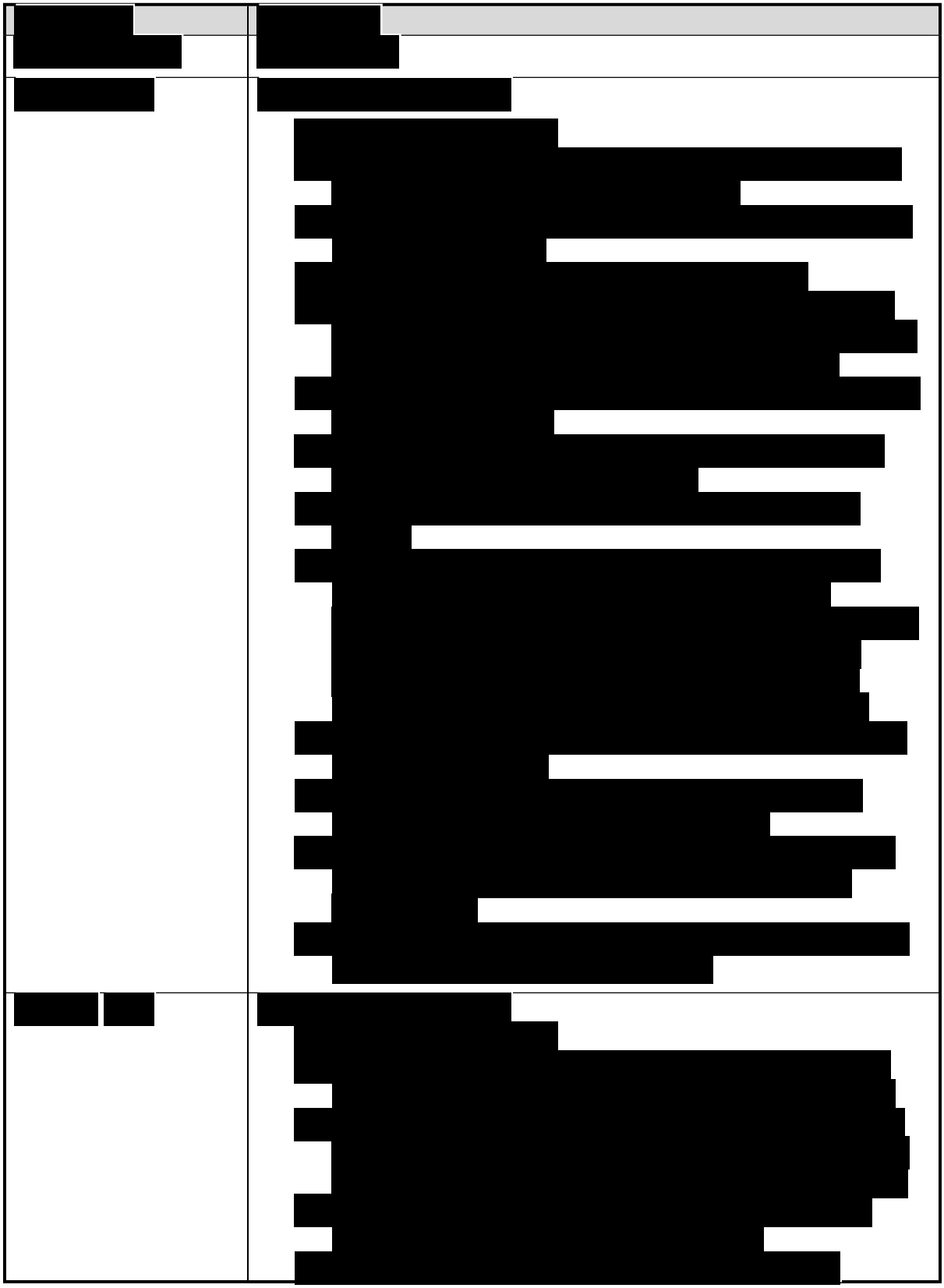
CLINICAL STUDY PROTOCOL

Title	**SYN**120 a Dual 5-HT_6/5-HT_{2A} **A**ntagonist **P**roof of Concept Study to Evaluate its **S**afety, Tolerability and **E**fficacy in Parkinson's Disease Dementia (SYNAPSE)
Protocol Number	SYN120-CL03
Phase	2a
IND Number	77,435
Date of Amendment 2	14 April 2016
Date of Amendment 1	16 April 2015
Original Date of Issue	02 October 2014
Sponsor	Biotie Therapies, Inc. 701 Gateway Boulevard, Suite 350 South San Francisco, CA 94080 USA [redacted]
Sponsor Study Director	[redacted]
Sponsor Chief Medical Officer	[redacted]

Confidential Material

[redacted]



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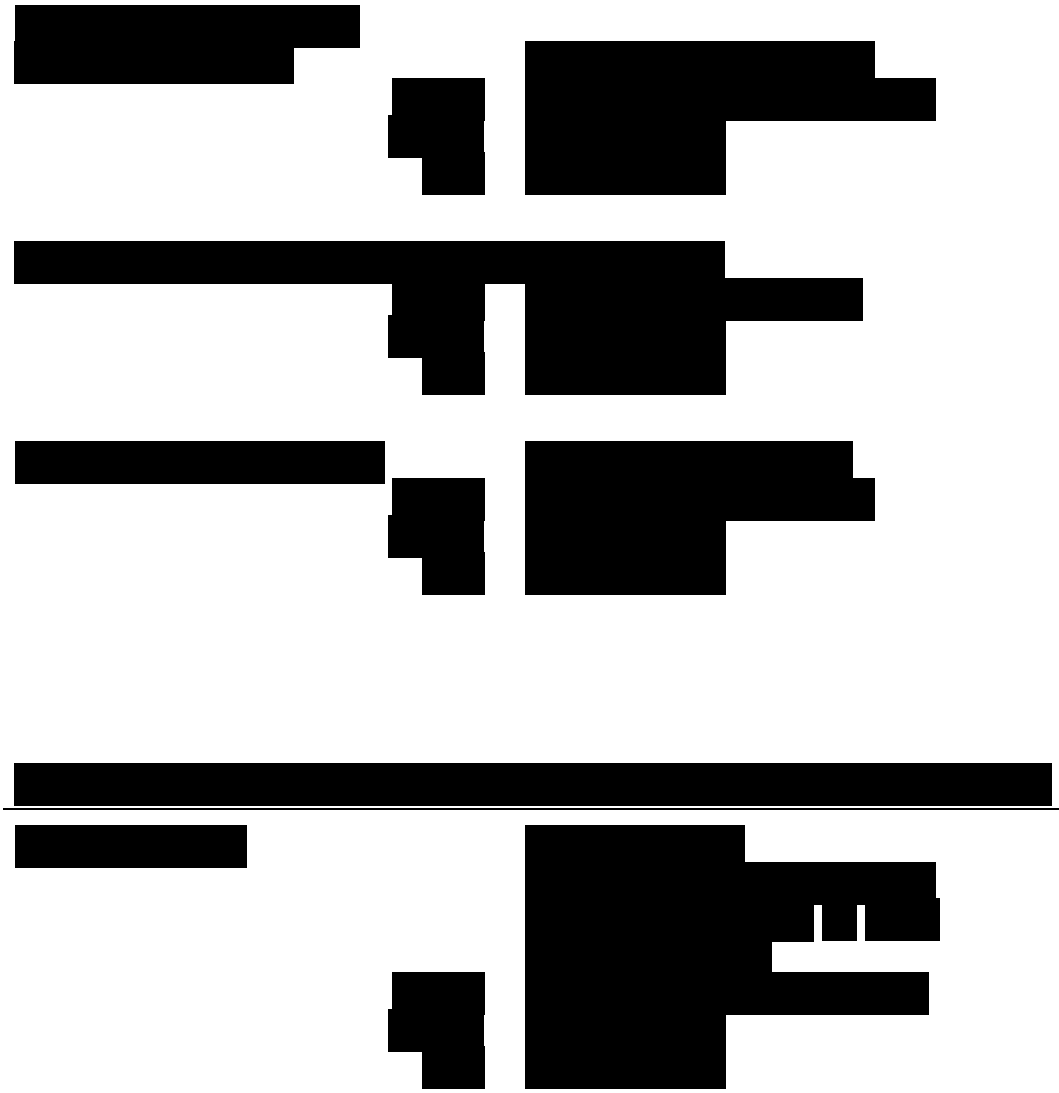
STUDY CONTACT INFORMATION

Biotie Therapies, Inc. – Sponsor



REPORTING OF SERIOUS ADVERSE EVENTS

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

1) Results in death.
2) Is life-threatening, i.e., places the patient, in the view of the Investigator, at immediate risk of death at the time of the event.
   a) Life-threatening does not refer to an event that hypothetically might have caused death if it were more severe.
3) Requires inpatient hospitalization or prolongation of existing hospitalization.
4) Results in persistent or significant disability/incapacity, i.e., results in a substantial disruption of a person's ability to conduct normal life functions.
5) Is a congenital anomaly or birth defect, i.e., an adverse event (AE) that occurs in the child or fetus of a patient exposed to a study drug prior to conception or during pregnancy
6) Is an important medical event, i.e., an event that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require medical or surgical intervention to prevent one of the other serious outcomes listed above.
   a) Examples of important medical events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions. Interruption, discontinuation, or adjustment of dose level of study drug alone will not be considered an intervention that satisfies the definition of important medical event.

Although fulfilling the above listed criteria, the following events are not regarded as being serious for this study:

1) Hospitalizations for:
   a) Facilitation of assessments specific to this protocol not associated with any deterioration in condition (e.g., when travel time between a patient's home and the study site would otherwise preclude adequate evaluation).
   b) Elective or preplanned assessment or treatment for a preexisting condition that has not worsened since initiation of study drug administration.

Any SAE meeting above criteria that occurs during the course of the study or within 4 weeks after the last dose of study drug must be reported within 24 hours (1 working day) of site awareness by **email** and/or fax by completing the SAE form.

[redacted]

Refer to additional SAE reporting instructions in **Section 8.9**.

CLINICAL STUDY PROTOCOL SIGNATURE PAGE

The undersigned have reviewed the format and content of this protocol and have approved Clinical Study Protocol SYN120-CL03 entitled "**SYN**120 a Dual 5-HT_6/5-HT_{2A} **A**ntagonist **P**roof of Concept Study to Evaluate its **S**afety, Tolerability and **E**fficacy in Parkinson's Disease Dementia (SYNAPSE)." Any modification of the clinical study protocol must be agreed upon by the Sponsor and the Investigator and must be documented in writing.

Sponsor: Biotie Therapies, Inc.

Protocol Number: SYN120-CL03

Amendment No.: **2**

Date of Amendment: **14 April 2016**

[redacted]

INVESTIGATOR'S STUDY ACKNOWLEDGMENT/DISCLOSURE

By my signature, I confirm that my staff and I understand that the protocol and Investigator's Brochure are the confidential and proprietary property of Biotie Therapies, Inc. Further, I/we have carefully read and understand this protocol and agree to comply with the conduct and terms of the study specified therein. In particular, I/we have agreed to:

1) Abide by all obligations per the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines and applicable country regulations.
2) Conduct the study according to the protocol, its amendments and study procedure manuals and study guides.
3) Assure that written and dated approval/favorable opinion from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the protocol, any amendments to the protocol, written informed consent form, any consent form updates, and Investigator's Brochure is available prior to initiation of any study-related procedure, and assure periodic review by the IRB/IEC as required per local and country regulations.
4) Obtain witnessed, written informed consent from each study participant or his/her legal representative.
5) Report all SAEs to Biotie Therapies, Inc. or its agents and to the IRB/IEC, as required by the protocol, country and IRB/IEC regulations.
6) Assure access by study monitors to original source documents.
7) Cooperate fully with any study-related Good Clinical Practice (GCP) audit as performed by Biotie Therapies, Inc. or its agents, the US Food and Drug Administration (FDA) and/or the Regulatory Health Authorities of the participating countries.
8) Maintain confidentiality and assure security of confidential documents such as the protocol, informed consent, case report forms, Investigator's Brochure, final study reports, study data, study procedure manuals, study guides, manuscript, and/or unpublished data and correspondence.
9) Maintain confidentiality of any supplemental information that may be added to this document.

Protocol Number: SYN120-CL03 **Date of Amendment 2**: **14 April 2016**

Principal Investigator's Signature Date

Principal Investigator's Name
(printed first and last name)

LIST OF ABBREVIATIONS

6-OHDA	6-hydroxydopamine
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale – cognitive subscale
ADCS	Alzheimer's Disease Cooperative Study
ADL	activity of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase (alanine aminotransferase)
ANOVA	analysis of variance
ANCOVA	analysis of covariance
AST	aspartate transaminase (aspartate aminotransferase)
ARO	academic research organization
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CIBIC+	Clinician's Interview Based Impression of Change Plus Caregiver Input
CDR	Cognitive Drug Research Computerized Cognition Battery
CGIC	Clinician's Global Impression of Change
CK	creatine phosphokinase
COMT	catechol-*O*-methyltransferase
CRA	Clinical Research Associate
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
eCRF	electronic case report form
ET	early termination
FDA	US Food and Drug Administration
FSH	follicle stimulating hormone
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase (gamma-glutamyl transferase)
GMP	Good Manufacturing Practice
hCG	human chorionic gonadotropin
hERG	human ether-a-go-go-related gene
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identifier
IEC	Independent Ethics Committee

IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
LDH	lactate dehydrogenase
MAD	multiple ascending dose
MAO-B	monoamine oxidase type B
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat analysis set (mITT sample)
MMRM	mixed model repeated measurement
MoCA	Montreal Cognitive Assessment
msec	Millisecond
NPI	Neuropsychiatric Inventory
PD	Parkinson's disease
PDD	Parkinson's disease dementia
PDAQ	Brief Penn Daily Activity Questionnaire
PET	positron emission tomography
PK	pharmacokinetic(s)
PP	per-protocol analysis set (PP set)
PR	interval from onset of P wave to start of QRS complex in electrocardiogram
PRN	as needed
RO	receptor occupying
QA	quality assurance
QD	once a day
QRS	interval from onset of Q wave to end of S wave in electrocardiogram
QT	interval between Q and T waves in electrocardiogram
QTc	heart rate-corrected QT
QTcF	heart rate-corrected QT calculated using Fridericia's correction formula
RR	interval between successive peaks of R wave in electrocardiogram
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SS	safety analysis set (safety sample)
ST	interval from end of QRS complex to beginning of T wave in electrocardiogram
T3	Triiodothyronine
T4	Thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
UK	United Kingdom

ULN	upper limit of normal
UPDRS	Unified Parkinson's Disease Rating Scale
US/USA	United States of America
UTI	urinary tract infection
V	Visit
W	Week
WHO	World Health Organization

PROTOCOL SYNOPSIS	
Title	**SYN**120 a Dual 5-HT_6/5-HT_{2A} **A**ntagonist **P**roof of Concept Study to Evaluate its **S**afety, Tolerability and **E**fficacy in Parkinson's Disease Dementia (SYNAPSE)
Protocol Number	SYN120-CL03
Phase	2a
Number of Sites/ Location	The study will take place in approximately 12 sites in the United States.
Test Product, Dose and Mode of Administration	Test Product: SYN120 tablets are manufactured in 10 mg and 50 mg dosage strengths. SYN120 Doses to be Administered: 1. 20 mg QD (1 week titration) 2. 50 mg QD (1 week titration) 3. 100 mg QD (14 weeks of maintenance) Comparator: Placebo Mode of Administration: Oral; each daily dose is taken once in the morning, approximately 30–60 min after breakfast.
Indication	Parkinson's disease dementia (PDD)
Study Objectives	Primary Efficacy Objective: The primary efficacy objective of this study is to assess the efficacy of a fixed dose of SYN120 on cognition as determined by the Cognitive Drug Research Computerized Cognition Battery (CDR) Continuity of Attention in patients with PDD treated with a stable dose of a cholinesterase inhibitor. Key Secondary Efficacy Objective: 1. To assess the effects of SYN120 on CDR Quality of Episodic Memory. Other Secondary Efficacy Objectives: 1. To assess the effects of SYN120 on the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC). 2. To assess the effects of SYN120 on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog). 3. To assess the effects of SYN120 on CDR Power of Attention. 4. To assess the effects of SYN120 on CDR Speed of Memory

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	Retrieval. 5. To assess the effects of SYN120 on the Brief Penn Daily Activity Questionnaire (PDAQ). 6. To assess the effects of SYN120 on the Scales for Outcomes in Parkinson's Disease-Sleep Scale (SCOPA-SLEEP) (nighttime sleep and daytime sleepiness). 7. To assess the effects of SYN120 on the Parkinson's Disease-Adapted Scale for Assessment of Positive Symptoms (SAPS-PD). 8. To assess the effects of SYN120 on the Neuropsychiatric Inventory (NPI). 9. To assess the effects of SYN120 on the Montreal Cognitive Assessment (MoCA). <u>Exploratory Objectives</u>: To assess the effects of SYN120 on the individual component tasks of the CDR, i.e., Word Presentation, Immediate Word Recall, Picture Presentation, Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Numeric Working Memory, Spatial Working Memory, Delayed Word Recall, Word Recognition, and Picture Recognition. <u>Safety Objectives</u>: The safety objectives are to assess the safety and tolerability of SYN120 by assessing adverse events (AEs), vital signs (including orthostatic blood pressure measurements), laboratory assessments, Unified Parkinson's Disease Rating Scale (UPDRS) Parts I-IV, Columbia-Suicide Severity Rating Scale (C-SSRS), and ECGs.
Study Population	Men or women at least 50 years old who have received a diagnosis of probable PDD according to the Movement Disorder Society Task Force clinical diagnostic criteria for dementia associated with Parkinson's disease (Emre et al., 2007) and who are taking a cholinesterase inhibitor.
Study Design	This is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled, parallel-group, two-arm, 16-week study in PDD patients taking a cholinesterase inhibitor. This includes a Screening Period of up to 6 weeks that starts with a Screening Visit, a 16-week Treatment Period, and a 2-week Safety Follow Up Period. After providing written informed consent, patients will undergo a screening evaluation. Patients must meet all inclusion criteria and none of the exclusion criteria. Final eligibility will be determined at

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	the Baseline Visit. Eligible patients will be randomized to receive placebo or SYN120 100 mg QD in a ratio of 1:1. Investigational Medicinal Product (IMP) will be dispensed to patients at each onsite visit and will be taken once daily for 16 consecutive weeks. SYN120 will be titrated as follows: 20 mg QD for the first 7 days, 50 mg QD for the next 7 days, and 100 mg QD for the remaining 14 weeks. Patients and caregivers will return to the study site for evaluations at Weeks 4, 8, and 16. Patients and caregivers will be telephoned at Weeks 2 and 12 to assess for AEs. Participants who discontinue IMP will remain on study following the normal schedule of assessments. Patients withdrawing consent will undergo an Early Termination Visit, ideally while still taking study medication, and return for a Safety Follow Up Visit approximately 2 weeks after their last dose administration.
Number of Patients to be Randomized	Approximately 80 patients will be randomized.
Randomization	At the Baseline Visit, patients will be randomly allocated in equal proportion to one of two treatment groups, SYN120 100 mg QD or placebo, according to a permuted-block randomization schedule, stratified by site.
Dose Groups	Group A: SYN120 100 mg QD. Group B: Placebo QD.
Dose Regimen	Randomized patients will be instructed to take 2 tablets of the dispensed blinded IMP in the morning, approximately 30-60 minutes after breakfast, preferably at the same time each day. After randomization, patients assigned to Group A will have their dose increased in a double-blind manner starting with 20 mg QD for the first 7 days, 50 mg QD for the next 7 days, and 100 mg QD for the remaining 14 weeks. Participants in Group B will take matching placebo tablets at each step of the titration. This is a fixed-dose study and study drug dosage may not be changed. Patients experiencing adverse effects considered study drug-related and not tolerated by the patient will discontinue IMP but remain on study.

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Concomitant Anti-Dementia and Anti-Parkinson Medications	Patients must be on a stable regimen of a cholinesterase inhibitor for at least 12 weeks before randomization. Treatment with memantine (Ebixa® or generic equivalents) is permitted, provided the dose has been stable for a minimum of 8 weeks prior to randomization. After randomization, all efforts should be made to maintain patients on the same stable dose of every anti-dementia and anti-Parkinson medication throughout the study. The addition of a new anti-dementia or anti-Parkinson medication is not permitted during the study; however, a decrease in total daily anti-dementia or anti-Parkinson medication dose because of medication-related AEs is permitted. Following a dose decrease of any anti-dementia or anti-Parkinson medication, the dose may be increased again but cannot exceed the total daily dosage at randomization.
Study Duration	Each patient will participate in the study for approximately 24 weeks: • Screening period: up to 6 weeks. • Treatment period: 16 weeks of dosing. • Safety Follow Up Visit: 2 weeks after the last dose of IMP.
Enrollment Period	Approximately 12 months.
Efficacy Endpoints	The primary efficacy endpoint is the change from Baseline to Week 16 on the CDR Computerized Cognition Battery Continuity of Attention captured in the ON state. The key secondary efficacy endpoint is the change from Baseline to Week 16 on the CDR Quality of Episodic Memory, captured in the ON state. The other secondary efficacy endpoints are the change from Baseline to Week 16 on the following measures: 1. Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC) captured in the ON state. 2. Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) total score captured in the ON state by an evaluator blinded to the results of all cognitive assessments. 3. CDR Power of Attention in the ON state. 4. CDR Speed of Memory Retrieval in the ON state. 5. PDAQ (reported by caregiver). 6. SCOPA-SLEEP (nighttime sleep and daytime sleepiness). 7. SAPS-PD.

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	8. NPI (reported by caregiver). 9. MoCA. Exploratory efficacy endpoints include the change from Baseline to Week 16 on the individual component tasks of the CDR, i.e., Word Presentation, Immediate Word Recall, Picture Presentation, Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Numeric Working Memory, Spatial Working Memory, Delayed Word Recall, Word Recognition, and Picture Recognition.
Inclusion and Exclusion Criteria	**Inclusion Criteria** Patients must fulfill all the following inclusion criteria in order to be included in the study: 1. Male or female and aged ≥ 50 years. 2. Caregivers and patients (or legal representative) must understand and have signed an Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent form to participate in this study. 3. Caregivers and patients (or legal representative) must be able to understand study requirements and be willing to follow instructions, attend all required study visits, and undergo all planned tests. 4. Patients are required to have contact with a responsible caregiver at least 3 days per week. 5. Patient has a documented history of idiopathic Parkinson's disease (PD) consistent with the UK Parkinson's Disease Society Brain Bank Diagnostic criteria. 6. The patient and/or caregiver have noted a cognitive decline and the patient has a diagnosis of probable PD dementia (PDD) according to the Movement Disorder Society Task Force clinical diagnostic criteria for dementia associated with PD (**Section 14.2**), with the onset of PDD symptoms occurring at least one year after the diagnosis of PD. 7. Patient has a Montreal Cognitive Assessment (MoCA) score of 10 to 23, inclusive, at Screening. 8. Patients must be on a stable regimen of cholinesterase inhibitor (Exelon®, Aricept®, or Reminyl® or their generic equivalent) for a minimum of 12 weeks prior to randomization. Treatment with memantine (Ebixa® or generic equivalents) is permitted, provided the dose has been stable for a minimum of 8 weeks prior to randomization. 9. Patient is maintained on a regimen of permitted anti-Parkinson medications (containing levodopa, dopamine agonists, MAO-B

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	inhibitors, or the COMT inhibitor entacapone), that has been stable for at least 4 weeks prior to Baseline. 10. Contraception: a. Women of childbearing potential must use an acceptable method of contraception starting 4 weeks prior to study drug administration and for a minimum of 1 month after study completion). Otherwise, women must be postmenopausal (at least one year absence of vaginal bleeding or spotting) as confirmed by FSH greater than or equal to 40 mIU/mL or 40 IU/L or be surgically sterile. b. Men with a potentially fertile partner must have had a vasectomy or be willing to use an acceptable method of contraception for the duration of the study and for 3 months after study drug discontinuation. Note: For men and women, acceptable methods of contraception include use of a condom with spermicide or use of oral, implantable or injectable contraceptives, or IUD, or a diaphragm with spermicide or diaphragm with condom. 11. Patients receiving treatment for depression may be enrolled if they have been on a stable daily dose of the antidepressant for ≥8 weeks before Baseline.
	Exclusion Criteria Patients with any of the following characteristics will be excluded from the study: 1. History of any significant neurologic or psychiatric disease other than PD not limited to, but including Alzheimer's disease (before onset of PD symptoms), multi-infarct or vascular dementia, Huntington's disease, normal pressure hydrocephalus, progressive supranuclear palsy, multiple sclerosis, intellectual disability/intellectual developmental disorder, Lewy body dementia, fronto-temporal dementia, major cortical stroke, major head trauma, primary or secondary cerebral neoplasia (except for benign stable extra-axial meningiomas), history of significant head trauma followed by persistent neurologic deficits, known structural brain abnormalities, delirium, schizophrenia or schizoaffective disorder. 2. Treatment with any other investigational drug within 5 half-lives or 30 days prior to screening (whichever is longer) or any investigational device within 30 days. 3. Any other condition or clinically significant abnormal findings on the physical or neurological examination, medical and

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	psychiatric history, at screening or at baseline that, in the opinion of the Investigator, would make the patient unsuitable for the study or put the patient at additional risk or prejudice evaluation of safety and efficacy of study drug. 4. Women who are pregnant or lactating. 5. Orthostatic hypotension requiring medication. 6. Hyperthyroidism or hypothyroidism, unless they meet all of the following conditions: a. They have received a stable dose of thyroid medication for at least 3 months prior to Baseline Visit. b. TSH concentrations are normal or within 10% of the upper or lower limit of the normal range. c. They are clinically euthyroid. 7. Clinically significant abnormal Vitamin B12 levels at Screening. 8. Any other out-of-range laboratory value at screening that have not been reviewed, approved, and documented as not clinically relevant by the Investigator. 9. Have a known allergy or sensitivity to SYN120 or any of its components. 10. Suicidal ideation on the C-SSRS of type 4 or type 5, or any suicidal behavior, in the past 6 months. Type 4 indicates active suicidal ideation with some intent to act, without a specific plan. Type 5 indicates active suicidal ideation with specific plan and intent. 11. Use of centrally acting anticholinergic drugs [redacted] (**Section 14.3**). 12. Treatment with any dopamine receptor blocking medication with the exception of low dose quetiapine (≤50 mg/day). 13. History of neurosurgical intervention for PD. 14. QTcF interval of ≥ 500 msec at Screening or an average QTcF interval ≥ 450 msec for males and ≥ 470 msec for females at Baseline (**Section 7.16**). 15. Unpredictable motor fluctuations that would interfere with administering all cognitive assessments in the ON state.
Overview of Study Procedures	Consenting patients will be screened for eligibility. Eligible patients who meet all entry criteria after completion of all screening assessments will return within 6 weeks. Patients meeting all eligibility criteria at Baseline will be randomized to double-blind treatment which will consist of two tablets every morning. Patients

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	randomized to SYN120 100 mg QD will receive two 10 mg tablets for the first 7 days, one placebo tablet and one 50 mg tablet for the next 7 days, and two 50 mg tablets every day for the remaining 14 weeks. Participants randomized to placebo will receive the same number of placebo tablets on the same titration schedule. After randomization, patients will be evaluated at clinic visits at Week 4 (28 ± 3 days), Week 8 (56 ± 3 days), and Week 16 (112 ± 3 days), and again 2 weeks (14 ± 3 days) following the Week 16 Visit (or at Early Termination, if applicable). Patients will also be contacted by the study site by telephone at Week 2 (14 ± 3 days) and Week 12 (84 ± 3 days) for assessment of AEs. At the clinic visits, patients will be asked to bring their study drug to the study site. Blood pressure and pulse (supine and standing) will be measured at each outpatient visit. Patients will be assessed for safety and tolerability in a blinded fashion regularly throughout the study and 2 weeks after their last dose of study drug. Please refer to the Schedule of Events/Evaluations in **Table 1** for specific timing of assessments.
Criteria for Withdrawal from Study	Investigational medicinal product may be discontinued for a given participant at any time if clinically significant out-of-range laboratory values or clinically significant abnormal findings on physical examination or intolerable AEs put the patient at additional risk, as judged by the Investigator. Patients will also discontinue IMP if their cognitive dysfunction or motor function worsens to the extent that in the judgment of the Investigator they require the addition of new medication to control their symptoms. Patients may withdraw consent and discontinue from the study for any reason. The Study Sponsor (Biotie Therapies) has the right to terminate the study at any time. All patients who withdraw consent prematurely will be requested to return for an onsite visit that includes all safety procedures as outlined for early termination in **Table 1**. For any early discontinuation, the patient should be requested to return for a Safety Follow Up Visit 2 weeks after the last dose of study drug, unless the Early Termination Visit itself occurs 2 or more weeks after the last dose of study drug.

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Safety Evaluations	Please refer to **Table 1** for Schedule of Events/Evaluations. Safety evaluations include: • AE reports • UPDRS • Supine and standing pulse and blood pressure • 12-lead ECGs • Safety labs: hematology, chemistry, urinalysis • C-SSRS • Concomitant medication assessment
SYN120 Plasma Concentrations	Blood samples will be collected for determination of SYN120 plasma concentrations [redacted] at Baseline (before the initiation of dosing), at Weeks 4, 8 and 16, and at Early Termination (if applicable). In addition, samples may be collected during unscheduled visits performed for AEs (optional, at the discretion of the Investigator).
Sample Size Justification	The primary efficacy measure is the change from Baseline to Week 16 in the total score on the CDR Computerized Cognition Battery Continuity of Attention. Based on a two-tailed test at alpha = 0.05 and assuming up to 15% loss to follow up, a total sample size of 80 randomized participants provides at least 80% power for a true treatment-dependent difference in 16-week change in CDR Continuity of Attention equal to an effect size of 0.69. Additional power will be obtained from analysis using a shared-baseline repeated measures analysis of variance (ANOVA).
Analysis Populations	Safety Analysis Set: The safety analysis set (SS) will consist of all randomized patients who received at least one dose of IMP. Modified Intention-to-Treat Analysis Set: The modified intention-to-treat (mITT) analysis set will consist of all randomized patients who received at least one dose of IMP and who have at least one valid baseline and at least one valid post-baseline assessment of the primary efficacy endpoint. Per-Protocol Analysis Set: The per-protocol (PP) analysis set will consist of a subset of the mITT analysis set, excluding any participants or observations potentially affected by important protocol deviations that might influence the validity of the data for testing efficacy and as specified in the Statistical Analysis Plan prior to breaking the blind.

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Statistical Analysis	Primary Outcome Variable The primary analysis will be performed on the mITT analysis set and will use a shared-baseline repeated measures ANOVA that includes fixed effects for visit and the interaction between treatment group and post-baseline visit, random center-specific intercepts, and unstructured within-person covariance. Secondary and Exploratory Outcome Variables Outcomes that are approximately normally distributed will be analyzed as described above for the primary outcome variable. Outcomes that are not normally distributed will be transformed or compared between the treatment groups using a van Elteren test that incorporates stratification by center. The key secondary outcome of CDR Quality of Episodic Memory will be tested for significance using the mITT analysis set at two-tailed alpha = 0.05. Other secondary outcomes will also be tested at two-tailed alpha = 0.05 using the mITT analysis set, recognizing that the totality of results will be evaluated in judging the potential of SYN120 as a therapeutic agent for PDD. Safety Analysis The assessment of safety will focus on the frequencies of individual AEs, vital signs (particularly orthostatic hypotension), UPDRS, abnormal laboratory test results, and ECG abnormalities, particularly treatment-emergent events. The frequency and type of any observed suicidal ideation will be described. The analyses will use the SS, Fisher's exact test for comparison of the proportion of participants in each treatment group experiencing a given AE or abnormal finding, and negative binomial regression for total counts of AEs. Tolerability Tolerance to SYN120 will be evaluated by recording the proportion of participants who discontinue IMP and by testing for a treatment-dependent difference in the time to discontinuation.

Table 1: Schedule of Events/Evaluations

Study Period	Screening [a]	Baseline Predose	16-Week Treatment Period (Double-blinded Dosing) (Days 1–112)					Safety Follow Up (Post Dose Follow Up)	Early Term.	Unscheduled
Study Week	−6 to −1	0	2 (±3 days)	4 (±3 days)	8 (±3 days)	12 (±3 days)	16 (±3 days)	18 (± 3 days)		
Assessments / Study Visit	V1	V2	V3 (phone call)	V4	V5	V6 (phone call)	V7	V8	V99	V98
Onsite clinic visit	X	X		X	X		X	X	X	X
Obtain patient and caregiver informed consent	X									
Demographics; medical history including neurological and PD/PDD history	X									
Concomitant medications including anti-dementia and anti-Parkinson meds	X [b]	X		X	X		X	X	X	X
BP and pulse (supine and standing) [c]	X x 3	X		X	X		X	X	X	X [d]
Weight (include height at Screening)	X						X		X	
Physical and neurological examination	X	X [d]		X	X		X		X	X [d]
MoCA	X						X		X	
Preliminary eligibility assessment by Investigator	X									
CDR Computerized Cognition Battery [e]	X x 2	X			X		X		X	
ADAS-cog [e]		X					X		X	
ADCS-CGIC [e]							X		X	
PDAQ (reported by caregiver)		X					X		X	
SCOPA-SLEEP		X					X		X	
SAPS-PD		X					X		X	
NPI (reported by caregiver)		X					X		X	
UPDRS Parts I–IV [f]		X		X	X		X	X	X	
Study drug accountability		X		X	X		X		X	X
Recording of AEs	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X		X	X		X	X	X	X [d]
Dispense IMP to patient/caregiver and provide dosing instructions		X		X	X					X [d]
FSH (♀ who are not surgically sterile and are postmenopausal, only)	X									
Urine hCG (♀ of childbearing potential, only) [g]	X	X		X	X		X		X	X [d]
Hematology [h], chemistry (including liver function) [i]	X	X		X	X		X		X	X [d]
TSH, freeT3 and free T4	X									
Vitamin B12	X									
Urinalysis [j]	X	X		X	X		X		X	X [d]
SYN120 blood sampling [k]		X		X [l]	X [l]		X		X [l]	X [d, l]
12-lead electrocardiogram [m]	X	X [n]		X	X		X		X	X [d]
Pharmacogenetic sample collection (optional)		**X [o]**		**X [p]**	**X [p]**		**X [p]**			

Table 1: Schedule of Events/Evaluations (cont.)

♀ = female; AEs, adverse events; ADAS-cog, Alzheimer's Disease Assessment Scale–cognitive subscale; ADCS-CGIC, Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change; BP, blood pressure; CDR, Cognitive Drug Research; C-SSRS, Columbia-Suicide Severity Risk Scale; ECG, electrocardiogram; FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin; IMP, investigational medicinal product; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; PD, Parkinson's disease; PDAQ, Brief Penn Daily Activities Questionnaire; PDD, Parkinson's disease dementia; SAPS-PD, PD-Adapted Scale for Assessment of Positive Symptoms; SCOPA-SLEEP, Scales for Outcomes in Parkinson's Disease-Sleep Scale; TSH, thyroid stimulating hormone; UPDRS, Unified Parkinson's Disease Rating Scale.

Footnotes:

[a] Screening period may not exceed 6 weeks. Note: For screen failures, document demographics and reason for ineligibility in source documents and eCRF.

[b] At Screening, obtain complete medication history including anti-dementia and anti-Parkinson medications (current and those received within the past year). Record the date and time of the most recent dose of each anti-dementia and anti-Parkinson medication taken prior to the Screening assessment.

[c] BP and pulse are to be measured after at least 5 minutes supine rest and again after standing for 1 and 3 minutes. At Screening Visit three sets of readings are performed approximately 10 minutes apart. This is the only visit with 3 sets of BP readings.

[d] Optional assessments that may be performed for evaluation of AEs, at the Investigator's discretion.

[e] Perform all cognitive and dementia-related assessments while patient is in ON state. Complete two training sessions during the screening period, as close to the Baseline visit as possible.

[f] UPDRS is to be measured in ON approximately 1 to 3 hours after patients have taken a scheduled dose of levodopa (preferably their morning dose of levodopa). Patients will be instructed to have already taken their normally scheduled dose of levodopa before arriving at the study site in order to have their UPDRS Part III evaluated in the ON state. UPDRS in the ON state will be measured at a time representative of the ON state in that patient, not in the patient's "best" ON.

[g] For female patients of childbearing potential, perform a urine hCG pregnancy test and document method of contraception at Screening and verify continuation of contraceptive method at each visit.

[h] Hematology: hemoglobin, hematocrit, red blood cell count, total and differential white blood cell, and platelet count.

[i] Chemistry: aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (conjugated and unconjugated), albumin, creatinine, urea/BUN, bicarbonate, uric acid, total protein, sodium, chloride, potassium, calcium, phosphate, glucose, cholesterol, and creatine phosphokinase (CK).

[j] Urinalysis: specific gravity, pH, ketones, blood, protein, and glucose. If urine dipstick positive for leukocytes, protein or erythrocytes, microscopic evaluation will be performed.

[k] Blood sample for determination of SYN120 plasma concentration [redacted] to be obtained at Baseline (Day 1) prior to initiation of dosing, Visit 4 (Week 4), Visit 5 (Week 8), Visit 7 (Week 16), Early Termination (if applicable), and Unscheduled Visit (optional, as per footnote d). Record date and time of SYN120 sample collection.

[l] For blood sample collections at Visit 4 (Week 4), Visit 5 (Week 8), Visit 7 (Week 16), and Early Termination or Unscheduled Visit (if applicable), record the date and time when the patient took the last dose of IMP.

[m] Resting supine 12-lead ECGs will be collected after the patient has been in a supine, or if unable, semi-supine (no more than 45 degrees) position for a minimum of 5 minutes. ECGs should be collected at a time during study visit when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

[n] At Baseline, obtain triplicate 12-lead ECGs (3 serial readings performed several minutes apart).

[o] **At Baseline, for patients who give consent for optional pharmacogenetic substudy, collect single blood sample (approximately 10 mL) for pharmacogenetic assessment. (If this sample is not collected at Baseline, it will be collected at the next possible in-clinic visit, i.e., Visit 4, 5 or 7.) See Section 7.13.**

[p] **For patients who give consent for optional pharmacogenetic substudy but sample not collected at Baseline (or during previous visit), collect single blood sample (approximately 10 mL) for pharmacogenetic assessment. See Section 7.13.**

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1.0 BACKGROUND AND RATIONALE

1.1 Background

Parkinson's disease (PD) is a chronic, progressive, neurodegenerative movement disorder characterized clinically by resting tremor, rigidity, bradykinesia and gait disturbance with postural instability. Other features can include masked faces, micrographia, and non-motor features including hyposmia, autonomic dysfunction, mood disturbances, and cognitive dysfunction. Estimates of the incidence and prevalence of PD vary considerably among studies due to differences in study populations, case ascertainment and diagnostic criteria. However, it is recognized that the incidence and prevalence of PD increase with age; and it is estimated that 1−2% of the population aged over 65 years are affected (**Von Campenhausen et al., 2005**).

The characteristic pathological findings in the brains of patients with PD are loss of dopaminergic neurons of the substantia nigra pars compacta coupled with the presence of intracytoplasmic inclusions (Lewy bodies). It is now appreciated that neurodegeneration also involves the olfactory system, the cerebral hemispheres, the lower brain stem, the spinal cord, and the peripheral autonomic nervous system.

The epidemiology of cognitive impairment in PD suggests that impairments occur in a range of cognitive domains, including memory, executive, visuo-spatial, attentional/working memory, and language functions; dementia is a common outcome; and other non-motor symptoms (e.g., hallucinations and depression) are risk factors for dementia. Cognitive deficits are associated with neurotransmitter impairment, including acetylcholine, dopamine, and norepinephrine.

1.2 Primary Target: 5-HT6R

Serotonin (5-HT) plays an important role in the regulation of many functions, including cognition, mood, sleep, and in pathological states such as Alzheimer's disease (AD) and PD (**Meneses et al., 2011**). 5-HT_6 receptors (5-HT_6R) are coupled to G proteins, inducing cAMP production through stimulation of adenylate cyclase activity. Human 5-HT_6 receptors are localized in brain regions involved in learning and memory processes including hippocampus, amygdala, striatum and neocortex (**King et al., 2008**). Using the radiolabelled 5-HT_6R antagonist [^{125}I] SB-258585, autoradiographic binding studies in rat brain show high receptor levels in striatum. Similarly, immunohistochemical staining shows high receptor levels in striatum, cortex, and hippocampus (**Yun et al., 2007**). The 5-HT_6R primary location in the striatum is relevant as cognitive dysfunction in PD links to striatal changes, particularly fronto-striatal alterations.

While the mechanism by which 5-HT_6R antagonists improve cognition in preclinical models and AD clinical studies is unknown, possible explanations relevant to Parkinson's disease dementia (PDD) involve multiple neurotransmitter systems. 5-HT_6R modulates cholinergic, dopaminergic, and glutamatergic function (**Dawson et al., 2001**; **Hirst et al., 2006**; **King et al., 2008**; **Riemer et al., 2003**; **Woolley et al., 2004**). Immunohistochemical staining for 5-HT_6R reveal

that it is localized on dendrites, cell bodies, and postsynaptic sites, and is expressed in cholinergic, glutamatergic and GABAergic neurons (**Woolley et al., 2004**; **Yun et al., 2007**). It has been consistently described that the influence of 5-HT$_6$R on memory is mediated, at least partially, by increased cholinergic neurotransmission (**Ramirez, 2013**). 5-HT$_6$R antagonists increase acetylcholine release in vitro (**Marcos et al., 2006**) and in vivo (**Riemer et al., 2003**).

Woolley et al. reported on the co-localization of 5-HT$_6$R with GABAergic neurons (**Woolley et al., 2004**); the co-localization together with microdialysis data suggest that 5-HT$_6$R antagonists modulate cholinergic and glutamatergic systems via disinhibition of GABAergic neurons. The 5-HT$_6$R agonist, WAY-181187, elicits robust increases in extracellular levels of GABA and attenuates long term potentiation. West et al. conclude that 5-HT$_6$R plays a role in the modulation of synaptic plasticity in hippocampal area CA1 and that the regulation of GABAergic interneuron activity may underlie the cognition enhancing effects of 5-HT$_6$R antagonists (**West et al., 2009**).

1.2.1 Preclinical Cognitive Data Using 5-HT$_6$R Antagonists (Other than SYN120)

A large body of preclinical data supports the use of 5-HT$_6$R antagonists to improve cognition (**Ramirez, 2013**; **Meneses et al., 2011**; **Fone, 2008**). Blocking 5-HT$_6$R produces anti-amnesic effects in the water maze, passive avoidance, autoshaping, fear conditioning, novel object recognition, and social memory (**Meneses et al., 2001**). 5-HT$_6$R antagonists have been reported to be active in the novel object discrimination test in rats and to improve water maze retention in aged rat (**Hirst et al., 2006**). Consistently, 5-HT$_6$R antagonists reverse scopolamine-induced cognitive deficits in the Morris water maze and novel object recognition test (**de Bruin et al., 2011**). 5-HT$_6$R blockade alleviates memory deficits more than improving memory in normal animals (**Ramirez, 2013**).

Combining SB-271046 with a cholinesterase inhibitor produces an additive increase in passive avoidance and scopolamine-induced amnesia (**Marcos et al., 2008**). The combined administration of sub-threshold doses of two 5-HT$_6$R antagonists, CMP X & CMP Y, with donepezil enhanced memory performance in rats with cognitive deficits induced by scopolamine (**de Bruin et al., 2011**).

1.2.2 Clinical Data in AD Using 5-HT6R Antagonists (Other than SYN120)

SB-742457 (15 mg and 35 mg) was evaluated in a 3-arm, double-blind, placebo-controlled study in 684 mild to moderate AD patients taking donepezil. At 24 weeks, significant differences in favor of the 35 mg dose group were seen using ADAS-cog with a placebo-corrected change from baseline of 1.5 points, and a favorable trend on the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL) (**GlaxoSmithKline [GSK] Study AZ3110866**).

As monotherapy, SB-742457 was evaluated in three 6-month AD studies. In one, 371 patients received placebo or 5, 15, or 35 mg/day. A significant linear trend in response across increasing doses on the Clinician's Interview Based Impression of Change Plus Caregiver Input (CIBIC+)

was seen, and a near-significant linear trend in ADAS-cog compared to placebo was noted for the 35 mg/day group (**Maher-Edwards et al., 2010**). The second study was an exploratory study evaluating the efficacy of a dose of 35 mg/day that was titrated from 15 mg/day for the first 4 weeks, with donepezil titrated from 5 mg/day to 10 mg/day during the first 4 weeks, and placebo. The differences from placebo at Week 24 for SB-742457 on CIBIC+ and ADAS-cog in this study were consistent with those observed in the previous Phase 2 study. There were also differences from placebo observed for donepezil. This study was not powered for formal hypothesis testing of superiority of either drug to placebo (**Maher-Edwards et al., 2011**). In the third study, 574 patients with mild to moderate AD received placebo, donepezil titrated from 5 mg/day to 10 mg/day during the first 4 weeks, and SB-742457 at 15 or 35 mg/day. SB-742457 at either dose did not show improvements in ADAS-cog and CIBIC+; donepezil showed a statistically significant improvement on CIBIC+, but not on ADAS-cog. In summary, this study was considered to partially flawed (**GSK Study AZ3110865**).

A placebo-controlled study of AE58054 in 278 moderate AD patients on donepezil for 24 weeks demonstrated placebo-adjusted ADAS-cog changes from baseline of 2.2 (p=0.004). The ADCS-ADL, AD Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC), and Neuropsychiatric Inventory (NPI) all showed favorable trends (**Colding-Jørgensen et al., 2014**).

1.2.3 [redacted]

[redacted]

1.3 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.4 [redacted]

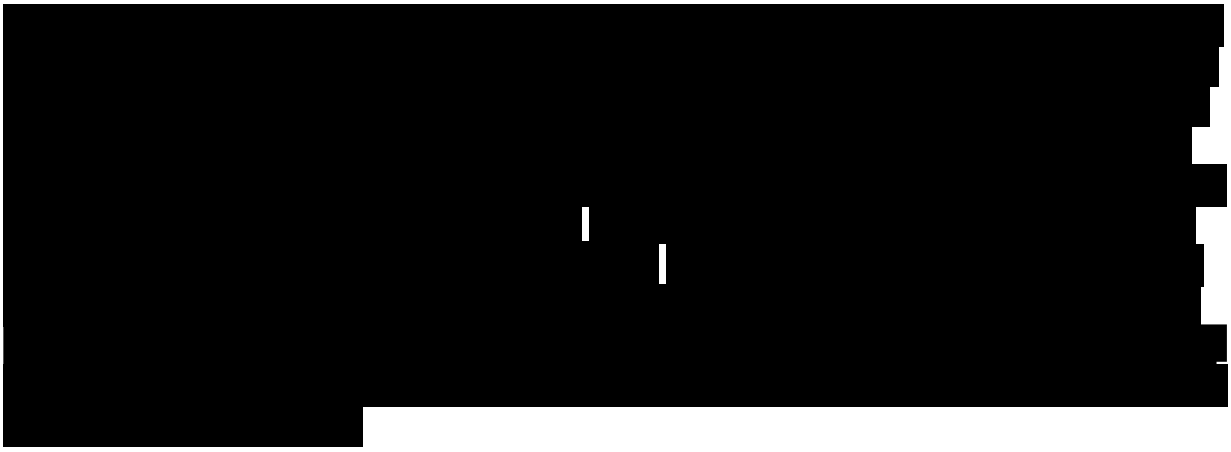
[redacted]

[redacted]

1.5 Trial Design/Methods

This placebo-controlled, randomized, double-blind study will assess the safety and efficacy of SYN120 in PDD patients as adjunctive therapy to a cholinesterase inhibitor. This 16-week study will randomize 80 patients to placebo or SYN120 100 mg daily in a 1:1 ratio. Patients will be required to be taking a cholinesterase inhibitor because this is largely considered to be the standard of care; furthermore, both preclinical and clinical data suggest that 5-HT_6R antagonists exert a more robust efficacy signal as adjunct to cholinesterase inhibitors.

The primary endpoint will be based on the CDR Computerized Cognition Battery Continuity of Attention. The key secondary endpoint is CDR Quality of Episodic Memory. Several secondary outcome variables will be used to further elucidate SYN120's anti-dementia activity including the ADCS-CGIC, ADAS-cog, CDR Power of Attention, and CDR Speed of Memory Retrieval. ADCS-CGIC is a seven-point scale that provides a global rating of change from baseline. The ADAS-cog subscale consists of 11 tasks measuring alterations of memory, language, praxis, attention and other cognitive abilities. To assess function, the 15-item Brief Penn Daily Activities Questionnaire (PDAQ) will be used (**Weintraub et al., 2013**). The Scales for Outcomes in Parkinson's Disease-Sleep Scale (SCOPA-SLEEP) will be used to assess if SYN120 improves nighttime sleep and daytime sleepiness. The Parkinson's Disease-Adapted Scale for Assessment of Positive Symptoms (SAPS-PD) and NPI will be used to determine if SYN120 improves psychosis or neurobehavioral disturbances.



Overall, the safety and efficacy data collected to date support further evaluation of SYN120 as a treatment for patients with PDD.

Please refer to the current SYN120 Investigator's Brochure (IB) for further information.

2.0 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Efficacy Objective

The primary efficacy objective of this study is to assess the efficacy of a fixed dose of SYN120 on cognition as determined by the Cognitive Drug Research Computerized Cognition Battery (CDR) Continuity of Attention in patients with PDD treated with a stable dose of a cholinesterase inhibitor.

2.1.2 Key Secondary Efficacy Objective

The key secondary efficacy objective is to assess the effects of SYN120 on CDR Quality of Episodic Memory.

2.1.3 Other Secondary Efficacy Objectives

The other secondary efficacy objectives are:

1. To assess the effects of SYN120 on the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC).

2. To assess the effects of SYN120 on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog).

3. To assess the effects of SYN120 on CDR Power of Attention.

4. To assess the effects of SYN120 on CDR Speed of Memory Retrieval.

5. To assess the effects of SYN120 on the PDAQ.

6. To assess the effects of SYN120 on the SCOPA-SLEEP (nighttime sleep and daytime sleepiness).

7. To assess the effects of SYN120 on the SAPS-PD.

8. To assess the effects of SYN120 on the NPI.

9. To assess the effects of SYN120 on the Montreal Cognitive Assessment (MoCA).

2.1.4 Safety Objectives

The safety objectives of this study are to assess the safety and tolerability of SYN120 by assessing AEs, vital signs (including orthostatic blood pressure measurements), laboratory assessments, Unified Parkinson's Disease Rating Scale (UPDRS) Parts I-IV, Columbia-Suicide Severity Rating Scale (C-SSRS), and ECGs.

2.2 Efficacy Endpoints

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline to Week 16 on the CDR Computerized Cognition Battery Continuity of Attention captured in the ON state.

2.2.2 Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the change from Baseline to Week 16 on the CDR Quality of Episodic Memory captured in the ON state.

2.2.3 Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints are the change from Baseline to Week 16 on the following measures:

1. Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change (ADCS-CGIC) captured in the ON state.

2. Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) total score captured in the ON state by an evaluator blinded to the results of all cognitive assessments.

3. CDR Power of Attention in the ON state.

4. CDR Speed of Memory Retrieval in the ON state.

5. PDAQ(reported by caregiver).

6. SCOPA-SLEEP (nighttime sleep and daytime sleepiness).
7. SAPS-PD.
8. NPI (reported by caregiver).
9. MoCA.

2.2.4 Exploratory Endpoints

Exploratory efficacy endpoints include the change from Baseline to Week 16 on the individual component tasks of the CDR, i.e., Word Presentation, Immediate Word Recall, Picture Presentation, Simple Reaction Time, Digit Vigilance, Choice Reaction Time, Numeric Working Memory, Spatial Working Memory, Delayed Word Recall, Word Recognition, and Picture Recognition.

2.2.5 Safety Endpoints

The safety of SYN120 will be evaluated using the following measures:

1. AE reports.
2. Supine and standing blood pressure (BP) and pulse.
3. Safety labs: hematology, chemistry, and urinalysis.
4. UPDRS Parts I-IV.
5. C-SSRS.
6. 12-lead ECGs.
7. Concomitant medication assessment.

2.2.6 Tolerability

Tolerability of SYN120 will be evaluated using the following measures:

1. Proportion of participants discontinuing IMP.
2. Proportion of participants discontinuing IMP due to an AE.
3. Time to discontinuation of IMP.

3.0 STUDY DESIGN

3.1 Study Description

This is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 2-arm study in patients with PDD treated with a stable dose of a cholinesterase inhibitor. The study includes a Screening Period of up to 6 weeks that starts with a Screening Visit, followed by a 16-week Treatment Period and a 2-week post dose Safety Follow Up Period. After providing legally effective written informed consent, patients will undergo screening evaluations. Patients must meet all inclusion criteria and none of the exclusion criteria to be considered for randomization. Final eligibility will be determined at the Baseline Visit.

Eligible patients will be randomized at the Baseline Visit (Week 0) to receive placebo or SYN120 (100 mg QD), in a ratio of 1:1. Double-blind investigational medicinal product (IMP) will be dispensed to patients upon randomization and at each clinic visit, with instructions to take 2 tablets of IMP daily for 16 consecutive weeks. Patients will return to the study site for evaluation at Weeks 4, 8 and 16. They will be contacted by telephone at Weeks 2 and 12 for assessment of AEs. Patients will return to the study site for a Safety Follow Up Visit approximately 2 weeks after their last dose administration (i.e., 14 ± 3 days after the Week 16 Visit).

Unscheduled visits to the clinic because of AEs or lost or stolen IMP can be arranged as considered necessary by the Investigator. Patients terminating early will undergo an Early Termination Visit, ideally under study medication, and should return for a Safety Follow Up Visit approximately 2 weeks after their last dose administration.

3.1.1 Study Duration Per Patient

Each patient will participate in the study for up to 24 weeks, which includes a Screening Period of up to 6 weeks, followed by a Baseline Visit, 16 weeks of double-blind treatment, and a 2-week post dosing Safety Follow-Up Visit:

- Screening Period: 1–6 weeks.
- Treatment Period: 16 weeks.
- Safety Follow-Up Period: 2 weeks.

The end of the study is defined as the date of the last visit of the last patient in the study.

3.1.2 Planned Number of Patients and Sites

Approximately, 120 patients will be screened, assuming a 33% screen failure rate, to randomize 80 patients.

Approximately 12 sites will participate in the study.

3.1.3 Anticipated Regions and Countries

This study will be conducted in the US.

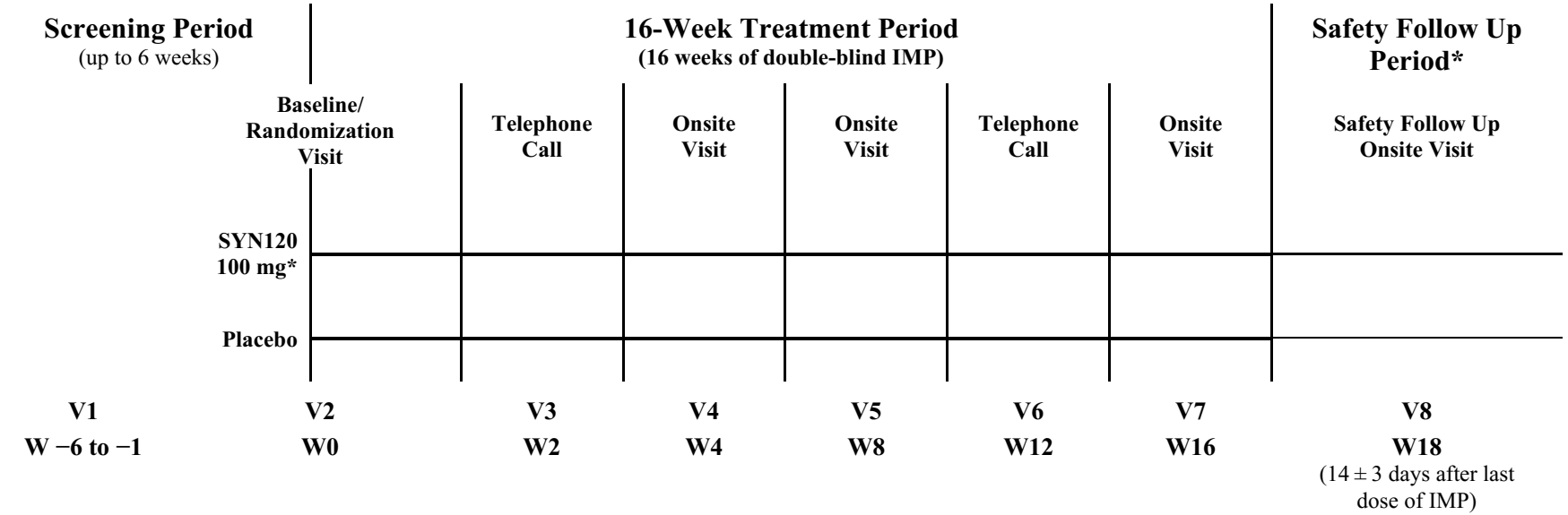
3.2 Schedule of Events/Evaluations

The Schedule of Events/Evaluations is shown in **Table 1**.

3.3 Schematic Diagram

A schematic diagram of the study design is provided in **Figure 6**, below.

Figure 6: Schematic Diagram of Study Design



V=Visit; W=Week.

* For each patient, dose escalation will proceed as follows: Total daily dose of 20 mg QD for the first 7 days, 50 mg QD for the next 7 days, and 100 mg QD for the remaining 14 weeks.

3.4 Rationale for Dose Selection and Placebo Control

Placebo was chosen as a comparator to establish a clear effect of SYN120 in patients with PDD.

4.0 SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

Patients must fulfill all of the following inclusion criteria in order to be included in the study:

1. Male or female and aged ≥ 50 years.

2. Caregivers and patients (or legal representative) must understand and have signed an Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent form to participate in this study.

3. Caregivers and patients (or legal representative) must be able to understand study requirements and be willing to follow instructions, attend all required study visits, and undergo all planned tests.

4. Patients are required to have contact with a responsible caregiver at least 3 days per week.

5. Patient has a documented history of idiopathic Parkinson's disease (PD) consistent with the UK Parkinson's Disease Society Brain Bank Diagnostic criteria.

6. The patient and/or caregiver have noted a cognitive decline and the patient has a diagnosis of probable PD dementia (PDD) according to the Movement Disorder Society Task Force clinical diagnostic criteria for dementia associated with PD (**Section 14.2**), with the onset of PDD symptoms occurring at least one year after the diagnosis of PD.

7. Patient has a Montreal Cognitive Assessment (MoCA) score of 10 to 23, inclusive, at Screening.

8. Patients must be on a stable regimen of cholinesterase inhibitor (Exelon®, Aricept®, or Reminyl® or their generic equivalent) for a minimum of 12 weeks prior to randomization. Treatment with memantine (Ebixa® or generic equivalents) is permitted, provided the dose has been stable for a minimum of 8 weeks prior to randomization.

9. Patient is maintained on a regimen of permitted anti-Parkinson medications (containing levodopa, dopamine agonists, MAO-B inhibitors, the COMT inhibitor entacapone, or the NMDA receptor antagonist amantadine), that has been stable for at least 4 weeks prior to Baseline.

10. Contraception:

    a. Women of childbearing potential must use an acceptable method of contraception starting 4 weeks prior to study drug administration and for a minimum of 1 month after study completion). Otherwise, women must be postmenopausal (at least one year absence of vaginal bleeding or spotting) as confirmed by FSH greater than or equal to 40 mIU/mL or 40 IU/L or be surgically sterile.

    b. Men with a potentially fertile partner must have had a vasectomy or be willing to use an acceptable method of contraception for the duration of the study and for 3 months after study drug discontinuation.

       Note: For men and women, acceptable methods of contraception include use of a condom with spermicide or use of oral, implantable or injectable contraceptives, or IUD, or a diaphragm with spermicide or diaphragm with condom.

11. Patients receiving treatment for depression may be enrolled if they have been on a stable daily dose of the antidepressant for ≥8 weeks before Baseline.

4.2 Exclusion Criteria

Patients with any of the following characteristics will be excluded from the study:

1. History of any significant neurologic or psychiatric disease other than PD not limited to, but including Alzheimer's disease (before onset of PD symptoms), multi-infarct or vascular dementia, Huntington's disease, normal pressure hydrocephalus, progressive supranuclear palsy, multiple sclerosis, intellectual disability/intellectual developmental disorder, Lewy body dementia, fronto-temporal dementia, major cortical stroke, major head trauma, primary or secondary cerebral neoplasia (except for benign stable extra-axial meningiomas), history of significant head trauma followed by persistent neurologic

deficits, known structural brain abnormalities, delirium, schizophrenia or schizoaffective disorder.

2. Treatment with any other investigational drug within 5 half-lives or 30 days prior to screening (whichever is longer) or any investigational device within 30 days.

3. Any other condition or clinically significant abnormal findings on the physical or neurological examination, medical and psychiatric history, at screening or at baseline that, in the opinion of the Investigator, would make the patient unsuitable for the study or put the patient at additional risk or prejudice evaluation of safety and efficacy of study drug.

4. Women who are pregnant or lactating.

5. Orthostatic hypotension requiring medication.

6. Hyperthyroidism or hypothyroidism, unless they meet all of the following conditions:

    a. They have received a stable dose of thyroid medication for at least 3 months prior to Baseline Visit.

    b. TSH concentrations are normal or within 10% of the upper or lower limit of the normal range.

    c. They are clinically euthyroid.

7. Clinically significant abnormal Vitamin B12 levels at Screening.

8. Any other out-of-range laboratory value at screening that have not been reviewed, approved, and documented as not clinically relevant by the Investigator.

9. Have a known allergy or sensitivity to SYN120 or any of its components.

10. Suicidal ideation on the C-SSRS of type 4 or type 5, or any suicidal behavior, in the past 6 months. Type 4 indicates active suicidal ideation with some intent to act, without a specific plan. Type 5 indicates active suicidal ideation with specific plan and intent.

11. Use of centrally acting anticholinergic drugs [redacted] during the 4 weeks before randomization (**Section 14.3**).

12. Treatment with any dopamine receptor blocking medication with the exception of low dose quetiapine (≤50 mg/day).

13. History of neurosurgical intervention for PD.

14. QTcF interval of ≥ 500 msec at Screening or an average QTcF interval ≥ 450 msec for males and ≥ 470 msec for females at Baseline (**Section 7.16**).

15. Unpredictable motor fluctuations that would interfere with administering all cognitive assessments in the ON state.

4.3 Criteria for Withdrawal from Study Drug or Study Participation

4.3.1 Study Drug Withdrawal

Investigators must contact the Medical Monitor to discuss any of the following events which may lead to the patient discontinuing study drug:

1. Patient is noncompliant with the study procedures or medications.

2. Patient takes prohibited concomitant medications as defined in this protocol or receives prohibited neurosurgical intervention for PD.

3. Patient has a clinically significant out-of-range laboratory value(s) or clinically significant abnormal finding(s) on physical examination or intolerable AEs (as determined by the patient) or that put the patient at additional risk as judged by the Investigator.

4. Patient's PDD symptoms worsen to the extent that, in the judgment of the Investigator, they require the addition of new anti-dementia medication or an increase in the dose of their concomitant cholinesterase inhibitor medication.

Any withdrawal of a patient from the study or discontinuation of study drug should be discussed with the Medical Monitor. Patients must discontinue study drug if any of the following events occur:

1. Patient develops an illness that would interfere with his or her continued participation.

2. Patient or caregiver (or legal representative, if applicable) withdraws consent.

3. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.

4. The Sponsor/Sponsor's designee or a regulatory agency requests withdrawal of the patient.

5. The Sponsor or a regulatory agency terminates the study.

6. Patient has active suicidality since last visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS, or reports any suicidal behavior since their last C-SSRS assessment. The patient should be referred immediately to a Mental Healthcare Professional.

7. The patient has a QTcF interval consistently ≥ 500 msec and/or a QTcF interval consistently increased by ≥ 60 msec compared to the average baseline QTcF interval (see **Section 7.16**). The average baseline QTcF interval is defined as the average of the three QTcF interval values obtained at Visit 2. Fridericia's method must be used for correction of QT intervals.

8. Investigators must follow guidelines provided related to monitoring hepatic parameters in relation to investigation guidelines and stopping rules. The following necessitate immediate cessation of dosing with IMP:

    a. Patients with alanine transaminase (ALT) or aspartate transaminase (AST) > 8x upper limit of normal (ULN).

    b. Patients with ALT or AST ≥ 3x ULN and co-existing total bilirubin ≥ 2x ULN*.

    c. Patients with ALT or AST ≥ 3x ULN who exhibit a temporally associated fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever (without clear alternative cause), rash or eosinophilia (> 5%) must be immediately temporarily or permanently discontinued from investigational product.

* Patients with significant elevation of ALP (ALP > 2x ULN) indicating biliary obstruction to be discussed with Study Physician.

4.3.2 Withdrawal from Study Participation

Patients are free to withdraw from the study at any time, without prejudice to their continued care.

All patients who discontinue prematurely from the study will be requested to return for a clinic visit that includes all safety procedures and efficacy measures as outlined for the Early Termination Visit in the Schedule of Events/Evaluations (**Table 1**). The Early Termination Visit should be done under IMP treatment, if possible.

For any early discontinuation, the patient will be requested to return for a Safety Follow-Up Visit 14 days after the last dose of IMP, unless the Early Termination Visit itself occurs 14 or more days after the last dose of IMP. All treatment-emergent, clinically significant AEs will be followed until resolution, return to Baseline level, or stabilization.

Patients who prematurely withdraw from the study will not be replaced.

Investigators should attempt to obtain information on patients in the case of study withdrawal. Participants who discontinue study drug but do not withdraw consent should continue to be followed according to the normal schedule of assessments. For patients considered lost to follow up, the Investigator should make an effort (at least one phone call and one written message to the patient) and document his or her effort (include the date and summary of the phone call(s) and a copy of the written message(s) in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the patient, must be recorded in the source documents. The electronic case report form (eCRF) must document the primary reason for study withdrawal or discontinuation.

Investigators should contact the Medical Monitor, whenever possible, to discuss in advance the withdrawal of a patient from the study.

5.0 STUDY TREATMENT(S)

5.1 Description of Investigational Medicinal Products

Table 4: Description of Investigational Medicinal Products

	SYN120	Placebo for SYN120
Dosage Form	Tablets (yellow, film-coated) containing 10 or 50 mg SYN120	Tablets (yellow, film-coated), matched to 10 or 50 mg SYN120 tablets (active)
Route of Administration	Oral	
Batch Number	Will be assigned according to Good Manufacturing Practice (GMP)	
Re-test Date	Will be assigned according to GMP	

5.2 Treatment(s) to be Administered

Investigational medicinal products are comprised of immediate-release, active and placebo tablets for oral administration, as described above. Placebo tablets are visually and physically indistinguishable from the active drug product and contain no active ingredient.

5.3 Packaging

The IMP will be packaged in a double-blind fashion according to current GMP guidelines and applicable national laws and regulations. They will be packaged in such a way as to protect the products from deterioration during transport and storage.

IMP will be packaged in blister cards containing **twenty-eight (28) days** per card. Each blister card will be labeled with a unique number corresponding to the randomization assignment. In addition, for each dispensing event one (1) reserve wallet will be provided to accommodate visit windows. The first blister card to be dispensed has an orange label designated as Weeks 1-4 and contains the doses during titration.

Sites will be supplied with an initial stock and resupply will be provided throughout the duration of the study in order to ensure sufficient supplies are available on site.

5.4 Labeling

Investigational medicinal product will be labeled in accordance with current FDA requirements and GMP.

5.5 Handling and Storage Requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site in accordance with labeling and written storage instructions. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access.

SYN120 tablets and placebo tablets should be stored at temperatures between 15°C and 25°C (59°F to 77°F) or under conditions meeting the US Pharmacopeial Convention (USP) requirements for Controlled Room Temperature. Appropriate storage conditions must be ensured either by controlled room temperature or by completion of a temperature log in accordance with local requirements on a regular basis (e.g., once a week), showing minimum and maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately communicated to the Sponsor (or designee) before further use of the IMP. The Sponsor (or designee) will transmit the out-of-range temperature (copy of the temperature log and duration of the out-of-range temperature, if available) to the Sponsor's Quality Assurance (QA) representative. Based on discussion with the Sponsor's QA representative, the Sponsor (or designee) will then provide the site with instructions regarding use of the IMP.

The Investigator (or designee) will instruct the patient to store the IMP following the instructions on the label.

5.6 Dosing Instructions

Randomized patients, **after taking the first dose in the clinic**, will be instructed to take 2 tablets of the dispensed blinded IMP in the morning, approximately 30-60 minutes after breakfast, preferably at the same time each day, using the blister cards dispensed by study site personnel for a given study week.

5.7 Drug Accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-patient basis and will serve as source documentation during the course of the study. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for Sponsor (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and **either** returned to Sponsor (or designee), preferably in their original package**, or destroyed on-site according to the site's SOP(s). Refer to the Pharmacy Manual for instructions**. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

5.8 Procedures for Monitoring Patient Compliance

At each visit after IMP is dispensed, patients must return all unused IMP and empty IMP containers. Drug accountability must be done in the patient's presence in order to obtain explanations regarding discrepancies in compliance with the dosing regimen. Drug accountability must be recorded on the Drug Accountability form. Upon the patient's Safety Follow Up Visit (or Early Termination Visit, if applicable), the authorized study staff will enter the date of the last dose of IMP into the eCRF registering the end of treatment for that patient.

If a patient is found to be persistently noncompliant (≤ 80 to $\geq 120\%$ of the assigned dose), the Sponsor or designee, in conjunction with the Investigator, will make a decision as to whether the patient should remain on study drug.

5.9 Concomitant Medications/Treatments

5.9.1 Allowed Anti-Dementia Medications/Treatments

Patients must be on a stable regimen of a cholinesterase inhibitor for at least 12 weeks before randomization. Treatment with memantine (Ebixa® or generic equivalents) is permitted, provided the dose has been stable for a minimum of 8 weeks prior to randomization.

After randomization, all efforts should be made to maintain patients on the same stable dose of every anti-dementia and anti-Parkinson medication throughout the study. The addition of a new anti-dementia or anti-Parkinson medication is not permitted during the study; however, a

decrease in total daily anti-dementia or anti-Parkinson medication dose because of medication-related AEs is permitted. Following a dose decrease of any anti-dementia or anti-Parkinson medication, the dose may be increased again but cannot exceed the total daily dosage at randomization. Patients will use their own supply of cholinesterase inhibitor and anti-Parkinson medications.

5.9.2 Prohibited Concomitant Medications/Treatments

The following concomitant medications and therapies are prohibited during the study:

1. Neurosurgical intervention for PD, including but not limited to deep brain stimulation.
2. Centrally acting anticholinergic drugs are prohibited for 4 weeks before randomization and throughout the study. See **Section 14.3**.
3. [redacted]

5.9.3 Other Concomitant Medications/Treatments

Patients taking thyroid medication for hypothyroidism or hyperthyroidism must be on a stable dose for at least 3 months prior to the Screening Visit.

Restrictions on pre-study use of medications are described in **Section 4.2**, Exclusion Criteria, and these restrictions will continue throughout the study.

During the study, patients are asked to refrain from the use of any concomitant medication, including herbal and over-the-counter medicines, without the specific prior approval by the Investigator. Any medication taken by a patient during the course of the study and the reason for its use will be recorded in the source documents and eCRF.

5.10 Blinding

The randomization schedule will be produced by an unblinded statistician who is otherwise not involved with the study team, Steering Committee, or Sponsor. The randomization schedule will use permuted blocks, stratified by site. The IMP vendor will generate unblinding **scratch-off labels** for patients' randomization assignments based on the randomization schedule produced by the unblinded statistician. The randomization schedule and unblinding **scratch-off labels** will be kept strictly confidential until the time of unblinding and should not be **scratched off** without authorization. Blinding will not be compromised for individuals involved with operational aspects of the study or individuals involved with the planning and conduct of the final statistical analyses, including an independent statistician. **Scratch-off labels should be removed from the kit and adhered in the patient's source document.**

The identity of the dosing group assignments will be concealed by identical appearance, packaging, labeling, and schedule of administration.

5.10.1 Procedures for Breaking the Treatment Blind in an Emergency Situation

In the event of an emergency, during which knowledge of the IMP received would affect the medical management of the patient, or for a regulatory requirement, it will be possible for the Investigator to determine to which treatment arm and dose the patient has been allocated by accessing the unblinding **scratch-off label** for the given patient, **which must be maintained in the source documentation**. All sites will be provided with details of how to perform unblinding on an emergency basis at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

All events resulting in an unblinding event will be recorded and reported by the Investigator to the Medical Monitor and the Sponsor or designee. If the blind is broken for an individual patient due to a medical emergency, the date and time of unblinding together with the reason for the unblinding will be recorded in the patient's source records, and all associated AE information will be included. The unblinding event and the date of unblinding will be noted in the eCRF to enable censoring of any data as appropriate.

5.11 Randomization and Numbering of Patients

Assignment of the next available sequentially numbered kit at a given site will be used for assigning eligible patients to a treatment regimen based on a predetermined randomization schedule. The final randomization schedule will be created and sent to the clinical supply packaging vendor. The clinical supply packaging vendor is responsible for packaging blister cards of the blinded IMP into numbered kits according to the randomization and the visit schedule.

To enroll a patient (Visit 1), the Investigator will assign a screening number to each patient, which serves as the patient identifier throughout the study. The patient number will be required in all communication between the Investigator (or designee) and the Sponsor or academic research organization (ARO) regarding a particular patient. Patient numbers and assigned IMP kit numbers will be tracked by the electronic data management system.

To randomize a patient (Visit 2), the Investigator (or designee) will assign the next available sequentially numbered kit at the site to the patient. The assigned kit number will be recorded in the source and eCRF. The Investigator or a designated study coordinator or pharmacist will dispense the assigned IMP kit to the patient.

6.0 STUDY PROCEDURES BY VISIT

6.1 Overview of Study Procedures

An overview of the conduct of the study, including the timing of visits and assessments performed, may be found in **Table 1**. Details of assessment methods can be found in **Section 7.0** and **Section 8.0**, respectively, and in the applicable appendices. Pharmacokinetic sample collection is described in **Section 7.12**. Detailed procedures by study visit are provided in **Section 6.2**.

Note: Laboratory supplies that are needed for protocol-specified tests will be provided by the central laboratory.

Consenting patients will be screened for eligibility. Eligible patients who meet all the entry criteria at Baseline will be randomized to receive double-blind IMP for 24 weeks. The first dose of IMP will be administered at the study site during the Baseline Visit, **approximately 30-60 minutes after lunch or a substantial snack. It is recommended that patients remain at the clinic for 2-4 hours after initial dosing for observation**. Patients will return to the study site for evaluation at Weeks 4, 8 and 16. They will be contacted by telephone at Weeks 2 and 12 for assessment of AEs. Patients and their caregivers will be requested to bring the IMP blister cards (used and unused) dispensed at the previous visit to the next clinic visit, to take their IMP in the morning, approximately 30 – 60 min after breakfast, before the clinic visit (as applicable), and to bring their other medications with them to the clinic visit.

Enrolled patients treated with levodopa who have end-of-dose motor fluctuations will be instructed to have already taken their normally scheduled dose of levodopa and their IMP prior to arriving at the study site in order to have their UPDRS Part III evaluated in ON. UPDRS in OFF will not be evaluated. The Investigator or Sub-Investigator will perform the full UPDRS Parts I, II III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in ON will be measured at a time representative of the ON state in that patient, not in “best” ON. All cognitive and dementia-related assessments will be performed while the patient is in ON state.

Blood pressure and pulse (supine and standing) will be taken at each outpatient visit.

Patients will be assessed for safety and tolerability in a blinded fashion regularly throughout the study and approximately 2 weeks after their last dose of IMP.

Please refer to the Schedule of Events/Evaluations in **Table 1** for specific timing of assessments. At each visit, the investigator or Sub-Investigator will assess ON/OFF status only at the initiation of each assessment for each of the 3 cognitive scales (CDR, ADAS-cog and MoCA).

6.2 Detailed Study Procedures

6.2.1 Recruitment and Written Informed Consent

Interested patients and their caregivers (or legal representatives, if applicable) will be scheduled to meet with a qualified investigative staff member and receive an explanation of the study purpose and requirements in lay language. If still interested in participating after receiving an explanation of the study, patients and their caregivers (or legal representatives, if applicable) will be given an opportunity to review and inquire about the study-specific written informed consent form. Patients and their caregivers (or legal representatives, if applicable) should have ample time to think about the information in the written informed consent form and have a chance to discuss it with family members or other people.

Any patient and caregiver (or legal representative, if applicable) who has difficulty understanding the information contained in the written informed consent form will be asked to reread the misunderstood portion(s) of the consent and discuss it with a research staff member until s/he shows complete understanding of the information discussed in the informed consent form, and may thus give full consent. Research staff will work closely with patients and their caregivers in an effort to help them understand the requirements of study participation. Patients' and caregivers' (or legal representatives') questions must be answered fully by trained and qualified staff. Any patient or caregiver (or legal representative, if applicable) who is unable to demonstrate understanding of the information contained in the informed consent form will be excluded from study participation.

Prior to a patient's participation in the study, the written IRB/IEC-approved informed consent form will be signed and personally dated by the patient (or legal representative, if applicable) and by the person who conducted the informed consent discussion. In addition, a statement to document the informed consenting process will be recorded in the patient's source documents.

The consent form and any other information provided to patients (or legal representative, if applicable) will be revised whenever important new information becomes available that is relevant to a patient's consent and continued participation in the study. The revised consent form and information will receive IRB/IEC approval/favorable opinion prior to use, and a copy of said IRB approval/favorable opinion should be returned to the Sponsor. The Investigator, or a person designated by the Investigator, should fully inform all patients of all pertinent aspects of the study and any new information relevant to the patients' willingness to continue participation in the study. This communication with the patient should be documented by the patient (or legal representative, if applicable) signing and personally dating the revised consent form and by written documentation of this discussion with the patient (or legal representative, if applicable) in the Investigator's study files available to Sponsor for onsite review.

Each patient (or legal representative, if applicable) who consents to participate in the study will receive a copy of the signed and dated written informed consent form and any other information provided to patients prior to the participation in the study. The original signed forms will be maintained in the Investigator's study file.

After providing and documenting consent on the IRB/IEC-approved written informed consent form, patients will be assigned their patient screening number and proceed to the Screening Period.

6.2.2 Visit 1 (Week -6 to -1) Screening and Baseline Predose

The following assessments will be obtained during the Screening Period and used to determine whether patients meet eligibility criteria for the study. Patients meeting eligibility criteria at Screening must also meet eligibility criteria at the Baseline Visit.

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Screening Visit with the courier (see Central Laboratory Procedures Manual).

6.2.2.1 Screening Assessments

1. Verify written informed consent has been signed and a copy provided to the patient and caregiver (or legal representative, if applicable).

2. Obtain demographics and previous medical history including neurological and PD history.

3. Assess and record any co-existing pretreatment AEs.

4. Obtain complete medication history including anti-dementia and anti-Parkinson medications (current and those received within the past year). Record the date and time of the most recent dose of each anti-dementia and anti-Parkinson medication taken prior to the Screening assessment.

5. Obtain and record BP and pulse after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes, on 3 occasions approximately 10 minutes apart.

6. Obtain weight and height.

7. Perform physical and neurological exam.

8. Administer the MoCA.

9. Administer the Cognitive Drug Research Computerized Cognition Battery (CDR) two times during the screening period, as close to the Baseline visit as possible. (Note: The CDR sample version administered at Screening will not be evaluated, but will be used to familiarize patients with the test procedures and reduce the risk of practice effects as a potential confounder.)

10. Administer C-SSRS.

11. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

12. Obtain samples for the following laboratory tests and record the date and time of collection:

    a. Females who are not surgically sterile and are postmenopausal < 2 years: Obtain a blood sample for FSH.

    b. Females of childbearing potential: Obtain urine hCG pregnancy test; document method of contraception.

    c. Hematology and chemistry (including liver function tests).

    d. TSH, free T3, and free T4.

    e. Serum vitamin B12.

    f. Urine sample for urinalysis.

13. If the patient does not meet the criteria for study participation, or if a laboratory result disqualifies the patient from participation in the study, the patient is considered a screen failure. Record the primary reason for screen failure in the appropriate eCRF module and on the Patient Screening/Enrollment Log. Schedule the patient's next routine non-study visit as appropriate.

14. For patients who appear to be eligible, proceed with scheduling the Baseline Visit, and instruct the patient and caregiver to bring the patient's medications (including anti-dementia and anti-Parkinson medications) to the next study visit and to maintain their regular treatment schedule.

15. If the patient is a screen failure, record the primary reason for screen failure in the appropriate eCRF module and on the Patient Screening/Enrollment Log.

16. The following data must be collected for all consented individuals, even if they fail screening: demographics, and reason for ineligibility.

6.2.3 Visit 2 (Week 0) Baseline

6.2.3.1 Pre-dosing Baseline Procedures

Randomization will occur at the Baseline (Visit 2), after the patient's eligibility for the study has been confirmed and all pre-dosing Baseline procedures have been performed.

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Baseline Visit with the courier (see Central Laboratory Procedures Manual).

Note: Patients will continue to take their anti-dementia and anti-Parkinson medications and other medications according to their regular treatment schedule.

Note: Due to the time involved with the visit, the patient will need to eat lunch or a substantial snack during the visit approximately 30-60 minutes before dosing in the clinic.

6.2.3.2 Confirm Patient's Eligibility for Study Participation

1. Assess for any co-existing pretreatment AEs by asking open-ended queries and record the assessments. Evaluate pretreatment AEs (including any AEs noted during the Screening Visit plus any new onset AEs) to ensure patient's continued eligibility for the study.

    a. If appropriate, a physical or neurological examination should be performed for an ongoing pretreatment AE.

2. Record concomitant medication use and ensure there have been no changes in medication (particularly anti-dementia medication) since preliminary screening that would make the patient ineligible for the study.

3. If the patient does not meet the criteria for study participation, the patient is considered a screen failure. Record the primary reason for screen failure in the appropriate eCRF module and on the Patient Screening/Enrollment Log. Schedule the patient's next routine non-study visit as appropriate.

6.2.3.3 Perform Baseline Assessments

1. Obtain and record BP and pulse after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.

2. Administer the following assessment instruments, in the order shown. The order may be adjusted to keep the physician assessments together; however, it is imperative that the CDR and ADAS-cog are performed first and second, in order to reduce the chance of patient fatigue. Perform all cognitive and dementia-related assessments while patient is in ON state. ON will be measured at a time representative of the ON state in that patient, not in "best" ON.

   a. CDR.

   b. ADAS-cog.

   c. Perform full UPDRS Parts I, II III (motor) and IV.

      For patients with motor fluctuations: Perform full UPDRS Parts I, II III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in ON will be measured at a time representative of the ON state in that patient, not in "best" ON.

   d. PDAQ (reported by caregiver).

   e. SCOPA-SLEEP.

   f. SAPS-PD.

   g. NPI (reported by caregiver).

3. Administer C-SSRS.

4. Obtain triplicate 12-lead ECGs (3 serial readings performed several minutes apart) and ensure the ECGs are collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

5. Obtain samples for the following laboratory tests and record the date and time of collection:

   a. Females of childbearing potential: Obtain urine hCG pregnancy test; verify method of contraception has not changed since Screening.

   b. Hematology and chemistry (including liver function tests).

   c. Blood sample for SYN120 plasma concentration [redacted] Record the date and time of SYN120 sample collection.

d. Blood sample for optional pharmacogenetic substudy (only if patient gave consent for the pharmacogenetic substudy): A single blood sample (approximately 10 mL) will be collected per patient. (If the sample is not collected at Baseline, it will be collected at the next possible visit.) See **Section 7.13.**

e. Urine sample for urinalysis.

6. If the patient does not meet the criteria for study participation, the patient is considered a screen failure. Record the primary reason for screen failure in the appropriate eCRF module and on the Patient Screening/Enrollment Log. Schedule the patient's next routine non-study visit as appropriate.

6.2.3.4 Randomization and Dosing with Investigational Medicinal Product

1. For patients meeting all entry criteria, obtain the randomization assignment by following the randomization procedures provided.

2. Dispense the blister cards assigned according to the patient's randomization assignment.

   a. Record the dates the patient should take IMP onto each blister card.

3. Review the dosing instructions for the IMP with the patient and caregiver, answer any questions, and remind the patient and caregiver to return the blister cards at the next clinic visit.

   a. Patients and caregivers will be instructed that the patient is to take 2 tablets of the dispensed blinded IMP by mouth once daily, approximately 30-60 minutes after breakfast, preferably at the same time each day.

   b. Document patient and caregiver understood dosing instructions and the use of the extra days if visit delayed and/or use of visit window.

4. Record the following information: patient randomization number, date and time blister card dispensed.

   a. Patient to take the first dose of IMP at study site, approximately 30 to 60 minutes after having consumed lunch or a substantial snack. All future doses will be taken 30-60 minutes following breakfast.

   b. It is recommended that patients remain at the clinic for 2-4 hours for observation following dosing. If the patient develops symptoms consistent with hypotension, blood pressure and pulse readings should be performed.

5. Schedule the Week 2 visit (telephone call).

6. Transcribe the randomization number on the paperwork for the laboratory samples that were drawn prior to receipt of IMP.

7. Complete eCRF information in the designated modules.

6.2.4 Visit 3 (Week 2) Telephone Call

1. Patients and caregivers will be reminded of the following:

   a. Instructions for taking the IMP.

   b. Need to bring the blister cards (used and unused) dispensed at the previous visit to the next clinic visit.

   c. Need to take the IMP in the morning, approximately 30 – 60 min after breakfast, before the next clinic visit.

   d. Need to take all doses of their routine medications (including anti-dementia and anti-PD medications) according to their normal schedule on the day of the next clinic visit and to bring their medications with them to the visit.

   e. Date and time of the next clinic visit (Week 4).

2. Assess AEs by asking open-ended queries and record the assessments.

3. Complete eCRF information in the designated modules.

6.2.5 Visit 4 (Week 4) Study Visit

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 4 visit with the courier (see Central Laboratory Procedures Manual).

1. Assess AEs by asking open-ended queries and record the assessments.

2. Record concomitant medication use; assess and record any changes to anti-dementia or anti-Parkinson medication doses or regimens.

3. Obtain and record BP and pulse after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.

4. Perform physical and neurological exam.

5. Perform full UPDRS Parts I, II III (motor) and IV.

   For patients with motor fluctuations: Perform full UPDRS Parts I, II III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in ON will be measured at a time representative of the ON state in that patient, not in "best" ON.

6. Administer C-SSRS.

7. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

8. Obtain samples for the following laboratory tests and record the date and time of collection:

   a. Females of childbearing potential: Obtain urine hCG pregnancy test; verify method of contraception has not changed since Screening.

   b. Hematology and chemistry (including liver function tests).

   c. Blood sample for SYN120 plasma concentration [redacted] Obtain and record the date and time when the patient took the last dose of IMP. Record the date and time of SYN120 sample collection.

   d. Blood sample for optional pharmacogenetic substudy (only if patient gave consent for the pharmacogenetic substudy and specimen was NOT collected during a previous visit): A single blood sample (approximately 10 mL) will be collected per patient. See **Section 7.13**.

   e. Urine sample for urinalysis.

   Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

9. Obtain the returned blister cards dispensed at the Baseline Visit:

   a. Assess and document the IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).

   b. Review and reconcile any discrepancies with the patient and caregiver.

10. Dispense blister card numbers per the patient's randomization assignment (7 days per card) to the patient (includes 1 extra blister pack in case of delayed visit and/or use of visit window).

    a. Record the dates the patient should take IMP onto the blister cards.

11. Review the dosing instructions for the IMP with the patient and caregiver, answer any questions, and remind the patient and caregiver to return blister cards at the next clinic visit.

    a. Document patient understood dosing instructions and the use of extra days if visit delayed and/or use of visit window.

12. Schedule the next visit (Week 8).

13. Complete eCRF information in the designated modules.

6.2.6 Visit 5 (Week 8) Study Visit

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 8 visit with the courier (see Central Laboratory Procedures Manual).

1. Assess AEs by asking open-ended queries and record the assessments.

2. Record concomitant medication use; assess and record any changes to anti-dementia or anti-Parkinson medication doses or regimens.

3. Obtain and record BP and pulse after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.

4. Perform physical and neurological exam.

5. Administer the CDR while patient is in ON state.

6. Perform full UPDRS Parts I, II III (motor) and IV.

   For patients with motor fluctuations: Perform full UPDRS Parts I, II III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in ON will be measured at a time representative of the ON state in that patient, not in "best" ON.

7. Administer C-SSRS.

8. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

9. Obtain samples for the following laboratory tests and record the date and time of collection:

    a. Females of childbearing potential: Obtain urine hCG pregnancy test; verify method of contraception has not changed since Screening.

    b. Hematology and chemistry (including liver function tests).

    c. Blood sample for SYN120 plasma concentration [redacted] Obtain and record the date and time when the patient took the last dose of IMP. Record the date and time of SYN120 sample collection.

    d. Blood sample for optional pharmacogenetic substudy (only if patient gave consent for the pharmacogenetic substudy and specimen was NOT collected during a previous visit): A single blood sample (approximately 10 mL) will be collected per patient. See **Section 7.13**.

    e. Urine sample for urinalysis.

    Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

10. Obtain the returned blister cards dispensed at the Week 4 Visit:

    a. Assess and document the IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).

    b. Review and reconcile any discrepancies with the patient and caregiver.

11. Dispense blister card numbers per the patient's randomization assignment (7 days per card) to the patient (includes 1 extra blister pack in case of delayed visit and/or use of visit window).

    a. Record the dates the patient should take IMP onto the blister cards.

12. Review the dosing instructions for the IMP with the patient and caregiver, answer any questions, and remind the patient and caregiver to return blister cards at the next clinic visit.

    a. Document patient and caregiver understood dosing instructions and the use of extra days if visit delayed and/or use of visit window.

13. Schedule the Week 12 visit (telephone call).

14. Complete eCRF information in the designated modules.

6.2.7 Visit 6 (Week 12) Telephone Call

1. Patients and caregivers will be reminded of the following:

    a. Instructions for taking the IMP.

    b. Need to bring the blister cards (used and unused) dispensed at the previous visit to the next clinic visit.

    c. Need to take the IMP in the morning, approximately 30 – 60 min after breakfast, before the next clinic visit.

    d. Need to take all doses of their routine medications (including anti-dementia and anti-PD medications) according to their normal schedule on the day of the next clinic visit and to bring their medications with them to the visit.

    e. Date and time of the next clinic visit (Week 16).

2. Assess AEs by asking open-ended queries and record the assessments.

3. Complete eCRF information in the designated modules.

6.2.8 Visit 7 (Week 16) End of Dosing

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 16 Visit with the courier (see Central Laboratory Procedures Manual).

1. Assess AEs by asking open-ended queries and record the assessments.

2. Record concomitant medication use; assess and record any changes to anti-dementia or anti-Parkinson medication doses or regimens.

3. Obtain and record BP and pulse after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes..

4. Obtain weight.

5. Perform physical and neurological exam.

6. Administer the following assessment instruments, in the order shown except for the ADCS-CGIC (see note, below). The order may be adjusted to keep the physician assessments together; however, it is imperative that the CDR and ADAS-cog are performed first and second, in order to limit patient fatigue. Perform all cognitive and dementia-related assessments while patient is in ON state. ON will be measured at a time representative of the ON state in that patient, not in “best” ON.

a. CDR.

b. ADAS-cog.

c. ADCS-CGIC. (Note: The ADCS-CGIC evaluation may be performed at any point during the study visit based on clinical interview by an Investigator who is blinded to the cognitive evaluations.)

d. Perform full UPDRS Parts I, II III (motor) and IV.

   For patients with motor fluctuations: Perform full UPDRS Parts I, II III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in ON will be measured at a time representative of the ON state in that patient, not in "best" ON.

e. PDAQ (reported by caregiver).

f. SCOPA-SLEEP.

g. SAPS-PD.

h. NPI (reported by caregiver).

i. MoCA.

7. Administer C-SSRS.

8. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

9. Obtain samples for the following laboratory tests and record the date and time of collection:

   a. Females of childbearing potential: Obtain urine hCG pregnancy test; verify method of contraception has not changed since Screening.

   b. Hematology and chemistry (including liver function tests).

   c. Blood sample for SYN120 plasma concentration [redacted] Obtain and record the date and time when the patient took the last dose of IMP. Record the date and time of SYN120 sample collection.

d. Blood sample for optional pharmacogenetic substudy (only if patient gave consent for the pharmacogenetic substudy and specimen was NOT collected during a previous visit): A single blood sample (approximately 10 mL) will be collected per patient. See **Section 7.13.**

e. Urine sample for urinalysis.

10. Obtain the returned blister cards dispensed at the Week 8 Visit:

    a. Assess and document the IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).

    b. Review and reconcile any discrepancies with the patient and caregiver.

11. Schedule the Week 18 post dose Safety Follow-Up Visit.

12. Complete eCRF information in the designated modules.

6.2.9 Safety Follow-Up Visit, Visit 8 (Week 18)

The post dose Safety Follow-Up Visit should be scheduled 14 ± 3 days after the last dose of IMP. If the patient was terminated early from the study and the Early Termination Visit took place 4 weeks or more after the last dose of IMP, this visit should not be conducted.

Note: Confirm the arrangement for laboratory sample pick-up on the day of the Week 18 visit with the courier (see Central Laboratory Procedures Manual).

1. Assess AEs by asking open-ended queries and record the assessments.

2. Record concomitant medication use; assess and record any changes to anti-dementia or anti-Parkinson medication doses or regimens.

3. Perform full UPDRS Parts I, II III (motor) and IV.

   For patients with motor fluctuations: Perform full UPDRS Parts I, II III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in ON will be measured at a time representative of the ON state in that patient, not in “best” ON.

4. Administer C-SSRS.

5. Obtain and record BP and pulse after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.

6. Complete eCRF information in the designated modules.

6.2.10 Early Termination Visit

Note: Confirm the arrangement for laboratory sample pick-up on the day of the patient's termination visit with the courier (see Central Laboratory Procedures Manual).

If the patient withdraws consent, perform this visit as soon as possible after the last dose of IMP.

1. Assess AEs by asking open-ended queries and record the assessments.

2. Record concomitant medication use; assess and record any changes to anti-dementia or anti-Parkinson medication doses or regimens.

3. Obtain and record BP and pulse after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.

4. Obtain weight.

5. Perform physical and neurological exam.

6. Administer the following assessment instruments, in the order shown except for the ADCS-CGIC (see note, below). The order may be adjusted to keep the physician assessments together; however, it is imperative that the CDR and ADAS-cog are performed first and second, in order to limit patient fatigue. Perform all cognitive and dementia-related assessments while patient is in ON state. ON will be measured at a time representative of the ON state in that patient, not in "best" ON.

    a. CDR.

    b. ADAS-cog.

    c. ADCS-CGIC. (Note: The ADCS-CGIC evaluation may be performed at any point during the study visit based on clinical interview by an Investigator who is blinded to the cognitive evaluations.)

    d. Perform full UPDRS Parts I, II III (motor) and IV.

    For patients with motor fluctuations**:** Perform full UPDRS Parts I, II III (motor) and IV, approximately 1 to 3 hours after the patient has taken a scheduled dose of levodopa (preferably their morning dose of levodopa). UPDRS in ON will be measured at a time representative of the ON state in that patient, not in "best" ON.

    e. PDAQ (reported by caregiver).

    f. SCOPA-SLEEP.

g. SAPS-PD.

h. NPI (reported by caregiver).

i. MoCA.

7. Administer C-SSRS.

8. Obtain 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording.

9. Obtain samples for the following laboratory tests and record the date and time of collection:

   a. Females of childbearing potential: Obtain urine hCG pregnancy test; verify method of contraception has not changed since Screening.

   b. Hematology and chemistry (including liver function tests).

   c. Blood sample for SYN120 plasma concentration [redacted] Obtain and record the date and time when the patient took the last dose of IMP. Record the date and time of SYN120 sample collection.

   d. Urine sample for urinalysis.

10. Obtain the returned blister cards dispensed at the previous visit:

    a. Assess and document the IMP accountability and compliance (document any missed dose(s), lost tablets and number of tablets taken).

    b. Review and reconcile any discrepancies with the patient and caregiver.

11. Complete eCRF information in the designated modules.

6.2.11 Unscheduled Visit

Note: Confirm the arrangement for laboratory sample pick-up on the day of an Unscheduled Visit with the courier (see Central Laboratory Procedures Manual).

An Unscheduled Visit is defined as any additional visit performed at the Investigator's discretion, at any time between Baseline (Visit 2) and the Safety Follow Up Visit (Week 18).

6.2.11.1 Required Assessments for Unscheduled Visit

The following assessments must be performed:

1. Assess AEs by asking open-ended queries and record the assessments.

2. Record concomitant medication use; assess and record any changes to anti-dementia or anti-PD medication doses or regimens.

3. Collect the dispensed IMP blister cards from the patient.

4. Obtain and record the date and approximate time when the patient took the most recent dose of IMP.

5. Assess and document the IMP accountability and compliance (document any missed dose[s], lost tablets, and number of tablets taken). In case of discrepancies, review and reconcile them with the patient/caregiver.

6. Complete the designated information in the designated eCRF modules.

6.2.11.2 Optional Assessments for Unscheduled Visit

The following additional assessments may be performed at an Unscheduled Visit for assessment of an adverse event, at the Investigator's discretion, depending on the type of AE (e.g., an out-of-range lab value):

1. Obtain and record BP and pulse after at least 5 minutes supine rest and again after standing for approximately 1 and 3 minutes.

2. Obtain the 12-lead ECG and ensure the ECG is collected at a time when the patient is not experiencing dyskinesia that would interfere with an adequate recording. Assess any changes from Baseline for clinical significance.

3. Perform physical and neurological examination, and assess any changes from Baseline for clinical significance.

4. Administer C-SSRS if suicide risk concern.

5. Obtain samples for the following laboratory tests and record the date and time of collection:

    a. Females of childbearing potential: Obtain urine hCG pregnancy test; verify method of contraception has not changed since Screening.

    b. Hematology and chemistry (including liver function tests).

c. Blood sample for SYN120 plasma concentration [redacted] Obtain and record the date and time when the patient took the last dose of IMP. Record the date and time of SYN120 sample collection.

d. Urine sample for urinalysis.

Note: For processing, labeling and shipping of samples, follow the instructions provided in the Central Laboratory Procedures Manual.

6. In consultation with the Medical Monitor, discuss any other appropriate diagnostic tests required to evaluate patient's AE.

7. Re-dispense remaining unused blister cards collected from the patient to continue IMP dosing to the next scheduled visit (if applicable).

8. Complete eCRF information in the designated modules.

7.0 ASSESSMENT METHODS

7.1 Cognitive Drug Research Computerized Cognition Battery

The Cognitive Drug Research Computerized Cognition Battery (CDR) (**Wesnes et al., 1992**; **Wesnes et al., 2000**) is a computerized neuropsychological test battery to assess cognitive tasks based on measures of choice reaction time, vigilance, and the sensitivity and speed of digit, word and picture recognition. The stimuli are presented on a computer screen and the subjects respond by pressing either a "Yes" or "No" on a response box. The CDR has been validated in demented patients and is provided through [redacted]. The CDR will be administered at Screening to all patients (two training sessions required) and to randomized patients at Baseline (before the initiation of dosing) and at Weeks 8 and 16 (or at Early Termination, if applicable). The CDR sample version administered at Screening will not be evaluated, but will be used to familiarize patients with the test procedures and reduce the risk of practice effects as a potential confounder.

The order of standard CDR System setup is:

- Word Presentation: A list of words is presented on the screen one at a time for the subject to remember.

- Immediate Word Recall: The subject is given 60 seconds to recall as many of the words as possible that were presented.

- Picture Presentation: A series of pictures is presented on screen for the subject to remember.

- Simple Reaction Time: The subject is instructed to press the 'YES' response button as quickly as possible every time the word 'YES' is presented on the screen. Stimuli are presented with a varying inter-stimulus interval.

- Digit Vigilance: A target digit is randomly selected and constantly displayed to the right of the screen. A series of digits is then presented in the center of the screen and the subject is required to press the 'YES' button as quickly as possible every time the digit in the series matches the target digit.

- Choice Reaction Time: Either the word 'NO' or the word 'YES' is presented on the screen and the subject is instructed to press the corresponding button as quickly as possible. Each stimulus word is chosen randomly with equal probability and there is a varying inter-stimulus interval.

- Numeric Working Memory: A series of digits is presented for the subject to hold in memory. This is followed by a series of probe digits in which the subject has to decide whether or not it was the original series and press the 'YES' or 'NO' response button (as appropriate), as quickly as possible.

- Spatial Working Memory: A picture of a house is presented on the screen with windows lit. The subject has to memorize the position of the lit windows. For each of the subsequent presentations of the house, the subject is required to decide whether or not the one window that was lit was also lit in the original presentation. The subject responds by pressing the ‘YES’ or ’NO’ buttons (as appropriate), as quickly as possible.

- Delayed Word Recall: The subject is given time to recall as many of the words as possible that were presented during word presentation.

- Word Recognition: The original words plus distracter words are presented one at a time in a randomized order. For each word the subject is required to indicate whether or not the subject recognizes it as being from the original list of words by pressing the 'YES' or 'NO' button (as appropriate), as quickly as possible.

- Picture Recognition: The original pictures, plus distracter pictures, are presented one at a time in a randomized order. For each picture, the subject has to indicate whether or not the subject recognizes it as being from the original series by pressing the 'YES' or 'NO' button (as appropriate), as quickly as possible.

The individual tasks measure the following cognitive domains:

Attentional Tasks

- Simple Reaction Time

- Digit Vigilance
- Choice Reaction Time

Working Memory Tasks

- Numeric Working Memory
- Spatial Working Memory

Episodic Secondary Memory Tasks

- Immediate Word Recall
- Delayed Word Recall
- Word Recognition
- Picture Recognition

These cognitive tasks are usually analyzed both separately and in different combinations to produce composite scores. The five composite scores were identified through a factor analysis and have been replicated in other studies (**Wesnes et al., 2000**).

The five composite scores are:

- Power of Attention: a measure of psychomotor/information processing speed. Indicates intensity of concentration at a particular moment.
- Continuity of Attention: a measure of attention/concentration. The ability to sustain attention and avoid error. The ability to keep mind on a single task over time.
- Quality of Working Memory: Assess ability to temporary store information.
- Quality of Episodic Secondary Memory: Measures ability to store, hold and retrieve information of episodic nature.
- Speed of Memory Retrieval: a measure of psychomotor/information processing speed. Time it takes to retrieve a memory.

Only Sponsor-accepted raters may administer the CDR Computerized Cognition Battery in accordance with the requirements for background, experience in a research setting and training in accordance with the rater experience form.

7.2 Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change (ADCS-CGIC)

The ADCS-CGIC (**Schneider et al., 1997**) is a validated scale for assessing clinically relevant global change in patients with dementia, which was originally developed for patients with AD. The ADCS-CGIC consists of an organized but unstructured assessment of the patient's function and mental status, a caregiver interview, and a standardized set of questions. Depending on a patient's level of impairment, raters consider several domains (e.g., global cognition, attention and wakefulness, psychiatric symptoms) in formulating a CGIC rating. The assessments are integrated in a 7-point categorical scale that gives a global rating of change in symptoms from a baseline level. A score of 1 = marked improvement; 2 = moderate improvement; 3 = minimum improvement; 4 = no change; 5 = minimum worsening; 6 = moderate worsening; and 7 = marked worsening. The ADCS-CGIC will be collected at Week 16 (or at Early Termination prior to Week 16, if applicable), and may be performed at any point during the study visit based on clinical interview by an Investigator who is blinded to the cognitive evaluations.

Only Sponsor-accepted raters may administer the ADCS-CGIC in accordance with the requirements for background, experience in a research setting and training in accordance with the rater experience form.

7.3 Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog) (Revised 10OCT13)

The ADAS-cog (**Mohs et al., 1988**; **Mohs et al., 1997**) is the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS), a validated instrument designed to measure the severity of the most prominent symptoms of dementia in patients with AD. The ADAS-cog subscale consists of 11 tasks measuring alterations of memory, language, praxis, attention and other cognitive abilities which comprise the core symptoms of AD and PDD. **This study utilizes** the original ADAS-cog **and does not include the supplemental maze** and number cancellation tasks. The ADAS-cog will be administered to randomized patients in this study at Baseline (before the initiation of dosing) and at Week 16 (or at Early Termination prior to Week 16, if applicable).

Only Sponsor-accepted raters may administer the ADAS-cog in accordance with the requirements for background, experience in a research setting and training in accordance with the rater experience form.

7.4 Brief Penn Daily Activity Questionnaire (PDAQ)

The PDAQ (**Weintraub et al., 2013**) is a 15-item questionnaire selected by an expert panel from a bank of 50 items. The PDAQ represents a new comprehensive instrument comprised of item-response theory scaled items for rating daily cognitive function in patients with PD. The questionnaire correlates highly with global cognitive performance in PD patients and shows good

discriminant validity across stages of cognitive impairment. The informant version of the PDAQ will be administered to the caregiver of randomized patients in this study at Baseline (before the initiation of dosing) and at Week 16 (or at Early Termination prior to Week 16, if applicable).

Only Sponsor-accepted raters may administer the Brief PDAQ in accordance with the requirements for background, experience in a research setting and training in accordance with the rater experience form.

7.5 Parkinson's Disease-Adapted Scale for Assessment of Positive Symptoms (SAPS-PD) (2013 Shortened Version)

The SAPS-PD is the Parkinson's disease-adapted version of the Scale for Assessment of Positive Symptoms (**Andreasen, 1984**) tailored to PDD. A shortened version of the SAPS-PD has recently been developed (**Voss et al., 2013**). The 2013 shortened version of the SAPS-PD will be administered to randomized patients in this study at Baseline (before the initiation of dosing) and at Week 16 (or at Early Termination prior to Week 16, if applicable).

Only Sponsor-accepted raters may administer the SAPS-PD in accordance with the requirements for background, experience in a research setting and training in accordance with the rater experience form.

7.6 Neuropsychiatric Inventory (NPI) (Version 12)

The NPI (**Cummings et al., 1994**) is a copyrighted validated instrument to assess dementia-related behavioral symptoms. The NPI originally examined 10 sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, and aberrant motor activity. Sub-domains subsequently added include night-time behavioral disturbances and appetite/eating abnormalities (**Cummings, 1997**), as well as a caregiver distress scale (**Kaufer et al., 1998**). Due to its wide variety of domains compared to dementia measures, the NPI is used to screen for multiple types of dementia in addition to that caused by AD. The NPI will be reported bythe subject's caregiver at Baseline (before the initiation of dosing) and at Week 16 (or at Early Termination prior to Week 16, if applicable).

Only Sponsor-accepted raters may administer the NPI in accordance with the requirements for background, experience in a research setting and training in accordance with the rater experience form.

A copy of the NPI is included in **Appendix 14.6**.

7.7 Scales for Outcomes in Parkinson's Disease-Sleep Scale (SCOPA-SLEEP)

The SCOPA-SLEEP (**Marinus et al., 2003**) is a validated instrument to evaluate nighttime sleep and daytime sleepiness developed for research in patients with PD, a population that frequently experience sleep disturbances. The SCOPA-SLEEP consists of two scales, one that evaluates nighttime sleep and one that assesses daytime sleepiness.

Only Sponsor accepted raters may administer the SCOPA-SLEEP in accordance with the requirements for background, experience in a research setting and training in accordance with the rater experience form.

A copy of the SCOPA-SLEEP is included in **Appendix 14.5**.

7.8 Montreal Cognitive Assessment (MoCA) (Original v7.1,Alternates v7.2 and v.7.3)

The MoCA (**Nasreddine et al., 2005**) is a validated brief screening instrument for cognitive dysfunction. The MoCA assesses the cognitive domains of attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The MoCA takes approximately 10 minutes to administer by a trained clinician and must be administered in the local language and scored by a trained clinician. The maximum score is 30; a score of 26 or above is considered normal. The MoCA has validated translations in many languages **[http://www.mocatest.org].**

Only Sponsor accepted raters may administer the MoCA in accordance with the requirements for background, experience in a research setting and training in accordance with the rater experience form.

Subjects may be given any version of the MoCA at the Screening Visit as long as they have NOT received the same MoCA version clinically within the last 3 months. A different version of the MoCA should be used at the Week 16 or Early Termination visit (if applicable). The MoCA version used at a study visit should be accurately documented in Source Document and within the EDC for each visit.

Re-screening**:** In cases where the subject screen fails due to the MoCA score being out of the required inclusionary range at the Screening Visit, the subject may be re-screened if the subject's score was **> 23**; a minimum of one month must have passed since their original MoCA assessment. If the subject's MoCA score was **< 10**, they must have had a change in therapy or intervention that (in the opinion of the Site Investigator) may have improved the subject's cognitive status. Subjects who move forward with a re-screen must be evaluated using a different MoCA version (7.1, 7.2 or 7.3) than was used at the original Screening Visit, and subjects may be re-screened only once.

7.9 Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS (**Fahn et al., 1987**) is a scale that was developed as an effort to incorporate elements from existing scales to provide a comprehensive but efficient and flexible means to monitor PD-related disability and impairment.

The scale itself has four components, largely derived from preexisting scales that were reviewed and modified by a consortium of movement disorders specialists (Part I, Mentation, Behavior and Mood; Part II, Activities of Daily Living; Part III, Motor Examination; Part IV, Complications of Therapy). One of the core advantages of the UPDRS is that it was developed as a compound scale to capture multiple aspects of PD. It assesses both motor disability (Part II: Activities of Daily Living) and motor impairment (Part III: Motor Examination). In addition, Part I addresses mental dysfunction and mood, and Part IV assesses treatment-related motor and non-motor complications. Of all available clinical scales for the assessment of Parkinsonian motor impairment and disability, the UPDRS is currently the most commonly used**.**

Patients with levodopa-related end-of-dose motor fluctuations will be instructed to have already taken their normally scheduled dose of levodopa and their study drug prior to arriving at the study site in order to have their UPDRS Part III evaluated in ON (within approximately 2 to 3 hours after taking their levodopa dose). UPDRS in ON will be measured at a time representative of the ON state in that patient, not in "best" ON. UPDRS Part III in OFF will be not be evaluated.

Only Sponsor accepted raters may administer the UPDRS subscales in accordance with the requirements for background, experience in a research setting and training in accordance with the rater experience form.

A copy of the UPDRS is included in **Appendix 14.4**.

7.10 Columbia-Suicide Severity Rating Scale (C-SSRS) (Revised 14JAN09)

Suicidality will be assessed by trained study personnel using the C-SSRS (**Posner et al. 2011**). The C-SSRS is a copyrighted standardized suicidal rating system conducted by a certified rater. The interview measures presence of suicidality and consists of four categories: suicide ideation, intensity of ideation, suicidal behavior and answer for actual attempts only. This scale will be used for screening as well as to assess for the occurrence of any suicidal ideation and/or behavior during the study.

Only Sponsor accepted trainers may administer the C-SSRS in accordance with the requirements for background, experience in a research setting and training in accordance with the rater experience form.

7.11 Laboratory Tests

The laboratory tests listed below (**Table 5**) are to be performed and analyzed as outlined in the Schedule of Events/Evaluations (**Table 1**).

Sample collection kits and the laboratory procedures manual with detailed sample processing and shipping instruction will be provided by the accredited central laboratory.

All laboratory samples will be destroyed upon authorization by the Sponsor or Sponsor's designee, at the finalization of the clinical study report.

The following laboratory parameters will be measured:

Table 5: Laboratory Measurements

Hematology	Chemistry	Thyroid [b]	Urinalysis [c]
basophils	calcium	TSH	protein
eosinophils	chloride	free T_3	glucose
lymphocytes	sodium	free T_4	pH
neutrophils	potassium		blood
monocytes	albumin		ketones
hemoglobin	phosphate		specific gravity
hematocrit	glucose		
platelet count	urea/BUN		
RBC count	bicarbonate		
WBC count	uric acid		
	total protein		
	creatinine		
	creatine phosphokinase with automatic troponin-I and CK-MB if value > 2x the ULN		
	AST		
	ALT		
	ALP		
	GGT		
	total bilirubin [a]		
	LDH		
	total cholesterol		
	serum FSH (at Screening, for female patients who are not surgically sterile and are postmenopausal)		
	urine hCG (for female patients of childbearing potential)		

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; CK-MB, creatine phosphokinase-MB fraction; FSH, follicle stimulating hormone; GGT, gamma-glutamyl transpeptidase; hCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; pH, reverse logarithmic representation of relative hydrogen proton (H+) concentration; RBC, red blood cell; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone; ULN, upper limit of normal; WBC, white blood cell.

[a] Conjugated and unconjugated.

[b] Assessed at Screening only.

[c] If urine dipstick is positive for leukocytes, protein, or erythrocytes, a microscopic evaluation and culture will be performed.

7.11.1 Hormones (Serum FSH and Urine HCG)

Follicle stimulating hormone (FSH) levels will be determined at Screening for all women who are not surgically sterile and are postmenopausal (at least one year absence of vaginal bleeding

or spotting). Postmenopausal status will be confirmed by an FSH level greater than or equal to 40 mIU/mL or 40 IU/L.

Urine human chorionic gonadotropin (hCG) pregnancy test will be performed for women of childbearing potential, at Screening and during the study as indicated in **Table 1**, Schedule of Events/Evaluations.

7.11.2 Hematology

Hematology tests will consist of hemoglobin, hematocrit, red blood cell count, white blood cell count and differential, and platelet count, at Screening and during the study as indicated in **Table 1**, Schedule of Events/Evaluations.

7.11.3 Chemistry

Serum chemistry tests will consist of aspartate aminotransferase (SGOT/AST), alanine aminotransferase, (SGPT/ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin (conjugated and unconjugated), albumin, creatinine, urea/BUN, bicarbonate, uric acid, total protein, sodium, chloride, potassium, calcium, phosphate, glucose, cholesterol, and creatine phosphokinase (CK), TSH, free T_3 and T_4, at Screening and during the study as indicated in **Table 1**, Schedule of Events/Evaluations.

7.11.4 Thyroid Function

Thyroid function tests will consist of thyroid stimulating hormone (TSH), free T3 and free T4, at Screening.

7.11.5 Urinalysis

Urinalysis will include specific gravity, pH, ketones, blood, protein, and glucose, at Screening and during the study as indicated in **Table 1**, Schedule of Events/Evaluations. If an urine dipstick is positive for leukocytes, protein or erythrocytes, a microscopic evaluation will be performed.

7.12 Blood Sampling for Bioanalytical Analysis

Blood samples will be collected for determination of SYN120 plasma concentrations [redacted] Baseline (before the initiation of dosing), at Weeks 4, 8 and 16, at Early Termination (if applicable), and at unscheduled visits (optional). For each collection, the time of sampling and of the most recent IMP dosing prior to sampling will be recorded.

Specific procedures for blood sample collection, plasma processing, storage, shipping, and analysis will be provided in the Central Laboratory Procedures Manual.

7.13 Pharmacogenetic Substudy (Optional)

Patients will be offered the option to participate in a pharmacogenetic substudy. Exploratory pharmacogenetic analyses are planned as a substudy with the objective of identifying inherited genetic factors which predict differential treatment response or intolerance to SYN120. Genetic polymorphisms related to the serotonin system (5HT6 and 5HT2a receptors) will be characterized. Other genetic features related to [redacted] Parkinson's disease and cognition may also be tested. The intent is to develop a better understanding of Parkinson's disease dementia and how patients respond to SYN120.

Blood samples will be taken for pharmacogenetic assessment from each patient who agrees, in writing, to participate in these exploratory assessments. A separate section on the ICF regarding the pharmacogenetic substudy will be provided. Patients who indicate on the ICF that they agree to the pharmacogenetic assessment will be eligible for extra blood collection and inclusion in pharmacogenetic analyses. A single blood sample will be collected per patient (approximately 10 ml) at Baseline or at the next possible visit.

A separate lab instruction will be provided with detailed information on sample collection, handling, and shipment for all pharmacogenetic assessments. The sample collection data must be entered on the sample collection CRF (eCRF) page.

Blood samples will be processed, DNA extracted, and samples stored [redacted] Samples may be shared with other investigators [redacted] Samples will be stored for up to 10 years. Participants may withdraw consent to use their samples at any time, in which case their samples and any derived biospecimens will be destroyed. Samples will be identified only by anonymous study ID number with linked phenotypic information gathered in the study.

7.14 Blood Pressure and Pulse

A full set of BP and pulse measurements will be obtained at Screening (3 sets) and during the study (1 set) as indicated in **Table 1**, Schedule of Events/Evaluations. Blood pressure and pulse rate should be obtained in a quiet room at a comfortable temperature, with the patient's arm unconstrained by clothing or other material. A full set of measurements consists of supine BP and pulse followed by standing BP and pulse. If repeats are performed for either supine or standing BP, the full set (BP and pulse) should be repeated after 5 minutes supine rest (i.e., supine followed by standing measurements). The measurements will be obtained with the appropriate cuff size from the non-dominant arm. All measurements will be obtained from the same arm and, if possible with the same cuff, using an automatic instrument with a digital readout, throughout the study. The automatic cuff should be placed on the designated arm at least 5 minutes prior to collection. Measurements will be made after a minimum of 5 minutes rest in the supine position. Patients will then stand up for 1 and 3 minutes, and a standing measurement

will be obtained. The 3 sets of readings collected during the Screening Visit should be taken approximately 10 minutes apart.

Supine and standing systolic and diastolic BP and pulse rate will be recorded at the nominal time points specified in **Table 1**, Schedule of Events/Evaluations. If for any reason (e.g., dyskinesia) an accurate reading cannot be obtained, collect the measurement as close to the nominal time point as feasible and record the date and time of collection.

7.15 Physical and Neurological Examination

Physical examination including neurological examination will be collected at Screening and during the study as indicated in **Table 1**, Schedule of Events/Evaluations. Physical examination includes evaluation of the heart, lungs, abdomen, extremities, and skin. Neurological exam will consist of assessment of the cranial nerves (I-XII), sensory and motor system functions and reflexes.

7.16 Twelve-lead Electrocardiogram

Resting supine 12-lead ECGs will be collected at the time points specified in **Table 1**, Schedule of Events/Evaluations, after the patient has been in a supine, or if unable, semi-supine (no more than 45 degrees) position for a minimum of 5 minutes.

The 12-lead electrocardiogram includes standard PR, QRS, QT and QTc intervals as read by the ECG machine provided by the cardiac core lab. Fridericia's correction (i.e., QTcF) must be used for the correction of the QT interval.

A central ECG core lab will overread all ECGs and provide the final interpretation. At Screening the results will be available within 72 hours of the visit. At Baseline, the overread of the 3 serial ECGs will be available within 24 hours. The Investigator should use the ECG machine recorded QTcF value to determine patient eligibility.

The ICH guideline E14 (section 2.1.1) suggests excluding from early phase studies subjects who have marked baseline prolongation of the QT interval, namely those in whom QTc interval has repeatedly been demonstrated to be > 450 milliseconds (msec). Therefore, to be eligible for this study patients must meet exclusion criteria #14 based on QTcF intervals as assessed at the Screening and Baseline Visits.

At subsequent visits, if the QTcF interval is noted to be ≥ 450 msec (for male patients) or ≥ 470 msec (for female patients), it is recommended that the ECG be repeated at 10 minute intervals, for a total of 3 ECGs, to determine if the QTcF prolongation is a consistent finding. If the patient is observed to have a QTcF interval consistently ≥ 500 msec and/or a QTcF interval consistently increased by ≥ 60 msec compared to the average baseline QTcF interval, study drug

should be discontinued (see **Section 4.3.1**, page 45). The average baseline QTcF interval is defined as the average of the three QTcF interval values obtained at Visit 2.

The eligibility or continued participation in the trial of any patient with potentially significant ECG abnormalities should be discussed the Medical Monitor.

7.17 Adverse Events

For details regarding AE assessments and reporting, please refer to **Section 8.0**.

7.18 Concomitant Medications

For details regarding concomitant medications, please refer to **Section 5.9** and **Section 14.3**.

8.0 ADVERSE EVENTS

8.1 Definition of Adverse Event

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

In order to ensure complete safety data collection, all AEs occurring during the study (i.e., after the signing of the informed consent form), including any pretreatment and post treatment periods required by the protocol, must be reported in the eCRF even if no investigational product was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the investigational product is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the patient's history or the Baseline Period.

8.2 Procedures for Reporting and Recording Adverse Events

The patient will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

> "Did you notice anything unusual about your health (since your last visit)?"

In addition, the Investigator should review any self-assessment procedures (e.g., diary cards) employed in the study.

8.3 Description of Adverse Events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the patient's own words on his/her own records (e.g., diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the AE eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

8.4 Follow Up of Adverse Events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the patient is lost to follow up.

If an AE is still ongoing at the end of the study for a patient, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the patient is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 30 days after the patient has discontinued his/her IMP.

8.5 Rule for Repetition of an Adverse Event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening".
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one.

8.6 Pregnancy

In the event a patient becomes pregnant after the first intake of any IMP, the Sponsor's drug safety representative should be informed immediately. The patient should discontinue study drug as soon as pregnancy is known, and the following should be completed:

- The patient should immediately stop the intake of the IMP or be down-titrated as instructed.

- A Safety Follow Up Visit should be scheduled 4 weeks after the patient has discontinued IMP.

The Investigator must inform the patient of information currently known about potential risks and about available treatment alternatives.

In cases where the partner of a male patient enrolled in a clinical study becomes pregnant, Sponsor will ask the Investigator or designee to contact the patient and his partner to request consent via the Partner Pregnancy Consent form. If the partner agrees to provide additional information, the Pregnancy Report and Outcome form will be forwarded to the patient's partner for completion.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed-up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. The health of the child must be followed for 30 days after birth for any significant medical issues.

In certain circumstances, Sponsor may request that follow up is continued for a period longer than 30 days.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be additionally reported using the Sponsor-provided SAE Report Form.

8.7 Overdose of Investigational Medicinal Product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the Drug Accountability module of the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (e.g., suicide attempt).

8.8 Safety Data Monitoring

Selected safety data from this study will be reviewed periodically to detect any clinical concern(s) potentially related to IMP so that Investigators, patients, and responsible oversight authorities including IRBs/IECs can be promptly informed of relevant safety-related findings. Responsibility for safety data monitoring will be assigned to a medically qualified, unblinded physician (Safety Data Monitor) who is independent from Biotie Therapies. The Safety Data Monitor will review reported SAEs and may identify additional safety data of interest (e.g., AEs, vital signs, laboratory or ECG results) to be requested from the unblinded biostatistician and reviewed periodically during the course of the study.

8.9 Serious Adverse Events

8.9.1 Definition of Serious Adverse Event

Once it is determined that a patient experienced an AE, the seriousness of the AE must be determined. An SAE must meet one or more of the following criteria:

- Death.
- Life-threatening.

  Note: Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.

- Significant or persistent disability/incapacity.
- Congenital anomaly/birth defect (including that occurring in a fetus).
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the definition of serious.

  Note: Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- Initial inpatient hospitalization or prolongation of hospitalization.

  Note: A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious (e.g., life-threatening adverse experience, important medical event).

  Hospitalizations for reasons not associated with the occurrence of an AE (e.g., preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner) do not qualify for reporting. For example, if a patient has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.

8.9.2 Procedures for Reporting Serious Adverse Events

If an SAE is reported, the Sponsor must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to the Sponsor (or its representative) a duly completed SAE Report Form provided by the Sponsor, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An SAE Report Form will be provided to the Investigator. The SAE Report Form must be completed in English.

It is important for the Investigator, when completing the SAE Report Form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for the Sponsor to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (e.g., autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the SAE Report Form.

The Investigator is specifically requested to collect and report to the Sponsor (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 4 weeks from the date of last IMP for each patient, and to also inform participating patients of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to the Sponsor regardless of the time between the event and the end of the study.

Upon receipt of the SAE Report Form, the Sponsor will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the current IB.

8.9.3 Follow Up of Serious Adverse Events

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the patient is lost to follow up.

Information on SAEs obtained after clinical database lock will be captured through the global safety database without limitation of time.

8.9.4 Immediate Reporting of Adverse Events

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the above definitions regardless of causality.
- Suspected transmission of an infectious agent via a medicinal product.

8.9.5 Anticipated Serious Adverse Events

[redacted]

Investigators are obliged to report all SAEs as detailed in **Section 8.9**.

9.0 STUDY MANAGEMENT AND ADMINISTRATION

9.1 Adherence to Protocol

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying the Sponsor (or its representative) and the IRB/IEC in writing regarding the type of emergency and the course of action taken.

9.2 Monitoring

Sponsor (or designee) will monitor the study in accordance with the ICH GCP guideline and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are

adequate. Monitoring of the study may be delegated by the Sponsor or Sponsor's designee to a contract research organization (CRO) or a contract monitor.

The Investigator and his/her staff are expected to cooperate with the Sponsor (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow Sponsor (or designee) to periodically review all eCRFs and corresponding source documents (e.g., hospital and laboratory records for each study participant). Monitoring visits will provide the Sponsor (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities' regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

9.2.1 Definition of Source Data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

None of the data will be recorded directly in the eCRF and therefore all source documentation will appear in a source document as defined above.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (e.g., ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the patient's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as ECG or electroencephalogram records, must be saved and stored as instructed by Sponsor (or designee).

9.2.2 Source Data Verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (e.g., patient files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in **Section 9.2.1**.

9.3 Data Handling

9.3.1 Case Report Form Completion

The study will be performed using remote data capture. The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/ electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF.

In accordance with the applicable regulatory requirements, the confidentiality of records that could identify patients must be protected, respecting the privacy and confidentiality rules.

The Investigator will maintain a Site Delegation Personnel Log to document signatures and initials of all persons qualified and authorized by the Investigator to make entries and/or corrections to the source documents. Any corrections to non-electronic source documents are made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be dated, initialed, and explained (if necessary) by the person making the correction and must not obscure the original entry.

For source documents such as automated pharmacy records, the Investigator will review during Screening and prior to randomization any pharmacy records in the medical chart and other physician medical notes and review the information with the patient and clarify with a note in the chart any items that are inconsistent or medications that may have been prescribed but the patient is not currently taking and have been discontinued.

Detailed instructions will be provided in the eCRF Completion Guidelines.

9.3.2 Database Entry and Reconciliation

Electronic case report forms will be available for review by the Clinical Research Associate (CRA), Sponsor and Sponsor's designee after completion by the site. The eCRFs will be monitored remotely and onsite by the CRO after documented training and in accordance with the monitoring plan. The CRA will review the eCRF data on a regular basis and post any queries for the site to complete prior to the scheduled onsite monitoring visits. Only those individuals who are qualified and authorized by the Investigator to complete eCRFs will trained and receive passwords allowing eCRF completion.

The completed eCRF must be electronically reviewed, signed, and dated by a qualified physician who is designated as Principal or Sub-Investigator for the study. The Investigator must retain the original source documents. A final PDF of the eCRFs will be provided to the study site by the CRO or designee at the end of the study for archival purposes.

If the patient is a screen failure, the primary reason for screen failure will be recorded in the eCRF and on the Patient Screening/Enrollment Log. No additional screening information will be entered into the eCRF.

An electronic audit trail system will be maintained within the eCRF to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

9.3.3 Patient Screening and Enrollment Log/Patient Identification Code List

The patient's screening and enrollment will be recorded into the eCRF and onto the paper Patient Screening and Enrollment Log. The Patient Screening/Enrollment Log will be sent to the Sponsor or the Sponsor's designee on a weekly basis.

The Investigator will keep a Patient Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each patient.

The patient's consent and enrollment in the study must be recorded in the patient's medical record. These data should identify the study and document the dates of the patient's participation.

9.4 Termination of the Study

Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, Sponsor (or its representative) will inform the Investigators/institutions and the regulatory authorities of the termination or suspension and

the reason(s) for the termination or suspension, in accordance with applicable regulatory requirements. The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirements. In addition, arrangements will be made for the return of all unused IMP and other material in accordance with Sponsor procedures for the study.

9.5 Archiving and Data Retention

The Investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, informed consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with Sponsor (**FDA, 1997** [Section 4.9.5]). The Investigator will contact Sponsor for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify Sponsor should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's study master file.

9.6 Audit and Inspection

The Investigator will permit study-related audits and inspections mandated by domestic or foreign regulatory authorities or study-related audits mandated by Sponsor (or designee), after reasonable notice.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the patients enrolled have been protected, that enrolled patients (i.e., those signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform the Sponsor (or designee).

9.7 Good Clinical Practice

Noncompliance with the protocol, ICH GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by the Sponsor (or designee) to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

10.0 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

10.1 Definition of Analysis Sets

Safety Sample (SS): The SS will consist of all randomized patients who received at least one dose of IMP.

Modified Intention-to-Treat (mITT) Sample: The mITT sample will consist of all randomized patients who received at least one dose of IMP and who have at least one valid baseline and at least one valid post-baseline assessment of the primary efficacy endpoint.

Per-Protocol Set (PP): The PP will consist of a subset of the mITT sample, excluding any participants or observations potentially affected by important protocol deviations that may influence the validity of the data for testing efficacy and as specified in the SAP prior to breaking the blind.

All safety variables will be summarized using the SS. All efficacy variables will be summarized using the mITT sample. The PP will be utilized for sensitivity analyses to estimate efficacy among participants tolerant of study drug and with less reliance on model assumptions required to extrapolate after any loss to follow up.

10.2 Study Variables

10.2.1 Efficacy Variables

10.2.1.1 Primary Efficacy Variable

The primary efficacy variable is the change from Baseline to Week 16 on the CDR Computerized Cognition Battery Continuity of Attention.

10.2.1.2 Key Secondary Efficacy Variable

The key secondary efficacy endpoint is the change from Baseline to Week 16 on the CDR Quality of Episodic Memory.

10.2.1.3 Other Efficacy Variables

The other secondary efficacy endpoints are the change from Baseline to Week 16 on the following measures:

1. ADCS-CGIC.
2. ADAS-cog (total score).
3. CDR Power of Attention.
4. CDR Speed of Memory Retrieval.
5. PDAQ.
6. SCOPA-SLEEP.
7. SAPS-PD.
8. NPI.
9. MoCA.

10.2.2 Exploratory Efficacy Variables

Exploratory efficacy endpoints include the change from Baseline to Week 16 on the individual component tasks of the CDR:

1. Word Presentation.
2. Immediate Word Recall.
3. Picture Presentation.
4. Simple Reaction Time.
5. Digit Vigilance.
6. Choice Reaction Time.
7. Numeric Working Memory.
8. Spatial Working Memory.
9. Delayed Word Recall.
10. Word Recognition.
11. Picture Recognition.

10.2.3 Pharmacokinetic Variables

- SYN120 plasma concentrations [redacted] and time point of IMP intake and blood sampling.

10.2.4 Safety Variables

Safety variables include the following:

- AEs.

Change from Baseline in:

- Vital sign parameters (pulse rate, systolic and diastolic BP).
- Change in body weight.
- Change from supine to standing BP (systolic and diastolic).
- UPDRS.
- C-SSRS.
- Standard 12-lead ECG (RR, PR, QRS, QT, and QT intervals corrected for heart rate using Fridericia's formula [QTcF]).
- Laboratory parameters: hematology, chemistry, and urinalysis.

10.3 General Statistical Considerations

Descriptive statistics will be displayed to provide an overview of the study results. For categorical variables, the number and percentage of patients in each category will be presented. The denominator for percentages will be based on the number of patients appropriate for the purpose of analysis. For continuous variables, descriptive statistics will include number of patients (n), mean, standard deviation (SD), median, minimum, and maximum.

In general, Baseline values for efficacy and safety variables will be determined from the last non-missing data collected prior to the first dose of study medication.

10.4 Planned Efficacy Analyses

10.4.1 Analysis of the Primary Efficacy Variable

The primary analysis will be performed on the mITT analysis set and will use a shared-baseline repeated measures analysis of variance (ANOVA) that includes fixed effects for visit (3 levels: baseline, Week 8, and Week 16) and the interaction between treatment group (2 levels: SYN120 and placebo) and post-baseline visit (2 levels), random center-specific intercepts, and unstructured within-person covariance. The repeated measures model yields estimates that are unbiased as long as loss to follow up and missing assessments are predictable from observed scores. Use of a shared baseline (i.e., no treatment main effect) reflects the true state of the population sampled prior to randomization and has the advantage of adjusting for any chance differences at baseline in a manner similar to analysis of covariance (ANCOVA) (**Liang and Zeger, 2000**) with potentially greater efficiency with more than one follow up visit and drop-out.

Treatment-dependent differences in the change from Baseline to Week 16 on the CDR Computerized Cognition Battery Continuity of Attention will be estimated by linear contrasts and tested using a two-tailed Wald-test at alpha = 0.05. A significant mean improvement over 16 weeks in CDR Continuity of Attention among participants randomized to SYN120 relative to mean changes among participants randomized to placebo would be considered evidence of therapeutic benefit from SYN120. As a sensitivity analysis if SYN120 is not found to be beneficial in the mITT sample, the same model will be applied to the PP sample and a nonparametric van Elteren test will be used to compare 16-week change scores in the PP sample, stratifying by center.

10.4.2 Key Secondary Efficacy Analyses

The key secondary efficacy variable will be analyzed in the mITT sample using the model specified for the primary analysis of the primary efficacy variable. Treatment-dependent differences in the change from Baseline to Week 16 on the CDR Quality of Episodic Memory will be estimated by linear contrasts and tested using a two-tailed Wald-test at alpha = 0.05. Equivalent sensitivity analyses as are planned for the primary efficacy variable will be applied to the key secondary efficacy variable.

10.4.3 Multiplicity Adjustment for Primary and Key Secondary Endpoints

If the effect of SYN120 on the primary outcome in the mITT sample is significant at alpha = 0.05, then testing the key secondary outcome at alpha = 0.05 maintains an overall type I error rate at 5% under a closed testing sequential analysis. When the primary analysis is not significant, we limit the overall type I error rate to 10% or less (depending on the magnitude of correlation between the primary and key secondary outcomes) when significance of the key secondary outcome alone is accepted as evidence of a therapeutic benefit from SYN120.

10.4.4 Other Efficacy Analyses

All continuous other (non-key) secondary and exploratory efficacy variables that are approximately normally distributed or can be made so by simple transformation will be analyzed using the model defined in the primary efficacy analysis (**Section 10.4.1**) using the mITT sample in a first round of testing. Outcomes that are not normally distributed will be transformed or compared between the treatment groups using a van Elteren test that incorporates stratification by center. Comparisons will be tested at two-tailed alpha = 0.05, recognizing that the totality of results will be evaluated in judging the potential of SYN120 as a therapeutic agent for PDD. If not significant in the mITT sample, additional sensitivity analyses of the other (non-key) secondary efficacy variables will use the PP sample.

10.5 Planned Safety and Other Analyses

10.5.1 Safety Analyses

Safety data, including AEs, vital signs, UPDRS, ECGs, physical examination, and clinical laboratory test results will be summarized descriptively for each treatment group. The frequency and type of any observed suicidal ideation will be described. Descriptive statistics of continuous measures will be provided for the observed data and for the change from Baseline at each measured time point. Adverse events will be summaries by dose group as counts of events and as the proportion of patients experiencing any given type of AE as classified by MedDRA system organ class and preferred term. Overall rates of AEs will be compared between treatments by negative binomial regression. Proportions of participants experiencing a given type of event will be compared between treatments by Fisher's exact test.

Laboratory test results will be classified as below the lower limit of normal, within normal limits and above the ULN. Shift tables will be used to summarize changes from Baseline to each visit by treatment group. Clinically significant physical or neurological exam findings and any clinically significant out-of-range laboratory tests are recorded as adverse events and will be documented in the AE summaries.

Analyses will be performed for the SS as treated.

10.5.2 Other Analyses

Patient Disposition

The number of patients who were screened, randomized, completed scheduled follow up, and prematurely withdrew study participation will be summarized overall and by treatment group. Reasons for non-participation and for withdrawal from study will also be presented.

Exposure to IMP/Compliance

The number of days of exposure to IMP will be summarized by treatment group. Compliance with IMP will be calculated as the number of doses taken divided by the scheduled number of doses taken, expressed as a percentage. Compliance will be summarized overall and by week for each treatment group. Time to discontinuation of IMP will be estimated using Kaplan-Meier product-limit estimates. Treatment-dependent differences will be tested by log-rank test.

Prior and Concomitant Medication Use

All prior and concomitant medications taken during the study period will be listed for each patient, including dosage and indication. Each medication will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced and classified as a past medication (last dose taken prior to the first dose of IMP), a concomitant medication ongoing at Baseline, or a

concomitant medication initiated after Baseline. The percentage of patients taking each medication (or class of medications) will be summarized overall and by treatment group.

Pharmacokinetic Samples

Results of the plasma assays of SYN120 will be descriptively analyzed and reported in the clinical study report. Separate population analysis on the data from this study alone or combined with data from other studies as deemed appropriate will be performed and reported separately.

Optional Pharmacogenetic Substudy Data Analysis

The exploratory pharmacogenetic analyses are designed to investigate the association between genetic factors (genotypes) and the prediction of treatment response or intolerance. The pharmacogenetic analyses are not intended to be used for regulatory judgments pertaining to the safety or efficacy of the investigational drug. However, these data may be considered for voluntary submission, consistent with applicable regulatory guidance on this topic, in order to develop the knowledge base necessary to establish the validity of genomic biomarkers.

Pharmacogenetic data will be analyzed to describe frequencies of pre-specified polymorphisms related to 5HT6 and 5HT2a receptors, [redacted] Parkinson's disease, and cognition. Exploratory analyses of association between specific genetic polymorphisms and treatment response will be performed by adding genotype, genotype × visit, and genotype × treatment × visit terms to models for primary and secondary efficacy outcomes. Exploratory analyses of association between specific genetic polymorphisms and treatment intolerance will be performed in logistic regression models with drug discontinuation or occurrence of specific adverse events as outcomes and genotype, treatment, and genotype × treatment interaction as predictors.

10.6 Handling of Protocol Deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on either the primary efficacy or safety. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined prior to unblinding. To the extent feasible, rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all patients.

10.7 Handling of Dropouts or Missing Data

Participants who discontinue study drug or withdraw consent will be included in mITT analyses if they received at least one dose of study drug. In the absence of a substantial difference in the

rate of withdrawal, the planned repeated measures analysis should prevent bias in estimating treatment differences. If rates of withdrawal are notably higher among participants randomized to SYN120, a nonparametric analysis that assigns the worst observed outcome to participants who withdraw prior to Week 16 will be used a conservative estimate of treatment benefit. Additional sensitivity analyses may be pursued to impute missing values or otherwise construct models for unobserved outcomes.

10.8 Determination of Sample Size

A total sample size of 80 or 40 in each group will provide at least 80% power to detect a true treatment difference equal to an effect size of 0.69 assuming up to 15% loss to follow up and using a two-tailed test at alpha = 0.05 based on a simple two-sample t-test. Additional power will be obtained from the proposed analysis using a shared-baseline repeated measures ANOVA.

Approximately 120 patients will be screened, assuming a 33% screen failure rate, to randomize 80 patients.

11.0 ETHICS AND REGULATORY REQUIREMENTS

11.1 Informed Consent

Patient's informed consent must be obtained and documented in accordance with local regulations, ICH GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the patient in both oral and written form by the Investigator (or designee). Each patient will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the written informed consent form should be signed and personally dated by the patient, and by the person who conducted the informed consent discussion (Investigator or designee). The patient must receive a copy of the signed and dated informed consent form. As part of the consent process, each patient must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the informed consent form is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended informed consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the United States that are considered "covered entities" according to the Health Insurance Portability and Accountability Act (HIPAA) must include the use of a HIPAA Authorization form.

The patient may withdraw his/her consent to participate in the study at any time. A patient is considered as enrolled in the study when he/she has signed the informed consent form. An eCRF must not be started, nor may any study-specific procedure be performed for a given patient, without having obtained his/her written consent to participate in the study.

11.2 Patient Identification Cards

Upon signing the informed consent the patient will be provided with a patient identification card in the language of the patient. The Investigator will fill in the patient identifying information and medical emergency contact information. The Investigator will instruct the patient to keep the card with him/her at all times.

11.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator and CRO will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator or if a central IRB/IEC is used, Sponsor (or designee) will forward copies of the protocol, informed consent form, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other patient-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human patients or others, and any protocol deviations, to eliminate immediate hazards to patients.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the patients. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of patient risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

Sponsor (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

11.4 Patient Privacy

Sponsor staff (or designee) will affirm and uphold the patient's confidentiality. Throughout this study, all data forwarded to Sponsor (or designee) will be identified only by the patient randomization number and/or site identifier (ID) and **3-digit alpha-numeric** patient screening number **(S##)**.

The Investigator agrees that representatives of Sponsor, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the patient's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a patient's study participation, and autopsy reports for deaths occurring during the study).

11.5 Protocol Amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by the Sponsor, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

12.0 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

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14.0 APPENDICES

14.1 UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria

Step 1: Diagnosis of Parkinsonian syndrome
-Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
-At least one of the following:
  -Muscular rigidity
  -4-6 Hz rest tremor
  -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 communicating hydrocephalus on CT scan
-Negative response to large doses of levodopa (if malabsorption excluded)
-MPTP exposure

Step 3: Supportive prospective positive criteria for Parkinson's disease
(Three or more required for diagnosis of definite Parkinson's disease)

-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 10 years or more

14.2 Movement Disorder Society Task Force – Clinical Diagnostic Criteria for Dementia Associated with Parkinson's Disease

Table 1. Features of Dementia Associated with Parkinson's Disease

I. Core Features

1. Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria
2. A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:
   - Impairment in more than one cognitive domain
   - Representing a decline from premorbid level
   - Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

II. Associated Clinical Features

1. Cognitive features:
   - Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
   - Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia)
   - Visuo-spatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
   - Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
   - Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present
2. Behavioral features:
   - Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
   - Changes in personality and mood including depressive features and anxiety
   - Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
   - Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
   - Excessive daytime sleepiness

III. Features Which Do Not Exclude PDD, but Make the Diagnosis Uncertain

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

IV. Features Suggesting Other Conditions or Diseases as Cause of Mental Impairment, Which, When Present Make It Impossible to Reliably Diagnose PDD

- Cognitive and behavioral symptoms appearing solely in the context of other conditions such as:

  - Acute confusion due to

  a. Systemic diseases or abnormalities
  b. Drug intoxication

  - Major Depression according to DSM IV

- Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN (dementia in the context of cerebrovascular disease as indicated by focal signs in neurological exam such as hemiparesis, sensory deficits, and evidence of relevant cerebrovascular disease by brain imaging AND a relationship between the two as indicated by the presence of one or more of the following: onset of dementia within 3 months after a recognized stroke, abrupt deterioration in cognitive functions, and fluctuating, stepwise progression of cognitive deficits)

Table 2. Criteria for the Diagnosis of Probable and Possible PDD

Probable PDD:

A. Core features: Both must be present

B. Associated clinical features:

- Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
- The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PDD, lack of behavioral symptoms, however, does not exclude the diagnosis

C. None of the group III features present

D. None of the group IV features present

Possible PDD:

A. Core features: Both must be present

B. Associated clinical features:

- Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
- Behavioral symptoms may or may not be present

OR

C. One or more of the group III features present

D. None of the group IV features present

Source: **Emre et al., 2007**.

14.3 Medications Prohibited Within 4 Weeks Before Randomization and During Study

Centrally Acting Anticholinergic Drugs

Anti-muscarinic agents, including but not limited to:

1. atropine
2. benztropine (Cogentin)
3. biperiden (Akineton)
4. brompheniramine (Dimetapp)
5. chlorpheniramine (Chlor-Trimeton)
6. dicyclomine (Dicycloverine)
7. dimenhydrinate (Dramamine)
8. diphenhydramine (Benadryl, Sominex, Advil PM, etc.)
9. doxylamine (Unisom)
10. orphenadrine (Norflex, Disipal, etc.)
11. oxybutynin (Ditropan, Driptane, Lyrinel XL)
12. tolterodine (Detrol, Detrusitol)
13. trihexyphenidyl (Artane, Tremin)
14. scopolamine (Pamine, Transderm Scop)

14.4 Unified Parkinson's Disease Rating Scale (UPDRS)

Part I MENTATION, BEHAVIOR AND MOOD (RATE ITEMS 1 TO 4 BY INTERVIEW)
When completing this section, indicate the patient's level of function during the past week.

A. The patient's PD symptoms during the past week were:
1 = Non Fluctuator
2 = Fluctuator

1. Intellectual Impairment
0 = None.
1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4 = Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (DUE TO DEMENTIA OR DRUG INTOXICATION)
0 = None.
1 = Vivid dreaming.
2 = "Benign" hallucinations with insight retained.
3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression
0 = Not present.
1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2 = Sustained depression (1 week or more).
3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative
0 = Normal.
1 = Less assertive than usual; more passive.
2 = Loss of initiative or disinterest in elective (nonroutine) activities.
3 = Loss of initiative or disinterest in day to day (routine) activities.
4 = Withdrawn, complete loss of motivation.

Part II. ACTIVITIES OF DAILY LIVING (RATE ITEMS 5 TO 17 BY INTERVIEW)
When completing this section, indicate the patient's level of function during the past week.

A. The patient's PD symptoms during the past week were:

1 = Non Fluctuator
2 = Fluctuator

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrostomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have start-hesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

Part III. MOTOR EXAMINATION (Acceptable responses are 0, 1, 2, 3, 4)
Instructions: All efforts should be made to conduct the motor exam while the patient is in a stable state (e.g., "On" for the entire exam or "Off" for the entire exam). If unstable, re-examine the patient in a stable state, if possible.

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

20a. Face, lips + chin: _____
20b. Right Hand: _____
20c. Left Hand:_____
20d: Right Foot:_____
20e: Left Foot: _____

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

21a. Right Hand:_____
21b. Left Hand: _____

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

22a. Neck
22b. RUE
22c. LUE
22d. RLE

22e. LLE

23. Finger Taps (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task
23a. Right Hand:_____
23b. Left Hand: _____

24. Hand Movements (Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.
24a. Right Hand:_____
24b. Left Hand: _____

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.
25a. Right Hand:_____
25b. Left Hand: _____

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be about 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.
26a. Right Leg:_____
26b. Left Leg _____

27. Arising from Chair (Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient is erect, with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

A. Indicate the patient's PD state during the examination:

1 = Fluctuator - "On" during exam
2 = Fluctuator - Fluctuated during the exam
3 = Fluctuator - "Off" during exam
4 = Non-fluctuator

Part IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)
0 = Not disabling.
1 = Mildly disabling.
2 = Moderately disabling.
3 = Severely disabling.
4 = Completely disabled.

34. Painful Dyskinesias: How painful are the dyskinesias?
0 = No painful dyskinesias.
1 = Slight.
2 = Moderate.
3 = Severe.
4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)
0 = No
1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods **predictable as to timing after a dose of medication?**
0 = No
1 = Yes

37. Are "off" periods **unpredictable as to timing after a dose of medication?**
0 = No
1 = Yes

38. Do "off" periods **come on suddenly, e.g. over a few seconds?**
0 = No
1 = Yes

39. What proportion of the waking day is the patient "off" on average?
0 = None
1 = 1-25% of day.
2 = 26-50% of day.
3 = 51-75% of day.
4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?
0 = No
1 = Yes

41. Does the patient have any sleep disturbances, e.g., insomnia or hypersomnolence?
0 = No
1 = Yes

42. Does the patient have symptomatic orthostasis?
0 = No
1 = Yes

Source: **Fahn et al., 1987**.

14.5 Scales for Outcomes in Parkinson's Disease-Sleep Scale (SCOPA-SLEEP)

SCOPA-SLEEP

By means of this questionnaire, we would like to find out to what extent in the past month you have had problems with sleeping. Some of the questions are about problems with sleeping at night, such as, for example, not being able to fall asleep or not managing to sleep on. Another set of questions is about problems with sleeping during the day, such as dozing off (too) easily and having trouble staying awake.

A. Use of sleeping tablets

A1. How often did you use sleeping tablets in the last months? (prescribed by a physician or not)

☐	☐	☐	☐
not at all	less than once a week	once or twice a week	more than 3 times a week

A2. Which sleeping tablets did you use in the last month?

name: _____ amount per month: _____ dose per tablet: _____

name: _____ amount per month: _____ dose per tablet: _____

name: _____ amount per month: _____ dose per tablet: _____

B. Sleeping at night

The questions below are for everyone and concern sleeping at night. If you have been using sleeping tablets, then the answer should reflect how you have slept while taking these tablets.

B1. In the past month, have you had trouble falling asleep when you went to bed at night?

☐ not at all ☐ a little ☐ quite a bit ☐ a lot

B2. In the past month, to what extent do you feel that you have woken *too often*?

☐ not at all ☐ a little ☐ quite a bit ☐ a lot

B3. In the past month, to what extent do you feel that you have been lying awake for *too long* at night?

☐ not at all ☐ a little ☐ quite a bit ☐ a lot

B4. In the past month, to what extent do you feel that you have woken up *too early* in the morning?

☐ not at all ☐ a little ☐ quite a bit ☐ a lot

B5. In the past month, to what extent do you feel you have had *too little* sleep at night?

☐ not at all ☐ a little ☐ quite a bit ☐ a lot

C1. Overall, how well have you slept at night during the past month?

☐ very well ☐ well ☐ rather well ☐ not well but not badly ☐ rather badly ☐ badly ☐ very badly

D. Sleeping during the day and the evening

D1. How often in the past month have you fallen asleep unexpectedly either during the day or in the evening?

☐ never ☐ sometimes ☐ regularly ☐ often

D2. How often in the past month have you fallen asleep while sitting peacefully?

☐ never ☐ sometimes ☐ regularly ☐ often

D3. How often in the past month have you fallen asleep while watching TV or reading?

☐ never ☐ sometimes ☐ regularly ☐ often

D4. How often in the past month have you fallen asleep while talking to someone?

☐ never ☐ sometimes ☐ regularly ☐ often

D5. In the past month, have you had trouble staying awake during the day or in the evening?

☐ never ☐ sometimes ☐ regularly ☐ often

D6. In the past month, have you experienced falling asleep during the day as a problem?

Source: **Marinus et al., 2003**.

14.6 Neuropsychiatric Inventory (NPI)

A. Delusions **(NA)**

Does the patient have beliefs that you know are not true (for example, insisting that people are trying to harm him/her or steal from him/her)? Has he/she said that family members are not who they say they are or that the house is not their home? I'm not asking about mere suspiciousness; I am interested if the patient is convinced that these things are happening to him/her.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient believe that he/she is in danger - that others are planning to hurt him/her? _____
2. Does the patient believe that others are stealing from him/her? _____
3. Does the patient believe that his/her spouse is having an affair? _____
4. Does the patient believe that unwelcome guests are living in his/her house? _____
5. Does the patient believe that his/her spouse or others are not who they claim to be? _____
6. Does the patient believe that his/her house is not his/her home? _____
7. Does the patient believe that family members plan to abandon him/her? _____
8. Does the patient believe that television or magazine figures are actually present in the home? [Does he/she try to talk or interact with them?] _____
9. Does the patient believe any other unusual things that I haven't asked about? _____

If the screening question is confirmed, determine the frequency and severity of the delusions.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - once or more per day.

Severity:
1. Mild - delusions present but seem harmless and produce little distress in the patient.
2. Moderate - delusions are distressing and disruptive.
3. Marked - delusions are very disruptive and are a major source of behavioral disruption. [If PRN medications are prescribed, their use signals that the delusions are of marked severity.]

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

B. Hallucinations **(NA)**

Does the patient have hallucinations such as seeing false visions or hearing imaginary voices? Does he/she seem to see, hear or experience things that are not present? By this question we do not mean just mistaken beliefs such as stating that someone who has died is still alive; rather we are asking if the patient actually has abnormal experiences of sounds or visions.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient describe hearing voices or act as if he/she hears voices? _____
2. Does the patient talk to people who are not there? _____
3. Does the patient describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc)? _____
4. Does the patient report smelling odors not smelled by others? _____
5. Does the patient describe feeling things on his/her skin or otherwise appear to be feeling things crawling or touching him/her? _____
6. Does the patient describe tastes that are without any known cause? _____
7. Does the patient describe any other unusual sensory experiences? _____

If the screening question is confirmed, determine the frequency and severity of the hallucinations.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - once or more per day.

Severity:
1. Mild - hallucinations are present but harmless and cause little distress for the patient.
2. Moderate - hallucinations are distressing and are disruptive to the patient.
3. Marked - hallucinations are very disruptive and are a major source of behavioral disturbance. PRN medications may be required to control them.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

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C. Agitation/Aggression **(NA)**

Does the patient have periods when he/she refuses to cooperate or won't let people help him/her? Is he/she hard to handle?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient get upset with those trying to care for him/her or resist activities such as bathing or changing clothes? _____
2. Is the patient stubborn, having to have things his/her way? _____
3. Is the patient uncooperative, resistive to help from others? _____
4. Does the patient have any other behaviors that make him hard to handle? _____
5. Does the patient shout or curse angrily? _____
6. Does the patient slam doors, kick furniture, throw things? _____
7. Does the patient attempt to hurt or hit others? _____
8. Does the patient have any other aggressive or agitated behaviors? _____

If the screening question is confirmed, determine the frequency and severity of the agitation.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than daily.
4. Very frequently - once or more per day.

Severity:
1. Mild - behavior is disruptive but can be managed with redirection or reassurance.
2. Moderate - behaviors are disruptive and difficult to redirect or control.
3. Marked - agitation is very disruptive and a major source of difficulty; there may be a threat of personal harm. Medications are often required.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

D. Depression/Dysphoria **(NA)**

Does the patient seem sad or depressed? Does he/she say that he/she feels sad or depressed?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have periods of tearfulness or sobbing that seem to indicate sadness? _____
2. Does the patient say or act as if he/she is sad or in low spirits? _____
3. Does the patient put him/herself down or say that he/she feels like a failure? _____
4. Does the patient say that he/she is a bad person or deserves to be punished? _____
5. Does the patient seem very discouraged or say that he/she has no future? _____
6. Does the patient say he/she is a burden to the family or that the family would be better off without him/her? _____
7. Does the patient express a wish for death or talk about killing him/herself? _____
8. Does the patient show any other signs of depression or sadness? _____

If the screening question is confirmed, determine the frequency and severity of the depression.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - essentially continuously present.

Severity:
1. Mild - depression is distressing but usually responds to redirection or reassurance.
2. Moderate - depression is distressing, depressive symptoms are spontaneously voiced by the patient and difficult to alleviate.
3. Marked - depression is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

E. Anxiety **(NA)**

Is the patient very nervous, worried, or frightened for no apparent reason? Does he/she seem very tense or fidgety? Is the patient afraid to be apart from you?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient say that he/she is worried about planned events? _____
2. Does the patient have periods of feeling shaky, unable to relax, or feeling excessively tense? _____
3. Does the patient have periods of [or complain of] shortness of breath, gasping, or sighing for no apparent reason other than nervousness? _____
4. Does the patient complain of butterflies in his/her stomach, or of racing or pounding of the heart in association with nervousness? [Symptoms not explained by ill health] _____
5. Does the patient avoid certain places or situations that make him/her more nervous such as riding in the car, meeting with friends, or being in crowds? _____
6. Does the patient become nervous and upset when separated from you [or his/her caregiver]? [Does he/she cling to you to keep from being separated?] _____
7. Does the patient show any other signs of anxiety? _____

If the screening question is confirmed, determine the frequency and severity of the anxiety.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - once or more per day.

Severity:
1. Mild - anxiety is distressing but usually responds to redirection or reassurance.
2. Moderate - anxiety is distressing, anxiety symptoms are spontaneously voiced by the patient and difficult to alleviate.
3. Marked - anxiety is very distressing and a major source of suffering for the patient.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

F. Elation/Euphoria **(NA)**

Does the patient seem too cheerful or too happy for no reason? I don't mean the normal happiness that comes from seeing friends, receiving presents, or spending time with family members. I am asking if the patient has a persistent and abnormally good mood or finds humor where others do not.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient appear to feel too good or to be too happy, different from his/her usual self? _____
2. Does the patient find humor and laugh at things that others do not find funny? _____
3. Does the patient seem to have a childish sense of humor with a tendency to giggle or laugh inappropriately (such as when something unfortunate happens to others)? _____
4. Does the patient tell jokes or make remarks that have little humor for others but seem funny to him/her? _____
5. Does he/she play childish pranks such as pinching or playing "keep away" for the fun of it? _____
6. Does the patient "talk big" or claim to have more abilities or wealth than is true? _____
7. Does the patient show any other signs of feeling too good or being too happy? _____

If the screening question is confirmed, determine the frequency and severity of the elation/euphoria.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - essentially continuously present.

Severity:
1. Mild - elation is notable to friends and family but is not disruptive.
2. Moderate - elation is notably abnormal.
3. Marked - elation is very pronounced; patient is euphoric and finds nearly everything to be humorous.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

G. Apathy/Indifference **(NA)**

Has the patient lost interest in the world around him/her? Has he/she lost interest in doing things or does he/she lack motivation for starting new activities? Is he/she more difficult to engage in conversation or in doing chores? Is the patient apathetic or indifferent?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient seem less spontaneous and less active than usual? _____
2. Is the patient less likely to initiate a conversation? _____
3. Is the patient less affectionate or lacking in emotions when compared to his/her usual self? _____
4. Does the patient contribute less to household chores? _____
5. Does the patient seem less interested in the activities and plans of others? _____
6. Has the patient lost interest in friends and family members? _____
7. Is the patient less enthusiastic about his/her usual interests? _____
8. Does the patient show any other signs that he/she doesn't care about doing new things? _____

If the screening question is confirmed, determine the frequency and severity of the apathy/indifference.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - nearly always present.

Severity:
1. Mild - apathy is notable but produces little interference with daily routines; only mildly different from patient's usual behavior; patient responds to suggestions to engage in activities.
2. Moderate - apathy is very evident; may be overcome by the caregiver with coaxing and encouragement; responds spontaneously only to powerful events such as visits from close relatives or family members.
3. Marked - apathy is very evident and usually fails to respond to any encouragement or external events.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

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H. Disinhibition **(NA)**

Does the patient seem to act impulsively without thinking? Does he/she do or say things that are not usually done or said in public? Does he/she do things that are embarrassing to you or others?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient act impulsively without appearing to consider the consequences? _____
2. Does the patient talk to total strangers as if he/she knew them? _____
3. Does the patient say things to people that are insensitive or hurt their feelings? _____
4. Does the patient say crude things or make sexual remarks that he/she would not usually have said? _____
5. Does the patient talk openly about very personal or private matters not usually discussed in public? _____
6. Does the patient take liberties or touch or hug others in way that is out of character for him/her? _____
7. Does the patient show any other signs of loss of control of his/her impulses? _____

If the screening question is confirmed, determine the frequency and severity of the disinhibition.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - essentially continuously present.

Severity:
1. Mild - disinhibition is notable but usually responds to redirection and guidance.
2. Moderate - disinhibition is very evident and difficult to overcome by the caregiver.
3. Marked - disinhibition usually fails to respond to any intervention by the caregiver, and is a source of embarrassment or social distress.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

I. Irritability/Lability **(NA)**

Does the patient get irritated and easily disturbed? Are his/her moods very changeable? Is he/she abnormally impatient? We do not mean frustration over memory loss or inability to perform usual tasks; we are interested to know if the patient has abnormal irritability, impatience, or rapid emotional changes different from his/her usual self.

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have a bad temper, flying "off the handle" easily over little things? _____
2. Does the patient rapidly change moods from one to another, being fine one minute and angry the next? _____
3. Does the patient have sudden flashes of anger? _____
4. Is the patient impatient, having trouble coping with delays or waiting for planned activities? _____
5. Is the patient cranky and irritable? _____
6. Is the patient argumentative and difficult to get along with? _____
7. Does the patient show any other signs of irritability? _____

If the screening question is confirmed, determine the frequency and severity of the irritability/lability.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - essentially continuously present.

Severity:
1. Mild - irritability or lability is notable but usually responds to redirection and reassurance.
2. Moderate - irritability and lability are very evident and difficult to overcome by the caregiver.
3. Marked - irritability and lability are very evident, they usually fail to respond to any intervention by the caregiver, and they are a major source of distress.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

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J. Aberrant Motor Behavior **(NA)**

Does the patient pace, do things over and over such as opening closets or drawers, or repeatedly pick at things or wind string or threads?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient pace around the house without apparent purpose? _____
2. Does the patient rummage around opening and unpacking drawers or closets? _____
3. Does the patient repeatedly put on and take off clothing? _____
4. Does the patient have repetitive activities or "habits" that he/she performs over and over? _____
5. Does the patient engage in repetitive activities such as handling buttons, picking, wrapping string, etc? _____
6. Does the patient fidget excessively, seem unable to sit still, or bounce his/her feet or tap his/her fingers a lot? _____
7. Does the patient do any other activities over and over? _____

If the screening question is confirmed, determine the frequency and severity of the aberrant motor activity:

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - essentially continuously present.

Severity:
1. Mild - abnormal motor activity is notable but produces little interference with daily routines.
2. Moderate - abnormal motor activity is very evident; can be overcome by the caregiver.
3. Marked - abnormal motor activity is very evident, usually fails to respond to any intervention by the caregiver, and is a major source of distress.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

K. Sleep (NA)

Does the patient have difficulty sleeping (do not count as present if the patient simply gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? Is he/she up at night? Does he/she wander at night, get dressed, or disturb your sleep?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Does the patient have difficulty falling asleep? _____
2. Does the patient get up during the night (do not count if the patient gets up once or twice per night only to go to the bathroom and falls back asleep immediately)? _____
3. Does the patient wander, pace, or get involved in inappropriate activities at night? _____
4. Does the patient awaken you during the night? _____
5. Does the patient awaken at night, dress, and plan to go out thinking that it is morning and time to start the day? _____
6. Does the patient awaken too early in the morning (earlier that was his/her habit)? _____
7. Does the patient sleep excessively during the day? _____
8. Does the patient have any other nighttime behaviors that bother you that we haven't talked about? _____

If the screening question is confirmed, determine the frequency and severity of the nighttime behavior disturbance.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - once or more per day (every night)

Severity:
1. Mild - nighttime behaviors occur but they are not particularly disruptive.
2. Moderate - nighttime behaviors occur and disturb the patient and the sleep of the caregiver; more than one type of nighttime behavior may be present.
3. Marked - nighttime behaviors occur; several types of nighttime behavior may be present; the patient is very distressed during the night and the caregiver's sleep is markedly disturbed.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

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L. Appetite and eating disorders **(NA)**

Has he/she had any change in appetite, weight, or eating habits (count as NA if the patient is incapacitated and has to be fed)? Has there been any change in type of food he/she prefers?

NO (If no, proceed to next screening question). YES (If yes, proceed to subquestions).

1. Has he/she had a loss of appetite? _____
2. Has he/she had an increase in appetite? _____
3. Has he/she had a loss of weight? _____
4. Has he/she gained weight? _____
5. Has he/she had a change in eating behavior such as putting too much food in his/her mouth at once? _____
6. Has he/she had a change in the kind of food he/she likes such as eating too many sweets or other specific types of food? _____
7. Has he/she developed eating behaviors such as eating exactly the same types of food each day or eating the food in exactly the same order? _____
8. Have there been any other changes in appetite or eating that I haven't asked about? _____

If the screening question is confirmed, determine the frequency and severity of the changes in eating habits or appetite.

Frequency:
1. Occasionally - less than once per week.
2. Often - about once per week.
3. Frequently - several times per week but less than every day.
4. Very frequently - once or more per day or continuously

Severity:
1. Mild - changes in appetite or eating are present but have not led to changes in weight and are not disturbing
2. Moderate - changes in appetite or eating are present and cause minor fluctuations in weight.
3. Marked - obvious changes in appetite or eating are present and cause fluctuations in weight, are embarrassing, or otherwise disturb the patient.

Distress: How emotionally distressing do you find this behavior?
0. Not at all
1. Minimally
2. Mildly
3. Moderately
4. Severely
5. Very severely or extremely

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