



AMENDED CLINICAL TRIAL PROTOCOL 06

COMPOUND: GZ/SAR402671

Multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of GZ/SAR402671 in patients with early-stage Parkinson's disease carrying a GBA mutation or other prespecified variant

Multicenter pharmacokinetics and interventional Study in Parkinson's Disease

STUDY NUMBER: ACT14820

STUDY NAME: MOVES-PD

Version number: 1	EudraCT number:	2016-000657-12
	NCT:	NCT02906020
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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/ countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 06 (Global)	All	09-Feb-2021, Version 01 (electronic 6.0)
Amended Clinical Trial Protocol 05 (Global)	All	03-Sep-2020, version 01 (electronic 5.0)
Amended Clinical Trial Protocol 04 (Global)	All	21-May-2020, version 01 (electronic 4.0)
Amended Clinical Trial Protocol 03 (Global)	All	20-Jul-2018, version 01 (electronic 1.0)
Amended Clinical Trial Protocol 04 (JP)	Japan only	06-Jun-2017, version 01 (electronic 1.0)
Amended Clinical Trial Protocol 03 (ISR)	Israel only	06-Jun-2017, version 01 (electronic 1.0)
Amended Clinical Trial Protocol 02 (Global)	All	06-Jun-2017, version 01 (electronic 1.0)
Protocol Amendment 05 (Global)	All	06-Jun-2017, version 01 (electronic 1.0)
Amended Clinical Trial Protocol 03 (JP)	Japan only	01-Feb-2017, version 01 (electronic 4.0)
Protocol Amendment 04 (JP)	Japan only	01-Feb-2017, version 01 (electronic 4.0)
Amended Clinical Trial Protocol 02 (ISR)	Israel only	08-Dec-2016, version 01 (electronic 2.0)
Amended Clinical Trial Protocol 02 (JP)	Japan only	08-Dec-2016, version 01 (electronic 3.0)
Amended Clinical Trial Protocol 01 (Global)	All	08-Dec-2016, version 01 (electronic 1.0)
Protocol Amendment 03 (Global)	All	08-Dec-2016, version 01 (electronic 1.0)
Amended Clinical Trial Protocol 02 (ISR)	Israel only	15-Aug-2016, version 01 (electronic 1.0)
Protocol Amendment 02 (ISR)	Israel only	15-Aug-2016, version 01 (electronic 1.0)
Amended Clinical Trial Protocol 01 (JP)	Japan only	15-Nov-2016, version 01 (electronic 1.0)
Protocol Amendment 01 (JP)	Japan only	15-Nov-2016, version 01 (electronic 2.0)
Clinical Trial Protocol		30-Jun-2016, version 01 (electronic 1.0)

Amended clinical trial protocol 06 (09 February 2021)

This amended protocol (amendment 06) is considered to be non substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The protocol is being amended to add MDS-UPDRS and BDI-II assessments at Visit 16 (Follow-up visit) and to increase the wash-out period before Visit 16 while allowing more flexibility on the visit window. This will help to better document the course of the disease after study treatment discontinuation.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary: Study design, Assessment schedule, Duration of the study; Section 1.2 Graphical study design for part 2; Section 1.3.3, Part 2: study schedule of assessments (Periods 3 and 4); Section 6.1 Description of the study; Section 6.2.1 Duration of study participation for each patient; Section 8.3.2 Randomization code breaking during Part 2; Section 9.1.2 Treatment phase; Section 9.3.3.3 Vital signs; Section 9.3.3.4 Physical examination, Section 9.3.3.5 Neurological examination; Section 9.3.3.6 Ophthalmological examination; Section 10.1.2 Part 2 : Treatment phase; Section 10.1.2.11 Eight week follow-up visit; Section 10.3.3 List of criteria for permanent discontinuation; Section 10.3.4 Handling of patients after permanent discontinuation; Section 10.3.5 Procedure and consequence for patient withdrawal from study;	Sections updated	Week 214 (Visit 16) changed to Week 216 with visit window increased to ± 2 weeks instead of ± 1 week. MDS-UPDRS and BDI-II added at Visit 16.
Appendix U Protocol amendment history	Revised to reflect current updates	Administrative changes

CLINICAL TRIAL SUMMARY

COMPOUND: GZ/SAR402671	STUDY No.: ACT14820 STUDY NAME: MOVES-PD
TITLE	Multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of GZ/SAR402671 in patients with early-stage Parkinson's disease carrying a GBA mutation or other prespecified variant.
INVESTIGATOR/TRIAL LOCATION	International, multicenter trial.
PHASE OF DEVELOPMENT	Phase 2
STUDY OBJECTIVES	<p><u>Part 1: Dose escalation phase</u></p> <p>Primary objective:</p> <ul style="list-style-type: none"> To determine the safety and tolerability of 4, 8, and 15 mg of GZ/SAR402671, as compared to placebo, when administered orally daily for 4 weeks in early-stage Parkinson's disease (PD) patients carrying a glucocerebrosidase gene (GBA) mutation or other pre-specified sequence variants (from now on both mutation types are referred to as 'GBA mutation'). This will allow selection of the dose for the second part of this study (this does not apply to Japanese patients). <p>Secondary objectives:</p> <ul style="list-style-type: none"> To assess the pharmacokinetic (PK) profile of daily oral dosing of GZ/SAR402671 in plasma when administered at doses of 4, 8, or 15 mg over a 4-week period in early-stage PD patients carrying a GBA mutation. To assess the exposure of GZ/SAR402671 in cerebrospinal fluid (CSF) when administered at doses of 4, 8, or 15 mg over a 4-week period in early-stage PD patients carrying a GBA mutation. <p>Exploratory Objectives:</p> <ul style="list-style-type: none"> To assess the pharmacodynamic response of daily oral dosing of GZ/SAR402671 in plasma and CSF when administered at doses of 4, 8 or 15 mg over a 4-week period, as measured by glucosylceramide (GL-1) in early-stage PD patients carrying a GBA mutation. To explore the effect of GZ/SAR402671 on scores from selected scales and questionnaires which will be used in this study over an 8-week period in early stage PD patients carrying a GBA mutation. <p><u>Part 2: Treatment phase</u></p> <p>Primary objective:</p> <ul style="list-style-type: none"> To determine the efficacy of GZ/SAR402671 in patients with early-stage PD carrying a GBA mutation when

	<p>administered orally daily at the dose selected in Part 1, over a 52-week period, as compared to placebo.</p> <p>Secondary objectives:</p> <ul style="list-style-type: none"> • To demonstrate the overall safety and tolerability of GZ/SAR402671 administered orally daily for 52 weeks in early-stage PD patients carrying a GBA mutation as compared to placebo. • To assess the pharmacodynamic response to daily oral dosing of GZ/SAR402671 in plasma and CSF as measured by GL-1 in early-stage PD patients carrying a GBA mutation over a 52-week period. <p>Exploratory objectives:</p> <ul style="list-style-type: none"> • To explore the effect of GZ/SAR402671 on scores from selected scales and questionnaires which will be used in this study. Of note, for patients receiving levodopa or other PD medication, assessment of scales and questionnaires will be performed during the OFF state (ie, no PD medication may be taken for at least 12 hours prior to the efficacy assessments) except for the Hoehn & Yahr (H&Y) scale which will be completed in "ON" state only at baseline visit (see inclusion criteria I 05). • To assess the effect of GZ/SAR402671 on neurologic functional status via functional neuroimaging over a 52-week period. • To assess the PK profile of GZ/SAR402671 in plasma and CSF of early-stage PD patients carrying a GBA mutation. • To evaluate the pharmacodynamic response to GZ/SAR402671 in plasma and CSF as measured by glucosylsphingosine (lyso-GL-1) in early-stage PD patients carrying a GBA mutation. • To explore the effect of GZ/SAR402671 on CSF biomarkers related to PD or neurodegeneration, including total α-synuclein (α-Syn), neurofilament light chain (NFL), tau, phospho-tau, as well as beta-amyloid (1-40 and 1-42). • To develop a Parkinson's disease progression model in early-stage PD patients carrying a GBA mutation. • To assess the long-term safety and efficacy of GZ/SAR402671 over a 156-week period.
<p>STUDY DESIGN</p>	<p>This is a two-part, multicenter, multiple-country, randomized, double-blinded, placebo-controlled study in early-stage PD patients carrying a GBA mutation. The study will be divided into 2 consecutive parts. Part 1 will be a randomized, double-blinded, placebo-controlled dose escalation study, utilizing a sequential cohort design. Part 1 will allow selection of the dose of GZ/SAR402671 for Part 2, a randomized, double-blind, placebo-controlled, 2-arm study of the efficacy and safety of GZ/SAR402671. Part 1 will be conducted only in selected sites (approximately 20 sites [including 4 Japanese sites]); Part 2 will be conducted at multiple sites (approximately 50). Part 2 will start after the appropriate dose for Part 2 is selected in Part 1.</p>

	<p>In Part 1, during the screening/baseline period, from Day -60 to Day -1, patients will provide informed consent and undergo screening assessments to determine trial eligibility and undergo baseline measurements. If all eligibility criteria are met, patients will enter the study. Part 1 will determine the safety and tolerability of GZ/SAR402671 at 4, 8, and 15 mg in early-stage PD patients carrying a GBA mutation by using a dose escalation scheme. There will be 3 sequential cohorts that will be placebo-controlled:</p> <ul style="list-style-type: none">• Cohort 1: 4 patients on GZ/SAR402671 4 mg and 1 patient on placebo.• Cohort 2: 4 patients on GZ/SAR402671 8 mg and 1 patient on placebo.• Cohort 3: 4 patients on GZ/SAR402671 15 mg and 1 patient on placebo. <p>No additional dose escalation of GZ/SAR402671 will occur above the highest proposed dose of 15 mg. All patients must complete the first 4-week course of therapy with subsequent data review, demonstrating safety/tolerability before dose escalation to the next higher level can occur. Patients will continue to be dosed daily and will be followed every 4 weeks until the completion of Part 1, allowing for additional safety and other exploratory endpoints to be collected. Each cohort will have a 4:1 randomization ratio, and the total sample size will be approximately 15 patients (including 12 on GZ/SAR402671 and 3 on placebo). In Japan, each cohort will have a 3:1 randomization ratio, and the total sample size will be approximately 12 Japanese patients (including 9 on GZ/SAR402671 and 3 on placebo). Therefore, the total sample size in Part 1 will be approximately 27 patients.</p> <p>If a serious adverse event (SAE) or \geqGrade 3 adverse event (AE, National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03) that is considered by the Investigator to be related to GZ/SAR402671 and not to underlying disease or concomitant medication is observed, the case will be communicated to the internal review committee and a decision should be reached regarding escalation to the next dose with GZ/SAR402671. If 2 patients receiving GZ/SAR402671 within the same cohort develop the same SAE or AE (\geqGrade 3), dosing within the cohort will be stopped. After stopping, the internal review committee will review the data and provide recommendations on how to proceed. In addition, SAE/adverse events of special interest (AESIs) will be communicated to the Data Monitoring Committee (DMC).</p> <p>At the end of 4 weeks of treatment during the dose escalation part, patients in each cohort will have a lumbar puncture (LP); CSF exposure of GZ/SAR402671 will be measured at 2 time points in Part 1: at pretreatment and Week 4. If there is no CSF exposure at the highest dose level, the study will be stopped.</p> <p>In Part 2, the GZ/SAR402671 dose will be the highest dose determined to be safe and well tolerated in Part 1. If patients from Part 1 continue to meet eligibility requirements, they may enroll in Part 2, but re-randomization will be required; furthermore, they will have to sign another informed consent form. All screening assessments will need to be repeated, except for the genetic</p>
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	<p>screening, magnetic resonance imaging (MRI), LP, and ioflupane I-123 injection DaTSCAN (DAT scan), to confirm eligibility of patients from Part 1 to enroll in Part 2.</p> <p>In Part 2, eligible patients will be stratified based on use of levodopa/PD medication (yes/no), cognitive function (Montreal Cognitive Assessment [MoCA]) score <26 [yes/no], and severe GBA mutation (yes/no). Patients will be randomized in a 1:1 ratio to receive GZ/SAR402671 or placebo for 52 weeks.</p> <p>Part 2 will include 4 main periods: the up to 60-day screening period (Period 1), the 52-week blinded treatment period (Period 2), the 156-week duration long-term follow-up (LTFU) period (Period 3), and the 8-week post-treatment observation period (Period 4).</p> <p>All patients who continue to meet inclusion criteria I 06, I 07, I 08, and I 09 and none of the exclusion criteria (exclusion criteria E 02, E 03, E 05, and E 06 will not need to be rechecked) at Week 52 will be eligible to receive GZ/SAR402671 treatment during the LTFU period (Period 3).</p>
<p>STUDY POPULATION</p> <p>Main selection criteria:</p>	<p>Inclusion criteria:</p> <p>I 01. Male or female subjects with a diagnosis of PD (with at least two of the following signs: resting tremor, postural instability, akinesia/hypokinesia, and muscle rigidity) and who are heterozygous carriers of a GBA mutation. Note: If the patient has a GBA mutation that is not on the list, a consult will always be required to determine the eligibility of the patient. OR</p> <p>I 02. Patients carrying known sequence variants associated with GBA-PD, in addition to having a diagnosis of PD (with at least 2 of the following signs: resting tremor, postural instability, akinesia/hypokinesia or muscle rigidity), must also have a diagnosis of rapid-eye movement sleep behavior disorder (RBD) confirmed by historically documented polysomnography or by RBD screening questionnaire.</p> <p>I 03. Age ≥18 years to 80 years, inclusive, at the time of signing the informed consent (FOR JAPANESE PATIENTS ONLY: Age ≥20 years to 80 years, inclusive, at the time of signing the informed consent. Note: Japanese patients refers only to Japanese patients enrolled and living in Japan).</p> <p>I 04. Has symptoms of PD for ≥2 years.</p> <p>I 05. Hoehn and Yahr (H&Y) stage of ≤2 for PD at baseline; for patients on a stable dose of PD medication, this should be done in the “ON” state.</p> <p>I 06. If on levodopa or any other PD medication (such as a dopamine agonist), the medication regimen must be stable for at least 30 days (at least 60 days for rasagiline) prior to randomization.</p> <p>I 07. Cooperative, able to ingest oral medication, and able to complete all aspects of the study and capable of doing so, alone, according to the Investigator’s judgment.</p> <p>I 08. The patient is willing to abstain from consumption of grapefruit, grapefruit juice, and/or grapefruit containing</p>

	<p>products for 72 hours prior to administration of the first dose of GZ/SAR402671 and for the duration of the entire treatment period (Part 1 and Part 2, Periods 2 and 3).</p> <p>I 09. Able to provide a signed written informed consent.</p> <p>Exclusion criteria:</p> <p>Exclusion criteria related to study methodology:</p> <ul style="list-style-type: none">E 01. Parkinsonism due to drug(s) and/or toxin(s).E 02. Patients carrying the LRRK2 G2019S mutation.E 03. Patients with Gaucher disease (GD) as defined by clinical signs and symptoms (ie, hepatosplenomegaly, cytopenia, skeletal disease) and/or marked deficiency of glucocerebrosidase (GCase) activity compatible with GD.E 04. MoCA score of <20.E 05. Patients who have past surgical history of deep brain stimulation.E 06. Patients who have a baseline MRI without contrast showing a structural abnormality that is a possible etiology of PD related signs and symptoms.E 07. Any medical disorders and/or clinically relevant findings in the physical examination, medical history, or laboratory assessments that, in the opinion of the Investigator, could interfere with study-related procedures (eg, heart failure, hypokalemia, etc). This includes condition(s) that precludes the safe performance of routine LP, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.E 08. Current participation in another investigational interventional study.E 09. Current treatment with anticoagulants (eg, coumadin, heparin) that might preclude safe completion of the LP.E 10. An investigational medicinal product (IMP), including ambroxol, within 3 months or 5 half-lives, whichever is longer, before study inclusion.E 11. Presence of severe depression as measured by Beck Depression Inventory, second edition (BDI-II) >28 and/or a history of a major affective disorder within 1 year of screening examination.E 12. A history of drug and/or alcohol abuse within the past year prior to the first screening visit.E 13. A known hypersensitivity to DAT scan (either the active substance of ioflupane I-123 or to any of the excipients).E 14. The patient is sexually active and is not willing to use 2 forms of birth control during the study and up to 90 days after the day of last dose. <p>- Women of childbearing potential (WOCBP) not</p>
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	<p>protected by 2 highly effective methods of birth control and/or who are unwilling or unable to be tested for pregnancy for up to 45 days after the day of last dose.</p> <ul style="list-style-type: none"> - Male participants must use 2 forms of birth control during the study and refrain from donating sperm up to 90 days after the day of last dose. If the patient has a female partner of childbearing potential, the patient must wear a condom and female partner must use at least 1 highly effective method of birth control. <p>E 15. The patient is scheduled for in-patient hospitalization including elective surgery during the study.</p> <p>E 16. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study. This includes any patient who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development.</p> <p>E 17. Any country-related specific regulation that would prevent the subject from entering the study.</p> <p>E 18. Any patient who is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.</p> <p>E 19. Know hypersensitivity to GZ/SAR402671 or any component of the excipients.</p> <p>Exclusion related to active comparator and/or mandatory background therapies:</p> <ul style="list-style-type: none"> E 20. Use of any medication specifically used for treating memory dysfunction, such as, but not limited to cholinesterase inhibitors or memantine within 30 days or 5 half-lives, prior to randomization, whichever is longer. E 21. The use of concomitant medications that prolong the time from ECG Q wave to the end of the T wave or corrected T wave corresponding to electrical systole (QT/QTc interval). <p>Exclusion criteria related to current knowledge of GZ/SAR402671 IMP:</p> <ul style="list-style-type: none"> E 22. Liver enzymes (alanine aminotransferase [ALT] /aspartate aminotransferase [AST]) or total bilirubin >2 times the upper limit of normal (ULN) at the time of screening. Patients with Gilbert's disease are excluded only from Part 1 participation. E 23. Renal insufficiency as defined by creatinine >1.5 times ULN at the screening visit. E 24. The patient has a documented diagnosis, as per local regulations, of any of the following infections: hepatitis B, hepatitis C, human immunodeficiency virus 1 or 2. E 25. The patient has received strong or moderate inducers
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	<p>or inhibitors of CYP3A4 within 30 days or 5 half-lives of these medications, prior to randomization, whichever is longer.</p> <p>E 26. Use of the following medications within 5-elimination half-lives prior to the DAT neuroimaging evaluation: amoxapine, amphetamine, benzotropine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norepinephrine, phentermine, phenylpropranolamine, selegiline, sertraline, citalopram, and paroxetine.</p> <p>E 27. The patient has, according to World Health Organization Grading, a cortical cataract >one-quarter of the lens circumference (Grade cortical cataract-2) or a posterior subcapsular cataract >2 mm (Grade posterior subcapsular cataract-2). Patients with nuclear cataracts will not be excluded.</p> <p>E 28. The patient is currently receiving potentially cataractogenic medications, including a chronic regimen (more frequently than every 2 weeks) of any dose or route of corticosteroids or any medication that may cause cataract or worsen the vision of patients with cataract (eg, glaucoma medications) according to the Prescribing Information.</p> <p>E 29. If female, pregnant (defined as positive beta-human chorionic gonadotropin blood test) or lactating or breastfeeding.</p> <p>E 30. A marked baseline prolongation of QT/QTc interval on screening electrocardiogram (ECG) (such as a QTc interval >450 msec in male subjects and >470 msec in female subjects).</p>
Total expected number of patients:	Approximately 27 (12 Japanese and 15 non-Japanese) patients will be treated in Part 1 of the study. The total number of patients will depend on the number of dose levels tested in Part 1. Patients who do not complete a minimum number of scheduled doses of study drug in Part 1 and withdraw for reasons other than safety may be replaced. At the end of Part 1, if patients continue to meet eligibility requirements, and are willing to continue in the study, they will be re-randomized and enrolled in Part 2. It is expected that an additional 216 patients (108 on active treatment and 108 on placebo), for a total of approximately 243 patients, will be enrolled into Part 2 of this study.
Expected number of sites:	Approximately 50 sites may be selected to participate in this study over the entire course of this trial.
STUDY TREATMENT(s)	
Investigational medicinal product:	GZ/SAR402671
Formulation:	GZ/SAR402671 is provided in capsule formulation containing 4 mg or 15 mg of GZ/SAR402671 (active moiety).
Route of administration:	Oral administration.
Dose regimen:	Part 1: placebo or 4, 8, or 15 mg of GZ/SAR402671 once per day for up to 36 weeks (or 52 weeks for Japanese patients).

	<p>Part 2: placebo or GZ/SAR402671 once per day (dose to be determined in Part 1) for 52 weeks (Period 2) and GZ/SAR402671 once per day for an additional 104 weeks (Period 3, LTFU).</p>
<p>ENDPOINTS</p>	<p>Part 1: Dose escalation phase</p> <p>Safety:</p> <ul style="list-style-type: none"> • Physical examination • Neurological examination • Clinical laboratory evaluations including hematology, biochemistry, urinalysis, serology • Vital signs • Assessment of AEs and concomitant medication • Ophthalmic examination • ECG <p>Pharmacodynamic:</p> <ul style="list-style-type: none"> • In plasma, GL-1 and lyso-GL1. Additional plasma and serum biomarkers may be included. • In CSF, GL-1 and lyso-GL1. Additional CSF biomarkers may be included. <p>Pharmacokinetic: Plasma parameters include:</p> <ul style="list-style-type: none"> • Day 1 (single dose administration): Maximum plasma concentration observed (C_{max}), time to reach C_{max} (t_{max}), and area under the plasma concentration versus time curve calculated using the trapezoidal method over a pre-defined time period (from time $t=0$ to 24 hours [AUC_{0-24}], and from $t=0$ to 48 hours [AUC_{0-48}]) • Week 2: Plasma concentration observed just before treatment administration during repeated dosing (C_{trough}) • Week 4: C_{trough}, C_{max}, t_{max}, AUC_{0-24}, and apparent total body clearance of a drug at steady state after oral administration (CL_{ss}/F; calculated using the following equation: $CL_{ss}/F = Dose/AUC_{\tau}$, where τ is the dosing interval) • Week 8: C_{trough} <p>Cerebrospinal fluid (CSF) parameters include:</p> <ul style="list-style-type: none"> • Day -14 to Day 1: pre-dose concentration • Week 4: Concentration at any time within 2 to 4 hours after administration of GZ/SAR402671 <p>NOTE: Plasma and CSF collections for the same time points at Week 4 should be performed in as close succession as possible.</p> <p>Efficacy:</p> <ul style="list-style-type: none"> • Change in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) PART II+III score, performed during the OFF state, from baseline to 4 weeks. • Change in MDS-UPDRS PART II+III score, performed during the OFF state, from baseline to 8 weeks. • Change in MDS-UPDRS PART I+II+III, performed during the OFF state, from baseline to 4 weeks.

	<ul style="list-style-type: none">• Change in MDS-UPDRS PART I+II+III, performed during the OFF state, from baseline to 8 weeks. <p>Part 2: Treatment phase</p> <p>Primary endpoint</p> <ul style="list-style-type: none">• Change in MDS-UPDRS PART II+III score, performed during the OFF state, from baseline to Week 52. <p>Secondary endpoints</p> <ul style="list-style-type: none">• Change in Parkinson's Disease-Cognitive Rating Scale (PD-CRS; total score) from baseline to Week 52.• Change in MDS-UPDRS PART I+II+III, performed during the OFF state, from baseline to Week 52.• Change in H&Y score from baseline to Week 52. <p>Exploratory endpoints</p> <p>Changes from baseline to Week 26 in the following (all patients):</p> <ul style="list-style-type: none">• Biomarkers GL-1 and lyso-GL-1 levels in plasma. <p>Changes from baseline to Week 52 in the following (all patients):</p> <ul style="list-style-type: none">• Change in DAT scan assessment score in predefined areas of interest, such as the caudate nucleus.• Time to initiation of levodopa or other PD therapy (for patients not on levodopa/other PD therapy at baseline) or to increased dose of levodopa/other PD therapy (for patients on levodopa/other PD therapy at baseline).• Reduction of levodopa/PD therapy (for patients on levodopa/other PD therapy at baseline).• GL-1, lyso-GL-1 levels in CSF and plasma.• GCcase activity in CSF and dried blood spot.• Biomarkers related to neurodegeneration in plasma and/or in CSF, such as α-Syn, NFL, tau, phospho-tau, as well as beta amyloid (1-40, and 1-42).• Change in MDS-UPDRS (total score), performed during the OFF state.• Change in MDS-UPDRS individual subscores (Parts I, II, III, and IV).• PD-CRS subscores (the subcortical scale [items 1, 3, 4, 5, 7, 8, 9]) and the cortical scale (items 2 and 6).• MoCA score.• Symbol Digit Modalities Test (SDMT) oral score.• Trail-Making Test A (TMT-A) and Trail-Making Test B (TMT-B) score including the change in the difference between TMT-B minus TMT-A score.• Clinical Global Impression (CGI) scale subscores (such as CGI of Improvement).• Beck Depression Inventory, second edition.• Parkinson's Disease Questionnaire - 39 (PDQ-39) score.• EuroQol five dimensions questionnaire (EQ-5D).
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	<ul style="list-style-type: none">• Health-Related Productivity Questionnaire (HRPQ).• Falls Efficacy Scale (FES) <p>Changes from baseline to Week 104, Week 156, and Week 208 in the following (all patients):</p> <ul style="list-style-type: none">• Change in MDS-UPDRS PART II+III score, performed during the OFF state.• Change in PD-CRS; total score.• Change in MDS-UPDRS PART I+II+III, performed during the OFF state.• Change in H&Y score.• Change in DAT scan assessment score in predefined areas of interest, such as the caudate nucleus.• Time to initiation of levodopa or other PD therapy (for patients not on levodopa/other PD therapy at baseline) or to increased dose of levodopa/other PD therapy (for patients on levodopa/other PD therapy at baseline).• Reduction of levodopa/PD therapy (for patients on levodopa/other PD therapy at baseline).• GL-1, lyso-GL-1 levels in plasma.• GCase activity in dried blood spot.• Biomarkers related to neurodegeneration in plasma, such as α-Syn, NFL, tau, phospho-tau, as well as beta amyloid (1-40, and 1-42).• Change in MDS-UPDRS (total score), performed during the OFF state.• Change in MDS-UPDRS individual subscores (Parts I, II, III, and IV).• PD-CRS subscores (the subcortical scale [items 1, 3, 4, 5, 7, 8, 9]) and the cortical scale (items 2 and 6).• MoCA score.• SDMT oral score.• TMT-A and TMT-B score including the change in the difference between TMT-B minus TMT-A score.• Beck Depression Inventory, second edition.• PDQ-39 score.• EQ-5D.• HRPQ.• FES. <p>The data collected during the study will be used to develop a Parkinson's disease progression model in early stage PD patients carrying a GBA mutation.</p> <p>Pharmacokinetic assessments</p> <p>Plasma parameters include:</p> <ul style="list-style-type: none">• Day 1 (single dose administration): C_{max}, t_{max}, AUC_{0-24}• Week 2: C_{trough}
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	<ul style="list-style-type: none"> • Week 26: <ul style="list-style-type: none"> - C_{through} - Concentration at any time within 2 to 4 hours after administration of GZ/SAR402671 on visit day. • Week 52: <ul style="list-style-type: none"> - C_{through} - Concentration at any time within 2 to 4 hours after administration of GZ/SAR402671 on visit day. <p>Cerebrospinal fluid parameters include:</p> <ul style="list-style-type: none"> • Day -14 to Day 1: pre-dose concentration • Week 52 (all patients): concentration at any time within 2 to 4 hours after administration of GZ/SAR402671 on visit days. <p>NOTE: Plasma and CSF collections for the same time points at Week 52 should be performed in as close succession as possible.</p> <p>Exploratory GZ/SAR402671 metabolite PK profiling and/or metabolite exposure analysis may be performed on plasma and CSF samples collected during Part 1 and Part 2 of the study.</p> <p>Safety endpoints</p> <ul style="list-style-type: none"> • Incidence, relationship to study drug and resolution of treatment-emergent adverse events (TEAEs), SAE, TEAE/SAE leading to study drug or study discontinuation. • Ophthalmological assessments. Visual acuity and lens evaluation will be performed according to the Lens Opacity Classification System II (LOCSII) for monitoring potential cataract development.
<p>ASSESSMENT SCHEDULE</p>	<p>See Study Flowcharts (Section 1.3).</p> <p>For Part 1, the study will comprise of at least 9 visits including the screening visit (V1: Day -60 to Day -1); V2 (Day 1), V3 (Day 2), V4 (Day 3), V5 (Week 2), V6 (Week 4/Day 1), V7 (Week 4/Day 2), V8 (Week 8), and V9. Visit 8 will be repeated every 4 weeks until the completion of Part 1. Visit 9 is a safety follow-up completion visit. See note below for further instructions for premature treatment discontinuation.</p> <p>Using Day 1 as reference, a time frame of ± 3 days is acceptable for Visits 5 to 9 of Part 1 study visits. (If one visit date is skipped/missed/changed, the next visit should take place according to the original schedule).</p> <p>Note: If there is no CSF exposure, the study may be stopped.</p> <p>For Part 2, the study will comprise 16 visits (22 visits in Japanese patients) including the screening visit (V1: Day -60 to Day -1); V2 (Day 1) through V9 (Week 52) for safety assessments and efficacy evaluations in the blinded treatment period; V10 (Week 78) (V9.1: Week 65 in Japanese patients) through V15 (Week 208) for safety assessments and efficacy evaluations in the LTFU period; and</p>

	<p>V16 (Week 216) for the post-treatment observation visit.</p> <p>Note: At the end of the 52-week blinded treatment period, all patients will be evaluated for safety and efficacy, and for eligibility to transition to the LTFU period and receive GZ/SAR402671.</p> <p>Note: For patients transitioning to a long-term study with GZ/SAR402671, Week 208 (V15) will be the last study visit.</p> <p>Using Day 1 as reference, a time frame of ± 3 days is acceptable from Visit 4 to 8 of Part 2 study visits, and ± 14 days for Visit 9 and 16. (If one visit date is skipped/missed/changed, the next visit should take place according to the original schedule).</p> <p>Patients will be followed in the LTFU period for 36 months (156 weeks).</p> <p>Note: All patients who prematurely discontinue study medication prior to Week 8 (Visit 8) in Part 1, or Week 52 (Visit 9) in Period 2 or Week 208 (Visit 15) in Period 3 of Part 2 will be asked to continue study visits for safety and efficacy assessments up to and including the last scheduled visit. At a minimum, the patient should be followed up for at least 8 weeks after their last scheduled received dose. Patients who prematurely and permanently discontinue study medication should complete an end of treatment assessment visit (similar to Week 8/Visit 8 in Part 1 or Week 52/Visit 9 in Part 2 [for either Period 2 or 3]) followed by a 8-week post-treatment follow-up visit (similar to Visit 9 in Part 1 or Visit 16 in Part 2 [for either Period 2 or 3]). If the following examinations including lumbar puncture, DAT scan, and PK analyses on plasma and CSF have been performed recently, then the Investigator can discuss with Sponsor the need to repeat these examinations. Repeat examination(s) will be done on a patient by patient basis.</p>
<p>STATISTICAL CONSIDERATIONS</p>	<p>Sample size determination</p> <p>Part 1: Dose escalation phase</p> <p>As Part 1 is an exploratory, dose-escalation study, the sample size is not based on the statistical power calculation. Each cohort (for non-Japanese patients only) will have a 4:1 randomization ratio, and the total sample size will be approximately 15 patients (including 12 on GZ/SAR402671 and 3 on placebo).</p> <p>For Japanese patients only, each cohort will have a 3:1 randomization ratio, and the total sample size will be approximately 12 Japanese patients (including 9 on GZ/SAR402671 and 3 on placebo). This sample size in Japanese Part 1 is considered based upon empirical and feasibility considerations.</p> <p>The total sample size in Part 1 will be approximately 27 patients.</p> <p>Part 2: Treatment phase</p> <p>Approximately 216 PD patients carrying a GBA mutation in total will be randomized in a 1:1 ratio to the GZ/SAR402671 or placebo group. A sample size of 108 patients for the GZ/SAR402671 group and 108 for the placebo group provides at least 80% power to detect a 4.06 points improvement compared to the placebo mean change in MDS-UPDRS Parts II+III score over 52 weeks. This sample size calculation assumes a 2-sided $\alpha = 0.05$, a standard deviation for the change from baseline to Week 52 in MDS-UPDRS Part II+III of 10.01 points (estimated from the Parkinson's Progression Markers Initiative [PPMI] database), and allows for an approximate 10% early</p>

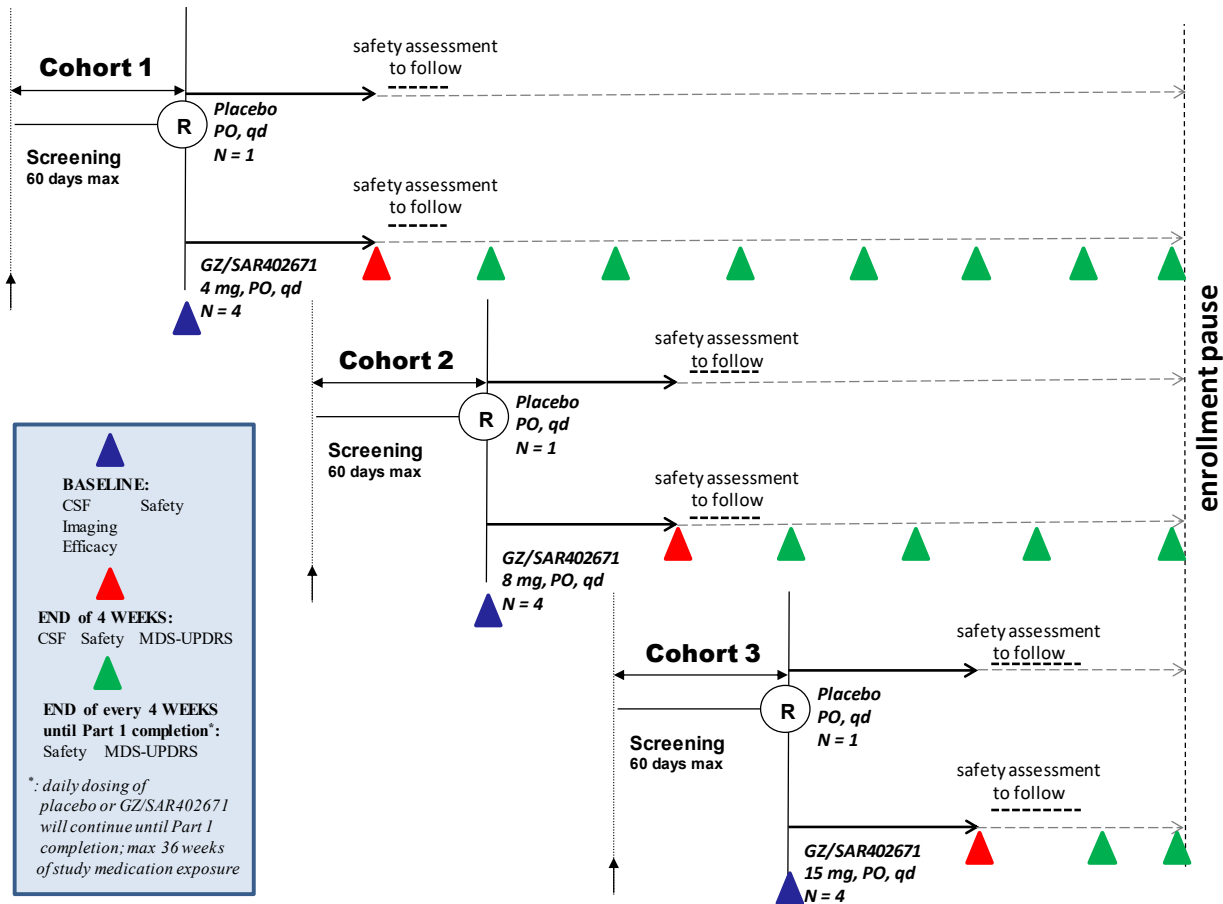
	<p>terminations/unevaluable patients.</p> <p>Of note, the approximate 27 early-stage PD patients carrying a GBA mutation from Part 1 may be re-randomized and participate in all of the assessments in Part 2 of this study; however, they will not contribute to the primary efficacy, safety, PK and pharmacodynamics analyses, and will be described separately.</p> <p>Analysis populations</p> <p>Part 1: Dose escalation phase</p> <p>The Part 1 safety population is defined as all randomized patients in Part 1 who received at least 1 dose of study medication. All safety analyses in Part 1 will be performed on the Part 1 safety population. Patients will be summarized based on the treatment they received.</p> <p>The Part 1 Japanese safety population will be defined as all Japanese randomized patients in Part 1 who received at least 1 dose of study medication in Part 1 of the study. All safety analyses in Japanese Part 1 of the study will be performed on the Part 1 Japanese safety population.</p> <p>The Part 1 pharmacodynamics and PK populations will be defined as all patients in Part 1 who received at least 1 dose of GZ/SAR402671 and who have at least one pharmacodynamics or PK assessment, respectively.</p> <p>The Part 1 Japanese pharmacodynamics and PK populations will be defined as all Japanese patients in Part 1 who received at least 1 dose of GZ/SAR402671 and who have at least one pharmacodynamics or PK assessment, respectively.</p> <p>Part 2: Treatment phase</p> <p>The Part 2 intent-to-treat (ITT) population is defined as all randomized patients in Part 2. Patients from Part 1 who are re-randomized in Part 2 will not be included in Part 2 ITT population. The Part 2 ITT population is the primary analysis population for all efficacy endpoints. Patients will be analyzed in the treatment group to which they were randomized.</p> <p>The Part 2 safety population is defined as all randomized patients in Part 2 who received at least 1 dose of study medication in Part 2 of the study. Patients from Part 1 who are re-randomized in Part 2 will not be included in Part 2 safety population, and will be described separately. All safety analyses in Part 2 will be performed on the Part 2 safety population. Patients will be summarized based on the treatment they received.</p> <p>The Part 2 pharmacodynamics and PK populations will be defined as all patients in Part 2 who received at least 1 dose of GZ/SAR402671 and who have at least one pharmacodynamics or PK assessment, respectively. Patients from Part 1 who are re-randomized in Part 2 will not be included in Part 2 pharmacodynamics and PK populations, and will be described separately.</p> <p>The Part 2 Japanese pharmacodynamics and PK populations will be defined as all Japanese patients in Part 2 who received at least 1 dose of GZ/SAR402671 and who have at least one pharmacodynamics or PK assessment, respectively. Patients from Part 1 who are rerandomized in Part 2 will not be included in Part 2 Japanese pharmacodynamics and PK populations, and will be described separately.</p>
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	<p>Analysis of efficacy (Part 2 only)</p> <p>The primary efficacy endpoint is the change from baseline to Week 52 in MDS-UPDRS Part II+III score.</p> <p>The primary analysis will be based on an ITT approach, including all data regardless of adherence to treatment and protocol. Change from baseline in MDS-UPDRS Part II+III score will be analyzed using a mixed effect model with repeated measures (MMRM). All postbaseline data available within Week 13 to Week 52 analysis windows will be used.</p> <p>Pharmacodynamics and pharmacokinetics analysis (Part 1 and Part 2)</p> <p>Pharmacodynamics and PK data will be described separately for Part 1 and Part 2 of the study, and separately for Japanese and non-Japanese patients.</p> <p>Pharmacodynamic parameters will be summarized and compared between GZ/SAR402671 and placebo administration using descriptive statistics at each time point, including assessment of observed values and percent change from baseline. p-Values for statistical comparisons will be provided for descriptive purpose. Plasma PK parameters will be summarized using descriptive statistics and also analyzed using noncompartmental methods. Cerebrospinal fluid exposure of GZ/SAR402671 will be summarized using descriptive statistics at each time point.</p> <p>PK parameters may be estimated for metabolites using noncompartmental methods and reported for individual patients and summarized using descriptive statistics.</p> <p>Safety (Part 1 and Part 2)</p> <p>Safety data will be described separately for Part 1, and Part 2 of the study, and separately for Japanese and non-Japanese patients.</p> <p>Treatment-emergent AEs will be tabulated (counts and percentages). Serious adverse events and discontinuations due to AEs will be summarized. Descriptive statistics will be generated by time point for selected safety parameters of interest. Data may include absolute and percent change from baseline values.</p>
<p>DURATION OF STUDY PERIOD (PER PATIENT)</p>	<p>Part 1</p> <p><i>Total duration:</i> up to approximately 50 weeks (or 68 weeks for Japanese patients), in total. Patients will receive either placebo or GZ/SAR402671. Dosing will be for minimum 8 weeks per cohort and maximum of 36 weeks (or 52 weeks for Japanese patients), for Cohort 1. After 4 weeks of dosing, an internal blinded data review will occur, ensuring no safety/tolerability issues, the next cohort of patients will be dosed.</p> <p>Part 2</p> <p><i>Total duration:</i> up to approximately 208 weeks (4 years), excluding Periods 1 and 4.</p> <p>There are 4 study periods:</p> <p>Period 1: up to 60 days of screening period;</p> <p>Period 2: up to 52 weeks of blinded treatment period;</p> <p>Period 3: up to 156 weeks LTFU period when all patients will be on active drug; and,</p>

	<p>Period 4: 8-week post-treatment observation period/end of study visit.</p> <p>Therefore, maximum duration for a patient will be approximately 224 weeks.</p> <p>At the end of Period 2, all patients will be evaluated for eligibility to transition to the LTFU period (Period 3) where they will continue to receive appropriate monitoring and will receive GZ/SAR402671. It is important to note that patients <u>will not</u> be informed of when the switch will occur, nor will the person(s) performing any of the evaluations.</p>
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1 FLOW CHARTS

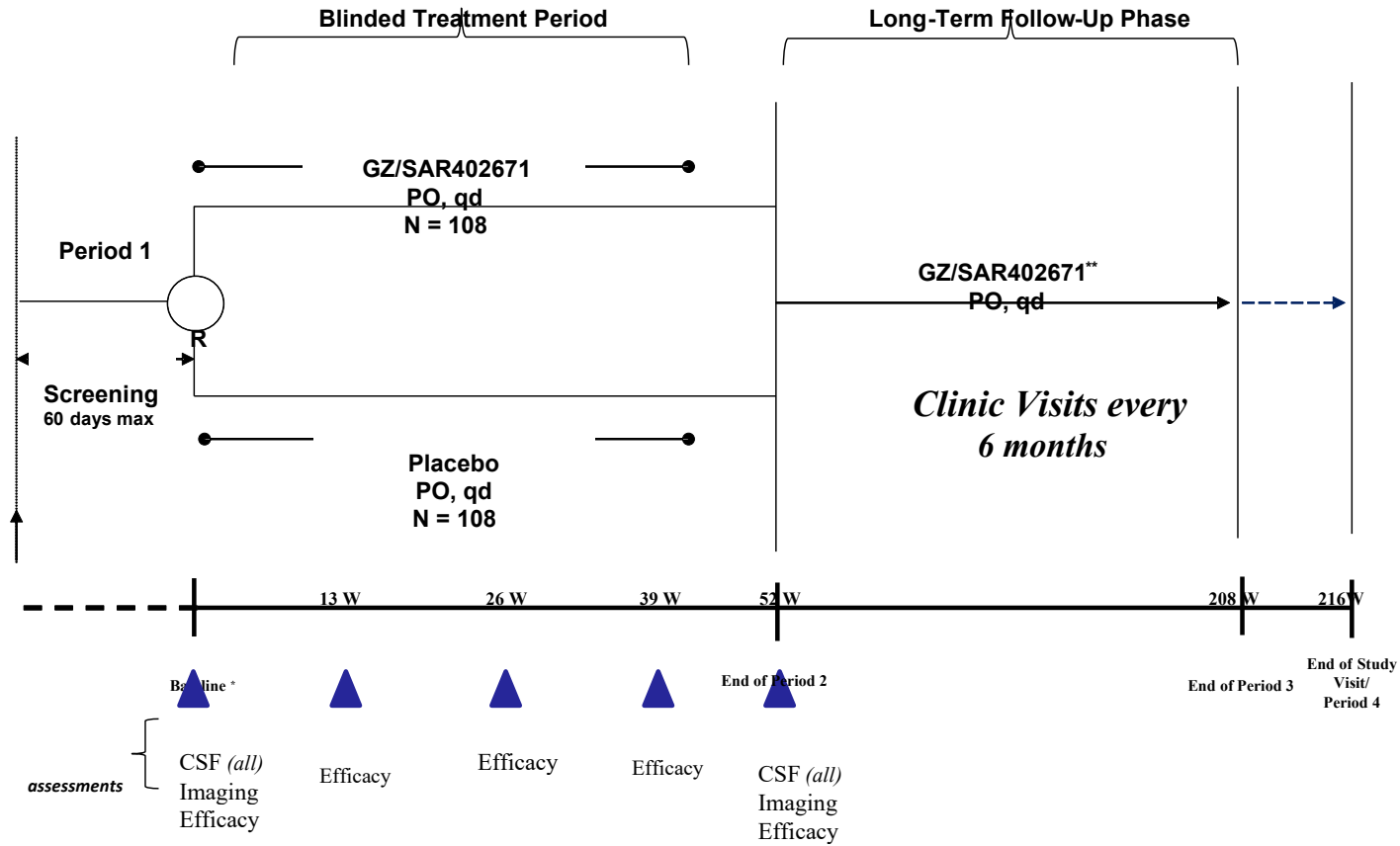
1.1 GRAPHICAL STUDY DESIGN FOR PART 1



Abbreviations: CSF: cerebrospinal fluid; LP: lumbar puncture; max: maximum; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; N: number of subjects; PO: oral; qd: once daily; R: randomization.

** The LP may be done during the screening period within 14 days prior to randomization (Day -14 to Day -1) or on the day of randomization (Day 1 pre-dose). Only 1 sample will be collected, during screening or at Day 1.

1.2 GRAPHICAL STUDY DESIGN FOR PART 2



Abbreviations: R: randomization; W: weeks; max: maximum; CSF: cerebrospinal fluid; pts: patients; LP: lumbar puncture.

- The LP may be done during the screening period within 14 days prior to randomization (Day -14 to Day -1) or on the day of randomization (Day 1 pre-dose). Only one sample will be collected, during screening or at Day 1
- The dose of GZ/SAR402671 will be determined in Part 1.

Abbreviations: CSF: cerebrospinal fluid; LP: lumbar puncture; max: maximum; N: number of patients; PO: oral; qd: once daily; R = randomized; W = weeks.

* The LP may be done during the screening period within 14 days prior to randomization (Day -14 to Day -1) or on the day of randomization (Day 1 pre-dose). Only 1 sample will be collected, during screening or at Day 1; LP at baseline will not be required to confirm eligibility of patients from Part 1 to enroll in Part 2.

** The dose of GZ/SAR402671 will be determined in Part 1.

1.3 STUDY FLOW CHART

1.3.1 Part 1: Study schedule of assessments

Study Period Day (D) or Week (W) (allowed range)	Screening D-60 to D-1	Blinded Treatment Period								
		D1	W0 D2	D3	W2 (±3 days)	W4 (±3 days) D1 D2	W8 (±3 days)	W12-36 (W12-52 for Japanese patients only) (±3 days) ^a	Part 1 Completion Visit (±3 days) ^b	
Visit number	1	2	3	4	5	6	7	8	8.1 – 8.7 (8.1 – 8.11, for Japanese patients only)	9
Site visit	X	X	X	X	X	X	X	X	X	X
Demography	X									
Informed consent	X									
Inclusion/exclusion criteria	X	X								
GBA complete gene sequencing and LRRK2 G2019S genotyping ^c	X									
Medical/surgical history and PD history	X									
Prior/concomitant medications	X	X	X	X	X	X		X	X	X
RBD history (if applicable) ^d	X									
Randomization		X								
MRI ^e (without contrast)	X									
Lumbar puncture ^e		X ^f					X			
Study treatment administration										
GZ/SAR402671 or placebo		X	Drug holiday	X	qd (min 8 weeks per cohort, max 36 weeks for Cohort 1, max 52 weeks for Japan Cohort 1)					
Dispense IMP		X				X		X	X	
Dispense/check patient diary	X	X	X	X	X	X	X	X	X	X ^g
Safety										
Physical examination	X	X				X		X	X	X
Neurological examination	X	X			X	X		X	X	X
Height	X									
Body weight	X									
Archival blood sample ^h		X								
Vital signs, body temperature ⁱ	X	X	X	X	X	X	X	X	X	X
Hematology and biochemistry	X	X			X	X			X	X

Study Period Day (D) or Week (W) (allowed range)	Screening D-60 to D-1	Blinded Treatment Period								
		D1	W0 D2	D3	W2 (±3 days)	W4 (±3 days) D1 D2	W8 (±3 days)	W12-36 (W12-52 for Japanese patients only) (±3 days) ^a	Part 1 Completion Visit (±3 days) ^b	
Visit number	1	2	3	4	5	6	7	8	8.1 – 8.7 (8.1 – 8.11, for Japanese patients only)	9
Urinalysis	X	X			X	X			X	X
Serum β-HCG pregnancy test (for WOCBP)	X									
Urine pregnancy test (for WOCBP)		X						X	X	X
Ophthalmology examination ^j	X					X		X	X	X
12-lead ECG	X	X ^k				X			X ^k	X
Adverse event collection	X	X	X	X	X	X	X	X	X	X
Biomarkers										
Biomarkers: CSF ^l		X ^f				X ^m				
Biomarkers: serum and plasma ⁿ		X			X	X				
GCase: dried blood spot ^o	X									
DNA (optional) (Not applicable in Israel)										
Pharmacogenetics DNA sample ^p		X								
Pharmacokinetics										
Plasma samples		X ^q	X	X	X	X ^q	X	X		
CSF samples		X ^{e,f}				X ^{m,r}				
Assessments^s										
DAT scan		X (Pre-dose) ^{e,t}								
MDS-UPDRS (including H&Y)	X ^u	X				X		X	X	
PD-CRS	X	X						X		
MoCA	X	X						X		
SDMT (Oral)		X						X		
TMT-A; TMT-B		X						X		
BDI-II	X ^v	X			X	X		X	X	X
CGI		X						X		
PGIC								X		
PDQ-39		X						X		

Study Period Day (D) or Week (W) (allowed range)	Screening D-60 to D-1	Blinded Treatment Period								
		D1	W0 D2	D3	W2 (±3 days)	W4 (±3 days) D1 D2	W8 (±3 days)	W12-36 (W12-52 for Japanese patients only) (±3 days) ^a	Part 1 Completion Visit (±3 days) ^b	
Visit number	1	2	3	4	5	6	7	8	8.1 – 8.7 (8.1 – 8.11, for Japanese patients only)	9
EQ-5D		X						X		
HRPQ		X						X		

Abbreviations: α -Syn: α -synuclein; β -HCG: beta-human chorionic gonadotropin; AE: adverse event; BDI-II: Beck Depression Inventory, second edition; CGI: Clinical Global Impression; CSF: cerebrospinal fluid; DAT: dopamine transporters; DAT scan, ioflupane I-123 injection DaTSCAN; DBS: dried blood spot; ECG: electrocardiogram; EQ-5D: EuroQol Five Dimensions questionnaire; GBA: glucocerebrosidase gene; GCase: glucocerebrosidase; GL-1: glucosylceramide; H&Y: Hoehn and Yahr; HRPQ: Health-Related Productivity questionnaire; IMP: investigational medicinal product; LP: lumbar puncture; lyso-GL-1: glucosylsphingosine; max: maximum; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; min: minimum; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging; NFL: neurofilament light chain; PD: Parkinson's disease; PD-CRS: Parkinson's Disease-Cognitive Rating Scale; PDQ-39: Parkinson's Disease Questionnaire - 39; PGIC: Patient Global Impression of Change; PK: pharmacokinetics; qd: once daily; RBD: rapid eye movement sleep behavior disorder; SDMT: Symbol Digit Modalities Test; TMT-A: Trail Making test A; TMT-B: Trail Making test B; WOCBP: women of childbearing potential.

- a This visit must be repeated for all ongoing patients every 4 weeks until all patients from Cohort 3 complete Part 1. A maximum of 36 weeks of treatment will be allowed (applicable to patients in Cohort 1), ie, up to 7 additional visits (8.1-8.7) may be required. In Japan, a maximum of 52 weeks of treatment will be allowed (applicable to patients in Cohort 1), ie, up to 11 additional visits (8.1-8.11) may be required.
- b This is the Part 1 completion visit and it should be done 6 weeks after last IMP dose; this visit also applies to early withdrawal or treatment discontinuation, if applicable.
- c Once the results of the GBA gene sequencing (positive for a GBA mutation) and the LRRK2 genotyping (negative for the G2019S mutation) are confirmed, the remaining of the screening activities can continue.
- d Confirmed by historically documented polysomnography or by RBD screening questionnaire.
- e Once patients demonstrate eligibility based on screening criteria, MRI, LP, and DAT scan will be performed. Baseline MRI must be done at least 7 days prior to the end of the screening period (Day -8). DAT scans will be performed only in countries where it is approved.
- f The LP may be done during the screening period within 14 days prior to randomization (Day -14 to Day -1) or on the day of randomization (Day 1 pre-dose). Only one LP will be performed, during screening or at Day 1. If the baseline LP coincides with the baseline MRI, MRI must be done prior to LP.
- g Retrieve patient diary.
- h This sample will be collected and stored for use if any unexpected safety issue occurs to ensure that a pre-dose baseline value is available for previously nonassessed parameters (eg, serology).
- i In addition to body temperature, other vital signs to be captured include: respiratory rate, heart rate, systolic, and diastolic blood pressure.
- j Full ophthalmology examination and photography must be done during screening, at Week 36 (or Week 52 for Japanese patients), if applicable, and at the completion visit, early withdrawal or treatment discontinuation, if applicable. Visual acuity check, slit lamp examination and funduscopy without pupil dilation are only required at Week 4, and at Weeks 12 and 28 (Week 36 for Japanese patients only), if applicable. Pupil dilation/full evaluation can be performed at any time if deemed medically necessary. When neurological and ophthalmological examinations are performed on the same day, the neurological examination should be performed **before** the ophthalmological examination. Please see [Section 9.3.3.6](#) for more details.
- k Electrocardiograms to be performed at multiple timepoints on Day 1: pre-dose, and 2, 4, and 6 hours postdose. If applicable, an ECG should be performed at Week 28.
- l Cerebrospinal fluid biomarkers, including GL-1, lyso-GL-1, α -Syn, NFL, tau, phospho-tau, as well as beta-amyloid (1-40, and 1-42).
- m Sample to be collected within 2 to 4 hours post GZ/SAR402671 administration (plasma and CSF samples in the same patient should be collected as close as possible). See detailed flowcharts in [Section 1.4.1](#) for timing of assessments.
- n Plasma or serum biomarkers, including plasma GL-1, lyso-GL-1. With respect to an unscheduled visit, plasma or serum biomarker samples should only be taken if the patient has a known AE.
- o One whole blood sample will be collected and spotted on cards at the clinical site and both the sample and the card must be sent to the laboratory doing the genetic testing.
- p DNA sample will be stored to support possible future investigation of potential biomarkers for response to GZ/SAR402671. The patient must sign a separate and optional consent form for pharmacogenetics (DNA) analysis only. Of note, the DNA sample should be collected at the baseline, but it may be collected at any visit during the study.
- q Multiple plasma PK assessments occur on this study day. See detailed flowcharts in [Section 1.4.1](#) for timing of assessments.

- r* Cerebrospinal fluid PK assessments. See detailed flowcharts in [Section 1.4.1](#) for timing of assessments.
- s* Baseline efficacy assessments should be conducted **prior to GZ/SAR402671 administration on Day 1**. For patients already on PD medications at the time of randomization, all efficacy assessments must be done in the patient's "OFF" state (no PD medication may be taken for at least 12 hours prior to the first efficacy assessment). See also footnote u.
- t* Baseline DAT scan may be done within 7 days prior to randomization (Day -7 to Day -1) or on the day of randomization (Day 1 pre-dose).
- u* Baseline H&Y for patients on a stable dose of PD medication must be done on the "ON" state (see inclusion criterion [I 05](#)).
- v* At screening, patients with BDI-II of 20-28, inclusive, should be evaluated by a mental health specialist before the Investigator can determine if the patient would be able to fully participate in the trial. Patients with a BDI-II of >28 (severe depression) at screening will be excluded.

Note: When several items take place at the same time, the following order should be respected: vital signs; plasma sampling for pharmacodynamics, PK, and safety; LP, IMP administration.

Note: Pregnancy testing after screening will be done by urine dipstick testing and **must** be conducted prior to imaging; pregnancy testing is required for all female patients capable of bearing children. Pregnancy tests may be performed more frequently in some countries due to local legislations related to WOCBP randomized in clinical trials.

Note: For Japan only, patients should be hospitalized for Visit 2 through 4, in principle; however, if hospitalization does not occur, the Investigator should follow up each day with a phone call to check if the patients experience any AEs (patients living alone must be hospitalized for Visit 2 through 4).

1.3.2 Part 2: Study schedule of assessments (Periods 1 and 2)

Study Period Day (D) or Week (W) (allowed range)	Screening ^a D-60 to D-1	Blinded Treatment Period							
		W0 D1 D2		W2 (±3 days)	W4 (±3 days)	W13 _u (±3 days)	W26 _u (±3 days)	W39 _u (±3 days)	W52 _{b,u} (±14 days)
Visit number	1	2	3	4	5	6	7	8	9
Site visit	X	X	X	X	X	X	X	X	X
Demography	X								
Informed consent	X								
Inclusion/exclusion criteria	X	X							X
GBA complete gene sequencing and LRRK2 G2019S genotyping ^{a,c}	X								
Medical/surgical history and PD history	X								
RBD history (if applicable) ^d	X								
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Randomization		X							
MRI ^{a,e} (without contrast)	X								
Lumbar puncture ^{a,e}		X ^f							X
Study treatment administration									
GZ/SAR402671 or placebo		qd							
Dispense IMP		X			X	X	X	X	X ^g
Dispense/check patient diary	X	X	X	X	X	X	X	X	X
Safety									
Physical examination	X	X					X		X
Neurological examination	X	X				X	X	X	X
Height	X								
Body weight	X								X
Archival blood sample ^h		X							
Vital signs, body temperature ⁱ	X	X	X	X	X	X	X	X	X
Hematology and biochemistry	X	X		X	X	X	X	X	X
Urinalysis	X	X		X	X	X	X	X	X
Serum β-HCG pregnancy test (for WOCBP)	X								

Study Period Day (D) or Week (W) (allowed range)	Screening ^a	Blinded Treatment Period							
	D-60 to D-1	W0		W2 (±3 days)	W4 (±3 days)	W13 _u (±3 days)	W26 _u (±3 days)	W39 _u (±3 days)	W52 _{b,u} (±14 days)
	D1	D2							
Visit number	1	2	3	4	5	6	7	8	9
Urine pregnancy test (for WOCBP)		X				X	X	X	X
Ophthalmology exam ⁱ	X				X	X	X	X	X
12-lead ECG	X				X		X		X
Adverse event collection	X	X	X	X	X	X	X	X	X
Biomarkers									
Biomarkers: CSF ^k		X ^f							X
Biomarkers: serum and plasma ^l		X		X	X	X	X	X	X
GCase: dried blood spot ^{a,m}	X								X
DNA (optional) (Not applicable in Israel)									
Pharmacogenetics DNA sample ⁿ		X							X
Pharmacokinetics									
Plasma samples		X ^o	X	X			X ^o		X ^o
CSF samples		X ^{f,p}							X
Assessments^q									
DAT scan ^{a,e}		X (Pre-dose) ^{e,r}							X
MDS-UPDRS (including H&Y)	X ^s	X				X	X	X	X
PD-CRS	X	X				X	X	X	X
MoCA	X	X				X	X	X	X
SDMT (oral)		X				X	X	X	X
TMT-A; TMT-B		X				X	X	X	X
BDI-II	X ^t	X		X	X	X	X	X	X
CGI		X							X
PGIC						X	X	X	X
PDQ-39		X				X	X	X	X
EQ-5D		X				X	X	X	X
FES		X				X	X	X	X
HRPQ		X				X	X	X	X

Abbreviations: α -Syn: α -synuclein; β -HCG: beta-human chorionic gonadotropin; AE: adverse event; BDI-II: Beck Depression Inventory, second edition; CGI: Clinical Global Impression; CSF: cerebrospinal fluid; DAT: dopamine transporters; DAT scan, ioflupane I-123 injection DaTSCAN; DBS: dried blood spot; ECG: electrocardiogram; EQ-5D: EuroQol Five Dimensions questionnaire; FES: Falls Efficacy Scale; GBA: glucocerebrosidase gene; GCase: glucocerebrosidase; GL-1: glucosylceramide; H&Y: Hoehn and Yahr; HRPQ: Health-Related Productivity Questionnaire; IMP: investigational medicinal product; LP: lumbar puncture; lyso-GL 1: glucosylsphingosine; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; MRI: magnetic resonance imaging; NFL: neurofilament light chain; PD: Parkinson's disease; PD-CRS: Parkinson's Disease-Cognitive Rating Scale; PDQ-39: Parkinson's Disease Questionnaire - 39; PGIC: Patient Global Impression of Change; PK: pharmacokinetics; qd, daily; RBD: rapid eye movement sleep behavior disorder; SDMT: Symbol Digit Modalities Test; TMT-A: Trail Making test A; TMT-B: Trail Making test B; WOCBP: women of childbearing potential.

- a For patients who have previously completed Part 1, the following will NOT have to be repeated: GBA mutation and LRRK2 screening, GCase: dried blood spot, MRI, LP, and DAT scan.
- b This visit will serve as the screening for patients enrolling into Period 3.
- c Genetic screening will not need to be repeated to confirm eligibility of patients from Part 1 to enroll in Part 2. Once the results of the GBA gene sequencing (positive for a GBA mutation) and the LRRK2 genotyping (negative for the G2019S mutation) are confirmed, the remaining of the screening activities can continue.
- d Confirmed by historically documented polysomnography or by RBD screening questionnaire.
- e Once patients demonstrate eligibility based on screening criteria, MRI, LP, and DAT scan will be performed, except for the patients who completed these baseline assessments in Part 1. Baseline MRI must be done at least 7 days prior to the end of the screening period (Day -8). DAT scans will be performed only in countries where it is approved.
- f The LP may be done during the screening period within 14 days prior to randomization (Day -14 to Day -1) or on the day of randomization (Day 1, pre-dose). Only one LP will be performed, during screening or at Day 1. If the baseline LP coincides with the baseline MRI, MRI must be done prior to LP. LP at baseline will not be required to confirm eligibility of patients from Part 1 to enroll in Part 2.
- g This dispensing is only for patients moving on to Period 3.
- h This sample will be collected and stored for use if any unexpected safety issue occurs to ensure that a preadministration baseline value is available for previously nonassessed parameters (eg, serology). This sample will not be required for patients from Part 1 to enroll in Part 2.
- i Multiple assessments occur on this study day. In addition to body temperature, other vital signs to be captured include: respiratory rate, heart rate, systolic, and diastolic blood pressure. Orthostatic vital signs will be done at screening, Weeks 4 and 52; at all other time points, vital signs will be done in the supine position.
- j Full ophthalmology examination and photography must be done during screening and at Week 52, early withdrawal or treatment discontinuation, as applicable. Visual acuity check, slit lamp examination and fundoscopy without pupil dilation are only required at Week 4, Week 13, Week 26, and Week 39. Pupil dilation/full evaluation can be performed at any time if deemed medically necessary. At Visits 1, 6, 7, 8, and 9, when neurological and ophthalmological examinations are performed on the same day, the neurological examination should be performed **before** the ophthalmological examination.
- k Cerebrospinal fluid biomarkers, including GL-1, lyso-GL-1, α -Syn, NFL, tau, phospho-tau, as well as beta-amyloid (1-40, and 1-42).
- l Plasma or serum biomarkers, including plasma GL-1, lyso-GL-1. With respect to an unscheduled visit, plasma or serum biomarker samples should only be taken if the patient has a known AE.
- m One whole blood sample will be collected and spotted on cards at the clinical site and both the sample and the card must be sent to the laboratory doing the genetic testing.
- n DNA sample will be stored to support possible future investigation of potential biomarkers for response to GZ/SAR402671. The patient must sign a separate and optional consent form for pharmacogenetics (DNA) analysis only. Of note, the first DNA sample should be collected at baseline after eligibility criteria are met, but it may be collected at any visit during the study. This sample will not be required for patients from Part 1 to enroll in Part 2. The second DNA sample should be collected at Week 52 or at any visit after Week 52.
- o Multiple plasma PK assessments occur on this study day. See detailed flowcharts in [Section 1.4.2](#) for timing of assessments.
- p Cerebrospinal fluid PK assessments. See detailed flowcharts in [Section 1.4.2](#) for more detail with respect to the timing of assessments.
- q Baseline efficacy assessments should be conducted **prior to GZ/SAR402671 administration on Day 1**. For patients already on PD medications at the time of randomization, all efficacy assessments must be done in the patient's "OFF" state (no PD medication may be taken for at least 12 hours prior to the first efficacy assessment). See also footnote s.
- r Baseline DAT scan may be done within 7 days prior to randomization (Day -7 to Day -1) or on the day of randomization (Day 1 pre-dose).
- s Baseline H&Y for patients on a stable dose of PD medication must be done on the "ON" state (see inclusion criterion [I 05](#)).
- t At screening, patients with BDI-II of 20-28, inclusive, should be evaluated by a mental health specialist before the Investigator can determine if the patient would be able to fully participate in the trial. Patients with a BDI-II of >28 (severe depression) at screening will be excluded.
- u Visit window extended up to 3 months, during Covid-19 outbreak ([Section 10.1.2](#)).

Note: When several items take place at the same time, the following order should be respected: vital signs; plasma sampling for pharmacodynamics, PK, and safety; LP, IMP administration.

Note: Pregnancy testing after screening will be by urine dipstick testing and **must** be conducted prior to imaging; pregnancy testing is required for all female patients capable of bearing children. Pregnancy tests may be performed more frequently in some countries due to local legislations related to WOCBP randomized in clinical trials.

1.3.3 Part 2: Study schedule of assessments (Periods 3 and 4)

Study Period	Long-Term Follow-up Period (Period 3)												8-Week Follow-up Visit (Period 4)
	W65 ^f (±7 days)	W78 ^f (±7 days)	W91 ^f (±7 days)	W104 (2 years) ^f (±7 days)	W117 ^f (±7 days)	W130 ^f (±7 days)	W143 ^f (±7 days)	W156 ^f (3 years) (±7 days)	W169 ^f (±7 days)	W182 ^f (±7 days)	W195 ^f (±7 days)	W208 ^f (4 years) (±7 days)	
Visit number	9.1 (for Japanese patients only)	10	10.1 (for Japanese patients only)	11	11.1 (for Japanese patients only)	12	12.1 (for Japanese patients only)	13	13.1 (for Japanese patients only)	14	14.1 (for Japanese patients only)	15	16
Visit at clinical site	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Study treatment administration													
GZ/SAR402671	qd												
Dispense IMP		X		X		X		X		X			
Dispense/check patient diary		X		X		X		X		X		X ^b	X ^b
Biomarkers^c													
Biomarkers: serum and plasma				X				X				X	
Safety													
Physical examination				X				X				X	X

Study Period	Long-Term Follow-up Period (Period 3)												8-Week Follow-up Visit (Period 4)
	W65 ^f (±7 days)	W78 ^f (±7 days)	W91 ^f (±7 days)	W104 (2 years) ^f (±7 days)	W117 ^f (±7 days)	W130 ^f (±7 days)	W143 ^f (±7 days)	W156 ^f (3 years) (±7 days)	W169 ^f (±7 days)	W182 ^f (±7 days)	W195 ^f (±7 days)	W208 ^f (4 years) (±7 days)	
Visit number	9.1 (for Japanese patients only)	10	10.1 (for Japanese patients only)	11	11.1 (for Japanese patients only)	12	12.1 (for Japanese patients only)	13	13.1 (for Japanese patients only)	14	14.1 (for Japanese patients only)	15	16
Neurological examination		X		X		X		X		X		X	X
Vital signs, body temperature	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight				X				X				X	
Hematology				X				X				X	
Biochemistry, urinalysis				X				X				X	
Urine pregnancy test (for WOCBP)		X		X		X		X		X		X	
Ophthalmology examination ^d		X		X		X		X		X		X	X
12-lead ECG				X				X				X	
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessments^e													
DAT scan				X				X				X	

Study Period	Long-Term Follow-up Period (Period 3)												8-Week Follow-up Visit (Period 4)
	Day (D) or Week (W) (allowed range)	W65 ^f (±7 days)	W78 ^f (±7 days)	W91 ^f (±7 days)	W104 (2 years) ^f (±7 days)	W117 ^f (±7 days)	W130 ^f (±7 days)	W143 ^f (±7 days)	W156 ^f (3 years) (±7 days)	W169 ^f (±7 days)	W182 ^f (±7 days)	W195 ^f (±7 days)	
Visit number	9.1 (for Japanese patients only)	10	10.1 (for Japanese patients only)	11	11.1 (for Japanese patients only)	12	12.1 (for Japanese patients only)	13	13.1 (for Japanese patients only)	14	14.1 (for Japanese patients only)	15	16
MDS-UPDRS (including H&Y)		X		X		X		X		X		X	X
PD-CRS		X		X		X		X		X		X	
MoCA		X		X		X		X		X		X	
SDMT (oral)		X		X		X		X		X		X	
TMT-A; TMT-B		X		X		X		X		X		X	
BDI-II		X		X		X		X		X		X	X
PDQ-39		X		X		X		X		X		X	
EQ-5D		X		X		X		X		X		X	
FES		X		X		X		X		X		X	
HRPQ		X		X		X		X		X		X	

Abbreviations: AE, adverse event; BDI-II: Beck Depression Inventory, second edition; CGI: Clinical Global Impression; DAT: dopamine transporters; DAT scan, ioflupane I-123 injection DaTSCAN; ECG: electrocardiogram; EQ-5D: EuroQol Five Dimensions questionnaire; FES: Falls Efficacy Scale; GL-1: glucosylceramide; H&Y: Hoehn and Yahr; HRPQ: Health-Related Productivity questionnaire; IMP, investigational medicinal product; lyso-GL-1: glucosylsphingosine; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; PD: Parkinson's disease; PD-CRS: Parkinson's Disease-Cognitive Rating Scale; PDQ-39: Parkinson's Disease Questionnaire – 39; qd, daily; SDMT: Symbol Digit Modalities Test; TMT-A: Trail-Making Test A; TMT-B: Trail Making Test B; WOCBP: women of childbearing potential.

- a* This is the study completion visit, and it should be done 8 weeks after last IMP dose; this visit also applies to early withdrawal or treatment discontinuation, if applicable. This does not apply to patients who will transition to a long-term study with GZ/SAR402671 (last visit will be week 208).
- b* Retrieve patient diary. For patients transitioning to a long-term study with GZ/SAR402671 the patient diary will be retrieved at week 208.
- c* Plasma biomarkers, including plasma GL-1 and lyso-GL-1.
- d* After 52 weeks, the patient is required to have a full ophthalmological examination at Weeks 104, 156, 208, and early withdrawal or treatment discontinuation, if applicable. Visual acuity check, slit lamp examination and funduscopy without pupil dilation are only required at Weeks 78, 130, 182, and 216 (at the 8-week follow-up [Period 4] visit). Pupil dilation/full evaluation can be performed at any time if deemed medically necessary.
- e* For patients already on PD medications at the time of randomization, all efficacy assessments must be done in the patient's "OFF" state (no PD medication may be taken for at least 12 hours prior to the first efficacy assessment).
- f* Visit window extended up to 3 months, during Covid-19 outbreak ([Section 10.1.2](#)).

Note: Visits in Weeks 65, 91, 117, 143, 169, and 195 are for Japanese patients only.

1.4 PHARMACOKINETIC SAMPLING FLOW CHARTS

1.4.1 Part 1: Dose escalation phase

Time (hour)	Week 0/day 1						Week 0 /day 2	Week 0 /day 3		Week 2 (±3 days)		Week 4/day 1 (±3 days)						Week 4 /day 2		Week 8 (±3 days)	
	Pre dose	0 h	1 h ^a	2 h ^b	4 h ^c	8 h ^d	24 h ^e	48 h ^f	0 h	Pre dose	0 h	Pre dose	0 h	1 h ^a	2 h ^b	4 h ^c	8 h ^d	24 h ^e	0 h	Pre dose	0 h
GZ/SAR402671 or placebo		X					DRUG HOLIDAY		X		X		X						X		X
Plasma sample for PK	P01 ^g		P02	P03	P04	P05	P06	P07 ^g		P08 ^g		P09 ^g		P10	P11	P12	P13	P14 ^{e,g}		P15 ^g	
CSF sample for PK	C01 ^h														C02 ⁱ						

Abbreviations: CSF: cerebrospinal fluid; LP: lumbar puncture; PK: pharmacokinetics.

a Blood sample must be collected within 1 hour ±10 minutes.

b Blood sample must be collected within 2 hours ±15 minutes.

c Blood sample must be collected within 4 hours ±30 minutes.

d Blood sample must be collected within 8 hours ±60 minutes.

e Blood sample must be collected within 24 hours ±60 minutes after the Day 1 dose.

f Blood sample must be collected within 48 hours ±120 minutes after the Day 1 dose.

g Sample must be collected within 1 hour before oral administration of GZ/SAR402671. On these days, patients will take GZ/SAR402671 at the clinical site.

h The LP may be done during the screening period within 14 days prior to randomization (Day -14 to Day -1) or on the day of randomization (Day 1, pre-dose). The CSF sample for PK will be done at the same time.

i Sample to be collected within 2 to 4 hours post GZ/SAR402671 administration (plasma and CSF samples in the same patient should be collected as close as possible).

1.4.2 Part 2: Treatment phase

	Week 0/day 1						Week 0/ day 2		Week 2 (±3 days)		Week 26 (±3 days)			Week 52 (±14 days)		
Time (hour)	Pre-dose	0 h	1 h ^a	2 h ^b	4 h ^c	8 h ^d	24 h ^e	0 h	Pre-dose	0 h	Pre-dose	0 h	2 ^b - 4 ^c h	Pre-dose	0 h	2 ^b - 4 ^c h
GZ/SAR402671 or placebo		X						X (NO DRUG HOLIDAY)		X		X			X	
Plasma sample for PK	P01 ^f		P02	P03	P04	P05	P06 ^f		P07 ^f		P08 ^f		P09 ^g	P10 ^f		P11 ^g
CSF sample for PK	C01 ^h															C02 ^g

Abbreviations: CSF: cerebrospinal fluid; LP: lumbar puncture; PK: pharmacokinetics.

a Blood sample must be collected within 1 hour ±10 minutes.

b Blood sample must be collected within 2 hours ±15 minutes.

c Blood sample must be collected within 4 hours ±30 minutes.

d Blood sample must be collected within 8 hours ±60 minutes.

e Blood sample must be collected within 24 hours ±60 minutes after the Day 1 dose.

f Sample must be collected within 1 hour before oral administration of GZ/SAR402671. On these days, patients will take GZ/SAR402671 at the clinical site.

g Sample to be collected within 2 to 4 hours post GZ/SAR402671 administration (plasma and CSF samples in the same patient should be collected as close as possible).

h The LP may be done during the screening period within 14 days prior to randomization (Day -14 to Day -1) or on the day of randomization (Day 1, pre-dose). The CSF sample for PK will be done at the same time. LP at baseline will not be required to confirm eligibility of patients from Part 1 to enroll in Part 2.

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3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
AUC _t :	area under the plasma concentration versus time curve calculated using the trapezoidal method over a predefined time period
BDI-II:	Beck Depression Inventory, second edition
CBC:	complete blood count
CGI:	Clinical Global Impression
CL _{ss} /F:	apparent total body clearance of a drug at steady state after oral administration
C _{max} :	maximum plasma concentration observed
CNS:	central nervous system
CSF:	cerebrospinal fluid
CTCAE:	Common Terminology Criteria for Adverse Events
C _{trough} :	plasma concentration observed just before treatment administration during repeated dosing
DAT:	dopamine transporter
DAT scan:	ioflupane I-123 injection DaTSCAN
DMC:	Data Monitoring Committee
DME:	drug metabolizing enzyme
ECG:	electrocardiogram
eCRF:	electronic case report form
EQ-5D:	EuroQol Five Dimensions Questionnaire
FDA:	Food and Drug Administration
FES:	Falls Efficacy Scale
GBA:	β-glucocerebrosidase gene
GBA-PD:	Parkinson's disease patient carrying a GBA mutation
GCase:	glucocerebrosidase
GCP:	Good Clinical Practice
GCS:	glucosylceramide synthase
GD:	Gaucher disease
GD1:	GD type 1
GGT:	gamma-glutamyl transferase
GL-1:	glucosylceramide
H&Y:	Hoehn and Yahr
HRPQ:	Health-Related Productivity Questionnaire
IB:	Investigator's brochure
ICH:	International Council for Harmonisation
IEC:	Independent ethics committee
IMP:	investigational medicinal product
INR:	international normalized ratio
IRB:	Institutional review board

ITT:	intent-to-treat
IVRS:	Interactive Voice Response System
IWRS:	Interactive Web Response System
LOCSII:	Lens Opacity Classification System II
LP:	lumbar puncture
LTFU:	long-term follow-up
lyso-GL-1:	glucosylsphingosine
MCID:	minimal clinically important difference
MDS-UPDRS:	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MMRM:	mixed effect model with repeated measures
MoCA:	Montreal Cognitive Assessment
MRI:	magnetic resonance imaging
NCI:	National Cancer Institute
NFL:	neurofilament light chain
PCSA:	potentially clinically significant abnormality
PD:	Parkinson's disease
PD-CRS:	Parkinson's Disease-Cognitive Rating Scale
PDQ-39:	Parkinson's Disease Questionnaire – 39
PGIC:	Patient Global Impression of Change
PI:	Principal Investigator
PK:	pharmacokinetics
PP:	per-protocol
PPMI:	Parkinson's Progression Markers Initiative
PR interval:	the time from the onset of the P wave to the start of the QRS complex
PT:	prothrombin time
PTT:	partial thromboplastin time
qd:	once daily
QRS interval:	time from ECG Q wave to the end of the s wave corresponding to ventricular depolarization
QT/QTc interval:	time from ECG Q wave to the end of the T wave or corrected T wave corresponding to electrical systole
RBD:	rapid eye movement sleep behavior disorder
SAC:	Scientific Advisory Committee
SAE:	serious adverse event
SAP:	statistical analysis plan
SDMT:	Symbol Digit Modalities Test
SRT:	substrate reduction therapy
ST deviation:	ECG ST-segment deviation
SUSAR:	Suspected Unexpected Serious Adverse Reaction
TEAE:	treatment-emergent adverse event
t_{\max} :	time to reach C_{\max}
TMT:	Trail-Making Test
ULN:	upper limit of normal
WOCBP:	women of childbearing potential
α -Syn:	α -synuclein
β -HCG:	beta-human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Gaucher disease (GD) is the most common lysosomal storage disorder and results from the deficiency of the lysosomal enzyme glucocerebrosidase (GCCase) that resides in lysosomes. Gaucher disease is caused by bi-allelic mutations in the human β -glucocerebrosidase gene (GBA) and follows an autosomal recessive mode of inheritance. GCCase deficiency leads to the accumulation of its major substrate, glucosylceramide (GL-1), within the lysosomes of a variety of cell types, including macrophages and neurons (1), which in some patients can lead to rapid neurodegeneration with death by late infancy. In addition, glucosylsphingosine (lyso-GL-1), the deacylated form of GL-1, also accumulates as a minor substrate.

The human GBA gene is located on chromosome 1q21 in a gene rich area. The GBA gene comprises 11 exons and 10 introns, spanning 7.6 kb of sequence. A nonprocessed pseudogene which shares 96% exonic sequence homology is located 16 kb downstream of the functional GBA gene (2). The presence of this highly homologous pseudogene along with another 6 genes at the locus increases the occurrence of chromosomal rearrangements and misalignments in this region. These processes provide an explanation for the high number of complex recombinant alleles that have been detected in GD (3).

Parkinson's disease (PD) is a progressive neurodegenerative condition, which is characterized primarily by the 4 cardinal motor symptoms: resting tremor, bradykinesia, rigidity, and postural instability. Nonmotor features include cognitive impairment, hallucinations, autonomic dysfunction, and sleep disorders.

Parkinsonism is one of the neurological symptoms described in GD, and affected individuals exhibit classical symptoms, including tremor, rigidity, and bradykinesia. An increased frequency of typical Parkinsonism was noted among otherwise healthy relatives of Gaucher patients who were obligate or confirmed carriers of GBA mutations (4). Further analysis of these Gaucher relatives revealed a possible association between heterozygous changes in GBA and parkinsonism, leading to subsequent mutational screening in patient cohorts with sporadic PD.

In 2009, a large international multicenter study with 16 participating centers compared 5,691 PD patients of different ethnic origin with 4,898 control individuals without PD. All patients were screened for at least the 2 most common GBA mutations (N370S and L444P), which were found in 15% of Ashkenazi Jewish PD patients and in 3% of PD patients of other ethnic origin. This study confirmed that heterozygous mutations in the GBA gene represent the most common genetic factor for PD so far. Carrier frequencies for GBA mutations differed between 10% and 31% in the Ashkenazi Jewish PD population, and 2.9% and 12% in PD cohorts of non-Ashkenazi-Jewish origin, such as North American (with European background), Taiwanese, and Italian. The lowest carrier frequency was reported to be 2.3% in Norwegian PD patients as compared to 1.7% in controls (5). Overall, approximately 7-10% of PD patients carry a GBA mutation (GBA-PD) that predisposes them to an earlier onset of PD symptoms with faster

cognitive and motor decline compared to sporadic PD (6), (7), (8), making them numerically the most important risk factor for the disease identified to date. Cognitive impairment in GBA-PD is characterized by impaired verbal fluency, visuospatial processing, executive planning, sustained attention, naming, and memory that declines rapidly over time.

Glucocerebrosidase is present, along with α -synuclein (α -Syn), in an average of 75% of the Lewy bodies in the brains of GBA-PD patients (9). One hypothesis is that GL-1, a substrate of GCase, may promote stabilization of α -Syn into oligomers similar to those found in Lewy bodies, and mutations in GBA correspondingly are associated with α -Syn accumulation; at the same time, α -Syn impairs GCase function within lysosomes, both in PD cells and in normal cells, promoting further accumulation of GL-1 (10). Furthermore, the accumulation of GCase lipid substrates (ie, GL-1) has been reported in cultured neurons and brain tissues from PD patients carrying GBA mutations (11).

4.2 RATIONALE

4.2.1 Study rationale

GZ/SAR402671 is a novel glucosylceramide synthase (GCS) inhibitor that decreases the synthesis of GL-1. In Phase 1 healthy volunteer studies, once daily (qd) oral administration of GZ/SAR402671 at free base doses ranging from 3.72 mg to 14.9 mg was shown to be safe and reduce plasma levels of GL-1 within 2 weeks in a dose-dependent manner. In these studies, GZ/SAR402671 was absorbed with a median time to reach maximum plasma concentration observed (t_{max}) of 2.00 to 3.00 hours and eliminated with a pooled geometric mean terminal elimination half-life ($t_{1/2z}$) of 31.3 hours on Day 14.

In vitro studies demonstrate that GZ/SAR402671 is a potent and selective inhibitor of murine and human GCS in biochemical and cell-based assays. In vivo pharmacology studies utilized plasma GL-1 lowering as a pharmacodynamic marker of GCS inhibition. In vivo activity was established in rodents and dogs with reductions in plasma (rodent and dog) and tissue (rodents only) GL-1 following oral administration of GZ/SAR402671. In both species, the effects of GZ/SAR402671 on plasma GL-1 were dose-dependent and correlated with plasma exposure of the compound. In rodents, GZ/SAR402671 has been shown to cross the blood brain barrier and reduce the synthesis of the major isoform of GL-1 in the central nervous system (CNS; ie, C18 GL-1). Exposure in CNS has also been confirmed in dogs where the cerebrospinal fluid (CSF) concentrations of GZ/SAR402671 following repeat oral dosing were approximately 2-fold greater than the unbound plasma concentration of drug.

To date, no large-scale studies have specifically addressed the relative benefits and risks of different treatments for GBA-associated PD. Thus, there is a medical need to address motor, cognitive, and/or neuropsychiatric manifestations in GBA-PD patients. Patients included in this study will be early-stage PD patients who are heterozygous carriers of a GBA mutation, aged 18 to 80 years.

A substrate reduction therapy (SRT) treatment approach for GD type 1 (GD1) was first demonstrated by miglustat (Zavesca®), which is a weak and nonspecific GCS inhibitor. Due to its

limited efficacy and tolerability profile, Zavesca was approved only for adult GD1 patients who are not candidates for enzyme replacement therapy, the standard of care. More recently, the therapeutic effect of SRT for the treatment of systemic disease in adults with GD1 was established clinically with eliglustat (Cerdelga[®], genzyme, a Sanofi company), in both treatment naïve and previously treated patients (12), (13). Cerdelga is a specific and potent GCS inhibitor that is structurally unrelated to Zavesca or GZ/SAR402671. By reducing substrate influx, eliglustat significantly improved disease manifestations in untreated GD1 patients with existing visceral and hematologic involvement. In GD1 patients stabilized on enzyme replacement therapy, oral eliglustat as monotherapy maintained hematological and organ volume stability (13). Cerdelga was approved by the Food and Drug Administration (FDA) in August 2014 and by the European Medicines Agency in January 2015. In contrast to GZ/SAR402671, eliglustat has no or only limited ability to cross the blood brain barrier with negligible exposure in brain, thus, it is not expected to impact neurological manifestations of GD or other neuropathic disease, such as PD.

Given the positive impact on visceral disease with Cerdelga, it is anticipated that GCS inhibitors with appropriate CNS exposure and activity could address neuronopathic forms of GD, ie, GD3, as well as GBA-PD. Preclinical investigations in mouse models of GBA-PD found viral vector mediated replacement of normal GBA genes in the CNS resulted in pharmacological reduction of GCase lipid substrates, decreased α -Syn pathology, and improved behavioral outcomes in 2 models of synucleinopathies (14). Treatment of Gaucher-related synucleinopathy mice (*Gba*^{D409V/D409V}) with the potent and selective GCS inhibitor Genz-667161 prevented CNS lyso-GL-1 accumulation. Notably, this treatment slowed the accumulation of hippocampal aggregates of α -Syn, ubiquitin and tau, and improved the associated memory deficits. In another set of studies, treatment of α -Syn overexpressing mice *PrP-A53T-SNCA* (harboring wild type alleles of GBA) with the GCS inhibitor also reduced membrane-associated α -Syn in the CNS and ameliorated cognitive deficits. Collectively, the data indicate that inhibition of GCS can modulate processing of α -Syn and reduce the progression of GBA-PD. GCS inhibition represents a new potentially disease-modifying treatment approach for GBA-associated PD (14).

This is a two-part, multicenter, multiple-country, placebo-controlled, randomized, double-blind study which will be divided into 2 consecutive major periods: 1) a placebo-controlled, randomized, double-blinded dose escalation study (using 3 different doses), utilizing a sequential cohort design, to be followed by 2) a randomized, double-blind, placebo-controlled, 2-arm study of the efficacy and safety of GZ/SAR402671 in early-stage PD patients carrying a GBA mutation. Part 1 will be only conducted in selected sites (approximately 20 sites [including 4 Japanese sites]); Part 2 will be conducted at multiple sites (approximately 50). Part 2 will start only after satisfactory Part 1 data is reviewed and considered satisfactory. The 3 doses being evaluated in Part 1 will be 4 mg, 8 mg, and 15 mg; all will be oral daily dosing. The maximum dose (15 mg) was selected based on data from a completed Phase 1 14-day repeated oral dose study (TDR12768) in which it provided proof of significant biological activity in humans (plasma GL-1 was reduced approximately 80%) and was safe and well tolerated. GZ/SAR402671 exposure in human CSF has not yet been investigated and will be done in Part 1 of this trial.

Of note, the highest administered dose in Study TDR12768 was a 20 mg capsule, which corresponds to a 15 mg base/active dose of GZ/SAR402671. A daily dose of greater than 15 mg has not been tested in humans. Therefore, in the absence of biomarkers and/or pharmacodynamic

data to guide human active dose estimation, evaluation of the maximum dose, as supported by the Phase 1 trial results, will first permit determination of efficacy.

Sanofi has considered it is scientifically appropriate to include Japanese patients in Part 1 of the multi-national study so that the safety and tolerability of GZ/SAR402671 in Japanese GBA-PD patients can be assessed, by stepwise approach, prior to enrollment of these patients into the main part of the study (Part 2). Understanding the safety and tolerability of GZ/SAR402671 in Japanese GBA-PD patients rather than in Japanese healthy subjects is important before enrolling Japanese GBA-PD patients into Part 2.

Comparison of pharmacokinetics (PK) and pharmacodynamics using plasma GL-1 as the biomarker between Japanese and non-Japanese patients can be conducted in the global clinical study as part of the dose escalation part of the study (Part 1), enabling PK and pharmacodynamics characterization in the Japanese target population and early participation of Japanese GBA-PD patients in a therapeutic, potentially disease modifying study.

4.2.2 Risk assessment

GZ/SAR402671 has not been studied in patients with GBA-PD. In the completed Phase 1 clinical trials in healthy volunteers, oral administration of GZ/SAR402671 was safe and generally well tolerated.

Based on toxicology data, the target tissues identified in rats were the lens, germinal epithelium of the testes, gastrointestinal tract, and the liver. Further analysis of data indicates that there seems to be no safety concern in humans involving the gastrointestinal tract and the liver.

In a juvenile toxicology study in rats given GZ/SAR402671, unilateral/bilateral degeneration of germinal epithelium in the testes of males and lenticular (eye lenses) degeneration in both sexes were observed. Lens swelling was also reported in adult female rats given a high dose of 20 mg/kg but no lens findings were observed in dog studies. Adult rodent and dog study data indicate no anticipated impact on adult male GBA-PD patient fertility. Additional information is provided in the GZ/SAR402671 Investigator's Brochure (IB).

As a result of rodent lens findings, GBA-PD patients with cataracts (excluding those with nuclear cataracts) are excluded from ACT14820. Furthermore, patients currently receiving potentially cataractogenic medications as listed in [Section 7.2](#) are excluded. The effect of GZ/SAR402671 on the lens will be closely monitored throughout the clinical trial through periodic ophthalmology examinations as detailed in [Section 9.3.3.6](#). Additionally, there is a theoretical risk of CNS effects given the compound's access through the blood-brain barrier to the CNS. However, preclinical studies in rats did not suggest the occurrence of untoward effects on the CNS at the no observed adverse effect level of 45 mg/kg/day (approximately 10-fold the above expected clinical exposure).

5 STUDY OBJECTIVES

5.1 PART 1: DOSE ESCALATION PHASE

5.1.1 Primary objective

To determine the safety and tolerability of 4, 8, and 15 mg of GZ/SAR402671, as compared to placebo, when administered orally daily for 4 weeks in early-stage PD patients carrying a GBA mutation or other prespecified sequence variants (from now on both mutation types are referred to as 'GBA mutation'). This will allow selection of the dose for the second part of this study (this does not apply to Japanese patients).

5.1.2 Secondary objectives

To assess the PK profile of daily oral dosing of GZ/SAR402671 in plasma when administered at doses of 4, 8, or 15 mg over a 4-week period in early-stage PD patients carrying a GBA mutation.

To assess the exposure of GZ/SAR402671 in CSF when administered at doses of 4, 8, or 15 mg over a 4-week period in early-stage PD patients carrying a GBA mutation.

5.1.3 Exploratory objectives

To assess the pharmacodynamic response of daily oral dosing of GZ/SAR402671 in plasma and CSF when administered at doses of 4, 8, or 15 mg over a 4-week period, as measured by GL-1 in early-stage PD patients carrying a GBA mutation.

To explore the effect of GZ/SAR402671 on scores from selected scales and questionnaires which will be used in this study over an 8-week period in early-stage PD patients carrying a GBA mutation.

5.2 PART 2: TREATMENT PHASE

5.2.1 Primary objective

To determine the efficacy of GZ/SAR402671 in patients with early-stage PD carrying a GBA mutation when administered orally daily at the dose selected in Part 1, over a 52-week period, as compared to placebo.

5.2.2 Secondary objectives

To demonstrate the overall safety and tolerability of GZ/SAR402671 administered orally daily for 52 weeks in early-stage PD patients carrying a GBA mutation as compared to placebo.

To assess the pharmacodynamic response to daily oral dosing of GZ/SAR402671 in plasma and CSF as measured by GL-1 in early-stage PD patients carrying a GBA mutation over a 52-week period.

5.2.3 Exploratory objectives

To explore the effect of GZ/SAR402671 on scores from selected scales and questionnaires which will be used in this study. Of note, for patients receiving levodopa or other PD medication, assessment of scales and questionnaires will be performed during the OFF state (ie, no PD medication may be taken for at least 12 hours prior to the efficacy assessments) except for the Hoehn & Yahr (H&Y) scale which will be completed in "ON" state only at baseline visit (see inclusion criteria [I 05](#))

To assess the effect of GZ/SAR402671 on neurologic functional status via functional neuroimaging over a 52-week period.

To assess the PK profile of GZ/SAR402671 in plasma and CSF of early stage PD patients carrying a GBA mutation.

To evaluate the pharmacodynamic response to GZ/SAR402671 in plasma and CSF as measured by lyso-GL-1 in early-stage PD patients carrying a GBA mutation.

To explore the effect of GZ/SAR402671 on CSF biomarkers related to PD or neurodegeneration, including total α -Syn, neurofilament light chain (NFL), tau, phospho-tau, as well as beta-amyloid (1-40, and 1-42).

To develop a Parkinson's disease progression model in early stage PD patients carrying a GBA mutation.

To assess the long-term safety and efficacy of GZ/SAR402671 over a 156-week period.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a two-part, multicenter, multiple-country, randomized, double-blinded, placebo-controlled study in early-stage PD patients carrying a GBA mutation. The study will be divided into 2 consecutive parts. Part 1 will be a randomized, double-blinded, placebo-controlled dose escalation study, utilizing a sequential cohort design. Part 1 will allow selection of the dose of GZ/SAR402671 for Part 2, a randomized, double-blind, placebo-controlled, 2-arm study of the efficacy and safety of GZ/SAR402671. Part 1 will be conducted only in selected sites (approximately 20 sites [including 4 Japanese sites]); Part 2 will be conducted at multiple sites (approximately 50). Part 2 will start after the appropriate dose for Part 2 is selected in Part 1.

In Part 1, during the screening/baseline period, from Day -60 to Day -1, patients will provide informed consent and undergo screening assessments to determine trial eligibility and undergo baseline measurements. If all eligibility criteria are met, patients will enter the trial. Part 1 will determine the safety and tolerability of GZ/SAR402671 at 4, 8, and 15 mg in early-stage PD patients carrying a GBA mutation by using a dose escalation scheme (4 weeks to assess safety and tolerability of dose and a minimum of an additional 4 weeks to further assess safety and tolerability and any potential changes in other exploratory endpoints in each dose cohort). There will be 3 sequential cohorts that will be placebo-controlled:

- Cohort 1: 4 patients on GZ/SAR402671 4 mg and 1 patient on placebo.
- Cohort 2: 4 patients on GZ/SAR402671 8 mg and 1 patient on placebo.
- Cohort 3: 4 patients on GZ/SAR402671 15 mg and 1 patient on placebo.

No additional dose escalation of GZ/SAR402671 will occur above the highest proposed dose of 15 mg. All patients must complete the first 4-week course of therapy with subsequent data review by an internal review committee whose purpose is to review data (such as safety, tolerability, and/or clinical endpoints), demonstrating safety/tolerability before dose escalation to the next higher level can occur. Patients will continue to be dosed daily and will be followed every 4 weeks until the completion of Part 1, allowing for additional safety and other exploratory endpoints to be collected. Each cohort will have a 4:1 randomization ratio, and the total sample size will be approximately 15 patients (including 12 on GZ/SAR402671 and 3 on placebo). In Japan, each cohort will have a 3:1 ratio, and the total sample size will be approximately 12 Japanese patients (including 9 on GZ/SAR402671 and 3 on placebo). Therefore, the total sample size in Part 1 will be approximately 27 patients.

If a serious adverse event (SAE) or \geq Grade 3 adverse event (AE, National Cancer Institute [NCI], Common Terminology Criteria for Adverse Events [CTCAE] Version 4.03) that is considered by the Investigator to be related to GZ/SAR402671 and not to underlying disease or concomitant medication is observed, the case will be communicated to the internal review committee and a decision should be reached regarding escalation to the next dose with GZ/SAR402671. If 2 patients receiving GZ/SAR402671 within the same cohort develop the same SAE or AE (\geq Grade 3), dosing within the cohort will be stopped. After stopping, this committee will review

the data and provide recommendations on how to proceed. In addition, SAE/adverse events of special interest (AEIs) will be communicated to the Data Monitoring Committee (DMC).

At the end of 4 weeks of treatment during the dose escalation part, patients in each cohort will have a lumbar puncture (LP); CSF exposure of GZ/SAR402671 will be measured at 2 time points in Part 1: at pretreatment and Week 4. If there is no CSF exposure at the highest dose level, the study will be stopped.

In Part 2, the GZ/SAR402671 dose will be the highest dose determined to be safe and well tolerated in Part 1. Moreover, CSF exposure must be known. If there is no CSF exposure of GZ/SAR402671, then that dose will not be used in Part 2.

If patients from Part 1 continue to meet eligibility requirements, and are willing to continue in the study, they may enroll in Part 2, but re-randomization will be required; furthermore, they will have to sign another informed consent form. All screening assessments will need to be repeated, except for the genetic screening, magnetic resonance imaging (MRI), LP, and ioflupane I-123 injection DaTSCAN (DAT scan), to confirm eligibility of patients from Part 1 to enroll in Part 2.

In Part 2, eligible patients will be stratified based on use of levodopa/PD medication (yes/no), cognitive function (Montreal Cognitive Assessment [MoCA] score <26 [yes/no]) and severe GBA mutation (yes/no). Patients will be randomized in a 1:1 ratio to receive GZ/SAR402671 or placebo for 52 weeks.

Part 2 will include 4 main periods: the up to 60-day screening period (Period 1), the 52-week blinded treatment period (Period 2), the 156-week duration long-term follow-up (LTFU) period (Period 3), and the 8-week post-treatment observation period (Period 4).

All patients who continue to meet inclusion criteria [I 06](#), [I 07](#), [I 08](#), and [I 09](#) and none of the exclusion criteria (exclusion criteria [E 02](#), [E 03](#), [E 05](#), and [E 06](#) will not need to be rechecked) at Week 52 will be eligible to receive GZ/SAR402671 treatment during the LTFU period (Period 3).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The maximum study duration per patient will be approximately 224 weeks (4.3 years, patients from Part 2 only) to 272 weeks (5.5 years, patients from Part 1 enrolling in Part 2), or to 288 weeks for Japanese patients (5.9 years, Japanese patients from Part 1 enrolling in Part 2).

Part 1: Dose escalation phase

The maximum study duration per patient will be approximately 50 weeks (or 66 weeks for Japanese patients), inclusive of the screening period. Three sequential cohorts are planned. Patients will receive either placebo or GZ/SAR402671 (4 mg, 8 mg, or 15 mg) for a minimum 8 weeks per cohort (and maximum of 36 weeks [or 52 weeks for Japanese patients], for Cohort 1).

Safety/tolerability data will be analyzed at the end of 4 weeks of treatment at each cohort before proceeding to the next cohort.

Part 2: Treatment phase

The total study treatment duration (Periods 2 and 3) is approximately 208 weeks (4 years).

The study comprises 4 main periods:

- Period 1: the up to 60-day screening period.
- Period 2: the 52-week double-blinded, randomized treatment period.
- Period 3: the 156-week LTFU period during which eligible patients will all receive GZ/SAR402671.
- Period 4: the 8-week post-treatment observation period with end of study visit.

Therefore, maximum duration for a patient will be approximately 224 weeks.

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is defined as being the “last patient last visit” planned with the protocol, including the follow-up visit (Visit 9 in Part 1 and Visit 16 in Part 2 or Visit 15 for patients who will transition to a long-term study with GZ/SAR402671). The Sponsor reserves the right to discontinue the study at any time.

6.3 INTERIM ANALYSIS

No interim analysis is planned for this study.

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

A DMC, operating independently from the Sponsor and Clinical Investigators, will be responsible for overseeing the safety of patients and the risk/benefit ratio throughout the study. This committee is composed of externally based individuals with expertise in the disease under study, biostatistics, and/or clinical research. The primary responsibilities of the DMC are to ensure the patients welfare as well as to evaluate and review the safety and other applicable data throughout the course of the study and make appropriate recommendations to the Sponsor regarding the conduct of the clinical trial. The specific responsibilities of the DMC will be described in the DMC Charter.

6.4.2 Scientific advisory committee

The Scientific Advisory Committee (SAC) is composed of field experts and Sponsor-based scientists with clinical and methodological expertise. This Committee, led by a Chairperson, selected by the Sponsor, will provide advice to the Sponsor regarding scientific issues and operational conduct of the study. The SAC will also review any amendments, and provide input

regarding interpretation of study results. The members will remain blinded until completion of the study.

Among its responsibilities, the SAC will receive blinded study status reports from the Sponsor, and will review the recommendations from the DMC throughout the study.

Moreover, the SAC will also be responsible for the primary publication(s) emanating from the study. The Principal Investigator (PI) of the study will be selected by the Sponsor and will be the first author for the primary publication(s). Principal Investigators at the 3 first sites enrolling the most patients will also be included as authors for the primary publication, in addition to the other SAC members.

Detailed activities and responsibilities of the SAC are provided in the SAC charter.

6.5 DISCUSSION OF STUDY DESIGN

Current treatment options for PD patients, with or without GBA mutations, are limited due to side effects. Despite the many therapeutic agents available for the treatment of PD, patients can still experience intolerable disability due to disease progression. Thus, there is a high unmet medical need for better treatment alternatives in PD. Participation in this placebo-controlled study, with a novel mechanism of action, would present a unique opportunity for the patients. Patients will be allowed to start on PD therapy (only an immediate release levodopa formulation is allowed) or to continue to take their medication as usual (if already taking PD medication at study start).

Of note, PD prescription medications permitted (see [Section 8.8](#)) in this trial include:

- Dopamine replacement therapies (eg; levodopa/carbidopa).
- Dopamine agonists (eg; pramipexole, ropinirole, bromocriptine).
- Monoamine oxidase B inhibitors (eg; rasagiline).
- Catechol-O-methyltransferase inhibitors (eg; entacapone, tolcapone).
- Anticholinergics (eg; artane, cogentin).

The following points were taken into consideration in the design of the study:

- **Screening:** Sequencing of the GBA gene and genotyping for a LRRK2 (G2019S) mutation to ensure patient eligibility will be conducted from a collected whole blood sample even if historical results are available.
- **Randomization (Day 1, pre-dose):** To reduce the risk of imbalance between treatment groups with respect to cognitive function and PD medication. In Part 2, randomization will be stratified based on use of levodopa/PD medication (yes/no), cognitive function (MoCA score <26 [yes/no]) and severe GBA mutation (yes/no).
- **Long-term follow-up (Part 2):** Upon completion of the 52-week treatment period, eligible patients will be followed in an LTFU period for 36 months. Patients in the placebo arm will be switched to GZ/SAR402671 treatment after completing the Week 52 study visit. During the LTFU period, study drug assignment will remain blinded and patients will continue to be assessed by a blinded rater, thus collecting important information and

data. This will allow not only the long-term safety to be assessed but can also support long-term efficacy of GZ/SAR402671. Importantly, patients who received placebo in Period 2 will have the opportunity to receive GZ/SAR402671 treatment. Analysis of efficacy and safety between those patients who were on GZ/SAR402671 treatment from the start of randomization and patients who began GZ/SAR402671 treatment 1 year later will potentially offer insightful information on delayed start of treatment in this patient population.

- **Primary and secondary efficacy endpoints:** The primary efficacy endpoint of the study is the change from baseline to Week 52 in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), PART II+III. The MDS-UPDRS was designed to be more comprehensive than the original UPDRS, with new items devoted to several nonmotor elements of PD, including cognitive function. Based on a published critique of the UPDRS, the 5-point range for each item was retained, and clinical anchors of normal (0), slight (1), mild (2), moderate (3), and severe (4) were added to provide a consistency across items. Importantly, the MDS-UPDRS places greater emphasis on distinguishing relatively mild impairments and disabilities, drawing distinctions between slight and mild, whereas former distinctions between severe and marked are now collapsed into the severe rating. The incorporation of 'slight' and 'moderate' ratings in the scale should result in an even more sensitive measure of disease progression in early stages. The subscales are now titled: (Part I) nonmotor experiences of daily living (13 items), (Part II) motor experiences of daily living (13 items), (Part III) motor examination (18 items), and (Part IV) motor complications (6 items).

An important addition to the MDS-UPDRS is a set of detailed instructions. These are officially part of the scale, so that international colleagues can perform ratings in a systematic manner within and across centers. The instructions are intended to standardize the method of application of the scale so that the MDS-UPDRS data are collected uniformly. The MDS-UPDRS tool includes clear definitions of 'ON' times, when dopaminergic medications are working properly, and 'OFF' times, when the dopaminergic therapies 'wear off', and patients experience decreased mobility, to ensure uniformity of rater assessments of ON/OFF status (Note: PD medication cannot be taken for at least 12 hours prior to the visits including efficacy assessment). The scale has been translated in many different languages, and, importantly, scale reliability, construct validity, and precision have been assessed. It performs extremely well in comparison with the original version with high internal consistency for the entire scale as well as high internal consistency on each part. In addition, even though restructured, each part of the MDS-UPDRS correlates highly with the corresponding part of the original scale.

In summary, the MDS-UPDRS is a reliable and sensitive measure of disease progression, particularly decline in motor function, in early stages of PD. Given the target population for this study is early-stage GBA-PD patients, the change in the motor parts of the MDS-UPDRS (PART II+III) is the most appropriate scale to use as a primary endpoint in this clinical trial.

GBA-PD patients also experience more rapid cognitive decline as compared with PD patients without GBA mutations. Cognition changes in GBA-PD patients will be captured via assessment of the Parkinson's Disease-Cognitive Rating Scale (PD-CRS), a scale that was designed to cover

the full spectrum of cognitive deficits associated with PD. This secondary endpoint will allow important data to be gathered in this patient population.

Given that GBA-PD patients experience nonmotor symptoms, another important secondary endpoint will be the MDS-UPDRS, PARTS I+II+III. Lastly, functional scales are important for assessment in clinical trials, allowing to support clinical meaningfulness of endpoints. The H&Y score has been shown to have moderate correlations with Parts I and IV, and high correlations with Parts II and III of the MDS-UPDRS.

- **Pharmacodynamic and exploratory biomarkers:** GBA-mutations and reduced GCase activity can lead to elevations in plasma and CSF concentrations of substrates including GL-1 and lyso-GL-1. GZ/SAR402671 has shown to reduce plasma concentrations even in normal healthy volunteers in the repeated-dose Phase 1 study (Study TDR12768). Plasma and CSF samples will be stored and will be used to assess changes in GL-1 and lyso-GL-1 to support the clinical endpoints. Glucocerebrosidase activity will be explored. In addition, biomarkers associated with PD and/or neurodegeneration may also be assessed in blood and/or CSF, such as total α -Syn, NFL, tau, phospho-tau, as well as beta-amyloid (1-40, and 1-42).
- **Imaging:** PD, including GBA-PD, has been associated with changes in dopamine transport density in the basal ganglia regions in the brain, as measured by ioflupane-I-123 injection DATSCAN™ (from now on referred to as DAT scan). Changes in DAT scans in predefined areas of interest, such as the caudate nucleus, from baseline to Week 52 and from baseline to Week 104, Week 156, and week 208 will be assessed as an exploratory endpoint. Please note that DAT scans will be performed only in countries where it is approved.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Male or female subjects with a diagnosis of PD (with at least two of the following signs: resting tremor, postural instability, akinesia/hypokinesia, and muscle rigidity) and who are heterozygous carriers of a GBA mutation. Please see [Section 17 \(Appendix A\)](#) for the list of most common mutations. Note: If the patient has a GBA mutation that is not on the list, a consult will always be required to determine the eligibility of the patient.

OR

I 02. Patients carrying known sequence variants associated with GBA-PD ([Section 17 \[Appendix A\]](#)), in addition to having a diagnosis of PD (with at least 2 of the following signs: resting tremor, postural instability, akinesia/hypokinesia or muscle rigidity), must also have a diagnosis of rapid eye movement sleep behavior disorder (RBD) (15) confirmed by historically documented polysomnography or by RBD screening questionnaire (see [Section 17 \[Appendix B\]](#)).

I 03. Age ≥ 18 years to 80 years, inclusive, at the time of signing the informed consent (FOR JAPANESE PATIENTS ONLY: Age ≥ 20 years to 80 years, inclusive, at the time of signing the informed consent. Note: Japanese patients refers only to Japanese patients enrolled and living in Japan [[Appendix T](#)]).

I 04. Has symptoms of PD for ≥ 2 years.

I 05. Hoehn and Yahr stage of ≤ 2 for PD at baseline; for patients on a stable dose of PD medication, this should be done in the "ON" state.

I 06. If on levodopa or any other PD medication (such as a dopamine agonist), the medication regimen must be stable for at least 30 days (at least 60 days for rasagiline) prior to randomization.

I 07. Cooperative, able to ingest oral medication, and able to complete all aspects of the study and capable of doing so, alone, according to the Investigator's judgment.

I 08. The patient is willing to abstain from consumption of grapefruit, grapefruit juice, and/or grapefruit containing products for 72 hours prior to administration of the first dose of GZ/SAR402671 and for the duration of the entire treatment period (Part 1 and Part 2, Periods 2 and 3).

I 09. Able to provide a signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the inclusion criteria listed in [Section 7.1](#) will be screened for the following exclusion criteria which are sorted and numbered in the following subsections.

7.2.1 Exclusion criteria related to study methodology

- E 01. Parkinsonism due to drug(s) and/or toxin(s).
- E 02. Patients carrying the LRRK2 G2019S mutation.
- E 03. Patients with GD as defined by clinical signs and symptoms (ie, hepatosplenomegaly, cytopenia, skeletal disease) and/or marked deficiency of GCase activity compatible with GD.
- E 04. MoCA score of <20.
- E 05. Patients who have past surgical history of deep brain stimulation.
- E 06. Patients who have a baseline MRI without contrast showing a structural abnormality that is a possible etiology of PD related signs and symptoms.
- E 07. Any medical disorders and/or clinically relevant findings in the physical examination, medical history, or laboratory assessments that, in the opinion of the Investigator, could interfere with study-related procedures (eg, heart failure, hypokalemia, etc). This includes condition(s) that precludes the safe performance of routine LP, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
- E 08. Current participation in another investigational interventional study.
- E 09. Current treatment with anticoagulants (eg, coumadin, heparin) that might preclude safe completion of the LP.
- E 10. An investigational medicinal product (IMP), including ambroxol, within 3 months or 5 half-lives, whichever is longer, before study inclusion.
- E 11. Presence of severe depression as measured by Beck Depression Inventory, second edition (BDI-II) >28 and/or a history of a major affective disorder within 1 year of screening examination.
- E 12. A history of drug and/or alcohol abuse within the past year prior to the first screening visit.
- E 13. A known hypersensitivity to DAT scan (either the active substance of ioflupane I-123 or to any of the excipients).

- E 14. The patient is sexually active and is not willing to use 2 forms of birth control during the study and up to 90 days after the day of last dose (see contraceptive guidance in [Section 17 \[Appendix C\]](#)).
- Women of childbearing potential (WOCBP) not protected by 2 highly effective methods of birth control and/or who are unwilling or unable to be tested for pregnancy for up to 45 days after the day of last dose.
 - Male participants must use 2 forms of birth control during the study and refrain from donating sperm up to 90 days after the day of last dose. If the patient has a female partner of childbearing potential, the patient must wear a condom and female partner must use at least 1 highly effective methods of birth control.
- E 15. The patient is scheduled for in-patient hospitalization including elective surgery during the study.
- E 16. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study. This includes any patient who, in the judgment of the Investigator, is likely to be noncompliant during the study, or unable to cooperate because of a language problem or poor mental development.
- E 17. Any country-related specific regulation that would prevent the subject from entering the study.
- E 18. Any patient who is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.
- E 19. Know hypersensitivity to GZ/SAR402671 or any component of the excipients.

7.2.2 Exclusion related to active comparator and/or mandatory background therapies

- E 20. Use of any medication specifically used for treating memory dysfunction, such as, but not limited to cholinesterase inhibitors or memantine within 30 days or 5 half-lives of these medications prior to randomization, whichever is longer.
- E 21. The use of concomitant medications that prolong the time from ECG Q wave to the end of the T wave or corrected T wave corresponding to electrical systole (QT/QTc interval) (see [Section 17 \[Appendix D\]](#) for a list of commonly used medications).

7.2.3 Exclusion criteria related to current knowledge of GZ/SAR402671 IMP

- E 22. Liver enzymes (alanine aminotransferase [ALT]/aspartate aminotransferase [AST]) or total bilirubin >2 times the upper limit of normal (ULN) at the time of screening. Patients with Gilbert's disease are excluded only from Part 1 participation.
- E 23. Renal insufficiency as defined by creatinine >1.5 times ULN at the screening visit.

- E 24. The patient has a documented diagnosis, as per local regulations, of any of the following infections: hepatitis B, hepatitis C, human immunodeficiency virus 1 or 2.
- E 25. The patient has received strong or moderate inducers or inhibitors of CYP3A4 (see [Section 17 \[Appendix E\]](#)) within 30 days or 5 half-lives of these medications, prior to randomization, whichever is longer.
- E 26. Use of the following medications within 5-elimination half-lives prior to the DAT neuroimaging evaluation: amoxapine, amphetamine, benztropine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norepinephrine, phentermine, phenylpropanolamine, selegiline, sertraline, citalopram, and paroxetine.
- E 27. The patient has, according to World Health Organization Grading, a cortical cataract > one-quarter of the lens circumference (Grade cortical cataract-2) or a posterior subcapsular cataract >2 mm (Grade posterior subcapsular cataract-2). Patients with nuclear cataracts will not be excluded.
- E 28. The patient is currently receiving potentially cataractogenic medications, including a chronic regimen (more frequently than every 2 weeks) of any dose or route of corticosteroids or any medication that may cause cataract or worsen the vision of patients with cataract (eg, glaucoma medications) according to the Prescribing Information.
- E 29. If female, pregnant (defined as positive beta-human chorionic gonadotropin [β -HCG] blood test) or lactating or breast-feeding.
- E 30. A marked baseline prolongation of QT/QTc interval on screening electrocardiogram (ECG) (such as a QTc interval >450 msec in male subjects and >470 msec in female subjects).

If the patient is a screen failure, all data obtained at screening including laboratory results of screening tests must be available in the patient's medical records. For screening failures, the following data obtained during screening will be transferred to the electronic case report form (eCRF) and entered into the database: informed consent date, visit date, patient's demographic data, inclusion and exclusion criteria, AE data (if available) and reason for failure.

A patient cannot be randomized more than once in the study, with the exception of those patients who have participated in and completed Part 1 of the trial and continue to meet eligibility criteria for Part 2. Patients who meet exclusion criteria in both Part 1 and Part 2 during the screening period may be rescreened once; a different patient identification will be issued. Rescreening is not permitted if the patient fails to meet inclusion criteria or if the patient carries the LRRK2 G2019S mutation (see exclusion criterion [E 02](#)) or has GD (see exclusion criterion [E 03](#)). There is no requirement for a waiting period between the screen-failure date and the rescreening date. The Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) report will flag rescreened patients. Patients that are rescreened must sign a new consent form and all Visit 1 procedures, except the genetic screening, MRI, LP, and DAT scan, must be repeated.

Note: Rescreening is possible in this study in cases where the original screening failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment. The patient may be rescreened once within 6 months from the time of the original screening failure to check whether or not they then meet all of the inclusion and none of the exclusion criteria. All screening assessments will need to be repeated, except the genetic screening, MRI, LP, and DAT scan, to confirm eligibility of the patient for the study.

Patients who do not adhere to treatment (at least 80% compliance rate) in Part 1 and withdraw for reasons other than safety may be replaced.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

GZ/SAR402671 or matching placebo will be provided for oral administration as brownish red, opaque, hard gelatin capsules. Each drug capsule will provide a dose of either 4 mg or 15 mg of GZ/SAR402671 (active moiety). Each placebo capsule will provide a dose of 0 mg.

GZ/SAR402671 can be administered without restriction to food, except for the consumption of grapefruit, grapefruit juice, and/or grapefruit containing products within 72 hours of starting GZ/SAR402671 administration. Patients should be instructed to ingest the capsules at approximately the same time of the day throughout the entire study.

In Part 1, the dose of GZ/SAR402671 will be 4, 8, or 15 mg or placebo once per day for up to 36 weeks (or 52 weeks for Japanese patients). Safety/tolerability and, eventually, CSF exposure, from Part 1 will determine the recommended dose for Part 2.

In Part 2, the dose of GZ/SAR402671 determined in Part 1 or placebo will be administered once per day for 52 weeks (Period 2); in Period 3 (LTFU), patients will receive GZ/SAR402671 once per day for an additional 156 weeks.

GZ/SAR402671 hard capsules will be packaged in blister packs.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT

Not applicable.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

GZ/SAR402671 and matching placebo for GZ/SAR402671 will be indistinguishable from one another and be provided in identically matched packaging which includes labeling to protect the blind.

In accordance with the double-blind design, study patients, Investigators and study site personnel will remain blinded to study treatment and will not have access to the randomization list (treatment codes) except under circumstances described in [Section 8.3.2](#). All samples for PK and biomarkers evaluation will be assessed blindly (treatment arm and timing) and results will not be communicated to the study personnel. The Investigators and the Sponsor will also be blinded to PK and biomarkers data. A Sanofi Clinical Supplies representative will remain unblinded throughout the study with respect to the study medication kits in order to provide the appropriate study drug to patients; however, sites and study teams must be blinded to PK and biomarker data throughout the study.

The blinded results at the end of 4 weeks of treatment for each patient in each dose cohort will be provided to an internal review committee.

The DMC will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review, which have to be handled strictly confidentially. None of these reports can be delivered to unauthorized persons.

8.3.2 Randomization code breaking during Parts 1 and 2

Blinding should only be broken for serious, unexpected, and related AEs, and only for the patient in question, or when required by local regulatory authorities. The Investigator must notify Sanofi genzyme before breaking the code for any patient as soon as possible.

The code may be broken only in the case of a serious, unexpected related AE. If possible, contact should be initiated with the Monitoring Team before breaking the code.

In case of an emergency, the IVRS can be contacted by the Investigator or Sub-Investigator to reveal the IMP assignment of a particular patient. In case of a Suspected Unexpected Serious Adverse Reaction (SUSAR), the Global Pharmacovigilance department of the Sponsor will contact IVRS to reveal IMP assignment for regulatory reporting requirements for the particular case. The IVRS unblinding procedures should be followed as outlined in the IVRS manual.

If the blind is broken by the Investigator he/she will document the date, time of day and reason for code breaking. The patient must discontinue study medication, but should be encouraged to continue in the study, completing all assessments at the scheduled timepoints. If in Part 2, the patient will not be allowed to enter the LTFU (Period 3) of the study. At a minimum, the patient may withdraw from the clinical trial and complete an end of treatment assessment visit (similar to Visit 8 in Part 1 or Visit 9 in Part 2) followed by a post-treatment follow-up visit (similar to Visit 9 in Part 1 or Visit 16 in Part 2). If this is done, then the patient should be followed up for at least 8 weeks after their last scheduled received dose or until resolution of the related SAE.

Patient withdrawal will only occur when the code break call is made at the site level and/or at the study level. This means that if the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level), then the patient will be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Sponsor (ie, at the study level), then the patient will not be withdrawn from treatment.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

A randomized treatment kit number list will be generated centrally by the Sponsor. The IMP (GZ/SAR402671 or placebo) will be packaged in accordance with this list.

The Sanofi Clinical Supplies team will provide the randomized treatment kit number list and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system. This centralized treatment allocation system will generate the patient randomization list according to which it will allocate the treatments to the patients.

The randomization and the treatment allocation will be performed centrally by an IVRS which will be available 24 hours a day, 7 days a week. In Part 1, randomization will not be stratified. In Part 2, randomization will be stratified based on use of levodopa/PD medication (yes/no), cognitive function (MoCA score <26 [yes/ no]), and severe GBA mutation (yes/no).

In order to maintain blinding, the Investigator or designee will contact the IVRS to obtain a patient number once the patient signs the informed consent form.

The patient number allocated by the IVRS is a specific 12-digit number consisting of: 3-digit country code (Independent System Operator), 4-digit site number, 5-digit sequential number at site with leading zeros (ie, 840-0001-00001, 840-0001-00002).

Once eligibility is confirmed, the pharmacist (or designee) will contact the IVRS at the time of patient randomization in order to obtain the randomization treatment kit assignment for the patient, and at subsequent patient scheduled visits to obtain the correct treatment kit assignment for the patient.

Patients will be allocated by the IVRS to either GZ/SAR402671 or placebo.

All kits must be retained for accountability.

8.5 PACKAGING AND LABELING

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP provided by the Sponsor in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

Batch and expiry date management will be assisted with IVRS.

8.7 RESPONSIBILITIES

The Investigator, the site pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be patient to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to-patient shipment, for which a courier company has been designated by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

The Investigator or designee will keep an accurate record of all IMP that is received, dispensed, and returned on a per patient basis using an IMP accountability log.

Measures taken to ensure and document treatment compliance and IMP accountability include:

- Accurate recording of treatment kit number as required on appropriate eCRF page for accounting purposes.
- All medication treatment kits (whether empty or unused) are returned by the patient at each visit.
- The Investigator or designee tracks treatment accountability/compliance, either by diary, or by counting the number of used treatment kits and fills in the appropriate page of the patient treatment log.
- The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the patient treatment log form.

A patient diary will be issued to the patient at the screening visit with instructions to record any safety issue. For eligible patients, the same diary will be used to record missing doses after randomization. A brief explanation should be provided if a dose is missed. The patient should bring their diary and any remaining capsules to each clinic visit.

The site staff will review the patient diary during each clinic visit and record excursions from treatment into the eCRF. The patient diary will be retrieved when the patient finishes their participation in the study.

8.7.2 Return and/or destruction of treatments

Reconciliation of all used, partially used or unused treatments must be performed at the site by the Investigator and the monitoring team using treatment log forms. The treatment log form will be countersigned by the Investigator and the monitoring team.

Authorization for destruction will be given by the Sponsor once the reconciliation has been completed. This destruction can be performed at the site depending on local regulations and site-specific capabilities; alternatively, study drug may be returned to the Sponsor or designee for destruction.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient during the study aside from the IMP. Concomitant medications should be kept to a minimum during the study. Furthermore, changes in concomitant medications should be kept to a minimum and only occur if considered to be absolutely necessary in the medical judgment of the Investigator. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given as rescue medication at the discretion of the Investigator and must be recorded in the eCRF.

Concomitant medications, including over-the-counter, dietary supplements (eg, herbal remedies) or prescriptions, are permitted during the study period, except for ambroxol use which is forbidden throughout the study and the medications listed in the following sections (see [Section 8.8.1](#), [Section 8.8.1.1](#), [Section 8.8.2](#), and [Section 8.8.3](#)). Any treatment not permitted at study entry will be forbidden throughout the study.

Patients will be allowed to continue with their PD medication as usual, if on stable PD therapy at study start. However, it may be considered necessary in the medical judgment of the Investigator to initiate or intensify PD medications. In such occurrence, this could apply only to an immediate release levodopa formulation.

The definition of stable PD therapy according to the longstanding gold standard worldwide is:

- At least 30 days on levodopa or other PD therapy, including dopamine agonists.
- At least 60 days on rasagiline.

All concomitant medications reported at the time of the screening visit and for the duration of the patient's participation should be recorded.

8.8.1 CYP3A4 inducers or inhibitors

GZ/SAR402671 should not be administered concomitantly with any strong or moderate inducers or inhibitors of CYP3A4 per FDA classification.

If a patient is inadvertently administered a strong or moderate CYP3A4 inducer or inhibitor, the Investigator should contact the Sponsor as soon as possible. The physician should switch the patient to an alternative medication that is not a strong or moderate CYP3A4 inducer or inhibitor.

Grapefruit, grapefruit juice, and/or grapefruit products are not permitted 72 hours prior to the first dose of GZ/SAR402671 and for the duration of the entire treatment period (Periods 2 and 3).

8.8.1.1 Temporary use of strong or moderate CYP3A4 inducers or inhibitors

GZ/SAR402671 dose interruptions will not be permitted during the first 4 weeks of Part 1 or Part 2, Period 2.

In Part 2, GZ/SAR402671 dose interruptions will be permitted for those patients who require temporary use (≤ 2 weeks) of strong or moderate inhibitors or inducers of CYP3A4 (see [Section 17 \[Appendix E\]](#)) for the treatment of acute illness. Such medications must not be used on more than a total of 2 occasions (ie, up to 2 weeks per occasion for a maximum of 4 weeks of GZ/SAR402671 interruptions) during the treatment Period 2 (Part 2).

In Part 2, patients must complete a minimum of 7 consecutive daily GZ/SAR402671 oral administrations prior to Weeks 26 and 52 assessments, except in the case of Covid-19 infection (see [Section 10.1.2](#)).

8.8.2 Medications with risk to cause or worsen cataract

Given nonclinical lens findings (see IB), a chronic regimen (ie, more frequent than once every 2 weeks) of the following medications is forbidden during the clinical trial:

- Corticosteroids:
 - May be used on a restricted basis in patients who require temporary use (≤ 1 week) for the treatment of any acute condition for which no appropriate substitute is found. Such medications must not be used on more than a total of 4 occasions (ie, up to 1 week per occasion) during the treatment periods (Period 2 and 3).
 - A special provision is made to allow enrollment of GBA-PD patients who require inhaled corticosteroids for the management of a stable medical condition (eg, allergies, asthma, etc), in which corticosteroid withdrawal would be detrimental. In this case, the Investigator would administer the lowest efficacious dose. The potential benefits expected by the administration of GZ/SAR402671 outweigh the potential drawbacks that can be observed by the initiation/worsening of cataracts.
- Psoralens used in dermatology with ultraviolet light therapy.
- Typical antipsychotics.

The Investigator should consider substituting medications listed in the previous paragraphs for noncataractogenic treatments, as appropriate.

In addition, glaucoma medications are excluded from the current trial since they can worsen the vision of patients with cataracts.

8.8.3 Medications with risk for dopamine transporters scan imaging

Medications that might interfere with dopamine transporter (DAT) single-photon emission computed tomography imaging and are restricted within 5 elimination half-lives prior to a DAT

scan injection include: amoxapine, amphetamine, benztropine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norepinephrine, phentermine, phenylpropanolamine, selegiline, sertraline, citalopram, and paroxetine.

8.8.4 Medication for treating memory dysfunction

Any medications specifically used for treating memory dysfunction, such as, but not limited to cholinesterase inhibitors or memantine, are prohibited.

8.8.5 Medications that can prolong the QT interval

The use of medications that prolong the time from ECG Q wave to the end of the T wave or corrected T wave corresponding to electrical systole (QT/QTc interval) (see Section 17 Appendix D) is forbidden throughout the study.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

For patients already on PD medications at the time of randomization, all efficacy assessments must be done in the patient's "OFF" state. No PD medication may be taken for at least 12 hours prior to any efficacy assessment. Study drug will be administered on-site on visit days.

Scales and questionnaires should be completed before dosing and before clinical procedures are performed by the study Investigator or other healthcare provider(s). Moreover, if possible, the patient completed instruments should be done prior to clinical interaction in order to try to minimize any influence this may have on the patient (either positive or negative). This includes the BDI-II, Patient Global Impression of Change (PGIC), Parkinson's Disease Questionnaire – 39 (PDQ-39), EuroQol Five Dimensions Questionnaire (EQ-5D), and Health-Related Productivity Questionnaire (HRPQ). The remainder of the scales/questionnaires (MDS-UPDRS [including H&Y], PD-CRS, MoCA, Symbol Digit Modalities Test [oral] (SDMT), Trail Making Tests A (TMT-A), TMT-B, and CGI) will be administered by individuals who will be blinded to study treatment and who are trained in the administration of standardized questionnaires.

The scales/questionnaires are provided in the appendices. Specific instructions for the administration of each scale/questionnaire are provided on each of the scales/questionnaires.

9.1 PRIMARY AND OTHER ENDPOINTS

The MDS-UPDRS is a multimodal scale assessing both impairment and disability and is separated into 4 subscales (Parts I to IV) with a total summed score. The MDS-UPDRS includes components assessed by the certified blinded rater, as well as sections completed by the patient. Every effort should be made to have the same neurologist perform the ratings for a patient throughout the course of the study.

- Part I: This assesses nonmotor experiences of daily living and is comprised of 2 components:
 - Part IA contains 6 questions that are assessed by the certified blinded rater and focuses on complex behaviors.
 - Part IB contains 7 questions that are part of the self-administered Patient Questionnaire.
- Part II: This assesses motor experiences of daily living. There are an additional 13 questions that are also part of the self-administered Patient Questionnaire.
- Part III: This assesses the motor signs of PD and is administered by the certified blinded rater.
- Part IV: This assesses motor complications, dyskinesias, and motor fluctuations using historical and objective information. The certified blinded rater will complete this assessment at each visit for a patient on PD medication.

Total score on the MDS-UPDRS is calculated by summing the 4 subscale scores.

9.1.1 Part 1: Dose escalation phase

The primary endpoint in Part 1 is safety of each dose cohort. The following additional exploratory endpoints will be evaluated:

- Change in MDS-UPDRS PART II+III score, performed during the OFF state, from baseline to 4 weeks.
- Change in MDS-UPDRS PART II+III score, performed during the OFF state, from baseline to 8 weeks.
- Change in MDS-UPDRS PART I+II+III, performed during the OFF state, from baseline to 4 weeks.
- Change in MDS-UPDRS PART I+II+III, performed during the OFF state, from baseline to 8 weeks.

The MDS-UPDRS will be performed by the certified blinded rater for all patients at screening, at Day 1, at Week 4 (Day 1), Week 8, and every 4 weeks thereafter, until completion. No PD medication may be taken for at least 12 hours prior to efficacy assessments. The maximum length of time a patient can be in Part 1 will be 50 weeks (or 66 weeks for Japanese patients), inclusive of the screening period.

9.1.2 Part 2: Treatment phase

The primary endpoint is the change in MDS-UPDRS (PART II+III score; [Section 17](#) [[Appendix F](#)]), performed during the OFF state, from baseline to Week 52. Of note, Part IA, IB, and II of the MDS-UPDRS do not have separate ON or OFF ratings. The OFF definition provided in this protocol is to ensure uniformity among raters and the score sheets should document the OFF status associated with the Part III assessment.

The MDS-UPDRS will be performed for all patients at screening, on Day 1, and at Weeks 13, 26, 39, 52, 78, 104, 130, 156, 182, 208, and 216 by the certified blinded rater. No PD medication may be taken for at least 12 hours prior to efficacy assessments.

Analysis of the change from baseline to Week 52 and from baseline to Week 104, Week 156, and Week 208 in the 4 subscale scores will be performed as an exploratory endpoint.

9.2 SECONDARY ENDPOINTS

9.2.1 Part 1: Dose escalation phase

Not applicable.

9.2.2 Part 2: Treatment phase

- Change in PD-CRS (total score) from baseline to Week 52.
- Change in MDS-UPDRS PART I+II+III, performed during the OFF state, from baseline to Week 52.
- Change in H&Y score from baseline to Week 52.

9.2.3 Scales and questionnaires (Part 1 and Part 2)

The scales and questionnaires will be administered at designated study visits as shown in [Section 1.3.1](#) (Part 1), and [Section 1.3.2](#) (Part 2, Periods 1 and 2), and [Section 1.3.3](#) (Part 2, Periods 3 and 4).

9.2.3.1 Parkinson's disease-cognitive rating scale

It has been suggested that impairment of the semantic memory and visuospatial functions, but not executive functions, predicts progression to dementia in PD. It is therefore relevant to identify those PD patients at risk of developing dementia by means of neuropsychological tools evaluating the whole spectrum of cognitive functions impaired over the course of the disease. The PD-CRS is a cognitive scale specifically designed to capture the whole spectrum of cognitive functions impaired over the course of PD ([Section 17 \[Appendix G\]](#)), specifically assessing fronto-subcortical and cortical cognitive functions.

It comprises a total of 9 tasks explicitly designed for a brief and separate scoring of:

- Frontal subcortical tasks (sustained attention, working memory, alternating and action verbal fluency, clock drawing, immediate, and delayed free recall verbal memory).
- Posterior cortical tasks (confrontation naming and clock copying).

Total scores on the PD-CRS are calculated by adding the subcortical and cortical PD-CRS scores.

In Part 1, analysis of the change in PD-CRS total score and subscores from baseline to Week 8 will be performed as an exploratory endpoint. The PD-CRS will be performed at screening, Day 1, and Week 8 by the certified blinded rater.

In Part 2, analysis of the change in PD-CRS subscores from baseline to Week 52 and from baseline to Week 104, Week 156, and Week 208 will be performed as an exploratory endpoint. The PD-CRS will be performed for all patients at screening, Day 1, Weeks 13, 26, 39, 52, 78, 104, 130, 156, 182, and 208 by the certified blinded rater.

9.2.3.2 Hoehn & Yahr scale

The H&Y scale is a widely used clinical rating scale, which defines broad categories of motor function in PD (see [Section 17 \[Appendix F\]](#)). Among its advantages, it is simple and easy to apply. It captures typical patterns of progressive motor impairment which can be applied whether or not patients are receiving dopaminergic therapy. Progression in H&Y stages has been found to correlate with motor decline, deterioration in quality of life, and neuroimaging studies of dopaminergic loss.

The scale allocates stages from 0 to 5 to indicate the relative level of disability. This scale is included within the MDS-UPDRS and will be completed for all patients.

- Stage 0: No symptoms.
- Stage 1: Symptoms on one side of the body only.
- Stage 2: Symptoms on both sides of the body. No impairment of balance.
- Stage 3: Balance impairment. Mild to moderate disease. Physically independent.

- Stage 4: Severe disability, but still able to walk or stand unassisted.
- Stage 5: Wheelchair-bound or bedridden unless assisted.

9.3 SAFETY ENDPOINTS

The observation period of safety endpoints will be divided into 3 segments:

- The **pretreatment period** is defined as the time between the date of the informed consent up to the first administration of double-blind IMP.
- The **on-treatment period** is defined as the period from the time of first IMP administration up to 6 weeks after the last administration of the IMP.
- The **post-treatment period** starts on the day after the end of the on-treatment period.

The **baseline value for safety endpoints** will be the last available value prior to the first administration of double-blind IMP.

9.3.1 Part 1: Dose escalation phase

Safety endpoints will be assessed by:

- Physical examination.
- Neurological examination.
- Clinical laboratory evaluations, including hematology, biochemistry, and urinalysis.
- Vital signs.
- Assessment of AEs and concomitant medication.
- Ophthalmological examination. Visual acuity and lens evaluation will be performed according to the Lens Opacity Classification System II (LOCSII) for monitoring potential cataract development.
- Electrocardiogram.

9.3.2 Part 2: Treatment phase

Safety endpoints will be assessed by:

- Incidence, relationship to study drug and resolution of treatment-emergent adverse events (TEAEs), SAE, TEAE/SAE leading to study drug or study discontinuation.
- Ophthalmological examinations. Visual acuity and lens evaluation will be performed according to the LOCSII for monitoring potential cataract development.

9.3.3 Safety assessments (Part 1 and Part 2)

9.3.3.1 Adverse events

Refer to [Section 10.4](#) to [Section 10.7](#) for details.

9.3.3.2 Laboratory safety variables

All laboratory data listed in this section, except for CSF cell count, will be measured at a central laboratory. The laboratory data will be collected at designated visits as shown in [Section 1.3](#). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

The following laboratory safety variables will be analyzed:

- Hematology: red blood cell count, hematocrit, hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), platelets, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).
- Biochemistry:
 - Plasma/serum electrolytes: sodium, potassium, chloride, calcium, bicarbonate;
 - Liver function: ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total and conjugated bilirubin;
 - Renal function: urea, serum creatinine;
 - Metabolism: glucose, albumin, total proteins;
- Urinalysis (microscopy if determined to be medically necessary).
- At screening, serum β -HCG test for WOCBP.

9.3.3.3 Vital signs

In Part 1, vital signs (including temperature, blood pressure, heart rate, and respiratory rate) will be collected at every visit (See [Section 1.3.1](#)).

In Part 2, vital signs (including temperature, blood pressure, heart rate, and respiratory rate) will be collected at screening and at Weeks 0, 2, 4, 13, 26, 39, 52, 78, 104, 130, 156, 182, 208, and 216. Vital signs will be collected for Japanese patients at Week 65, 91, 117, 143, 169, and 195 in addition to the above time points (refer to [Section 1.3.2](#) and [Section 1.3.3](#)). Orthostatic vital signs will be done at screening, Weeks 4 and 52; at all other time points, vital signs will be done in the supine position.

Supine vital signs will be taken after patients have remained supine for 5 minutes. Orthostatic vital signs will be taken once after patients have remained supine for 5 minutes, and then again after 2 minutes in the standing position. Patients should move from supine to standing without

sitting in between vital sign measurements. Systolic/diastolic blood pressure and heart rate will be measured in each position.

Body temperature (auricular or oral body temperature [Celsius °C]) will be collected using the same method for a given patient. Any fever (defined as: body temperature $\geq 38^{\circ}\text{C}$) should be recorded as an AE and the Investigator should perform all investigations necessary to rule out infection.

Blood pressure will be measured under standardized conditions using the same method for a given patient. It will be determined at each study visit using a well calibrated apparatus. Both systolic and diastolic blood pressure must be recorded.

9.3.3.4 Physical examination

Whenever possible, the same physician should perform the physical examination at all study visits. The findings of each examination will be recorded.

Each physical examination will include the following physical observations/measurements: general appearance; heart, skin, respiratory auscultation; head, eyes, ears, nose, and throat, extremities/joints, and abdomen.

A site physician will assess the physical examination findings as normal, abnormal but not clinically significant, or abnormal and clinically significant.

In Part 1, a physical examination will be performed at screening, Day 1, and Weeks 4 and 8, and if applicable, at Weeks 12, 16, 20, 24, 28, 32, and 36 and the completion visit. A physical examination will be collected for Japanese patients at Week 40, 44, 48, and 52 in addition to the above time points, if applicable (refer to Section 1.3.1). At screening, height will be measured without shoes and body weight will be measured without shoes or heavy clothing (See [Section 1.3.1](#)).

In Part 2, a physical examination will be performed at screening, Day 1, and Weeks 26, 52, 104, 156, 208, and 216. Any clinically significant abnormalities should be reported in the patient eCRF as medical history if observed at the screening visit (Day -60 to Day -1) or as an AE if observed during subsequent visits. Height will be measured at screening without shoes. Body weight will be measured without shoes or heavy clothing at screening and at Weeks 52, 104, 156, and 208 (See [Section 1.3.2](#) and [Section 1.3.3](#)).

9.3.3.5 Neurological examination

Each neurological examination will include, but not be limited to, assessments of the patient's mental status, cranial nerves, motor system (including muscle atrophy, tone and power), deep tendon reflex, sensation, and cerebellar function. The examination should be performed by the same neurologist throughout the study, if possible.

When neurological and ophthalmological examinations are performed on the same day, the neurological examination should be performed before ophthalmological examination.

In Part 1, a neurological examination will be performed at screening, Day 1, and Weeks 2, 4, and 8, and if applicable, at Weeks 12, 16, 20, 24, 28, 32, and 36, and the completion visit (See [Section 1.3.1](#)). A neurological examination will be collected for Japanese patients at Week 40, 44, 48, and 52 in addition to the above time points, if applicable (refer to [Section 1.3.1](#)).

In Part 2, a neurological examination will be performed at screening, Day 1, and Weeks 13, 26, 39, 52, 78, 104, 130, 156, 182, 208, and 216 (See [Section 1.3.2](#) and [Section 1.3.3](#)).

9.3.3.6 Ophthalmological examination

The full ophthalmological examination will include visual acuity, slit-lamp examination, and examination of the cornea, lens, and retina. The examination should include pupil dilation and evaluation of the lens according to the LOCSII. As part of the eye exam, a conventional confrontation visual field exam, such as the Donders' test, can be performed by the local ophthalmologist as needed. Systematic visual field test by perimetry is not required for this trial.

This evaluation should be accompanied by pictures of the lens for evaluation by the examining ophthalmologist. Photos of the lens will be reviewed/assessed by a central reader.

In Part 1, a full ophthalmological examination and photography will be performed during screening, at Week 36 (or Week 52 for Japanese patients), if applicable, and at the completion visit, early withdrawal or treatment discontinuation, if applicable. At Week 4 only, and if applicable, at Weeks 12 and 28 (Week 36 for Japanese patients only), only best corrected visual acuity, slit lamp examination and funduscopy without pupil dilation will be required; if a lens abnormality is found, the ophthalmologist at the site should perform pupil dilation and LOCSII evaluation, and document by photograph (see [Section 1.3.1](#)). Pupil dilation/full evaluation can be performed at any time if deemed medically necessary.

In Part 2, a full ophthalmological examination will be performed during screening, Weeks 52, 104, 156, 208, and early withdrawal or treatment discontinuation. For Weeks 4, 13, 26, 39, 78, 130, 182, and 216, only best corrected visual acuity, slit lamp examination, and funduscopy without pupil dilation will be required. In Part 2, if at any of the intermediate time points (Weeks 4, 13, 26, and 39) or during Period 3, a lens abnormality is found, the ophthalmologist at the site should perform pupil dilation and LOCSII evaluation, and document by photograph (See [Section 1.3.2](#) and [Section 1.3.3](#)). Pupil dilation/full evaluation can be performed at any time if deemed medically necessary.

The examination should be performed by the same ophthalmologist throughout the study, if possible. Abnormal findings reported by the clinical sites will be reviewed by the DMC and/or the clinical site to adjudicate these findings as AESI and assess their seriousness/severity.

9.3.3.7 Electrocardiogram (ECG)

Heart rate, ECG recordings, including time from ECG Q wave to the end of the s wave corresponding to ventricular depolarization (QRS interval), the time from the onset of the P wave to the start of the QRS complex (PR interval), QT interval, ECG ST-segment deviation (ST deviation), T-wave morphology, and U-wave presence or absence will be determined per local site procedure using automated and manual readings of all ECGs. All ECG recordings will be centrally read by independent experts. Refer to central ECG reading manual for more details.

Any clinically significant abnormality (eg, corrected QT or QTc >450 msec in males/ >470 msec in females) observed at the first screening visit (Day -60 to Day -1) upon Investigator review will be immediately rechecked for confirmation before making a determination regarding patient exclusion from the study. Additional ECGs may be performed if deemed clinically necessary by the Investigator (eg, diagnosis of AE) and will be documented in the eCRF.

In Part 1, a 12-lead ECG will be performed at screening, Day 1 (pre-dose and then 2, 4, and 6 hours postdose), and Week 4, and if applicable, at Week 28 and at the completion visit ([Section 1.3.1](#)).

In Part 2, an ECG will be performed at screening and Weeks 4, 26, 52, 104, 156, and 208 (See [Section 1.3.2](#) and [Section 1.3.3](#)).

9.4 EXPLORATORY AND OTHER ENDPOINTS

9.4.1 Pharmacodynamic and exploratory fluid biomarkers

In Part 1 and Part 2, CSF samples collected by means of a LP and plasma samples will be collected at the times specified in the schedule of assessments (see [Section 1.3](#)).

Pharmacodynamic biomarkers such as GL-1 and lyso-GL-1 in plasma and CSF, and GCase activity in dried blood spot will be measured at the Sponsor's laboratory or at a subcontracted laboratory. Additional pharmacodynamic biomarkers, such as chitotriosidase, cytokines, ceramide, and sphingomyelin in plasma and serum or chitotriosidase and cytokines in CSF may also be assessed. See [Section 17 \(Appendix H\)](#) for a list of exploratory pharmacodynamic biomarkers per body fluid.

Exploratory biomarkers to be evaluated may include:

- NFL
- α -Syn
- beta amyloid (1-40, and 1-42)
- Total tau and phospho-tau (181)

Other variables may also be assessed if available data during the course of the study suggests a relationship to disease course in PD patients or to GZ/SAR402671. Markers related to PD and/or neurodegeneration and/or GZ/SAR402671 may be assessed at the Sponsor's laboratory or at a contract research organization or an academic laboratory appointed by the Sponsor.

The number of samples per patient is shown in [Table 1](#).

Table 1 - Number of samples for pharmacodynamics assessment

Type of Samples	Plasma/Serum			Cerebrospinal Fluid		
	15 patients in Part 1	12 Japanese patients	216 patients in Part 2	15 patients in Part 1	12 Japanese patients	216 patients in Part 2
Total number of sample timepoints by patient ^a	3	3	7	2	2	2
Total number of samples for study ^a	45	36	1512	30	24	432

a Approximate total number of samples.

The assay methods will be detailed in a separate laboratory manual.

9.4.2 Pharmacokinetics

9.4.2.1 Sampling time

The sampling times for blood and CSF collection in Part 1 and Part 2 can be found in the study flow charts (Section 1.4) and in a separate laboratory manual.

Plasma and CSF collections for the same time points at Week 4 in Part 1 and at Week 52 in Part 2 should be performed in as close succession as possible.

Plasma parameters in Part 1 will include:

- Day 1 (single dose administration): maximum plasma concentration observed (C_{max}), t_{max} , and area under the plasma concentration versus time curve calculated using the trapezoidal method over a predefined time period (from time $t=0$ to 24 hours [AUC_{0-24}], and from $t=0$ to 48 hours [AUC_{0-48}])
- Week 2: plasma concentration observed just before treatment administration during repeated dosing (C_{trough})
- Week 4: C_{trough} , C_{max} , t_{max} , AUC_{0-24} , and apparent total body clearance of a drug at steady state after oral administration (CL_{ss}/F ; calculated using the following equation: $CL_{ss}/F = \text{Dose}/AUC_{\tau}$, where τ is the dosing interval)
- Week 8: C_{trough}

Cerebrospinal fluid parameters in Part 1 will include:

- Day -14 to Day 1: pre-dose concentration
- Week 4: Concentration at any time within 2 to 4 hours after administration of GZ/SAR402671

Plasma parameters in Part 2 will include:

- Day 1 (single dose administration): C_{max} , t_{max} , AUC_{0-24}
- Week 2: C_{trough}
- Week 26:
 - C_{trough}
 - Concentration at any time within 2 to 4 hours after administration of GZ/SAR402671 on visit day.
- Week 52:
 - C_{trough}
 - Concentration at any time within 2 to 4 hours after administration of GZ/SAR402671 on visit day.

Cerebrospinal fluid parameters in Part 2 will include:

- Day -14 to Day 1: pre-dose concentration
- Week 52 (all patients): Concentration at any time within 2 to 4 hours after administration of GZ/SAR402671 on visit day.

The number of samples per patient is shown in [Table 2](#).

Table 2 - Number of samples for pharmacokinetics assessment

Type of Samples	Plasma			Cerebrospinal Fluid		
	15 non-Japanese patients in Part 1	12 Japanese patients in Part 1	216 patients in Part 2	15 non-Japanese patients in Part 1	12 Japanese patients in Part 1	216 patients in Part 2
Total number of sample timepoints by patient ^a	15	15	11	2	2	2
Total number of samples for study ^a	225	180	2376	30	24	432

^a Approximate total number of samples.

9.4.2.1.1 Lumbar puncture

The LP will be performed by the site Investigator or another qualified clinician appointed by the Investigator.

An LP for the collection of approximately 15 to 20 mL of CSF will be conducted for all patients per the visit schedule unless there is evidence of clinically significant coagulopathy or thrombocytopenia that would interfere with the safe conduct of the procedure. It is expected that all patients will undergo an LP at baseline. The baseline LP can be done within 14 days prior to or on the day of randomization (pre-dose).

The first 1 to 2 mL of CSF will be discarded; the subsequent 2 to 4 mL will be processed at the site's local laboratory facility (unless the laboratory is not able to process the CSF within 4 hours) to conduct standard analyses on cell count, including red blood cell counts. The remaining CSF will be processed and shipped to a central laboratory for biomarker and PK assessments. Please refer to the laboratory manual provided by the central laboratory.

Patients will be closely monitored during the procedure and following the procedure.

9.4.2.2 Pharmacokinetics handling procedure

Special procedures for collection, storage, and shipment of plasma and CSF samples collected for GZ/SAR402671 concentrations which will be provided in a separate laboratory manual provided by the central laboratory.

An overview of PK sample handling procedure is provided in [Table 3](#).

Table 3 - Summary of plasma and cerebrospinal fluid samples collected for GZ/SAR402671 concentrations

Sample Type	Plasma	Cerebrospinal Fluid
Sample volume	2 mL blood	0.5 mL
Anticoagulant	K ₂ EDTA	NA
Handling procedures	See study specific laboratory manual	
Aliquot split	Yes (2)	
Storage conditions	Keep in upright position at -70°C	
Shipment conditions	Frozen, on dry ice	

Abbreviations: K₂EDTA: dipotassium ethylenediamine tetra-acetic acid; NA: not applicable.

9.4.2.3 Bioanalytical method

Bioanalytical analyses will be performed under the responsibility of the central laboratory. Only samples from patients on active study treatment will be analyzed.

Plasma GZ/SAR402671 concentrations will be determined using a validated liquid chromatography tandem mass spectrometry method (DMPK15-R012) with a lower limit of quantification of 0.500 ng/mL.

Cerebrospinal fluid concentrations of GZ/SAR402671 will be determined using a validated liquid chromatography tandem mass spectrometry method (DMPK15-R016) with a lower limit of quantification of 0.100 ng/mL.

9.4.2.4 Pharmacokinetic parameters

The following PK plasma parameters will be calculated, using noncompartmental methods from plasma GZ/SAR402671 concentrations obtained after single dose administration. The parameters will include, but may not be limited to the following:

Parameters	Drug/Analyte	Definition/Calculation
C _{max}	GZ/SAR402671	Maximum plasma concentration observed
C _{trough}	GZ/SAR402671	Plasma concentration observed just before treatment administration during repeated dosing
t _{max}	GZ/SAR402671	Time to reach C _{max}
AUC ₀₋₂₄ or AUC ₀₋₄₈	GZ/SAR402671	Area under the plasma concentration versus time curve calculated using the trapezoidal method over a predefined time period (from time t= 0 to 24 hours; AUC ₀₋₂₄ , and from t= 0 to 48 hours; AUC ₀₋₄₈)
AUC	GZ/SAR402671	Area under the plasma concentration versus time curve extrapolated to infinity according to the following equation: $AUC = AUC_{last} + \frac{C_{last}}{\lambda_z}$ Values with percentage of extrapolation >30% will not be reported
t _{1/2z}	GZ/SAR402671	Terminal half-life associated with the terminal slope (λ _z) determined according to the following equation: $t_{1/2z} = \frac{0.693}{\lambda_z}$ where λ _z is the slope of the regression line of the terminal phase of the plasma concentration versus time curve, in semilogarithmic scale. Half-life is calculated by taking the regression of at least 3 points.
CL _{ss} /F	GZ/SAR402671	Apparent total body clearance of a drug at steady state after oral administration; calculated using the following equation: CL _{ss} /F = Dose/AUCτ, where τ is the dosing interval

Exploratory GZ/SAR402671 metabolite PK profiling and/or metabolite exposure analysis may be conducted in the collected plasma PK and CSF samples during Part 1 and Part 2 of the study.

9.4.3 Dopamine transporters scan assessment

DAT scans will be performed only in countries where it is approved.

Women of childbearing potential must have a urine (or serum if required by the site) pregnancy test prior to injection of DAT scan. The result must be confirmed as negative prior to proceeding with the injection.

Before the DAT scan injection, patients will be pretreated with stable iodine (10 drops of a saturated solution of potassium iodide) to reduce the uptake of DAT scan by the thyroid, according to the local regulation.

Patients will be injected with 3 to 5 mCi of DAT. Within a 4-hour (± 30 minutes) window following the injection, patients will undergo standard brain single-photon emission computerized tomography imaging as per the Society of Nuclear Medicine Practice Guidelines.

A central reading center will be used to read the imaging from the patients to ensure consistency and accuracy between sites.

In Part 1, patients will undergo a DAT scan within 7 days prior to randomization (Day -7 to Day -1) or on the day of randomization (Day 1, pre-dose) (See [Section 1.3.1](#)).

In Part 2, patients will undergo a DAT scan at screening (within 7 days prior to randomization [Day -7 to Day -1] or on the day of randomization [Day 1, pre-dose]) and Weeks 52, 104, 156, and 208 (See [Section 1.3.2](#) and [Section 1.3.3](#)).

9.4.4 Levodopa or other Parkinson's disease therapy

9.4.4.1 Time to initiation/intensification of levodopa/PD therapy

It is anticipated that GBA-PD patients, if entering the study on a PD medication, will be able to remain on a stable dose of the PD medications for the entire duration of the study. However, it may be considered necessary in the medical judgment of Investigator to initiate or intensify PD medications. In such occurrence, this could apply only to an immediate release levodopa formulation. If PD medications are to be initiated or intensified, patients will be asked to return for an additional study visit on site. This also holds true if a patient requires a change in his/her PD medication. The Investigator will document any new medications or changes in medication at each study visit on the Concomitant Medication Log.

In Part 2 only, time to initiation of levodopa or other PD therapy (for patients not on levodopa/other PD therapy at baseline) or to increased dose of levodopa/other PD therapy (for patients on levodopa/other PD therapy at baseline) will be calculated.

9.4.4.2 Reduction of levodopa/PD therapy

In Part 2 only, there might be a possibility that GBA-PD patients, if entering the study on a PD medication, would be able reduce their dose of the PD medication. If PD medications are to be reduced or stopped, the Investigator will document these changes in medication at each study visit on the Concomitant Medication Log.

9.4.5 Scales and questionnaires

9.4.5.1 Montreal cognitive assessment score

In early PD, when cognitive deficits occur, they are subtle and mild and the patients usually perform in the normal range on the widely used Mini Mental State Examination. The MoCA is a rapid screening instrument like the Mini Mental State Examination but was developed to be more sensitive to patients presenting with mild cognitive complaints. It assesses short-term and working memory, visuospatial abilities, executive function, attention, concentration, language, and orientation. The total score ranges from 0 to 30 (see [Section 17 \[Appendix I\]](#)). This assessment will be scored by an independent blinded rater.

In Part 1, the changes from baseline to Week 8 in MoCA score will be assessed, separately for Japanese and non-Japanese patients.

In Part 2, the changes in MoCA score from baseline to Week 52 and from baseline to Week 104, Week 156, and Week 208 will be assessed.

9.4.5.2 Oral symbol digit modalities test score

The SDMT assesses divided attention, visual scanning, and motor speed. After being presented with a coding key, the patient is required to pair the number with the corresponding symbol as rapidly as possible and within 90 seconds (see [Section 17 \[Appendix J\]](#)). Symbol Digit Modalities Test requires the subject to substitute a number for its corresponding geometric figure. There are 9 figures. On the record form, there are a series of rows containing geometric figures in the top half, but the bottom half is left blank. When it is clear that the subject understands the task, he or she is told to fill in the remaining boxes as quickly as possible, completing one box at a time, one row at a time, before proceeding to the next. Skipping from box to box with the same geometric figure is not permitted. Subjects receive one point for each correctly completed box. The total score is the total number of correctly completed boxes in the time allowed. The practice items are not counted in the scoring. This assessment will be scored by an independent blinded rater.

The test can be administered by having the subject write out the correct response or by having the subject report the correct answer (ie, number) aloud. Higher scores are better scores and the range of scores can be from 0 to 110 for SDMT oral scores.

Parkinson's disease patients have motor skill deficits, therefore oral SDMT will be used in this study as this version has greater sensitivity than the written version. The blinded rater will read the instructions to the patient, point to the open spaces on the form and record the answer from the patient.

In Part 1, the changes from baseline to Week 8 in SDMT oral score will be assessed, separately for Japanese and non-Japanese patients.

In Part 2, the changes in SDMT oral score from baseline to Week 52 and from baseline to Week 104, Week 156, and Week 208 will be assessed.

9.4.5.3 Trail making test A and B score

The TMTs are popular neuropsychological instruments used either alone as a screening instrument for detecting neurological disease and neuropsychological impairment or as part of a larger battery of tests. The tests are believed to measure the cognitive domains of processing speed, sequencing, mental flexibility, and visual–motor skills (see [Section 17 \[Appendix K\]](#)). It consists of two parts in which the patient is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy. The test can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning. It is sensitive to detecting cognitive impairment associated with dementia. This assessment will be scored by an independent blinded rater.

Scoring will include total score for each TMT-A and TMT-B as well as the change in the difference between TMT-B score minus TMT-A score.

In Part 1, the changes from baseline to Week 8 in TMT-A and TMT-B score including the change in the difference between TMT-B minus TMT-A score will be assessed, separately for Japanese and non-Japanese patients.

In Part 2, the changes from baseline to Week 52 and from baseline to Week 104, Week 156, and Week 208 in TMT-A and TMT-B score including the change in the difference between TMT-B minus TMT-A score will be assessed.

9.4.5.4 Beck depression inventory, second edition

Depression will be monitored during the study by using the BDI-II; see [Section 17 \(Appendix L\)](#). Beck Depression Inventory, second edition is a 21-question, multiple-choice, self-report inventory. It is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and disinterest in sex.

The wording of the BDI-II is clear and concise. The test contains 21 items, most of which assess depressive symptoms on a Likert scale of 0-3. The two exceptions to this are questions 16 and 18. Question 16 addresses changes in sleeping pattern, while question 18 addresses changes in appetite. Patients will be asked to report their own feelings over the past 2 weeks instead of 1 week, as in the BDI and BDI-IA. The reason for this is to be consistent with the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition criteria for depression. There were also two items added to indicate any directional changes in eating and sleeping patterns. Finally, all forms of the inventory are written at the 5th grade reading level.

Clinical interpretation of scores is accomplished through criterion-referenced procedures utilizing the following interpretive ranges: total BDI-II scores of 0-13 indicate minimal depression, scores of 14-19 indicate mild depression, scores of 20-28 indicate moderate depression, and scores of 29-63 indicate severe depression. The BDI-II will be performed at every study visit in this trial.

If a patient has a score of ≥ 20 or if the patient has a score < 20 but answers “yes” to answer 2 or 3 of question 9, the patient must be referred to their health care professional for psychiatric evaluation. This will be captured as an AE. The participant may continue the study, but this is dependent on the judgment of the PI.

In Part 1, BDI-II will be administered at every study visit, except on Visits 3 and 4 (Week 0, Days 2 and 3) and Visit 7 (Week 4, Day 2).

In Part 2, the changes from baseline to Week 52 and from baseline to Week 104, Week 156, and Week 208 in BDI-II score will be assessed.

9.4.5.5 Clinical global impression scale

The CGI is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC), and therapeutic response (see [Section 17 \[Appendix M\]](#)). Each component of the CGI is rated separately; the instrument does not yield a global score. CGI will be scored by an independent blinded reader.

The CGIS is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). CGIC scores range from 1 (very much improved) through to 7 (very much worse). Treatment response ratings should take account of both therapeutic efficacy and treatment-related AEs and range from 0 (marked improvement and no side effects), and 4 (unchanged or worse and side-effects outweigh the therapeutic effects).

In Part 1, CGI scores will be assessed on Day 1 and Week 8, separately for Japanese and non-Japanese patients.

In Part 2, CGI scores will be assessed on Day 1 and Week 52.

9.4.5.6 Patient global impression of change scale

In 2004, Hurst and Bolton describe the PGIC scale as a more meaningful measure of health care system performance via direct feedback from the patient. The PGIC is particularly suited to capturing clinically meaningful change that makes a difference to the patient and has been used extensively in studies of musculoskeletal conditions.

This questionnaire (see [Section 17 \[Appendix N\]](#)) will be administered by individuals trained in the administration of standardized questionnaires. Score result should not be disclosed to the blinded rater.

In Part 1, PGIC will be administered on Week 8.

In Part 2, PGIC will be administered on Weeks 13, 26, 39, and 52.

9.4.5.7 Parkinson's disease questionnaire – 39 score

The PDQ-39 is a self-completion patient-reported outcome designed to address aspects of functioning and well-being over the last month for those affected by PD (see [Section 17 \[Appendix O\]](#)). This patient-reported outcome assesses how often patients experience difficulties across different quality of life dimensions:

- Mobility (10, #1-10);
- Activities of daily living (6, #11-16);
- Emotional well-being (6, #17-22);
- Stigma (4, #23-26)
- Social support (3, #27-29);
- Cognition (4, #30-33);
- Communication (3, #34-36);
- Bodily discomfort (3, #37-39).

Moreover, the PDQ-39 assesses impact of PD on specific dimensions of functioning and well-being, with a lower score reflecting a better quality of life.

In Part 1, the changes from baseline to Week 8 in PDQ-39 will be assessed, separately for Japanese and non-Japanese patients.

In Part 2, the changes from baseline to Week 52 and from baseline to Week 104, Week 156, and Week 208 in PDQ-39 scores will be assessed.

9.4.5.8 EuroQol five dimensions questionnaire

The EQ-5D is a standardized instrument for measuring generic health status. The health status measured with EQ-5D is used for estimating preference weight for that health status, then by combining the weight with time, quality-adjusted life year can be computed (see [Section 17 \[Appendix P\]](#)). The EQ-5D is made up for two components; health state description and evaluation. In the description part, health status is measured in terms of five dimensions (5D); mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Mobility dimension asks about the person's walking ability. Self-care dimension asks about the ability to wash or dress by oneself, and usual activities dimension measures performance in "work, study, housework, family or leisure activities". In pain/discomfort dimension, it asks how much pain or discomfort they have, and in anxiety/depression dimension, it asks how much anxious or depressed they are. The respondents self-rate their level of severity for each dimension using a five-level scale. In the evaluation part, the respondents evaluate their overall health status using the visual analogue scale.

In Part 1, the changes from baseline to Week 8 in EQ-5D score will be assessed, separately for Japanese and non-Japanese patients.

In Part 2, the changes from baseline to Week 52 and from baseline to Week 104, Week 156, and Week 208 in EQ-5D scores will be assessed.

9.4.5.9 Falls efficacy scale

The Falls Efficacy Scale (FES) is used to assess perception of balance and stability during activities of daily living and to assess the patient's fear of falling (see [Section 17 \[Appendix Q\]](#)). It is a 10-item questionnaire designed to assess confidence in a person's ability to perform 10 daily tasks without falling as an indicator of how one's fear of falling impacts physical performance. Each item is rated from 1 ("very confident") to 10 ("not confident at all"), and the per item ratings are added to generate a summary total score. Total scores can range from 10 (best possible) to 100 (worst possible). Thus, lower scores indicate more confidence and higher scores indicate lack of confidence and greater fear of falling. Of note, the FES appears to be a reliable and valid method for measuring fear of falling. This scale has excellent reliability, is correlated with measures of balance and gait, and predicts future falls and decline in functional capacity. Most importantly, the FES has proven sensitive to change in fears following clinical interventions.

In Part 2, the changes from baseline to Week 52 and from baseline to Week 104, Week 156, and Week 208 in FES scores will be assessed. FES will be administered at baseline, Weeks 13, 26, 39, 52, 78, 104, 130, 156, 182, and 208.

9.4.6 Parkinson's disease progression model

The data collected during the study will be used to develop a Parkinson's disease progression model in early-stage PD patients carrying a GBA mutation.

9.5 HEALTH-RELATED PRODUCTIVITY QUESTIONNAIRE

Health-related quality of life measures are currently essential for the evaluation of patients in clinical trials. Patients with PD are particularly vulnerable to deterioration of health-related quality of life resulting from significant motor disability and the burden of nonmotor symptoms. Assessment of health-related quality of life of persons with PD is thus of essential importance.

The HRPQ contains items related to productivity during paid work, but more importantly for this population, it also has questions about ability to be productive in the home at household chores (cooking, cleaning, gardening, repairs, etc) (see [Section 17 \[Appendix R\]](#)).

In Part 1, the changes from baseline to Week 8 in HRPQ scores will be assessed, separately for Japanese and non-Japanese patients.

In Part 2, the changes from baseline to Week 52 and from baseline to Week 104, Week 156, and Week 208 in HRPQ scores will be assessed.

9.6 PHARMACOGENETIC ASSESSMENT

During the screening period, 1 blood sample will be collected for investigation of GBA mutations and the LRRK2 G2019S mutation, which is required to include patients in the study (see [Section 17 Appendix A](#)).

Approximately 6 to 10 mL whole blood will be collected for pharmacogenetic analysis during the screening period. Special procedures for collection, storage, and shipping of DNA samples for investigation of GBA mutations will be described in detail in the laboratory manual provided to the study sites.

Once these analyses have been performed, all DNA material left over will be destroyed ([Section 9.6.1](#)).

9.6.1 Optional stored DNA sample (not applicable in Israel)

Once enrollment is confirmed, patients will be asked if they are willing to consent to long-term storage of DNA samples for future use. For those patients who signed the optional Pharmacogenetic Informed Consent Form, a blood sample will be collected as specified in the study flow chart ([Section 1.3.1](#)) for the purpose of additional pharmacogenetic analysis and this sample will be stored.

In Part 2, patients who initially consented, will be asked if they consent for a second blood sample. This sample will be collected at Week 52 or at any visit after Week 52.

The data from patient's genetic material may be used to understand PD disease pathogenesis, GZ/SAR402671 signaling, drug response or activity and toxicity, to determine a possible relationship between the genes and PD or diseases, to develop and/or validate a bioassay method, possibly to identify new drug targets or biomarkers, and investigate allelic variants of drug metabolizing enzymes (DMEs) and/or drug transporters. In addition, as new scientific knowledge is gained that may be related to GZ/SAR402671, patient response or association with PD, other genes may also be studied.

This blood sample will be transferred to a Sanofi site (or a subcontractor site) which could be located outside of the country where the study is conducted. Sanofi or its subcontractor will extract DNA from the sample.

This blood sample, and the DNA that is extracted from it, will be assigned a second number, a Genetic ID that is different from the Patient ID. This "double coding" is performed to separate a patient's medical information and DNA data.

The clinical study data (coded by Patient ID) will be stored in the clinical data management system (CDMS), which in a distinct database in a separate environment from the database containing the genetic data (coded by Genetic ID). The key linking Patient ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key,

which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The DNA will be stored for up to 15 years from the completion of the clinical study report.

If a patient, via written request, asks for destruction of his/her samples and the samples have not yet been double coded, the Sponsor will destroy the samples per applicable guidelines; however, any data already generated will not be destroyed. The Sponsor will notify the Investigator in writing that the samples have been destroyed. However, any analyses of the sample(s) that have already been performed or data generated prior to patient's request will continue to be used as part of the research in this project and will be kept by the Sponsor.

Special procedures for collection, storage, and shipping of DNA samples are summarized in [Table 4](#) and will be described in detail in the laboratory manual provided to the study sites.

Table 4 - Summary of handling procedures for stored DNA samples

Sample Type(s)	Pharmacogenetics
Blood sample volume	Up to 8.5 mL
Tube type	Tube provided by central laboratory for DNA sample storage
Anticoagulant	See laboratory manual for specific instructions
Blood handling procedures	See laboratory manual for specific instructions
Shipping conditions	See laboratory manual for specific instructions
DNA storage conditions	70°C or colder; may also be placed temporarily on dry ice (only if the sample is being shipped frozen)

Abbreviation: DNA: deoxyribonucleic acid.

9.7 FUTURE USE OF NON-GENOMIC SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For patients who have consented to it, the samples that are unused or left over after testing may be used for other research purposes (excluding genetic analysis) related to PD and/or to GZ/SAR402671 other than those defined in the present protocol, as per local regulations.

These other research analyses can help to better understand PD disease pathogenesis, GZ/SAR402671 signaling, drug response or activity, and toxicity, to develop and/or validate a bioassay method, and possibly to identify new drug targets or biomarkers.

These samples (excluding genetic analysis and long-term stored DNA sample) will remain labelled with the same identifiers as the one used during the study (ie, Patient ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the countries where the study is conducted and stored for up to 5 years and as per local regulations. The Sponsor has included safeguards for protecting patient confidentiality and personal data (see [Section 14.3](#) and [Section 14.5](#)).

If a patient, via written request, asks for destruction of his/her research samples, the Sponsor will destroy the samples per applicable guidelines; however, any data already generated will not be destroyed. The Sponsor will notify the Investigator in writing that the samples have been destroyed. However, any analyses of the sample(s) that have already been performed or data generated prior to patient's request will continue to be used as part of the research in this project and will be kept by the Sponsor.

10 STUDY PROCEDURES

In order to ensure proper evaluation of efficacy, the staff of each study center will include the following physicians: a primary treating neurologist, a neurologist Sub-Investigator and a minimum of 2 blinded examining neurologist/raters. The primary treating neurologist, who can serve as the PI, will have overall responsibility to lead the site study team (physicians, pharmacists, technicians, nurses, and clinical coordinators) in all aspects of the study. The primary treating neurologist/PI will also have a neurologist Sub-Investigator who can back up the PI when/if needed. The blinded examining neurologist/raters must be experienced neurologists, or qualified non-physician health professionals who meet a predetermined level of experience in evaluating GBA-PD patients including examining GBA-PD patients and scoring the various scales when permitted by local laws, health authority rules, and ethics committee requirements. This delineation assures that AEs or other health issues for any patient do not influence the neurological assessment. Both the treating neurologist and blinded examining neurologist/ rater must have a minimum of 2 years of PD clinical experience.

Treating neurologist

The treating neurologist will be responsible for evaluation of patient eligibility; supervision of IMP administration; assessing and treating of AEs; assessing, confirming, and managing any GBA-PD issues; and monitoring of safety assessments, including routine laboratory results and concomitant medications. As much as possible, the same treating neurologist, be it the PI or Sub-Investigator, must maintain that role for a given patient throughout the study.

Examining neurologist/blinded rater

Every effort should be made to maintain the same blinded raters throughout the study. In case the rater must change, new blinded raters must be trained and remain throughout the duration of the study. For a given patient, one blinded rater does not have to perform all the assessments. However, each questionnaire (MDS-UPDRS [including H&Y], PD-CRS, MoCA, SDMT [oral], TMT-A, TMT-B, and CGI) should be scored by the same blinded rater throughout the study. Of note, only MDS-UPDRS and PD-CRS require a certified blinded rater.

The examining neurologist/blinded rater will be responsible for conducting all the efficacy assessments and for determining the scores, and must be certified for MDS-UPDRS and PD-CRS rating prior to any involvement in the study. Throughout the study, the examining neurologist/rater must not be involved with any other aspect of patient care and management and must remain blinded to the patient's treatment and safety profile (AEs, concomitant medications and laboratory results). Moreover, he/she must also not read the protocol, ensuring accurate rater-blinded assessments. This person should instead refer to the schedule of assessments.

All other investigational site staff must refrain from discussing any aspects of the protocol and/or safety issues with the examining neurologist. The examining neurologist/blinded rater should maintain the role for a given patient throughout the study. The study site is responsible for appointing a backup examining neurologist/rater in the case the primary is unable to fulfill the

role and that person is responsible for conducting the remainder of the assessments for the patient throughout the remainder of the study. The role of the treating neurologist and the examining neurologist is NOT interchangeable throughout the study even for different patients.

The Clinical Coordinator may be a nurse or physician who will be responsible for coordinating and assisting all study site staff, including patient scheduling and completion and monitoring of all patients' case report forms. He/she will be responsible for coordinating IMP administration, and collect, process, and send all blood and other forms of biological samples and requests to the central laboratory. Additionally, he/she will be responsible for administering the patient-reported questionnaires, and coordinating the conduct of the baseline MRI (without contrast).

10.1 VISIT SCHEDULE

This is an outpatient study consisting of on-site visits. Additional, optional phone-call visits to monitor safety should be scheduled as often as deemed necessary by the Investigator. If a patient does not attend a scheduled visit, the study site personnel should contact the patient as soon as possible for rescheduling.

For patients already on PD medications at baseline, the H&Y scale must be done in the patient's "ON" state (see inclusion criterion I 05). For patients already on PD medications at the time of randomization, all efficacy assessments, and all scales and questionnaires must be done in the patient's "OFF" state. Therefore, PD medication cannot be taken for at least 12 hours prior to the visits including efficacy assessment. Study drug will be administered on-site on visit days.

Scales and questionnaires should be completed before dosing and before clinical assessments by the Study Investigator or other healthcare provider(s) are performed. At least two trained raters should be available at each site at all times.

When neurological and ophthalmological examinations are performed on the same day, the neurological examination should be performed before ophthalmological examination.

Before any screening assessment is performed, information regarding the aims and methods of the study, its constraints and risks will be explained to the patient and a written summary in the form of an informed consent will be provided. The patient must sign and date the informed consent before screening and before patient demography is recorded.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for these to be performed over more than one site visit if necessary, as long as the screening visit window prior to Day 1 (Visit 2) is respected. Rescreening is possible in this study, see [Section 7.2.3](#).

Further details of procedures/assessments listed in the following sections are captured in the study flow charts ([Section 1.3](#)).

10.1.1 Part 1: Escalated dose phase

Visit window: The randomization visit (Day 1) can be performed within 60 days from the screening visit. Using Day 1 as reference, a time frame of ± 3 days is acceptable for Visits 5 to 9 in Part 1. (If one visit date is skipped/missed/changed, the next visit should take place according to the original schedule).

10.1.1.1 Visit 1: Screening from Day -60 to -1

The following activities will be performed:

- An explanation of the purpose, procedures, potential risks, and benefits of this study will be provided to the patient.
- Informed consent signature and date will be collected.
- A patient diary will be issued with instructions to record any safety issues, and if the patient is eligible, missing doses will also be collected after randomization. The patient should bring their diary and any remaining capsules to each clinic visit. The site staff will review the patient diary during each clinic visit and record excursions from treatment into the eCRF. The patient diary will be retrieved when the patient finishes their participation in the study.
- One blood sample will be collected for investigation of GBA mutations required to include patients in the study (see [Section 9.6](#)). See [Section 17 \(Appendix A\)](#) for a list of GBA mutations. This gene will be sequenced even if historical results are available. Also, this sample will be investigated for a specific mutation in the LRRK2
- gene (G2019S) and patients carrying this mutation will be excluded. **Of note, if patient meets these two criteria, then the screening visit may proceed for all other items described below.**
- Patient demography will be recorded.
- BDI-II ([Appendix L](#)): At screening, patients with BDI-II of 20-28, inclusive, should be evaluated by a mental health specialist before the Investigator can determine if the patient would be able to fully participate in the trial. Patients with a BDI-II of >28 (severe depression) at screening will be excluded.
- Confirmation of eligibility by the Investigator.
- GBA complete gene sequencing and LRRK2 G2019S genotyping.
- Medical/surgical history and PD history.
- Review of prior medications.
- Confirmation of diagnosis of RBD (historically documented polysomnography or RBD screening questionnaire [[Appendix B](#)]).
- Physical examination.
- General neurological examination.

- Record of height and body weight measurements.
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C).
- 12-lead ECG.
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: Complete blood count (CBC), with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Serum β -HCG pregnancy test (for WOCBP).
- Full ophthalmology examination and photography.
- Review of current medical conditions, with AE/SAE reporting (if any).
- GCase activity: dried blood spot from whole blood sample for genetic testing.
- MDS-UPDRS ([Appendix F](#)).
- Hoehn and Yahr ([Appendix F](#)); for patients on a stable dose of PD medication, this should be done in the “ON” state.
- PD-CRS ([Appendix G](#)).
- MoCA ([Appendix I](#)).

If patients demonstrate eligibility based on all previous screening criteria:

- MRI (without contrast) scan will be performed (at least 7 days prior to the end of the screening period [Day -8]).
- LP for collection of CSF will be performed (within 14 days prior to randomization or at Day 1, pre-dose).
- DAT scan will be performed (within 7 days prior to randomization or at Day 1, pre-dose).

10.1.1.2 Visit 2: Randomization/baseline at Week 0/Day 1

Baseline assessments will be completed within the 60-day screening period. Eligibility will be reconfirmed prior to randomization/first dose administration on Day 1.

Patients will receive either placebo or GZ/SAR402671, orally, at the clinic.

In addition to recording any safety issue, the patient diary will also be used to record any missing doses after randomization. The patient should bring their diary and any remaining capsules to each clinic visit. The site staff will review the patient diary during each clinic visit and record

excursions from treatment into the eCRF. The patient diary will be retrieved when the patient finishes their participation in the study.

For Japan only ([Appendix T](#)), patients should be hospitalized for Visit 2 through 4, in principle; however, if hospitalization does not occur, the Investigator should follow up each day with a phone call to check if the patients experience any AEs (patients living alone must be hospitalized for Visit 2 through 4).

The baseline visit (Day 1) will include assessments and activities as listed in the study flow chart, [Section 1.3.1](#), which should be done in the following order:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
 - BDI-II ([Appendix L](#))
 - PDQ-39 ([Appendix O](#))
 - EQ-5D ([Appendix P](#))
 - HRPQ ([Appendix R](#))
- Reconfirmation of eligibility by the Investigator
- Review of concomitant medications
- Randomization via IVRS
- 12-lead ECG (at pre-dose and then at 2 hours, 4 hours, and 6 hours postdose)
- MDS-UPDRS, including H&Y ([Appendix F](#))
- PD-CRS ([Appendix G](#))
- Other questionnaires and scales:
 - MoCA ([Appendix I](#))
 - Oral SDMT ([Appendix J](#))
 - TMT-A; TMT-B ([Appendix K](#))
 - CGI ([Appendix M](#))
- Physical examination
- General neurological examination
- Archival blood sample collected prior to the start of IMP
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR

- Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urine pregnancy test (for WOCBP)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for biomarker analysis
- Blood sampling for PK analysis at multiple time points: at pre-dose and at 1, 2, 4, and 8 hours after IMP intake
- Pharmacogenetics DNA sample (optional; not applicable in Israel [[Appendix T](#)])
- DAT scan (only if not performed during the screening period, pre-dose)
- Lumbar puncture for collection of CSF (if not already done during the screening period) for biomarker and PK analyses
- Dispense IMP

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day.

10.1.1.3 Visit 3: Week 0/Day 2

Patients will not receive IMP on Day 2 (drug holiday), in order to better characterize the PK of the IMP, and will have a blood sample for PK analysis collected at 24 hours after first IMP intake.

The following assessments should be done as listed in the study flow chart, [Section 1.3.1](#), in the following order:

- Review of concomitant medications
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for PK analysis (24 hours post-Day 1 dose PK sample; [Section 1.4.1](#))

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.1.4 Visit 4: Week 0/Day 3

Before dosing, the following assessments will be performed as listed in the study flow chart, [Section 1.3.1](#):

- Review of concomitant medications
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for PK analysis (48 hours post-Day 1 dose PK sample or 1 hour before dosing; [Section 1.4.1](#))

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.1.5 Visit 5: Week 2 (±3 days)

The following assessments will be performed as listed in the study flow chart, [Section 1.3.1](#), which should be done in the following order:

- BDI-II ([Appendix L](#))
- Review of concomitant medications
- General neurological examination
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Blood sampling for biomarker analysis
- Blood sampling for PK analysis (1 hour before dosing)

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.1.6 Visit 6: Week 4/Day 1 (± 3 days)

The following assessments will be performed as listed in the study flow chart, [Section 1.3.1](#), which should be done in the following order:

- MDS-UPDRS, including H&Y ([Appendix F](#))
- BDI-II ([Appendix L](#))
- Review of concomitant medications
- Physical examination
- General neurological examination
- Visual acuity check, slit lamp examination and fundoscopy without pupil dilation
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature ($^{\circ}\text{C}$)
- 12-lead ECG
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for PK at multiple time points (pre-dose, 1, 2, 4, and 8 hours after IMP intake) and biomarker analyses
- Lumbar puncture for collection of CSF for PK and biomarker analyses
- Dispense IMP

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.1.7 Visit 7: Week 4/Day 2 (± 3 days)

The following assessments will be performed as listed in the study flow chart, [Section 1.3.1](#), which should be done in the following order:

- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature ($^{\circ}\text{C}$)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for PK (24 hours post-Week 4/Day 1 dose PK sample or 1 hour before dosing; [Section 1.4.1](#))

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.1.8 Visit 8: Week 8 (± 3 days)

The following assessments will be performed as listed in the study flow chart, [Section 1.3.1](#), which should be done in the following order:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
 - BDI-II ([Appendix L](#))
 - PGIC ([Appendix N](#))
 - PDQ-39 ([Appendix O](#))
 - EQ-5D ([Appendix P](#))
 - HRPQ ([Appendix R](#))
 - MDS-UPDRS, including H&Y ([Appendix F](#))
 - PD-CRS ([Appendix G](#))
- Other questionnaires and scales
 - MoCA ([Appendix I](#))
 - Oral SDMT ([Appendix J](#))
 - TMT-A; TMT-B ([Appendix K](#))
 - CGI ([Appendix M](#))
- Review of concomitant medications
- Physical examination
- General neurological examination

- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- Urine pregnancy test (for WOCBP)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for PK analyses (1 hour before dosing)
- Dispense IMP

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

*10.1.1.8.1 Visits 8.1 – 8.7 (Visits 8.8-8.11 for Japanese patients only): Weeks 12-36
(Weeks 40-52 for Japanese patients only) (±3 days)*

This visit must be repeated for all ongoing patients every 4 weeks until all patients from Cohort 3 complete Part 1. A maximum of 36 weeks of treatment will be allowed (applicable to patients in Cohort 1), ie, up to 7 additional visits (8.1-8.7) may be required. In Japan ([Appendix T](#)), a maximum of 52 weeks of treatment will be allowed (applicable to patients in Cohort 1), ie, up to 11 additional visits (8.1-8.11) may be required.

The following assessments will be performed as listed in the study flow chart, [Section 1.3.1](#), which should be done in the following order:

- MDS-UPDRS, including H&Y ([Appendix F](#))
- BDI-II ([Appendix L](#))
- Review of concomitant medications
- Physical examination
- General neurological examination
- Visual acuity check, slit lamp examination and fundoscopy without pupil dilation only at Weeks 12 and 28 (Week 36 for Japanese patients), if applicable
- Full ophthalmology examination and photography at Week 36 (or Week 52 for Japanese patients), if applicable
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- 12-lead ECG; Week 28, if applicable
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins

- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urine pregnancy test (for WOCBP)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Dispense IMP

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

10.1.1.9 Visit 9: Safety follow-up completion visit (± 3 days)

The Part 1 safety follow-up completion visit (Visit 9) should be done approximately 6 weeks after last IMP dose; this visit also applies to early withdrawal or permanent treatment discontinuation, if applicable.

The following assessments will be performed as listed in the study flow chart, [Section 1.3.1](#), which should be done in the following order:

- BDI-II ([Appendix L](#))
- Review of concomitant medications
- Physical examination
- General neurological examination
- Visual acuity check, slit lamp examination, and fundoscopy without pupil dilation
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature ($^{\circ}\text{C}$)
- 12-lead ECG
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urine pregnancy test (for WOCBP)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Retrieve patient diary

10.1.2 Part 2: Treatment phase

In Part 2, the GZ/SAR402671 dose will be the highest dose determined to be safe and well tolerated in Part 1. If patients from Part 1 continue to meet eligibility requirements, they may enroll in Part 2, but rerandomization will be required. All assessment at baseline will need to be repeated, except for the genetic screening, MRI, LP, and DAT scan, to confirm eligibility of patients from Part 1 to enroll in Part 2 (see study flowchart, [Section 1.3.2](#)).

Visit window: The randomization visit (Day 1) can be performed within 60 days from the screening visit. For Week 2 through Week 39 visits, a time frame of ± 3 days is acceptable using Day 1 as reference. For Week 52, a visit window of ± 14 days is acceptable using Day 1 as a reference. After Week 52 and throughout Period 3, a visit window of ± 7 days for all visits is acceptable using Day 1 as reference. For Week 216, a visit window of ± 14 days is acceptable using Day 1 as a reference. (If one visit date is skipped/missed/changed, the next visit should take place according to the original schedule).

Covid-19 outbreak

Due to Covid-19 outbreak, on-site visits may be delayed with visit window extended up to 3 months. In this case, IMP can be dispensed to the patient (via direct-to-patient) for a maximum duration of 6 months without on-site visit, but with a follow-up by phone (see [Section 10.1.2.12](#)). If Week 52 visit is delayed, the blinded treatment will be continued until Week 52 visit is performed and eligibility assessed for LTFU period.

Prior to dispensing the IMP, the Investigator will contact (phone, on-line) the patient to review AE/SAE/concomitant medication to ensure that no safety issues contraindicate the prolongation of the IMP. During the time of IMP prolongation, the Investigator will make every effort to contact the patient every 2 weeks to assess the safety. All examinations required for safety that can't be done at the site can be performed locally at a minimum laboratory assessment.

The on-site visit should be scheduled as close as possible to the theoretical visit date, particularly Week 52 which is mandatory.

In case a patient is infected by the Covid-19 virus and that his/her condition requires a treatment that is forbidden by the protocol, the study IMP should be temporarily discontinued. The IMP can be resumed once the patient's health status allows it and if the temporary discontinuation did not exceed 4 weeks. For patients who have not completed Week 52 visit, the patient should resume IMP for at least 4 weeks prior to Week 52 assessments.

For other patients infected by Covid-19 requiring concomitant medications not forbidden by the protocol, depending on the severity the investigator can decide to interrupt IMP after discussion with the Sponsor.

All the deviations due to the Covid-19 outbreak will be documented in the patient's file.

Note: In case the Week 52 visit is delayed and overlaps with the Week 65 visit (for Japanese patients only), perform the Week 52 assessments and record the Week 65 visit as a missed visit. If

Week 39 is delayed and overlaps with Week 52, perform the Week 52 assessments and record the Week 39 visit as a missed visit.

10.1.2.1 Visit 1: Screening from Day -60 to -1 (Period 1)

The following activities will be performed:

- An explanation of the purpose, procedures, potential risks and benefits of this study will be provided to the patient.
- Informed consent signature and date will be collected.
- In addition to recording any safety issue, the patient diary will also be used to record any missing doses after randomization. The patient should bring their diary and any remaining capsules to each clinic visit. The site staff will review the patient diary during each clinic visit and record excursions from treatment into the eCRF. The patient diary will be retrieved when the patient finishes their participation in the study.
- One blood sample will be collected for investigation of GBA mutations required to include patients in the study (see [Section 9.6](#)). See [Section 17 \(Appendix A\)](#) for a list of GBA mutations. This gene will be sequenced even if historical results are available. Also, this sample will be investigated for a specific mutation in the LRRK2 gene (G2019S) and patients carrying this mutation will be excluded. **Of note, if patient meets these two criteria, then the screening visit may proceed for all other items described below.**
- Patient demography will be recorded.
- BDI-II ([Appendix L](#)): At screening, patients with BDI-II of 20-28, inclusive, should be evaluated by a mental health specialist before the Investigator can determine if the patient would be able to fully participate in the trial. Patients with a BDI-II of >28 (severe depression) at screening will be excluded.
- Confirmation of eligibility by the Investigator
- GBA complete gene sequencing and LRRK2 G2019S genotyping
- Medical/surgical history and PD history
- Confirmation of diagnosis of RBD (historically documented polysomnography or RBD screening questionnaire)
- Review of prior medications
- Physical examination
- General neurological examination
- Record of height and body weight measurements
- Vital signs (orthostatic): systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- 12-lead ECG
- Laboratory assessments (to be performed by the central laboratory):

- Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
- Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Serum β -HCG pregnancy test (for WOCBP)
- Full ophthalmology examination and photography
- Review of current medical conditions, with AE/SAE reporting (if any)
- GCase activity: dried blood spot from whole blood sample for genetic testing
- MDS-UPDRS ([Appendix F](#))
- Hoehn and Yahr ([Appendix F](#)); for patients on a stable dose of PD medication, this should be done in the “ON” state.
- PD-CRS ([Appendix G](#))
- MoCA ([Appendix I](#))

If patients demonstrate eligibility based on all previous screening criteria:

- MRI (without contrast) scan will be performed (at least 7 days prior to the end of the screening period [Day -8]).
- LP for collection of CSF will be performed (within 14 days prior to randomization or at Day 1, pre-dose).
- DAT scan will be performed (within 7 days prior to randomization or at Day, 1 pre-dose).

10.1.2.2 Visit 2: Randomization/baseline at Week 0/Day 1

Baseline assessments will be completed within the 60-day screening period. Eligibility will be reconfirmed prior to randomization/first dose administration on Day 1.

Patients will receive either placebo or GZ/SAR402671, orally, at the clinic.

The baseline visit (Day 1) will include assessments and activities as listed in the study flow chart, [Section 1.3.2](#), which must be done in the following order:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
 - BDI-II ([Appendix L](#))
 - PDQ-39 ([Appendix O](#))
 - EQ-5D ([Appendix P](#))

- HRPQ ([Appendix R](#))
- CGI ([Appendix M](#))
- FES ([Appendix Q](#))
- Reconfirmation of eligibility by the Investigator
- Review of concomitant medications
- Randomization via IVRS
- MDS-UPDRS, including H&Y ([Appendix F](#))
- PD-CRS ([Appendix G](#))
- Other questionnaires and scales:
 - MoCA ([Appendix I](#))
 - Oral SDMT ([Appendix J](#))
 - TMT-A; TMT-B ([Appendix K](#))
- Physical examination
- General neurological examination
- Archival blood sample collected prior to the start of IMP
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urine pregnancy test (for WOCBP)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for biomarker analysis
- Blood sampling for PK analysis at multiple time points: at pre-dose and at 1, 2, 4, and 8 hours after IMP intake
- Pharmacogenetics DNA sample (optional; not applicable in Israel [[Appendix T](#)])
- DAT scan (only if not performed during the screening period, pre-dose)
- Lumbar puncture for collection of CSF (if not already done during the screening period) for biomarker and PK analyses

- Dispense IMP

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.2.3 Visit 3: Week 0/Day 2

The following assessments should be done before dosing:

- Review of concomitant medications
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for PK analysis (24 hours post-Day 1 dose PK sample or 1 hour before dosing)

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.2.4 Visit 4: Week 2 (± 3 days)

Before dosing, the following assessments will be performed as listed in the study flow chart, [Section 1.3.2](#), which should be done in the following order:

- BDI-II ([Appendix L](#))
- Review of concomitant medications
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature ($^{\circ}\text{C}$)
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for biomarker analysis
- Blood sampling for PK analysis (1 hour before dosing [pre-dose]) PK sample)

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.2.5 Visit 5: Week 4 (± 3 days)

Before dosing, the following assessments will be performed as listed in the study flow chart, [Section 1.3.2](#), which should be done in the following order:

- BDI-II ([Appendix L](#))
- Review of concomitant medications
- Visual acuity check, slit lamp examination, and fundoscopy without pupil dilation
- Vital signs (orthostatic): systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature ($^{\circ}\text{C}$)
- 12-lead ECG
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for biomarker analyses

- Dispense IMP

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.2.6 Visit 6: Week 13 (± 3 days)

Before dosing, the following assessments will be performed as listed in the study flow chart, [Section 1.3.2](#), which should be done in the following order:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
 - BDI-II ([Appendix L](#))
 - PGIC ([Appendix N](#))
 - PDQ-39 ([Appendix O](#))
 - EQ-5D ([Appendix P](#))
 - HRPQ ([Appendix R](#))
 - FES ([Appendix Q](#))
- MDS-UPDRS, including H&Y ([Appendix F](#))
- PD-CRS ([Appendix G](#))
- Other questionnaires and scales
 - MoCA ([Appendix I](#))
 - Oral SDMT ([Appendix J](#))
 - TMT-A; TMT-B ([Appendix K](#))
- Review of concomitant medications
- General neurological examination
- Visual acuity check, slit lamp examination, and fundoscopy without pupil dilation
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature ($^{\circ}\text{C}$)
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins

- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urine pregnancy test (for WOCBP)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for biomarker analysis
- Dispense IMP

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.2.7 Visit 7: Week 26 (±3 days)

Before dosing, the following assessments will be performed as listed in the study flow chart, [Section 1.3.2](#), which should be done in the following order:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
 - BDI-II ([Appendix L](#))
 - PGIC ([Appendix N](#))
 - PDQ-39 ([Appendix O](#))
 - EQ-5D ([Appendix P](#))
 - HRPQ ([Appendix R](#))
 - FES ([Appendix Q](#))
- MDS-UPDRS, including H&Y ([Appendix F](#))
- PD-CRS ([Appendix G](#))
- Other questionnaires and scales
 - MoCA ([Appendix I](#))
 - Oral SDMT ([Appendix J](#))
 - TMT-A; TMT-B ([Appendix K](#))
- Review concomitant medications
- Physical examination
- General neurological examination
- Visual acuity check, slit lamp examination, and funduscopy without pupil dilation

- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- 12-lead ECG
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urine pregnancy test (for WOCBP)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for biomarker and PK analyses as listed in study flow chart [Section 1.4.2](#)
- Dispense IMP

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.2.8 Visit 8: Week 39 (±3 days)

Before dosing, the following assessments will be performed as listed in the study flow chart, [Section 1.3.2](#), which should be done in the following order:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
 - BDI-II ([Appendix L](#))
 - PGIC ([Appendix N](#))
 - PDQ-39 ([Appendix O](#))
 - EQ-5D ([Appendix P](#))
 - HRPQ ([Appendix R](#))
 - FES ([Appendix Q](#))
- MDS-UPDRS, including H&Y ([Appendix F](#))
- PD-CRS ([Appendix G](#))
- Other questionnaires and scales
 - MoCA ([Appendix I](#))

- Oral SDMT ([Appendix J](#))
- TMT-A; TMT-B ([Appendix K](#))
- Review of concomitant medications
- General neurological examination
- Visual acuity check, slit lamp examination, and fundoscopy without pupil dilation
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urine pregnancy test (for WOCBP)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for biomarker analysis
- Dispense IMP

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.2.9 Visit 9: Week 52 (±14 days)

Visit 9 will be the last study visit of the blinded treatment period in Part 2.

Before dosing, the following assessments will be performed as listed in the study flow chart, [Section 1.3.2](#), which must be done in the following order:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
 - BDI-II ([Appendix L](#))
 - PGIC ([Appendix N](#))
 - CGI ([Appendix M](#))
 - PDQ-39 ([Appendix O](#))
 - EQ-5D ([Appendix P](#))

- HRPQ ([Appendix R](#))
- FES ([Appendix Q](#))
- MDS-UPDRS, including H&Y ([Appendix F](#))
- PD-CRS ([Appendix G](#))
- Other questionnaires and scales
 - MoCA ([Appendix I](#))
 - Oral SDMT ([Appendix J](#))
 - TMT-A; TMT-B ([Appendix K](#))
- Review concomitant medications
- Physical examination
- General neurological examination
- Record of body weight measurement
- Vital signs (orthostatic): systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- 12-lead ECG
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urine pregnancy test (for WOCBP)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Blood sampling for biomarker analyses, GCase activity and PK (as listed in study flow chart [Section 1.4.2](#))
- Pharmacogenetics DNA sample (optional; not applicable in Israel [[Appendix T](#)])
- Evaluate patients for eligibility (inclusion/exclusion criteria as listed in [Section 7.1](#), [Section 7.2](#), and [Section 10.1.2.10](#)) to transition to LTFU and receive GZ/SAR402671 treatment
- Full ophthalmology examination and photography (must be performed after the neurological examination)
- DAT scan

- Lumbar puncture for collection of CSF for PK (as listed in study flow chart [Section 1.4.2](#)) and biomarker analyses
- Dispense IMP (the results for all Week 52 assessments, required to check inclusion/exclusion criteria, must be received and reviewed before the Week 52 visit is registered in IVRS for Week 52 IMP dispensation)

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules, if patient is enrolled in the LTFU period.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

10.1.2.10 Long term follow-up period (Period 3)

Patients who complete the 52 weeks of double-blinded treatment and who continue to meet inclusion criteria [I 06](#), [I 07](#), [I 08](#), and [I 09](#) and none of the exclusion criteria (exclusion criteria [E 02](#), [E 03](#), [E 05](#), and [E 06](#) will not need to be rechecked) will be eligible to enroll to the LTFU period (Period 3) where they will continue to receive appropriate monitoring and will receive GZ/SAR402671 treatment after Visit 9. It is important to note that patients will not be informed of when the switch will occur, nor will the person(s) performing any of the evaluations.

Throughout Period 3, a visit window of ± 7 days for all visits is acceptable using Day 1 as reference.

During this period, a clinic visit will be scheduled at 6-month intervals (Weeks 78, 104, 130, 156, 182, and 208) and patients will receive GZ/SAR402671, orally, at the clinic. For Japanese patients only, additional clinic visit will be scheduled at Weeks 65, 91, 117, 143, 169, and 195 (Visits 9.1, 10.1, 11.1, 12.1, 13.1, and 14.1) in addition to the above 6-month interval visits.

Before dosing, the following assessments will be performed at each study visit (every 6 months), as listed in the study flow chart, [Section 1.3.3](#), which should be done in the following order:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
 - BDI-II ([Appendix L](#))
 - PDQ-39 ([Appendix O](#))
 - EQ-5D ([Appendix P](#))
 - HRPQ ([Appendix R](#))
 - FES ([Appendix Q](#))
- MDS-UPDRS, including H&Y ([Appendix F](#))
- PD-CRS ([Appendix G](#))
- Other questionnaires and scales
 - MoCA ([Appendix I](#))

- Oral SDMT ([Appendix J](#))
- TMT-A; TMT-B ([Appendix K](#))
- Review of concomitant medications (every 3 months [13 weeks] for Japanese patients only)
- General neurological examination
- Visual acuity check, slit lamp examination, and fundoscopy without pupil dilation at Visits 10, 12, and 14; at Visits 11, 13, and 15, patients will have a full ophthalmology examination and photography (must be performed after the neurological examination)
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C) (every 3 months [13 weeks] for Japanese patients only)
- Urine pregnancy test (for WOCBP)
- Review of current medical conditions, with AE/SAE reporting (if any) (every 3 months [13 weeks] for Japanese patients only)
- Dispense IMP

At Visit 11/Week 104, Visit 13/Week 156, and Visit 15/Week 208 (ie, yearly), the following additional assessments will be performed, as listed in the study flow chart, [Section 1.3.3](#):

- Blood sampling for biomarker analysis
- Physical examination and record of body weight measurement
- 12-lead ECG
- Laboratory assessments (to be performed by the central laboratory):
 - Hematology: CBC, with differential and platelet count; coagulation profile: PT, PTT, and INR
 - Biochemistry: Sodium, potassium, chloride, calcium, ALT, AST, GGT, ALP, total and conjugated bilirubin, urea, serum creatinine, glucose, albumin, total proteins
- Urinalysis (dipstick) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leucocytes. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- DAT scan
- Dispense IMP (except Visit 15/Week 208)
- Retrieve patient diary (at Visit 15/Week 208, only for patients who will transition to a long-term study with GZ/SAR402671).

Remind patient to return to the clinic for next visit.

Remind patient to not take the dose at home on the clinic visiting day, the IMP will be taken at clinic.

At Visit 15 (Week 208), patients will receive their last dose of GZ/SAR402671 at the clinic.

Visit 15 (Week 208) will be the last study visit for patients who will transition to a long-term study with GZ/SAR402671.

10.1.2.11 Eight-week follow-up visit (Period 4, end-of-study visit, Visit 16: Week 216 ±14 days)

This will be the last study visit. Patients who prematurely and permanently discontinue study medication should complete an end of treatment assessment visit (similar to Week 52/end of treatment visit for Period 2, Part 2) followed by a 8-week post-treatment follow-up visit (Visit 16). The following assessments will be performed as listed in the study flow chart, [Section 1.3.3](#), which should be done in the following order:

- BDI-II (Appendix L)
- MDS-UPDRS, including H&Y ([Appendix F](#))
- Review of concomitant medications
- Physical examination
- General neurological examination
- Visual acuity check, slit lamp examination, and fundoscopy without pupil dilation
- Vital signs: systolic and diastolic blood pressure (mm Hg), heart rate (bpm), respiratory rate (breaths/minute), and temperature (°C)
- Review of current medical conditions, with AE/SAE reporting (if any)
- Retrieve patient diary.

10.1.2.12 Contact for IMP dispensing during Covid-19 outbreak

In case of delayed visit, the IMP can be dispensed to a patient without on-site visit (see [Section 10.1.2](#)). Prior to dispensing the IMP, the Investigator will have to contact the patient to perform the following:

- Review of current medical conditions, with AE/SAE reporting (if any) including potential signs of depressed mood and changes in vision
- Review of concomitant medications
- IMP compliance
- Assess the patient's status for prolongation of IMP
- Dispense IMP

During the IMP prolongation, the Investigator will make every effort to contact the patient every 2 weeks to perform the following:

- Review of current medical conditions, with AE/SAE reporting (if any) including potential signs of depressed mood and changes in vision

- Review of concomitant medications
- IMP compliance
- Assess for patient's status for prolongation of IMP

10.2 DEFINITION OF SOURCE DATA

Source data are defined as original documents, data, and records. This includes, but is not limited to the following: hospital records, clinic and office charts, study-specific source document worksheets including MDS-UPDRS worksheets, phone logs, memoranda, evaluation checklists, laboratory requisitions, and reports, DAT scan reports and images, ECG tracings, and reports, local laboratory reports (if applicable), medication dispensing records, patient questionnaires, computer printouts, electronic data/information sources including IVRS/IWRS notifications, and any other documentation regarding the patient.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the eCRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to definitive treatment discontinuation in all cases.

10.3.1 Temporary treatment discontinuation with investigational medicinal products

Temporary treatment discontinuation because of suspected AEs may be considered by the Investigator. After close and appropriate clinical and/or laboratory monitoring, once the Investigator considers, according to his/her best medical judgment that the occurrence of the concerned event was unlikely due to the IMP, the safety of the patient is not affected, and if the selection criteria for the study are still met (refer to [Section 7.1](#) and [Section 7.2](#)), treatment with the IMP may be re-initiated. For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reason(s) for treatment discontinuation and this should be documented in the eCRF.

The patients who develop Grade 3 cataract or higher will be discontinued from study treatment.

The following may be justifiable reasons for the Investigator or Sponsor to discontinue a patient from treatment.

Patient specific:

- The patient experiences two similar SAE or one life-threatening SAE (assessed as related by the Investigator and/or the Sponsor)
- The patient meets criteria for Hy's law (confirmed ALT >5 x ULN range or confirmed ALT >3 x ULN and bilirubin >2 x ULN)
- The patient becomes pregnant
- The patient develops Grade 3 cataract or higher.

Trial specific:

- Any AEs, per Investigator judgment, that may jeopardize the patient's safety
- Any unblinding of the study treatment by the Investigator
- Any use of prohibited concomitant treatment (see [Section 8.8](#))
- At patient's request, ie, withdrawal of the consent for treatment

After the company representatives have been made aware of the SAE(s), relevant safety/laboratory data will be submitted to the DMC within 72 hours by Global Pharmacovigilance and Epidemiology, Clinical and other related departments as designated by the Company.

Any abnormal laboratory value or imaging reports will be immediately rechecked by the Sponsor and the central reader, respectively, for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

The DMC will also review data if applicable to assist in determining if AEs should preclude continued treatment with GZ/SAR402671.

If a patient decides to discontinue participation in the study, he/she should be contacted by the Study Investigator in order to obtain information about the reason(s) for discontinuation and collection of any potential AEs.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the Visit 9 (Part 1 Completion Visit) if in Part 1, Week 52/end of treatment visit if in Part 2 Period 2, or Week 216 if in Part 2 Period 3.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

All patients who prematurely and permanently discontinue study medication prior to Week 8 (Visit 8) in Part 1, or Week 52 (Visit 9) in Period 2 or Week 208 (Visit 15) in Period 3 of Part 2 will be asked to continue study visits for safety and efficacy assessments up to and including the last scheduled visit, if possible. If the patient refuses, at a minimum, they should be followed up for at least 8 weeks after their last scheduled received dose. Patients who prematurely and permanently discontinue study medication should complete an end of treatment assessment visit (similar to Visit 9 [Part 1 Completion Visit] if in Part 1, Week 52/end of treatment visit if in Part 2 Period 2, or Week 216 if in Part 2 Period 3) followed by a 8-week post-treatment follow-up visit (similar to Visit 9 in Part 1 or Visit 16 in Part 2 [for either Period 2 or 3]).

Patients who withdraw from the study due to pregnancy should be followed throughout the pregnancy up to approximately 6 to 8 weeks beyond the estimated delivery date so that the outcome of the pregnancy is determined. Additional follow-up information may be requested about the baby until at least one year after the birth of the baby, due to potential risk of abnormalities not present at birth. See [Section 17](#), [Appendix C](#) for guidance.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for nonpatient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study.

If possible, the patients are assessed using the procedure normally planned for Visit 9 in Part 1 or Week 52 in Part 2 Period 2, or Week 216 if in Part 2 Period 3. If the following examinations including lumbar puncture, DAT scan, and PK analyses on plasma and CSF have been performed recently, then the Investigator can discuss with Sponsor the need to repeat these examinations. Repeat examination(s) will be done on a patient by patient basis.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator should make the best effort to recontact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

All data collected up to the patient's withdrawal will be included in the analyses. The statistical analysis plan (SAP) will specify how early withdrawals from treatment will be accounted for in the analyses of efficacy endpoints.

Patients who have withdrawn from the study cannot be rerandomized (treated) in the study, nor, if applicable, can they enter the LTFU (Period 3). Their subject and treatment number must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

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

- Results in death, or
- Is life-threatening, or
Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
 - Allergic bronchospasm
 - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
 - Convulsions (seizures, epilepsy, epileptic fit, absence, etc)
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of an IMP on these diseases)

10.4.1.3 Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse event of special interest may be added, modified or removed during a study by protocol amendment.

The definition of AESI for this study are as follows:

- New or worsening lens opacities and cataracts.
- Pregnancy:
 - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial will be recorded as an AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see [Section 10.4.1.2](#)).
 - In the event of pregnancy in a female participant, IMP should be discontinued.
 - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see [Section 17 \[Appendix C\]](#)). Additional follow-up information may be requested about the baby

until at least one year after the birth of the baby, due to potential risk of abnormalities not present at birth.

- Increase in aminotransferase (ALT) (see the “Increase in ALT” flow diagram in [Section 17 \[Appendix S\]](#) of the protocol).
- Symptomatic overdose (serious or nonserious) with IMP:
 - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.

Of note, asymptomatic overdose has to be reported as a standard AE.

The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the eCRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per-protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs only if:
 - Symptomatic and/or
 - Requiring either corrective treatment or consultation, and/or
 - Leading to IMP discontinuation or modification of dosing, and/or
 - Fulfilling a seriousness criterion, and/or
 - Defined as an AESI

Instructions for AE reporting are summarized in [Table 5](#).

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In such case, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Company. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper Case Report Form process) is available and should be used when the eCRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in [Section 10.4.3](#), even if not fulfilling a seriousness criterion, using the corresponding pages of the eCRF (to be sent) or screens in the eCRF.

Instructions for AE reporting are summarized in [Table 5](#).

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in [Section 17 \[Appendix S\]](#).

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia
- Thrombocytopenia
- ALT increase
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

Table 5 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety complementary form	Other specific forms
AE (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
SAE (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
AESI	Expedited (within 24 hours)	New or worsening lens opacities and cataracts	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes ^a
		Symptomatic overdose with IMP	Yes	Yes	Yes
		ALT increase as defined in the protocol	Yes	Yes	Yes

Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AESI: adverse event of special interest; SAE: serious adverse events.

^a Pregnancy follow-up form (pharmacovigilance reporting form).

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, independent ethics committee (IECs)/institutional review boards (IRBs) as appropriate, and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

Adverse events that are expected will be specified in the reference safety information (IB).

The Sponsor will report all safety observations made during the conduct of the study in the clinical study report.

10.6 SAFETY INSTRUCTIONS

At any time during the study, patients who develop \geq Grade 3 cataracts will be discontinued from treatment.

In Part 1, the dose escalation study, if an SAE or \geq Grade 3 AE (NCI, CTCAE Version 4.03) that is considered by the Investigator to be related to GZ/SAR402671 and not to underlying disease or concomitant medication is observed, the case will be communicated to the DMC and a decision should be reached regarding escalation to the next dose with GZ/SAR402671. If 2 patients receiving GZ/SAR402671 within the same cohort develop the same SAE or AE (\geq Grade 3),

dosing within the cohort will be stopped. After stopping, the DMC will review the data and provide recommendations on how to proceed.

In Part 2, if an SAE or \geq Grade 3 AE (NCI, CTCAE v4.03) that is considered by the Investigator to be related to GZ/SAR402671 and not to underlying disease or concomitant medication, the dose may be temporarily discontinued.

Other theoretical potential risks considered for general development of any SRT therapy are included in the following subsections.

10.6.1 Liver function tests

Elevated liver function tests were observed during a 4-week toxicology study in rats.

In order to closely monitor the liver function, assessment of total protein, albumin, total bilirubin, AST, ALT, and ALP are measured as part of the clinical laboratory testing. Patients with a positive medical history of hepatitis B or hepatitis C antibody at the screening visit will be excluded from the study.

Guidance for the investigation of elevated liver function tests is provided in [Section 17 \(Appendix S\)](#).

10.6.2 Acute renal failure

See [Section 17 \(Appendix S\)](#). GZ/SAR402671 is not known to be associated with any renal effect; this algorithm is provided for informational purposes regarding the assessment of acute renal failure.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

An SAP will be written and finalized prior to database lock to give guidance to the statistical analysis. It will be in compliance with the International Council for Harmonisation (ICH) and the FDA's Guidance for Industry: Statistical Principles for Clinical Trials.

The Sponsor or its designee will perform the statistical analysis of the data from this study. The analysis will be performed using the SAS[®] statistical software system Version 9.1 or higher.

11.1 DETERMINATION OF SAMPLE SIZE

Part 1: Dose Escalation Phase

As Part 1 is an exploratory, dose-escalation study, the sample size is not based on the statistical power calculation. Each cohort (for non-Japanese patients only) will have a 4:1 randomization ratio, and the total sample size will be approximately 15 patients (including 12 on GZ/SAR402671 and 3 on placebo).

For Japanese patients only, each cohort will have a 3:1 randomization ratio, and the total sample size will be approximately 12 Japanese patients (including 9 on GZ/SAR402671 and 3 on placebo). This sample size in Japanese Part 1 is considered based upon empirical and feasibility considerations.

Therefore, the total sample size in Part 1 will be approximately 27 patients.

Patients who do not complete a minimum number of scheduled doses of study drug in Part 1 and withdraw for reasons other than safety may be replaced.

Part 2: Treatment Phase

Approximately 216 PD patients carrying a GBA mutation in total will be randomized in a 1:1 ratio to the GZ/SAR402671 or placebo groups. A sample size of 108 patients for the GZ/SAR402671 group and 108 for the placebo group provides at least 80% power to detect a 4.06 points improvement compared to the placebo mean change in MDS-UPDRS Parts II+III score over 52 weeks. This sample size calculation assumes a 2-sided alpha = 0.05, a standard deviation for the change from baseline to Week 52 in MDS-UPDRS Part II+III of 10.01 points (estimated from the Parkinson's Progression Markers Initiative [PPMI] database), and allows for an approximate 10% early terminations/unevaluable patients.

A previous study showed that a 3.25 points difference on MDS-UPDRS Part III represent the minimal clinically important difference (MCID) for detecting an improvement. It was estimated from the PPMI database that the standard deviation for change from baseline to Week 52 in MDS-UPDRS Part III was 8.01 points; therefore, the MCID of 3.25 points would represent an effect size of 0.406. Since no study evaluated the MCID for MDS-UPDRS Part II+III, the same effect size of 0.406 was assumed, resulting in an estimated MCID of 4.06 points, using the standard

deviation of 10.01 for change from baseline to Week 52 in MDS-UPDRS Part II+III also estimated from the PPMI database.

Of note, the approximate 27 (12 Japanese and 15 non-Japanese) early-stage PD patients carrying a GBA mutation from Part 1 may be re-randomized and participate in all of the assessments in Part 2 of this study; however, they will not contribute to the primary efficacy, safety, PK and pharmacodynamics analyses, and will be described separately.

Calculations were made using nQuery 7.0 Advisor software.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who signed the informed consent.

Randomized patients consist of all screened patients, with a double-blind treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not. Patients treated without being randomized or treated with a double-blind treatment kit before the randomization will not be considered as randomized and will not be included in any analysis population. The safety experience of patients treated and not randomized will be reported separately, and these patients will not be included in the safety population.

For any patient randomized more than once in Part 2 of the study, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent-to-treat population

The Part 2 intent-to-treat (ITT) population will be defined as all randomized patients in Part 2. Patients from Part 1 who are rerandomized in Part 2 will not be included in Part 2 ITT population. The Part 2 ITT population is the primary analysis population for all efficacy endpoints. Patients will be analyzed in the treatment group to which they were randomized.

In addition, exploratory efficacy endpoints in Part 1 of the study will be described separately for non-Japanese and Japanese patients:

- The Part 1 non-Japanese ITT population will be defined as all non-Japanese randomized patients in Part 1. Patients will be analyzed in the treatment group to which they were randomized.
- The Part 1 Japanese ITT population will be defined as all Japanese randomized patients in Part 1. Patients will be analyzed in the treatment group to which they were randomized.

11.3.1.2 Per-protocol population

The Part 2 PP population will be defined as a subset of the Part 2 ITT population that excludes patients with major protocol deviations that potentially impact the primary efficacy endpoint. The criteria for exclusion of patients from the Part 2 PP population will be determined and documented prior to database lock. The Part 2 PP population will be used for sensitivity analysis purposes.

11.3.2 Safety population

The safety populations considered for safety analyses will be the randomized population who did actually receive at least one dose or part of a dose of the double-blind IMP. Patients will be analyzed according to the treatment actually received (GZ/SAR402671 or placebo).

Safety populations will be defined separately for Part 1 and Part 2 of the study:

- The Part 1 non-Japanese safety population will be defined as all non-Japanese randomized patients in non-Japanese Part 1 who received at least 1 dose of study medication in Part 1 of the study. All safety analyses in Part 1 of the study will be performed on the Part 1 non-Japanese safety population.
- The Part 1 Japanese safety population will be defined as all Japanese randomized patients in Part 1 who received at least 1 dose of study medication in Part 1 of the study. All safety analyses in Japanese Part 1 of the study will be performed on the Part 1 Japanese safety population.
- The Part 2 safety population will be defined as all randomized patients in Part 2 who received at least 1 dose of study medication in Part 2 of the study. Patients from Part 1 who are re-randomized in Part 2 will not be included in Part 2 safety population, and will be described separately. All safety analyses in Part 2 of the study will be performed on the Part 2 safety population.

In addition:

- Nonrandomized but treated patients will not be part of the safety populations, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than one study treatment within the same part of the study, the treatment group allocation for as-treated analysis will be the one to which the patient was treated with the longest duration.

11.3.3 Pharmacokinetics/pharmacodynamics population

The PK and pharmacodynamics populations will be defined as all patients who received at least 1 dose of GZ/SAR402671 and who have at least one PK or pharmacodynamics assessment, respectively.

Pharmacokinetics and pharmacodynamics data will be described separately for Part 1 and Part 2 of the study, and separately for non-Japanese and Japanese patients:

- The Part 1 non-Japanese pharmacodynamics and PK populations will be defined as all non-Japanese patients in Part 1 who received at least 1 dose of GZ/SAR402671 and who have at least one pharmacodynamics or PK assessment, respectively.
- The Part 1 Japanese pharmacodynamics and PK populations will be defined as all Japanese patients in Part 1 who received at least 1 dose of GZ/SAR402671 and who have at least one pharmacodynamics or PK assessment, respectively.
- The Part 2 non-Japanese pharmacodynamics and PK populations will be defined as all patients in Part 2 who received at least 1 dose of GZ/SAR402671 and who have at least one pharmacodynamics or PK assessment, respectively. Patients from Part 1 who are rerandomized in Part 2 will not be included in Part 2 pharmacodynamics and PK populations, and will be described separately.
- The Part 2 Japanese pharmacodynamics and PK populations will be defined as all Japanese patients in Part 2 who received at least 1 dose of GZ/SAR402671 and who have at least one pharmacodynamics or PK assessment, respectively. Patients from Part 1 who are rerandomized in Part 2 will not be included in Part 2 Japanese pharmacodynamics and PK populations, and will be described separately.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed separately for Part 1 and Part 2 of the study, and summarized by actual treatment received within the Part 1 safety population and Part 2 safety population respectively.

Within each part of the study, duration of IMP exposure is defined as: last dose date - first dose date +1 day, regardless of unplanned intermittent discontinuations.

11.4.2 Analyses of efficacy endpoints

All analyses of efficacy endpoints will be done on Part 2 of the study and will not include patients from Part 1 who are rerandomized in Part 2. Efficacy data in patients from Part 1 will be described separately, with no formal statistical testing.

11.4.2.1 Analysis of primary efficacy endpoint

The primary efficacy endpoint is the change from baseline to Week 52 in MDS-UPDRS Part II+III score.

The primary analysis will be based on an ITT approach, including all data regardless of adherence to treatment and protocol. Change from baseline in MDS-UPDRS Part II+III score will be analyzed using a mixed effect model with repeated measures (MMRM). All postbaseline data

available within Week 13 to Week 52 analysis windows will be used and missing data will be accounted for by the MMRM model. The model will include the fixed categorical effects of treatment group (GZ/SAR402671 versus placebo), randomization strata, time point (Week 13, Week 26, Week 39, and Week 52), treatment-by-time point interaction as well as the continuous fixed covariates of baseline MDS-UPDRS Part II+III score. This model will provide baseline adjusted least squares means estimates at Week 52 for both treatment groups with their corresponding standard errors and 95% confidence intervals (CI). To compare the GZ/SAR402671 group to the placebo group, an appropriate contrast statement will be used to test the differences of these estimates, at the 2-sided 0.05 level.

The MMRM model relies on the “missing-at-random” (MAR) assumption. As the possibility for a not-missing-at-random (NMAR) missingness mechanism cannot be excluded, a sensitivity analysis to explore the impact of nonignorable missingness on the primary efficacy analysis will be conducted.

The sensitivity analysis will use a control-based pattern-mixture model (PMM) method. This PMM method will make the assumption that, in case of missing data after permanent treatment discontinuation, the MDS-UPDRS Part II+III scores for patients in the GZ/SAR402671 arm will follow the same trajectory as for patients in the placebo arm. As a consequence, missing data after permanent treatment discontinuation will be imputed using a model estimated solely from data observed in the placebo arm. Missing data during the treatment period will be imputed separately assuming MAR, using a model estimated from data observed during the treatment period within the same treatment arm. Missing values will be imputed 100 times to generate 100 complete data sets. Each completed dataset will be analyzed using an analysis of covariance (ANCOVA) of change from baseline to Week 52 in MDS-UPDRS Part II+III score, including the fixed categorical effects of treatment group (GZ/SAR402671 versus placebo), randomization strata, as well as the continuous fixed covariates of baseline value. The final results will be obtained by combining the least squares means and least squares mean differences from these 100 analyses, using Rubin’s formula.

The primary analysis will be repeated using a PP approach. Movement Disorder Society-Unified Parkinson’s Disease Rating Scale data collected after a major protocol deviation that potentially impacts the primary efficacy endpoint will be excluded from this analysis. The criteria for exclusion of data will be determined and documented prior to database lock. The PP analysis will be used for sensitivity analysis purposes.

11.4.2.2 Analyses of secondary efficacy endpoints

Secondary efficacy endpoints include:

- Change in PD-CRS (total score) from baseline to Week 52.
- Change in MDS-UPDRS Parts I+II+III from baseline to Week 52.
- Change in H&Y score from baseline to Week 52.

Secondary endpoints will be analyzed using the same MMRM model as for the primary efficacy endpoint.

11.4.2.3 Multiplicity considerations

In order to handle multiple secondary endpoints, the overall type-I error will be controlled by the use of a hierarchical approach. Statistical significance of the primary endpoint at the 2-sided 0.05 alpha level is required before drawing inferential conclusions about first secondary endpoint (refer to order of list in [Section 9.2.2](#)). Inferential conclusions about successive secondary endpoints require statistical significance of the prior one.

This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 2-sided 0.05 level.

No further adjustments will be made for exploratory endpoints for which p-values will be provided for descriptive purpose only.

11.4.3 Analyses of safety data

Safety data will be described separately for Part 1 and Part 2 of the study, and separately for Japanese and non-Japanese patients.

Safety and tolerability in the Japanese patients from Part 1 will be compared to the non-Japanese patients.

All safety analyses will be performed on the Part 1 safety population and Part 2 safety population respectively. The summary of safety results will be presented by treatment group actually received.

The baseline value is defined generally as the last available value before randomization, within each part of the study.

For all safety data, the observation period will be divided into 3 segments within each part of the study:

- The **pretreatment period** is defined as the time between the date of the informed consent and the first administration of double-blind IMP.
- The **on-treatment period** is defined as the period from the time of first IMP administration up to 6 weeks after the last administration of the IMP.
- The **post-treatment period** starts on the day after the end of the on-treatment period.

The following definitions will be applied to laboratory parameters, vital signs, and ECGs.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECGs.
- The PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.4.3.1 Adverse events

Adverse event incidence tables will be presented by system organ class (sorted by internationally agreed order), high-level group term, high-level term, and preferred term sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment period. The denominator for computation of percentages is the safety population within each treatment group.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities. The AEs will be classified into predefined standard categories according to chronological criteria:

- Pretreatment AEs: AEs that occurred or worsened during the pretreatment period;
- Treatment-emergent AEs: AEs that occurred or worsened during the on-treatment period;
- Post-treatment AEs: AEs that occurred or worsened during the post-treatment period.

11.4.3.2 Laboratory data and vital signs

The summary statistics (including mean, standard deviation, median, Q1, Q3, minimum, and maximum) of all laboratory variables and all vital sign parameters (raw data and changes from baseline) will be calculated for each visit, last and worst value assessed during the treatment period, and presented by treatment group. For selected parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) in each treatment group.

The incidence of PCSAs at any time during the TEAE period (on-treatment PCSAs) will be summarized by treatment group whatever the baseline level and/or according to the following baseline categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

For laboratory parameters for which PCSA criterion is not defined, similar table(s) using the normal range could be provided.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

Pharmacokinetic and pharmacodynamic data will be described separately for Part 1 and Part 2 of the study, and separately for Japanese and non-Japanese patients.

Pharmacokinetics and pharmacodynamics in the Japanese patients from Part 1 will be compared to the non-Japanese patients.

Pharmacodynamic parameters will be summarized and compared between GZ/SAR402671 and placebo administration using descriptive statistics at each time point, including assessment of observed values, and percent change from baseline. p-Values for statistical comparisons will be provided for descriptive purpose. Plasma PK parameters will be summarized using descriptive

statistics and also analyzed using noncompartmental methods. CSF exposure of GZ/SAR402671 will be summarized using descriptive statistics at each time point.

Pharmacokinetic parameters may be estimated for metabolites using noncompartmental methods and reported for individual patients and summarized using descriptive statistics.

With respect to biomarkers, levels of plasma, serum or CSF biomarkers, as well as changes from baseline, will be summarized descriptively by time point.

11.5 INTERIM ANALYSIS

11.5.1 Interim efficacy analysis

No interim analysis is planned for this study.

11.5.2 Two-step final analysis

The final analysis will be conducted in two steps:

- First step: analysis of the 52-week treatment period of Part 2 of the study:
 - The analysis of the 52-week treatment period of Part 2 of the study will be conducted when all patients from Part 2 have been randomized and have all their data up to Week 52 collected and validated, and will consist in the final analysis of the primary, secondary, and exploratory endpoints up to Week 52. The safety analysis will be performed on all safety data collected and validated at the time of the first analysis. This analysis will be conducted after a partial database lock and treatment unblinding.
- Second step: analysis up to Week 208 of Part 2 of the study:

The second analysis will be conducted at the end of the study and will consist of the final analysis up to Week 208. Specific analyses of efficacy and safety data up to Week 208 will be described in the SAP. This analysis will be conducted after the final database lock.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Sub-Investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for Good Clinical Practice (GCP), all applicable laws, rules, and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the IRB/IEC. All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

Prior to collection of blood for pharmacogenetics, the optional pharmacogenetics informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the patient.

All informed consent forms used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, IB with any addenda or labeling documents [summary of product characteristics, package insert], Investigator's curriculum vitae, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the IB or labeling information will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the IRB/IEC at least annually and a summary of the study's outcome at the end of the study.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the eCRF, Discrepancy Resolution Form or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-Investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-Investigators shall be appointed and listed in a timely manner. The Sub-Investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial with regards to ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the eCRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF ELECTRONIC CASE REPORT FORMS (eCRFs) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety in a cohesive manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

The computerized handling of the data by the Sponsor may generate additional requests (Discrepancy Resolution Form) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the eCRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification, and training of each Investigator and Sub-Investigator will be signed, dated, and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the eCRFs, the IB, and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-Investigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Sub-Investigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Sub-Investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations including GDPR (Global Data Protection Regulation)
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations

Patient race or ethnicity (eg, "American Indian or Alaska Native, Asian, Black/Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported or Unknown") will be collected if permitted by local regulations as these are required by several regulatory authorities (eg, on afro American population for FDA, or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan).

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any

obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the study or the participation of an individual site at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio
- Patient enrollment is unsatisfactory
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon
- Noncompliance of the Investigator or Sub-Investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP
- The total number of patients are included earlier than expected

- If the study no longer meets the development needs of the compound or business needs of the company

In any case, the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon 30 days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. In addition to the SAC, PIs at the 3 first sites enrolling the most patients will also be included as authors for the primary publication. However, if no multicenter publication is submitted, underway, or planned within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the study. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be recollected if necessary.

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17 APPENDICES

Appendix A List of common GBA mutations

Note: If the patient has a GBA mutation that is not on the list, a consult will always be required to determine the eligibility of the patient and severity of the novel variant.

Category	Allele Name	cDNA nucleotide substitution	Amino Acid substitution
Severe GBA Mutations	Frameshifts		
	122CC	122insC	Arg41ProfsX6
	148-149insGTAT	148-149insGTAT	Tyr50CysfsX15
	203Cdel	203delC	Pro68ArgfsX23
	329-333del CAGAA	329-333del CAGAA	Not determined
	330delA	330delA	Glu111AsnfsX7
	413delC	413delC	Pro138LeufsX62
	493insA	493insA	Not determined
	500insT	500insT	Ser168LeufsX12
	532delC	532delC	Not determined
	534delT	534delT	Asp179MetfsX21
	595-596delCT	595_596delCT	Leu199AspfsX62
	72delC	72delC	Leu25SerfsX66
	V214Stop	741delC	Trp248GlyfsX6
	84GG	84dupG	Leu29AlafsX18
	898delG	898delG	Ala300ProfsX4
	914Cdel	914delC	Pro305LeufsX31
	953delT	953delT	Leu318ProfsX18
	Tyr343Stop	1029delT	Tyr343X
	1093-1094insG	1093dupG	Glu365GlyfsX71
	1098insA	1098dupA	His367ThrfsX69
	1122-1123insTG	1121_1122dupTG	Leu375CysfsX20
	1147delG	1147delG	Not determined
119delC	119delC	Not determined	
1214delGC	1214_1215delGC	Ser405AsnfsX30	
1263-1317del	1263-1317del	Not determined	

Category	Allele Name	cDNA nucleotide substitution	Amino Acid substitution
	1284delA	1284delA	GlyAspfsX15
	1326insT	1326dupT	Val443CysfsX26
	1447-1466del20,insTG	1447_1466delinsTG	Leu483_Met489delinsTrp
	Substitutions		
	A190T	685G>A	Ala229Thr
	A190E	686C>A	Ala229Glu
	A341T	1138G>A	Ala380Thr
	A456P	1483G > C	Ala495Pro
	C16S	164G > C	Cys55Ser
	C342Y	1142G>A	Cys381Tyr
	D380A	1256A>C	Asp419Ala
	D399N	1312G>A	Asp438Asn
	D409H	1342G > C	Asp448His
	D409V	1343A>T	Asp448Val
	E41K	238G>A	Glu80Lys
	E233Stop	814G>T	Glu272X
	E388Stop	1279G>T	Glu427X
	F213I	754T > A	Phe252Ile
	F251L	870C>A	Phe290Leu
	G195E	701G>A	Gly234Glu
	G195W	700G>T	Gly234Trp
	G202R	721G > A	Gly241Arg
	G325R	1090G > A	Gly364Arg
	G355D	1181G>A	Gly394Asp
	G389E	1283G>A	Gly428Glu
	G390R	1285G>A	Gly429Arg
	H255Q	882T>G	His294Gln
	H311R	1049A>G	His350Arg
	I119T	473T > C	Ile158Thr
	I402F	1321A>T	Ile441Phe
	K74Stop	337A>T	Lys113X
	K157Q	586A>C	Lys196Gln
	K157N	588G>T	Lys196Asn
	K198E	709A>G	Lys237Glu

Category	Allele Name	cDNA nucleotide substitution	Amino Acid substitution
	K425E	1390A>G	Lys464Glu
	L197F	706C>T	Leu236Phe
	L240P	836T>C	Leu279Pro
	L385P	1271T>C	Leu424Pro
	L444P	1448T>C	Leu483Pro
	L444R	1448T>G	Leu483Arg
	N392I	1292A>T	Asn431Ile
	N462K	1503C>G	Asn501Lys
	P178S	649C > T	Pro217Ser
	P182L	662C > T	Pro221Leu
	P266L	914C>T	Pro305Leu
	P415R	1361C>G	Pro454Arg
	Q73Stop	334C>T	Gln112X
	Q169Stop	622C>T	Gln208X
	Q350Stop	1165C>T	Gln389X
	Q414Stop	1357C>T	Gln453X
	Q414R	1358A>G	Gln453Arg
	R47Stop	256C>T	Arg86X
	R120W	475C>T	Arg159Trp
	R120Q	476G > A	Arg159Gln
	R131C	508C > T	Arg170Cys
	R131L	509G > T	Arg170Leu
	R163Stop	604C>T	Arg202X
	R257Q	887G > A	Arg296Gln
	R257Stop	886C>T	Arg296X
	R285H	971G > A	Arg324His
	R353G	1174C>G	Arg392Gly
	R359Stop	1192C>T	Arg398X
	R463C	1504C > T	Arg502Cys
	R463Q	1505G>A	Arg502Gln
	S107L	437C > T	Ser146Leu
	S173Stop	635C>G	Ser212X
	S237P	826T>C	Ser276Pro
	S364R	1207A>C	Ser403Arg

Category	Allele Name	cDNA nucleotide substitution	Amino Acid substitution
	T231R	809C>G	Thr270Arg
	T491I	1589C > T	Thr530Ile
	V394L	1297G > T	Val433Leu
	V398L	1309G>C	Val437Leu
	V398F	1309G>T	Val437Phe
	W179Stop	653G>A	Trp218X
	W(-4)Stop	108G>A	Trp36X
	W378Stop	1250G>A	Trp417X
	Y135Stop	522T>A	Tyr174X
	Y304C	1028A>G	Tyr343Cys
	Y304Stop	1029T>G	Tyr343X
	841-842insTGA	839_841dupTGA	Leu280_Ser281insMet
	Splice variants		
	IVS10+2t>a	1505+2t>a	Not determined
	IVS10(+2)	1505+2t>g	Not determined
	IVS2+1g>a	115+1g>a	Not determined
	IVS2+1g>t	115+1g>t	Not determined
	(-203)a>g + IVS4-2a>g	(-203a>g; 455-2a>g)	Not determined
	IVS5+1g>t	588+1g>t	Not determined
Other GBA Mutations	222-224delTAC	222_224del TAC	Thr75del
	A90T	385G>A	Ala129Thr
	A232G	812C>G	Ala271Gly
	C342G	1141T>G	Cys381Gly
	C342R	1141T>C	Cys381Arg
	D127V	497A>T	Asp166Val
	D140H	535G > C	Asp179His
	D409G	1343A>G	Asp448Gly
	F37V	226T>G	Phe76Val
	F216Y	764T>A	Phe255Tyr
	F397S	1307T>C	Phe436Ser
	G46E	254G > A	Gly85Glu
	G189V	683G > T	Gly228Val
	G193W	694G>T	Gly232Trp

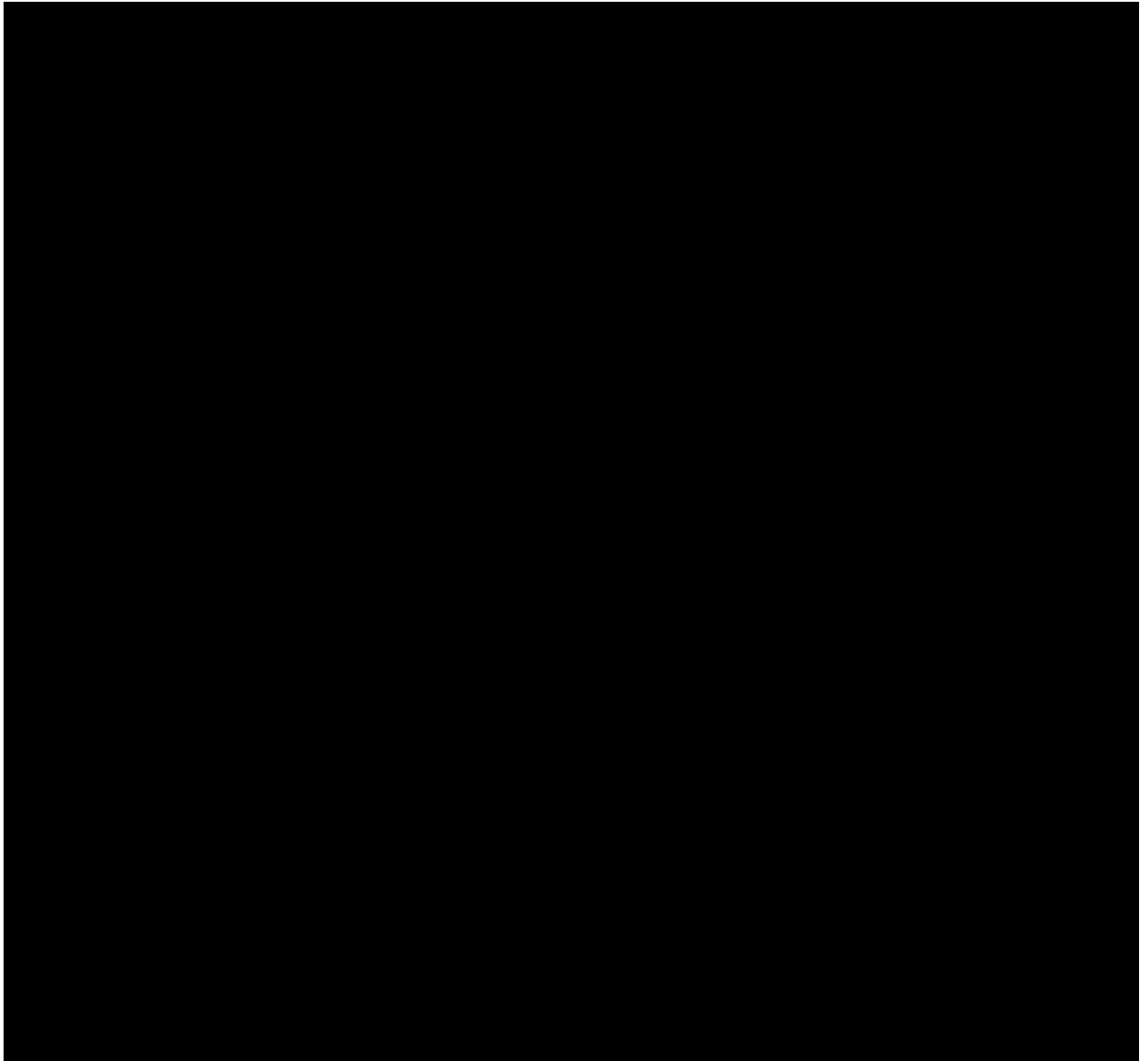
Category	Allele Name	cDNA nucleotide substitution	Amino Acid substitution
	G377S	1246G > A	Gly416Ser
	G377C	1246G>T	Gly416Cys
	I402T	1322T>C	Ile441Thr
	K79N	354G>C	Lys118Asn
	K413Q	1354A>C	Lys452Gln
	L66P	314T>C	Leu105Pro
	L371V	1228C>G	Leu410Val
	M123V	484A > G	Met162Val
	N117D	466A > G	Asn156Asp
	N188R	680_681 delinsGG	Asn227Arg
	N188S	680A > G	Asn227Ser
	N370S	1226A > G	Asn409Ser
	N396T	1304A>C	Asn435Thr
	P122S	481C>T	Pro161Ser
	P159L	593C > T	Pro198Leu
	P159T	592C > A	Pro198Thr
	P266R	914C > G	Pro305Arg
	P289L	983C>T	Pro328Leu
	P401L	1319C>T	Pro440Leu
	R48W	259C > T	Arg87Trp
	R170C	625C>T	Arg209Cys
	R170P	626G>C	Arg209Pro
	R359Q	1193G>A	Arg398Gln
	R395C	1300C>T	Arg434Cys
	R433G	1414A>G	Arg472Gly
	R496C	1603C>T	Arg535Cys
	R496H	1604G>A	Arg535His
	S271G	928A>G	Ser310Gly
	S271N	929G>A	Ser310Asn
	S364T	1208G>C	Ser403Thr
	S364N	1208G>A	Ser403Asn
	S366G	1213A>G	Ser405Gly
	T43I	245C>T	Thr82Ile
	T134I	518C>T	Thr173Ile

Category	Allele Name	cDNA nucleotide substitution	Amino Acid substitution
	T323I	1085C>T	Thr362Ile
	V15L	160G>T	Val54Leu
	V352L	1171G>C	Val391Leu
	V375L	1240G>T	Val414Leu
	V375G	1241T>G	Val414Gly
	W184R	667T>C	Trp223Arg
	W312C	1053G>T	Trp351Cys
	W378G	1249T>G	Trp417Gly
Sequence variants where history of RBD or co-occurrence of any mutation on the list are required	E326K	1093G>A	Glu365Lys
	T369M	1223C>T	Thr408Met

Note: If the patient has a GBA mutation that is not on this list, a consult will be required to determine the eligibility of the patient.

Abbreviation: cDNA: complementary deoxyribonucleic acid; GBA: β -glucocerebrosidase gene; RBD: rapid eye movement sleep behavior disorder.

Appendix B REM Sleep Behavior Disorder Screening Questionnaire



Appendix C Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:

NOTE: Documentation can come from the review of subject's medical records, medical examination, or medical history interview.

- Documented hysterectomy.
 - Documented bilateral salpingectomy.
 - Documented bilateral oophorectomy.
2. Postmenopausal
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
 - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Male subjects

- Male subjects with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:
 - Refrain from donating sperm
- and**
- At least 1 of the following conditions applies:
 - Are and agree to remain abstinent from penile-vaginal intercourse on a long-term and persistent basis, when this is their preferred and usual lifestyle.

or

- Agree to use a male condom plus an additional contraceptive method with a failure rate of <1% per year (see table for female subjects).
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol.

Highly Effective Contraceptive Methods That Are User Dependent
<ul style="list-style-type: none">• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation<ul style="list-style-type: none">- oral- intravaginal- transdermal
<ul style="list-style-type: none">• Progestogen-only hormone contraception associated with inhibition of ovulation<ul style="list-style-type: none">- oral- injectable
Highly Effective Methods That Are User Independent
<ul style="list-style-type: none">• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
<ul style="list-style-type: none">• Intrauterine device
<ul style="list-style-type: none">• Intrauterine hormone-releasing system
<ul style="list-style-type: none">• Bilateral tubal occlusion
<ul style="list-style-type: none">• Vasectomized partner
<ul style="list-style-type: none">• Sexual abstinence

Female subjects:

Highly Effective Contraceptive Methods That Are User Dependent
<ul style="list-style-type: none">• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation<ul style="list-style-type: none">- oral- intravaginal- transdermal

<ul style="list-style-type: none">• Progestogen-only hormone contraception associated with inhibition of ovulation<ul style="list-style-type: none">- oral- injectable
Highly Effective Methods That Are User Independent
<ul style="list-style-type: none">• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
<ul style="list-style-type: none">• Intrauterine device
<ul style="list-style-type: none">• Intrauterine hormone-releasing system
<ul style="list-style-type: none">• Bilateral tubal occlusion
<ul style="list-style-type: none">• Vasectomized partner
<ul style="list-style-type: none">• Sexual abstinence

Male subjects with partners of reproductive potential who become pregnant

- The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Additional follow-up information may be requested about the

baby until at least one year after the birth of the baby, due to potential risk of abnormalities not present at birth.

- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.

Appendix D Drugs that can prolong the QT interval

Antimicrobials	Antipsychotics (all have some risk)
Erythromycin	Risperidone
Clarithromycin	Fluphenazine
Moxifloxacin	Haloperidol
Fluconazole	Pimozide
Ketoconazole	Chlorpromazine
Antiarrhythmics	Quetiapine
Dronedarone	Clozapine
Sotalol	Antidepressants
Quinidine	Citalopram/escitalopram
Amiodarone	Amitriptyline
Flecainide	Clomipramine
	Dosulepin
Others	Doxepin
Methadone	Imipramine
Protein kinase inhibitors, eg, sunitinib	Lofepramine
Some antimalarials	Antiemetics
Some antiretrovirals	Domperidone
Telaprevir	Droperidol
Boceprevir	Ondansetron/Granisetron

NOTE: This list is not exhaustive but is designed to give examples of more commonly used drug classes.

Appendix E List of known CYP3A4 inducers/inhibitors

Please always check/confirm against the most up-to-date list on the FDA website:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling>

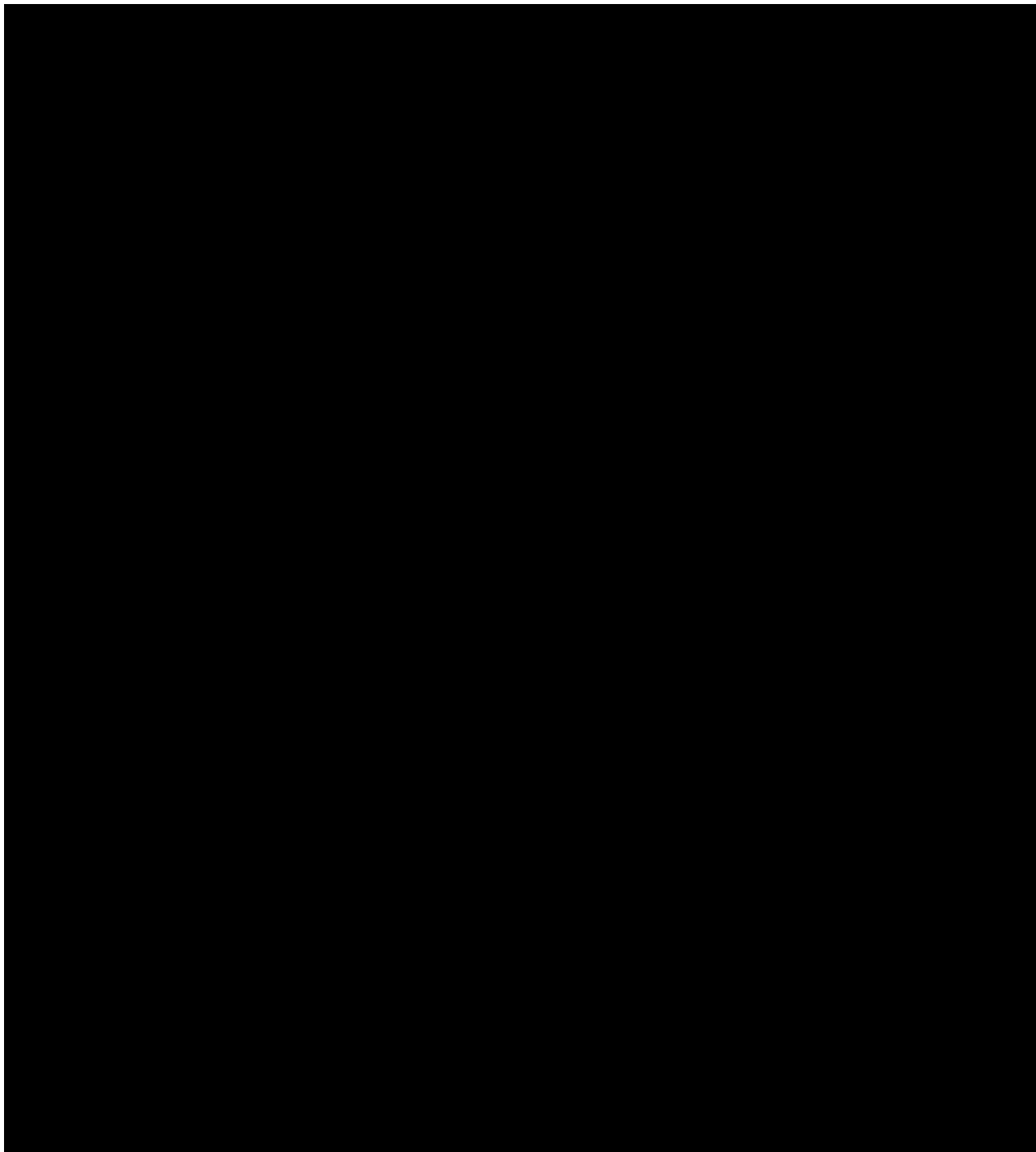
CYP3A4 Inducers

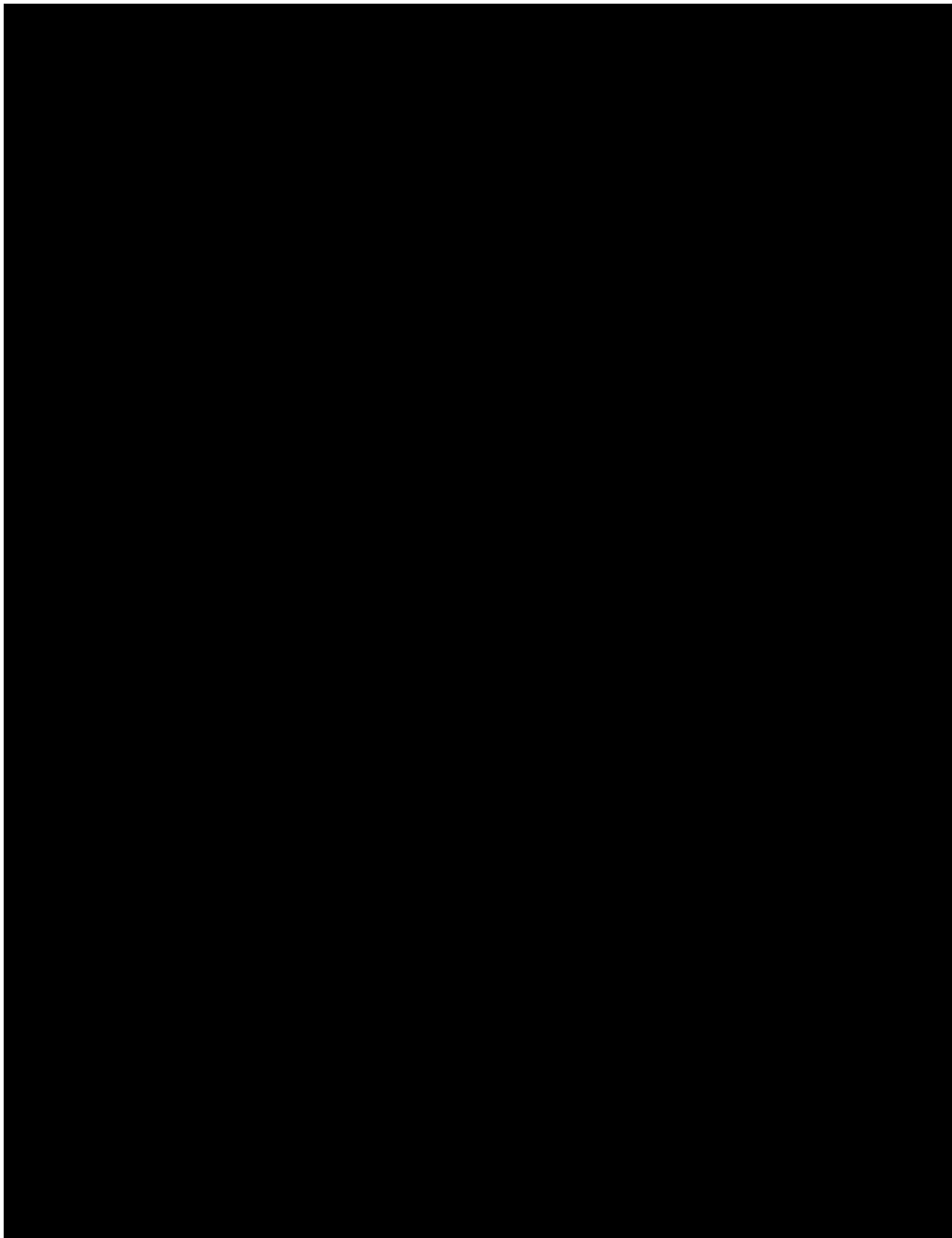
Aminoglutethimide	Nevirapine
Bexarotene	Oxcarbazepine
Bosentan	Phenobarbital
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Efavirenz	Rifabutin
Fosphenytoin	Rifampin
Griseofulvin	Rifapentine
Modafinil	St. John's wort
Nafcillin	

CYP3A4 Inhibitors

Amiodarone	Imatinib
Amprenavir	Indinavir
Atazanavir	Isoniazid
Chloramphenicol	Itraconazole
Clarithromycin	Ketoconazole
Conivaptan	Lapatinib
Cyclosporine	Miconazole
Darunavir	Nefazodone
Dasatinib	Nelfinavir
Delavirdine	Posaconazole
Diltiazem	Ritonavir
Erythromycin	Quinupristin
Fluconazole	Saquinavir
Fluoxetine	Tamoxifen
Fluvoxamine	Telithromycin
Fosamprenavir	Verapamil
Grapefruit juice	Voriconazole

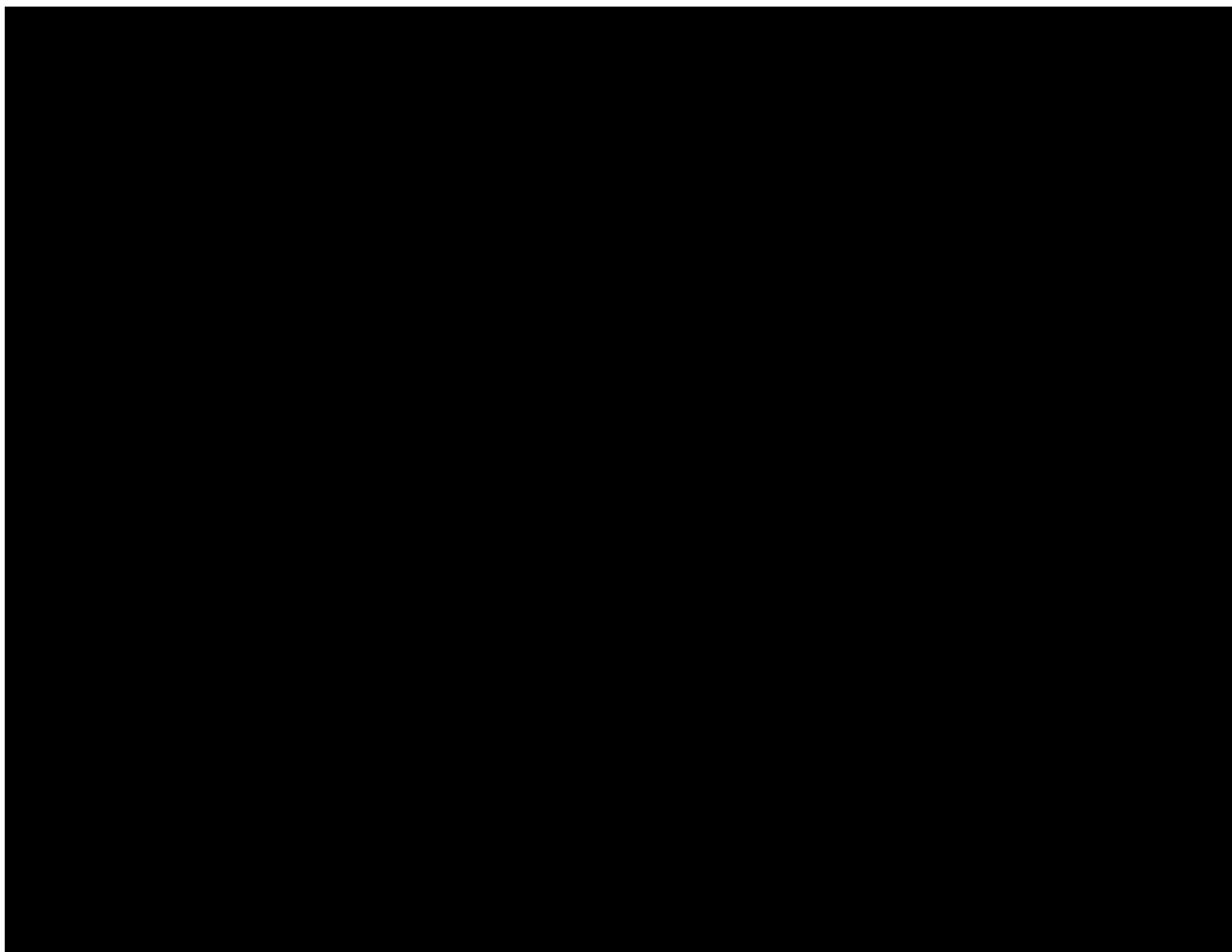
Appendix F Movement Disorder Society-Unified Parkinson's Disease Rating Scale, including Hoehn and Yahr

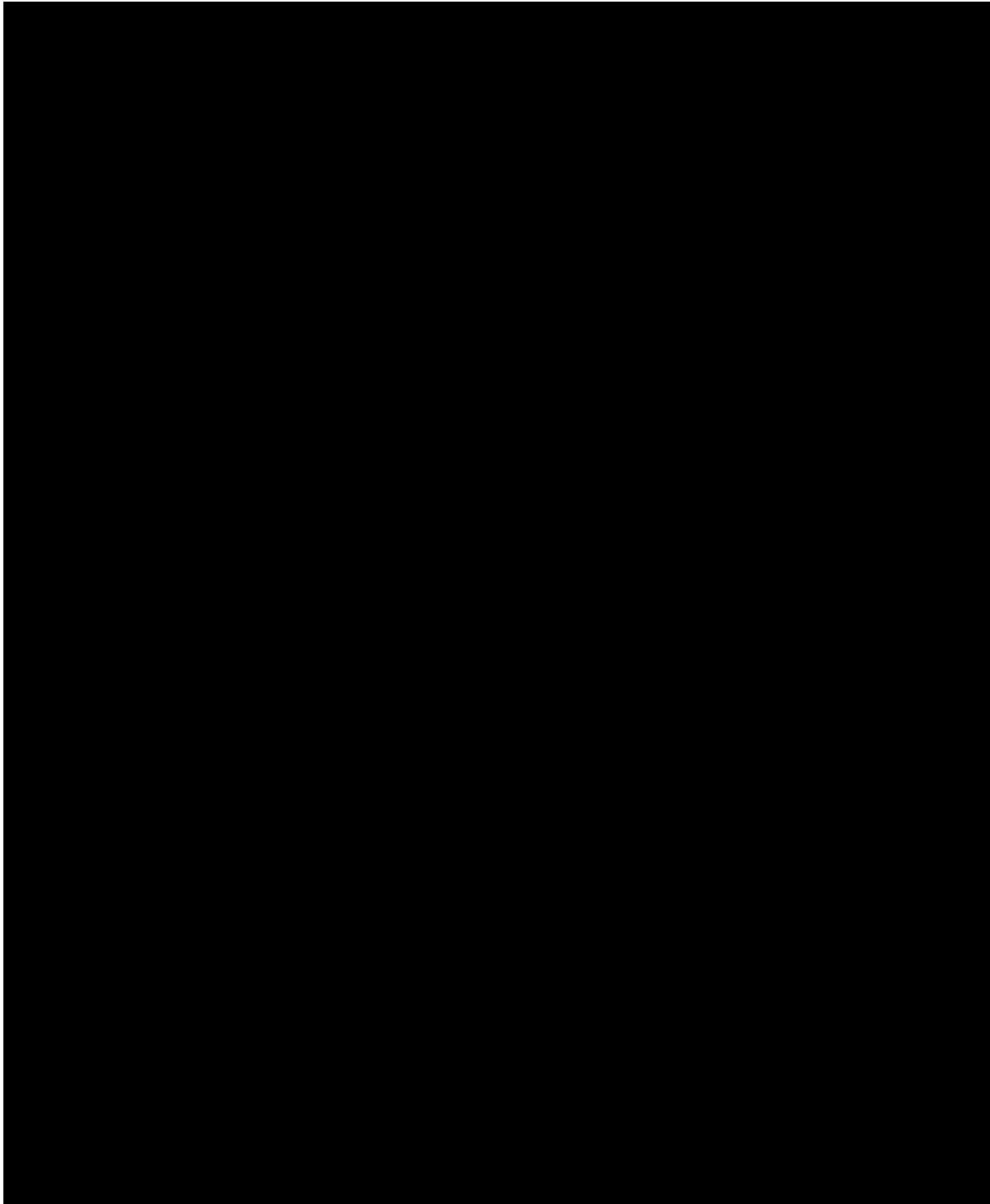




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Appendix G Parkinson's Disease-Cognitive Rating Scale





Appendix H Body fluid biomarkers

The following biomarkers in blood, dried blood spot and/or cerebrospinal fluid may be analyzed in samples collected during the study, at the discretion of the Sponsor:

Blood markers (plasma or serum)

- Glucosylceramide
- Glucosylsphingosine
- Neurofilament light chain

Other markers may also be assessed.

Dried blood spot

- Glucocerebrosidase activity

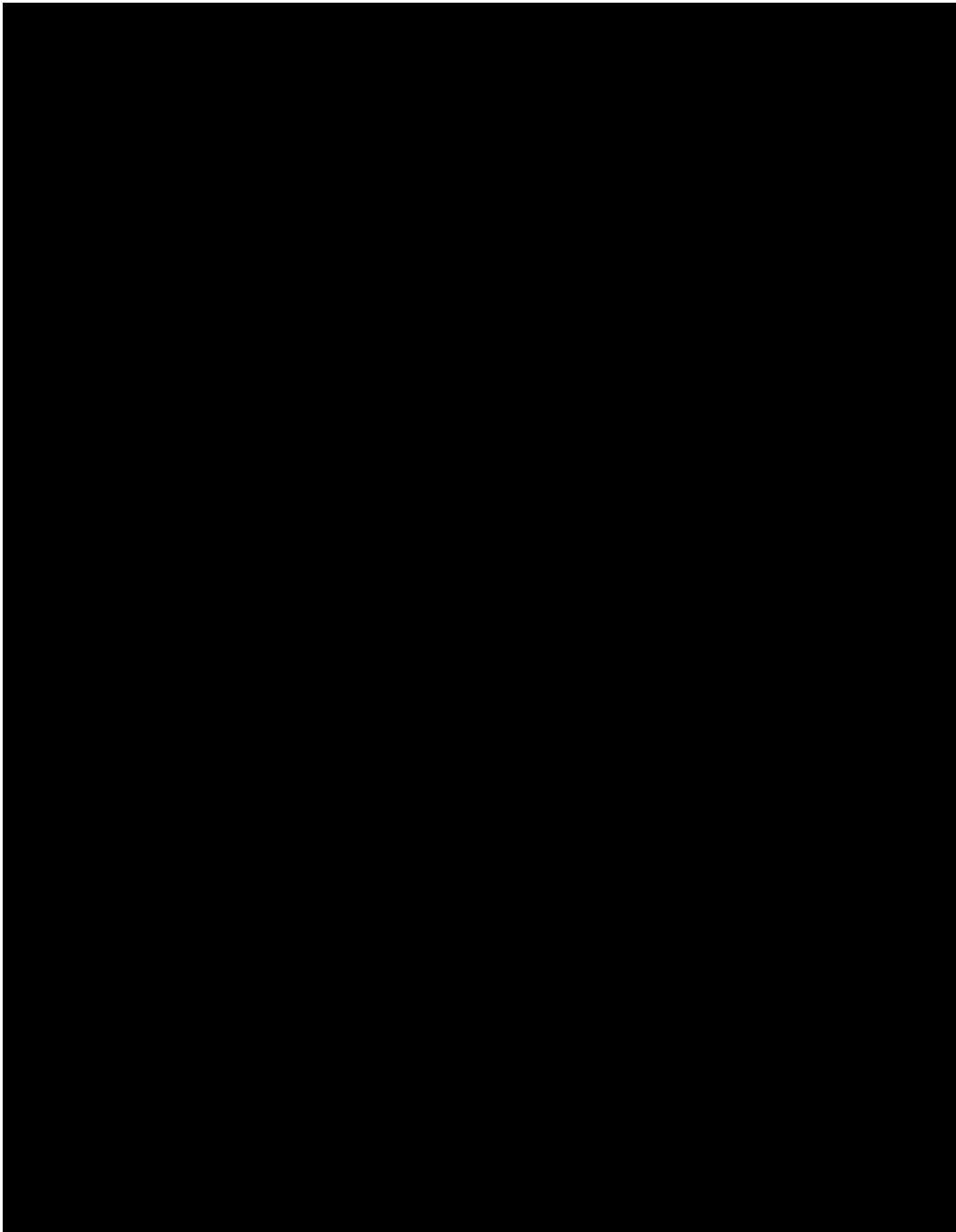
Other markers may also be assessed.

Cerebrospinal Fluid

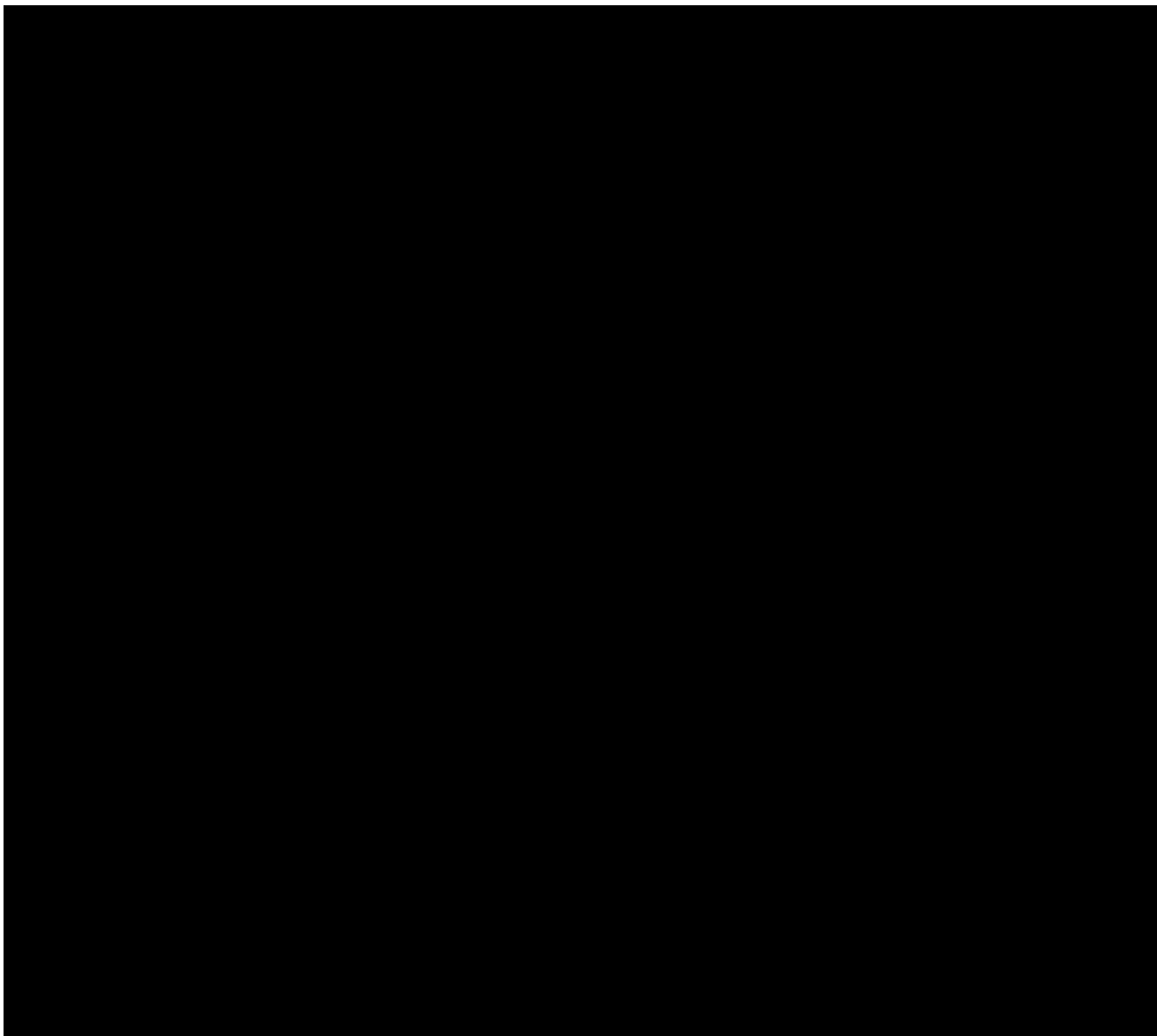
- Glucosylceramide
- Glucosylsphingosine
- Neurofilament light chain
- Glucocerebrosidase activity
- Total alpha-synuclein
- Tau and phospho-Tau₁₈₁
- Amyloid –beta₁₋₄₀, and Amyloid –beta₁₋₄₂

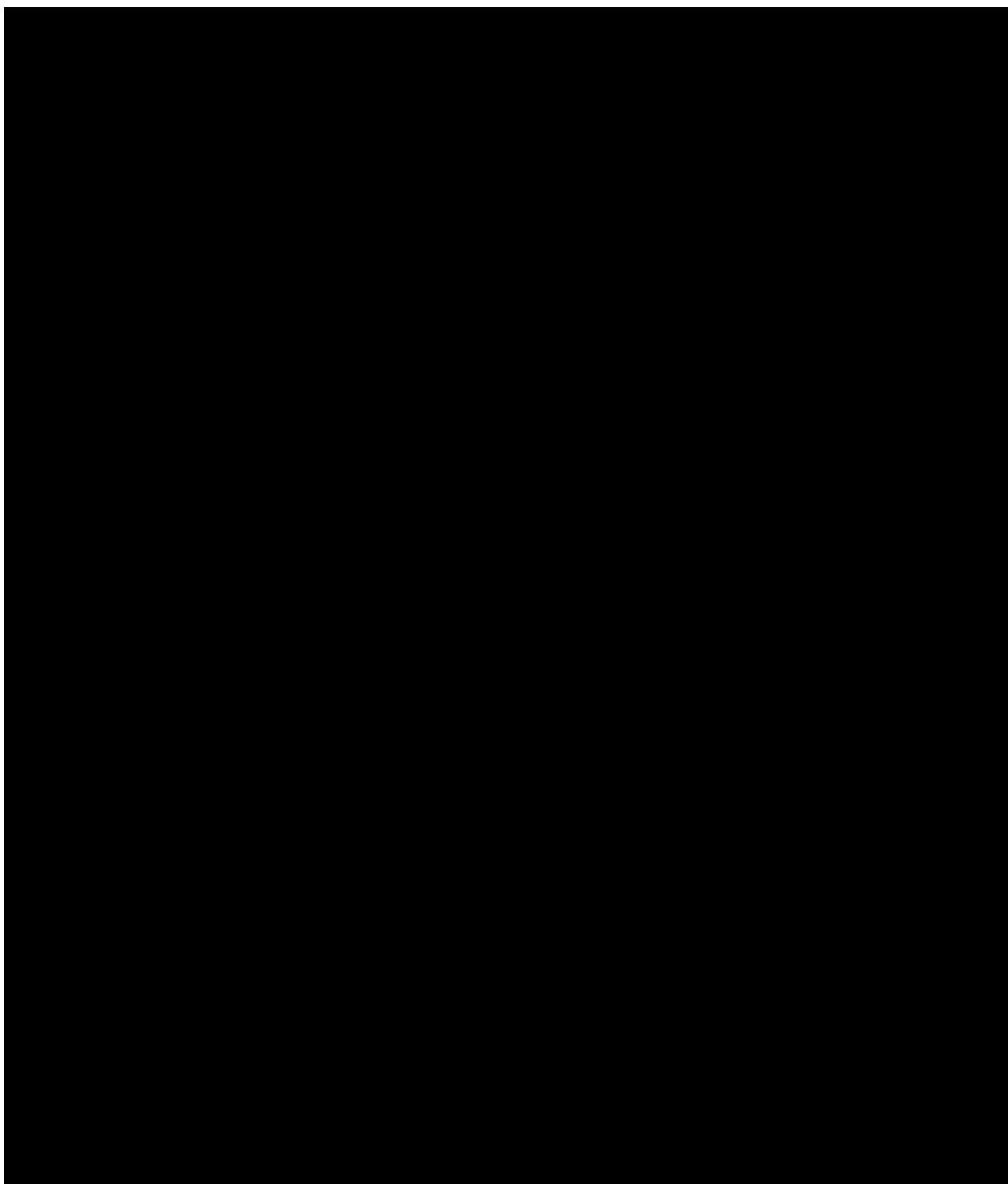
Other markers may also be assessed.

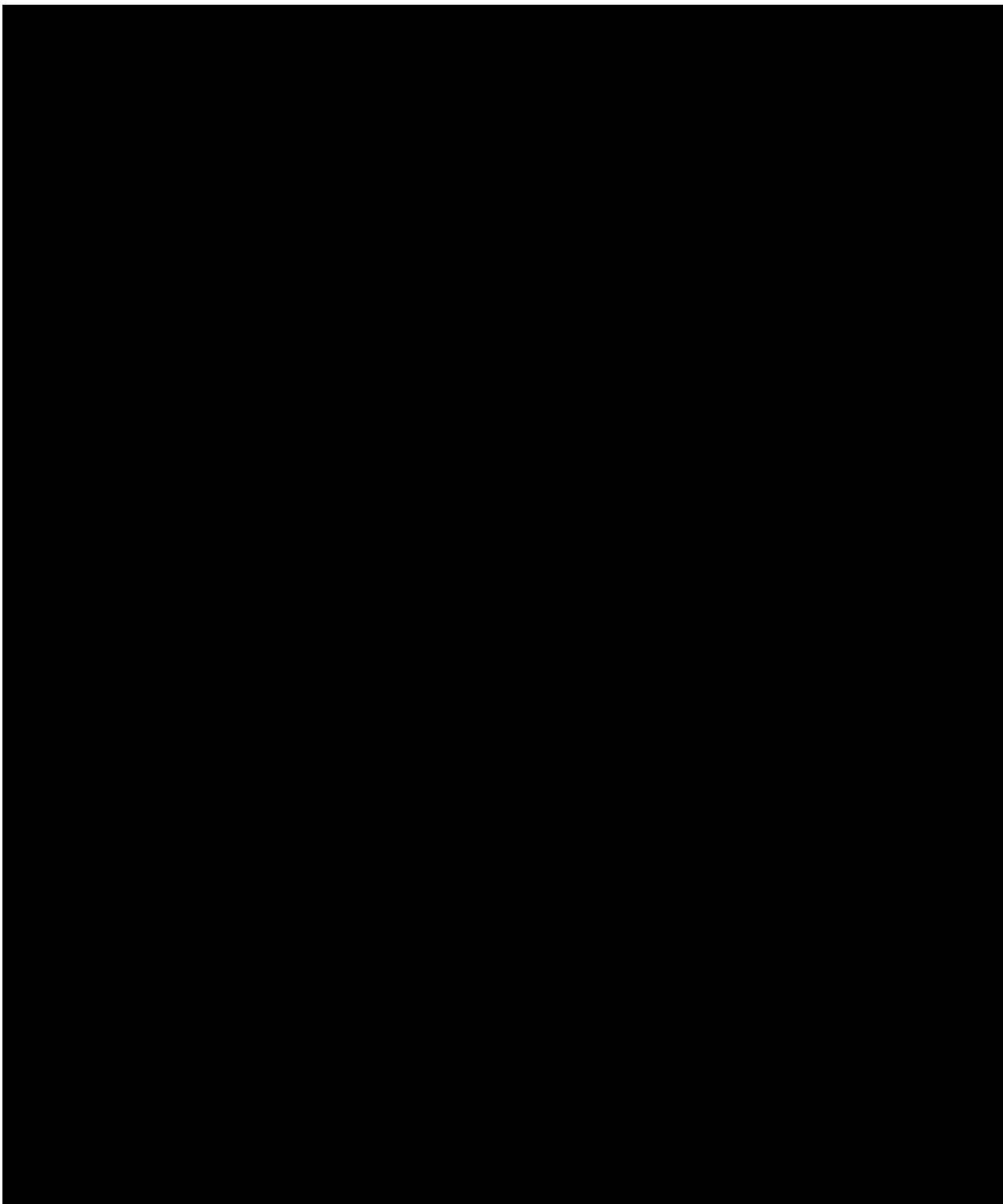
Appendix I Montreal Cognitive Assessment



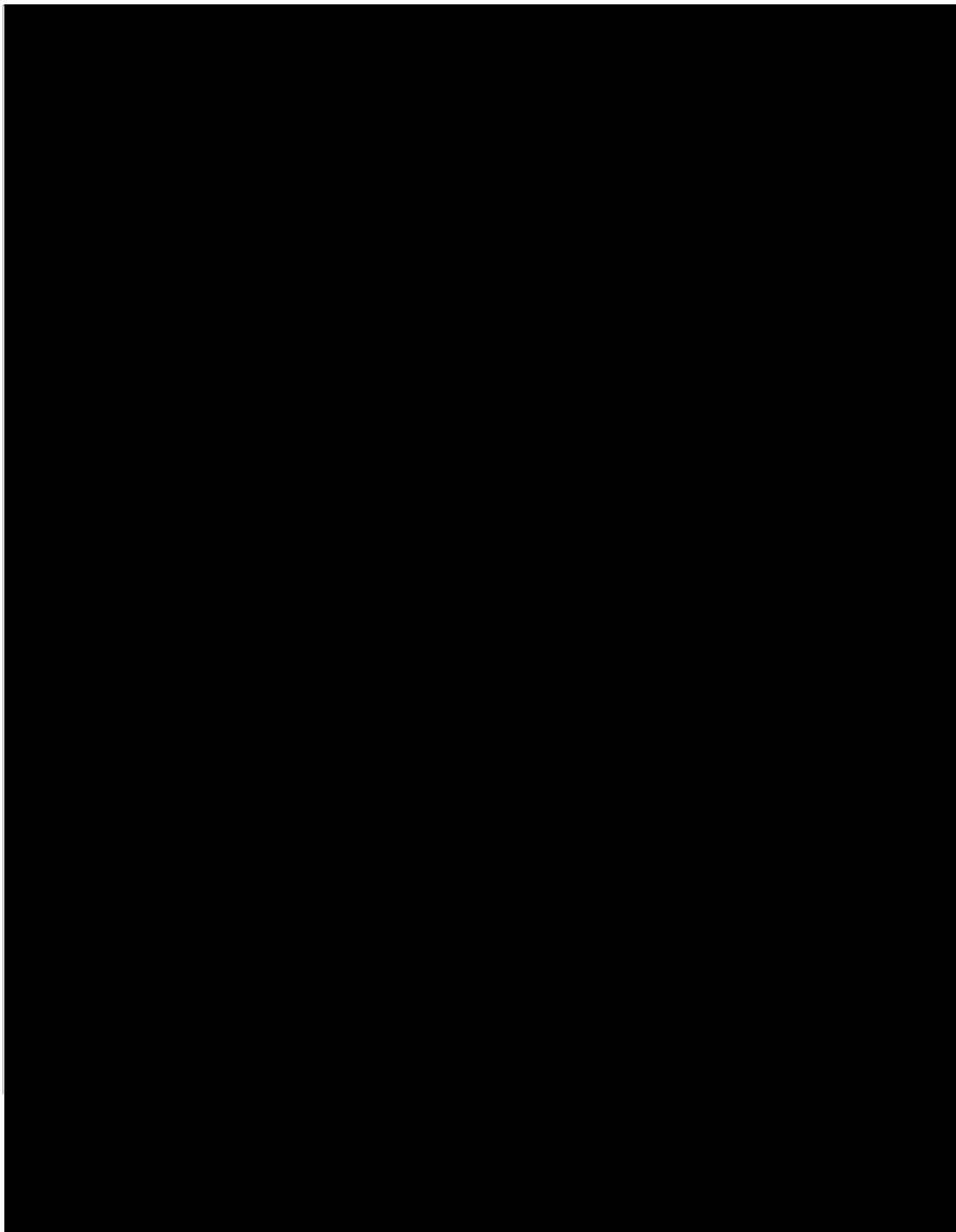
Appendix J Oral Symbol Digit Modalities Test

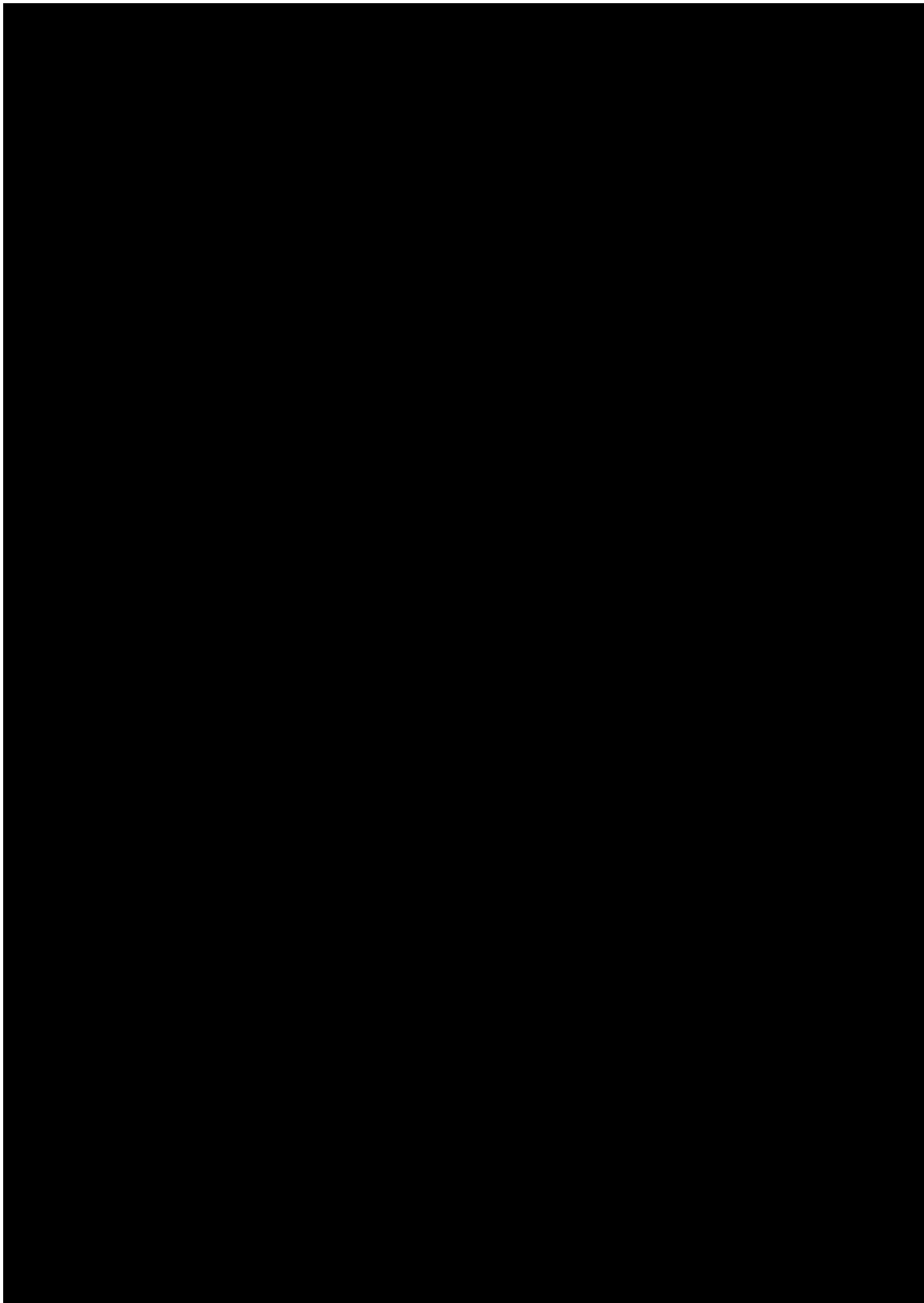


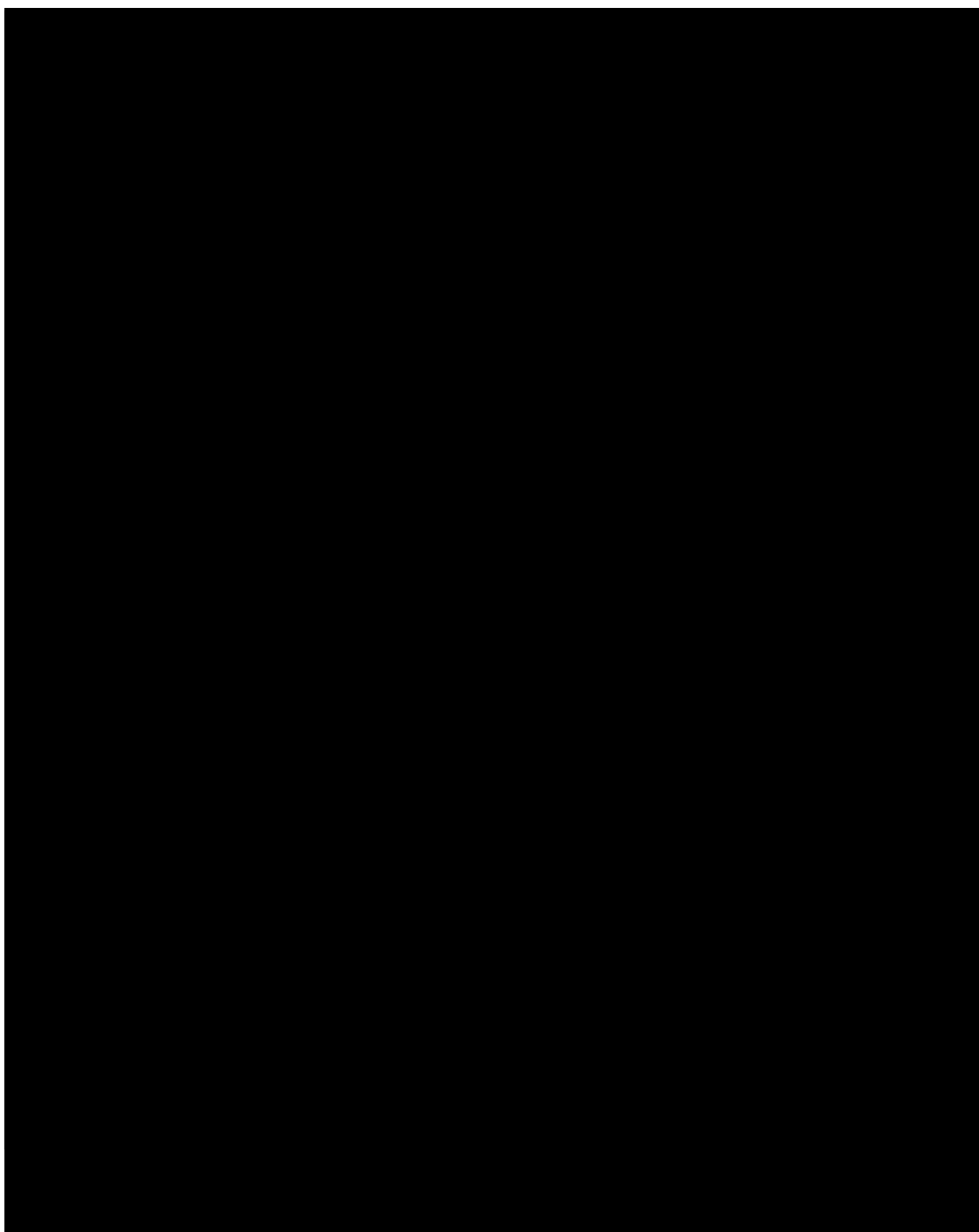


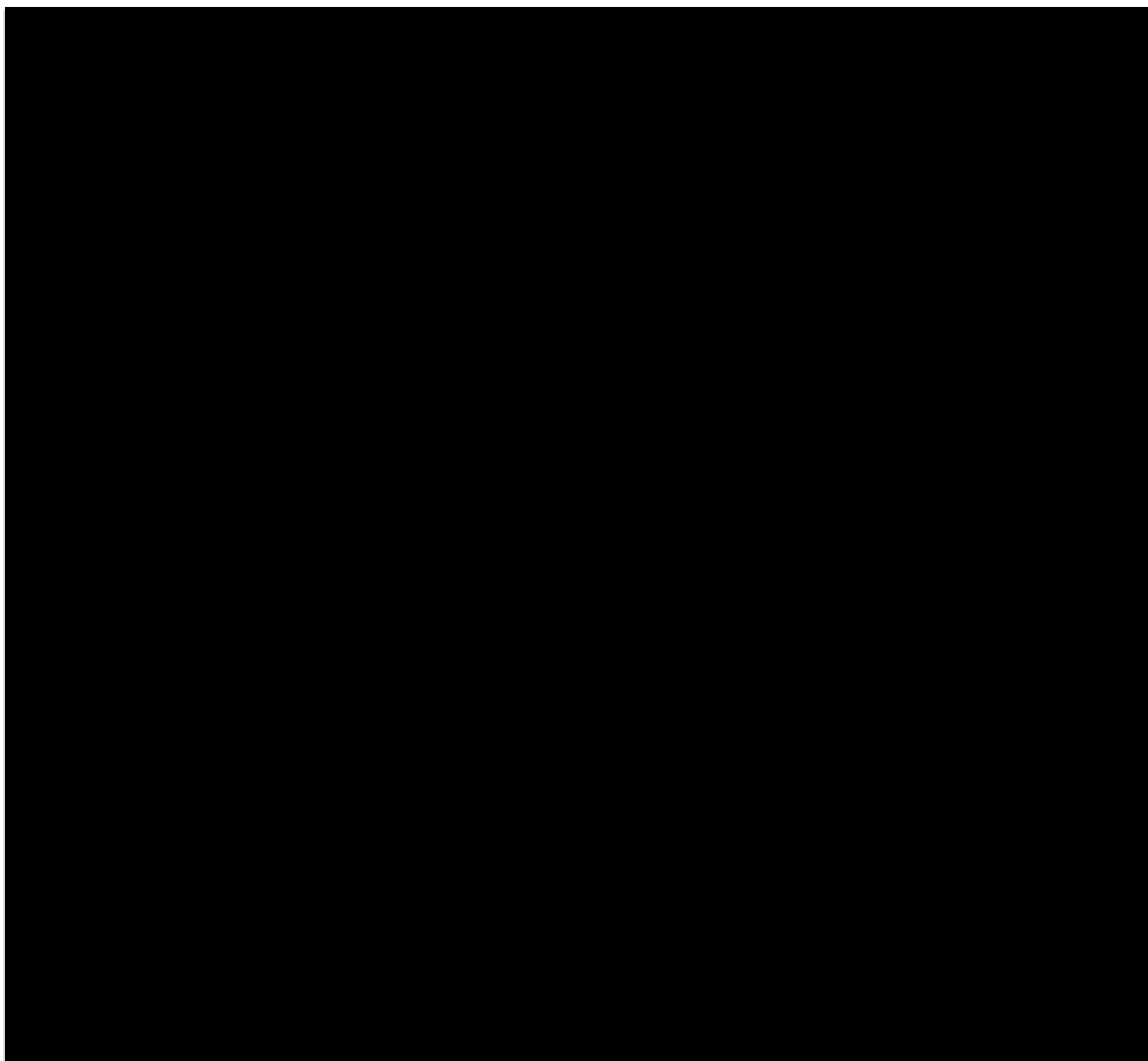


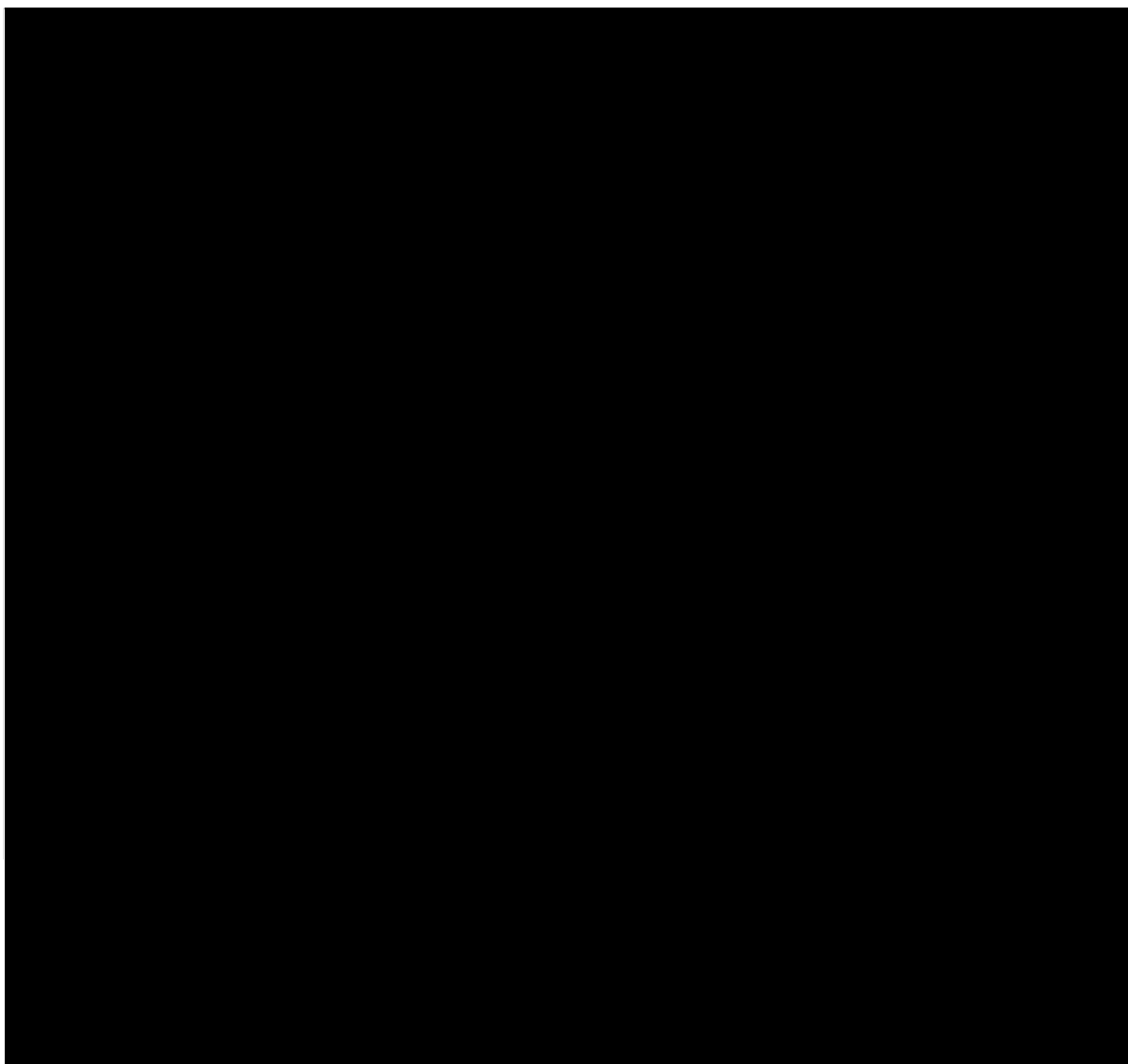
Appendix K Trail Making Test Parts A & B



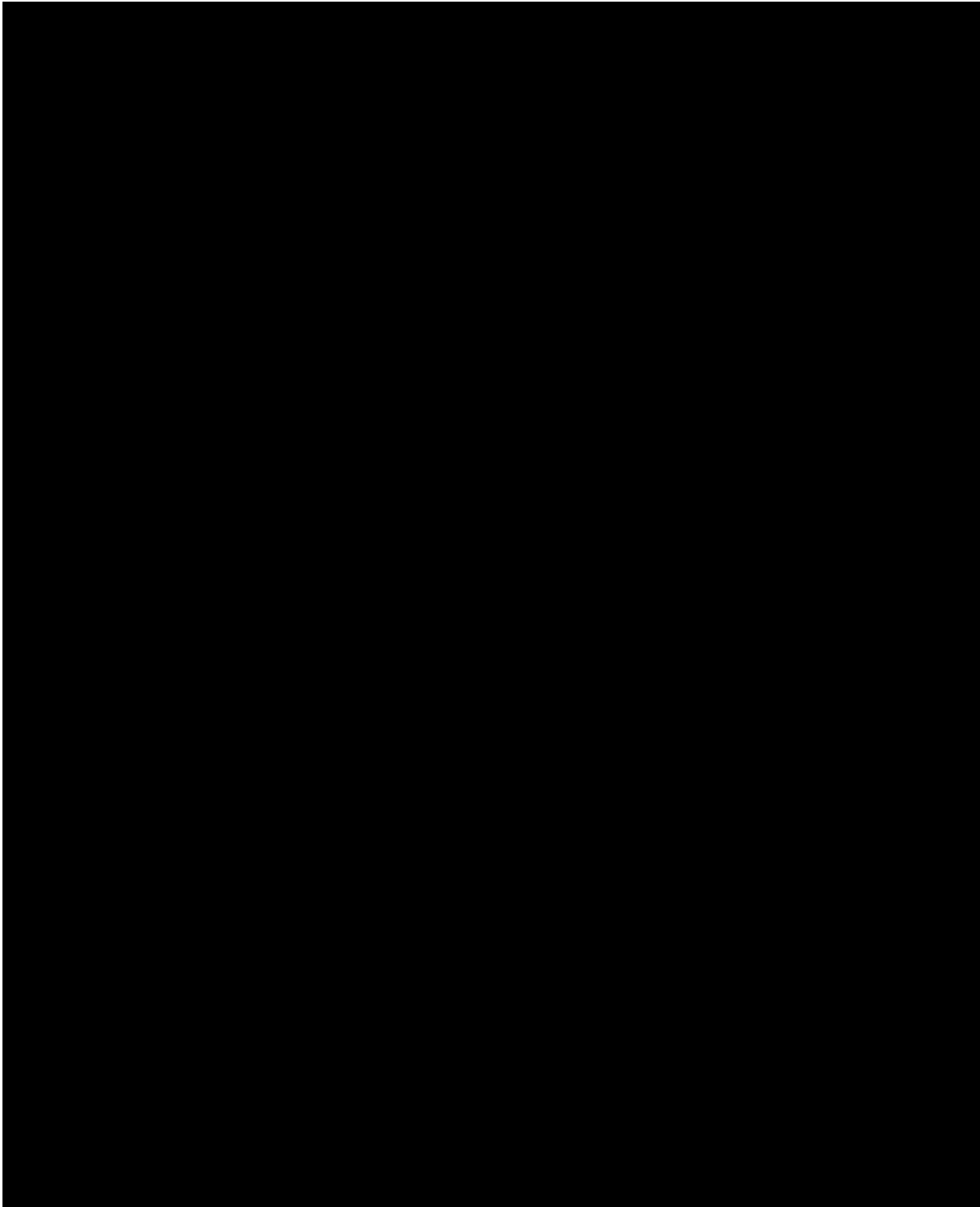








Appendix L Beck Depression Inventory, Second Edition



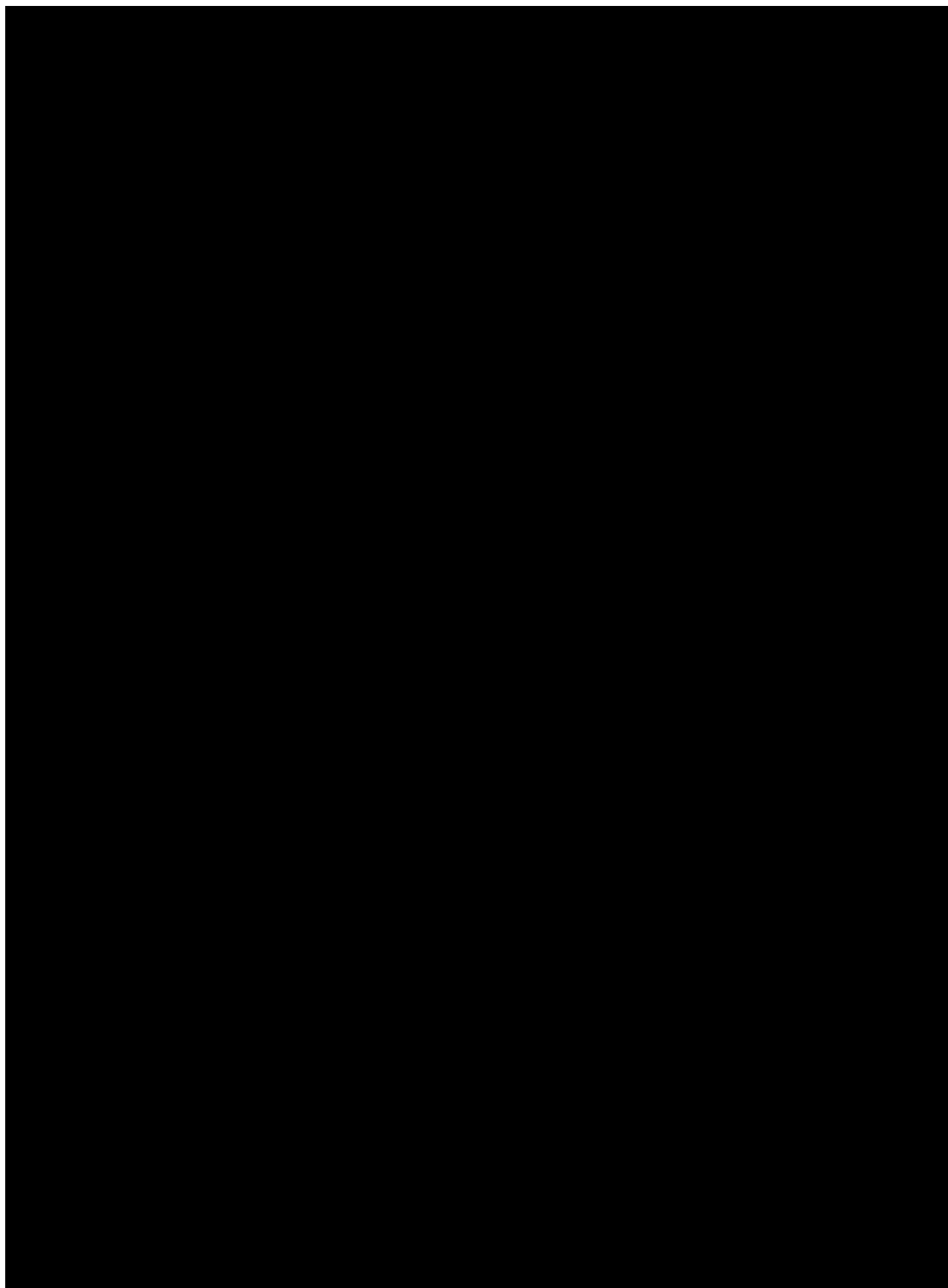
PEARSON

35 36 B C D E

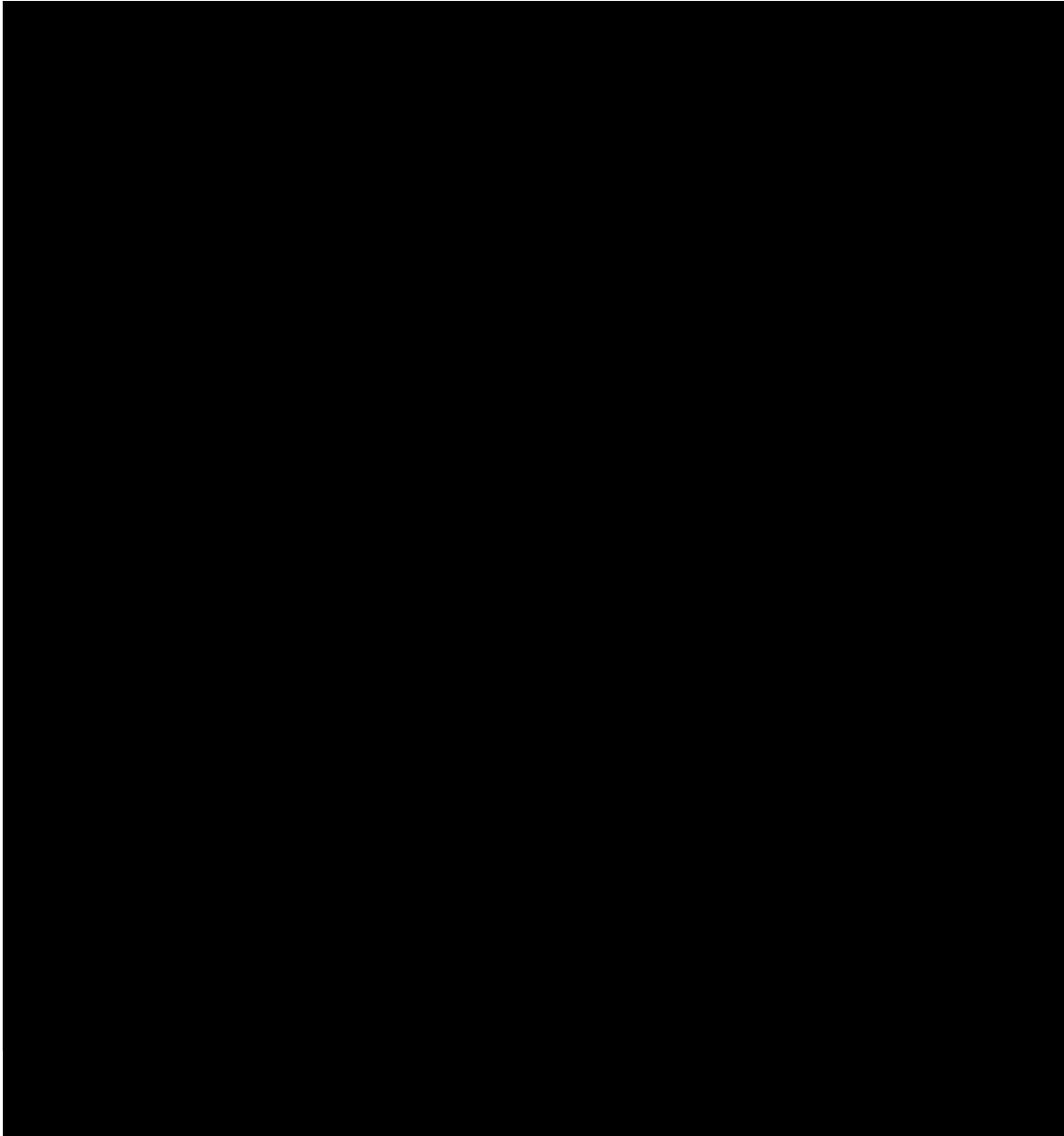
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Pearson Executive Office 5601 Green Valley Drive Bloomington, MN 55437
800.627.7271 www.PearsonClinical.com

 **PsychCorp**

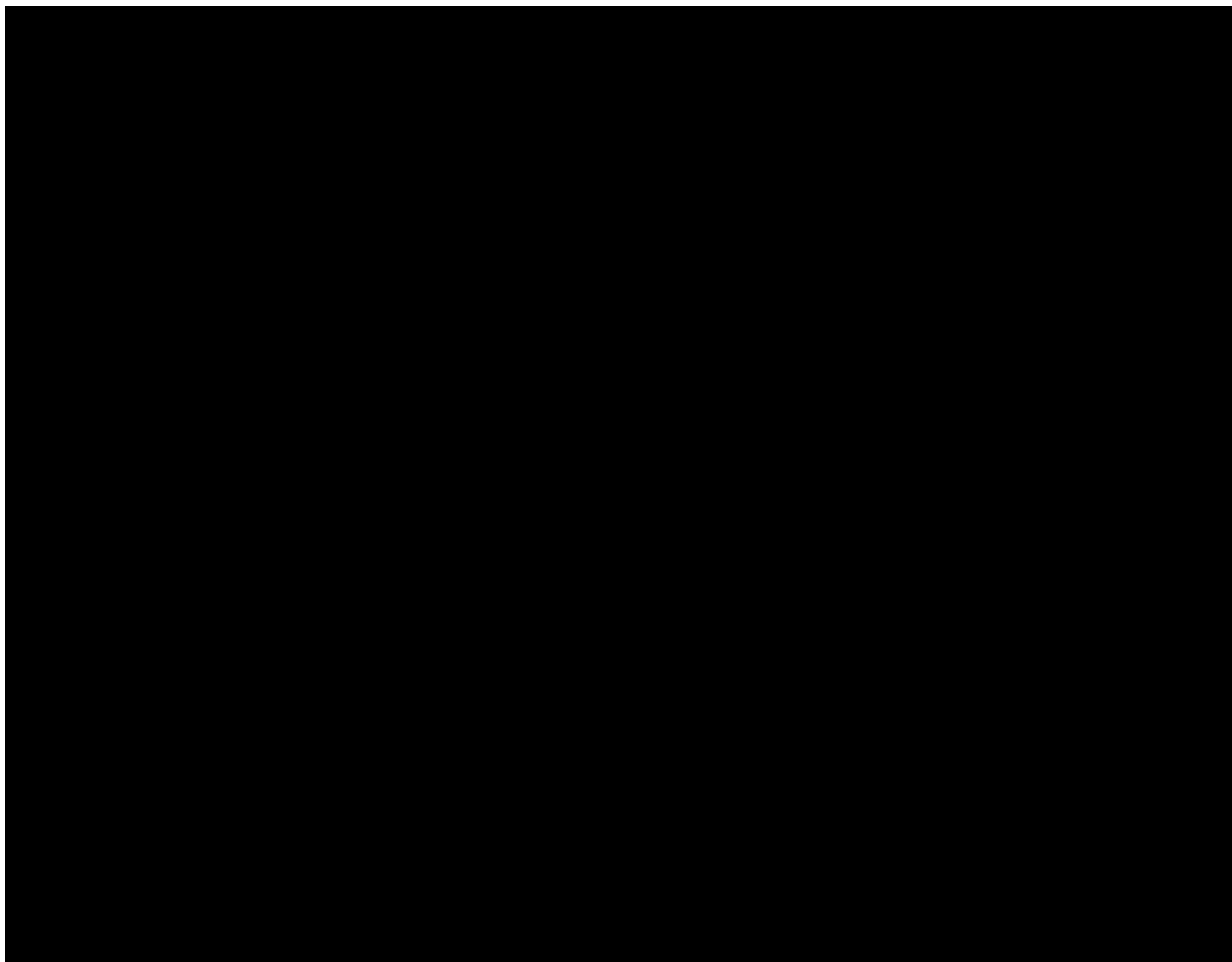




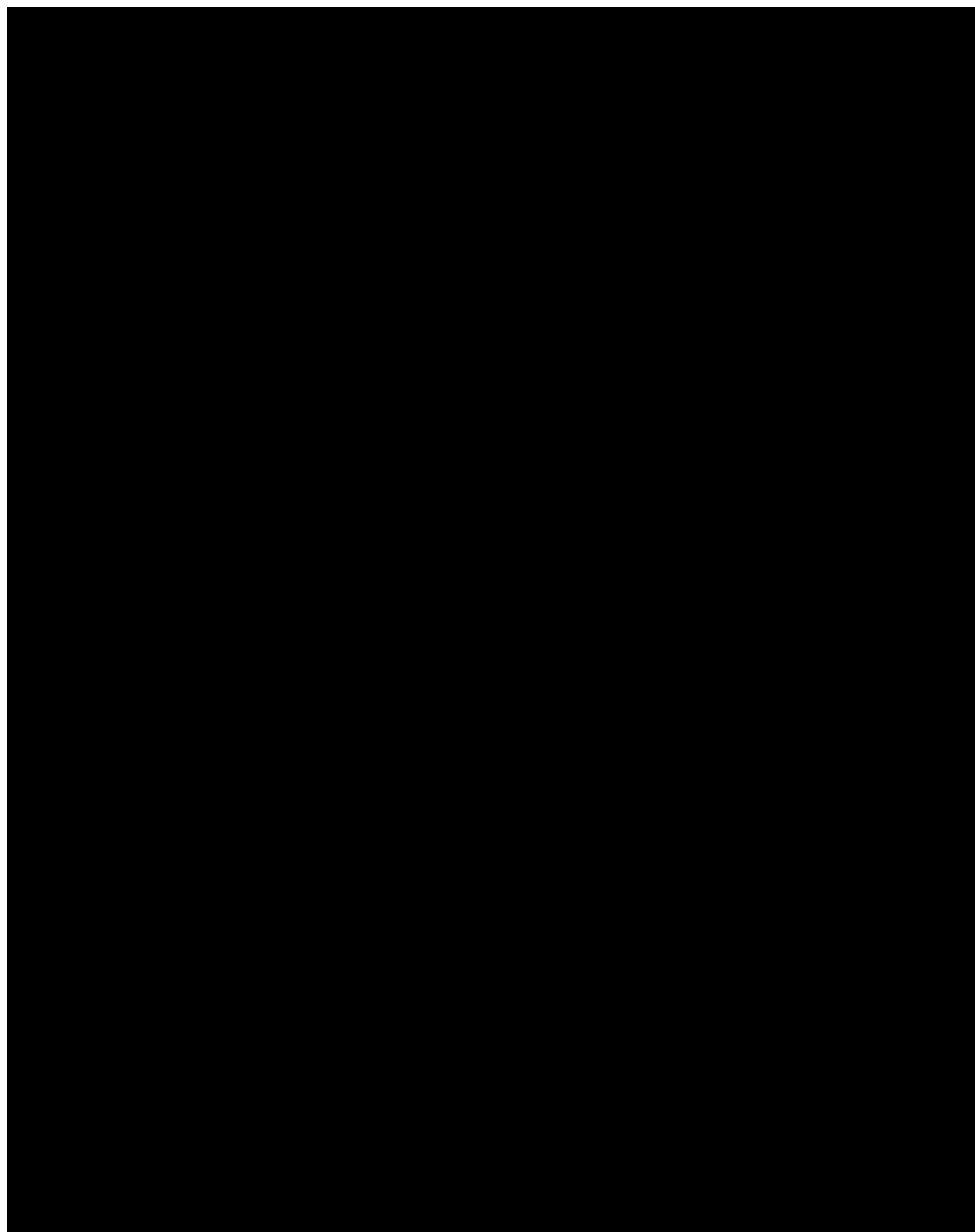
Appendix M Clinical Global Impression of Change

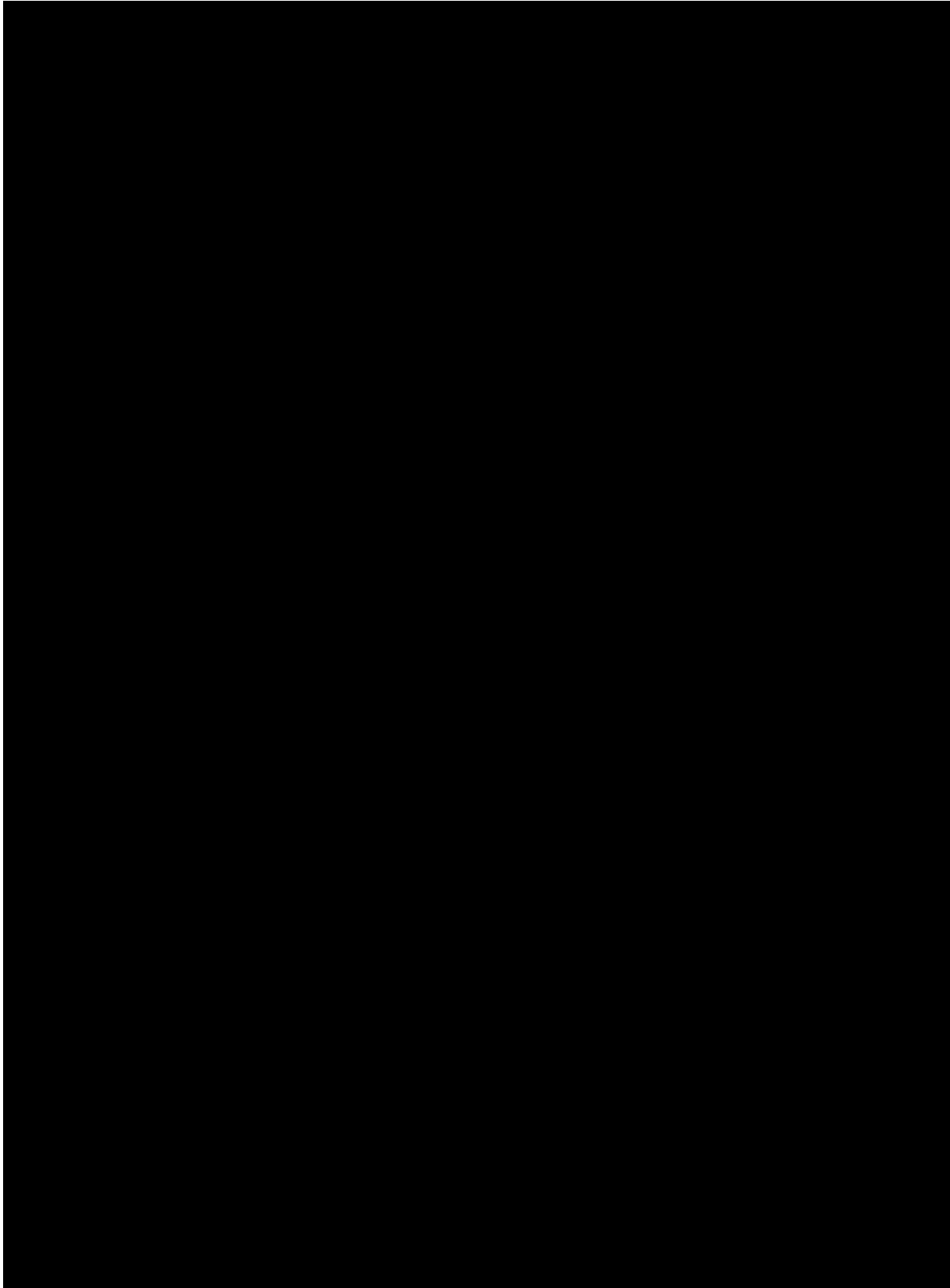


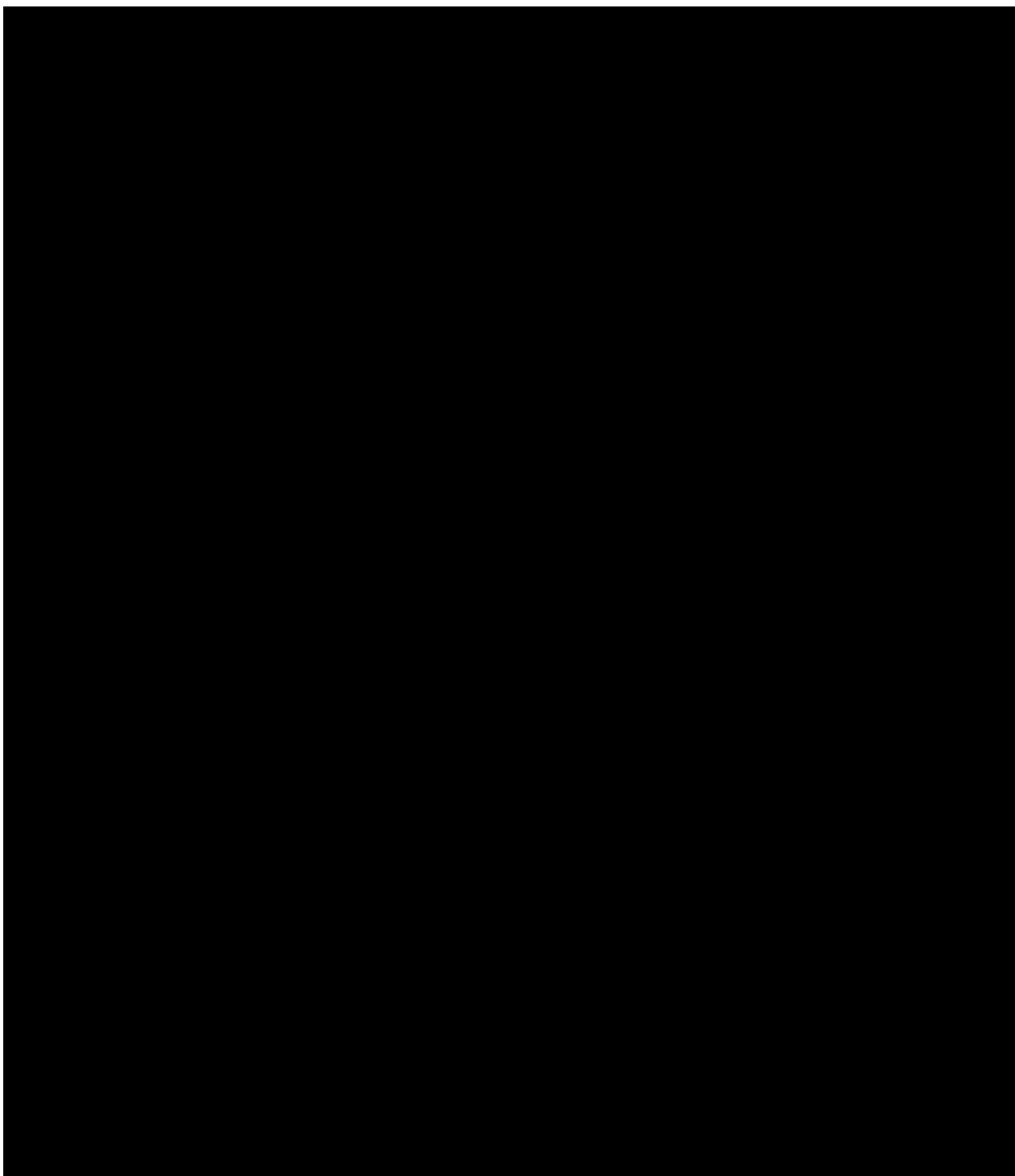
Appendix N Patient Global Impression of Change



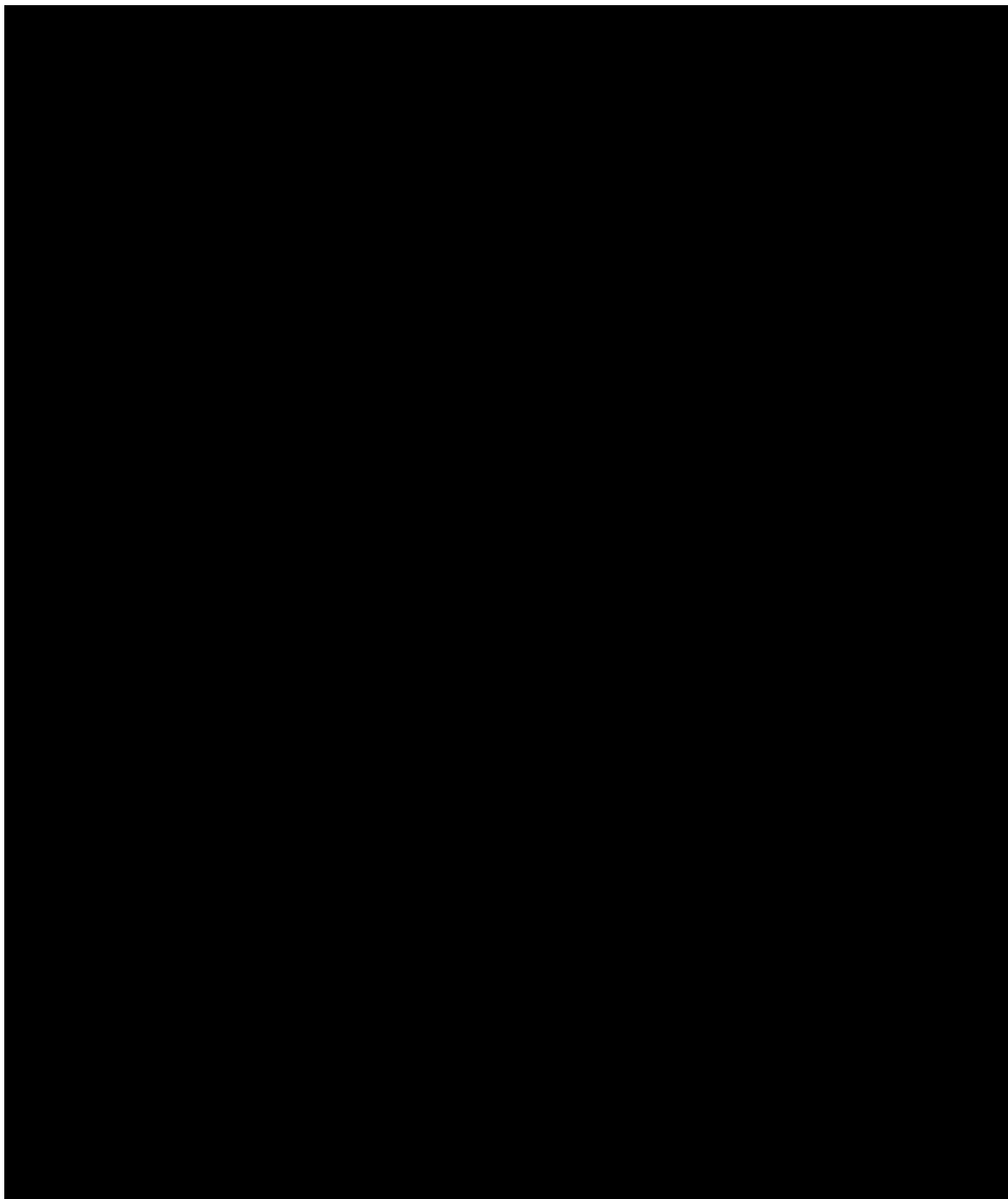
Appendix O Parkinson's Disease Questionnaire – 39



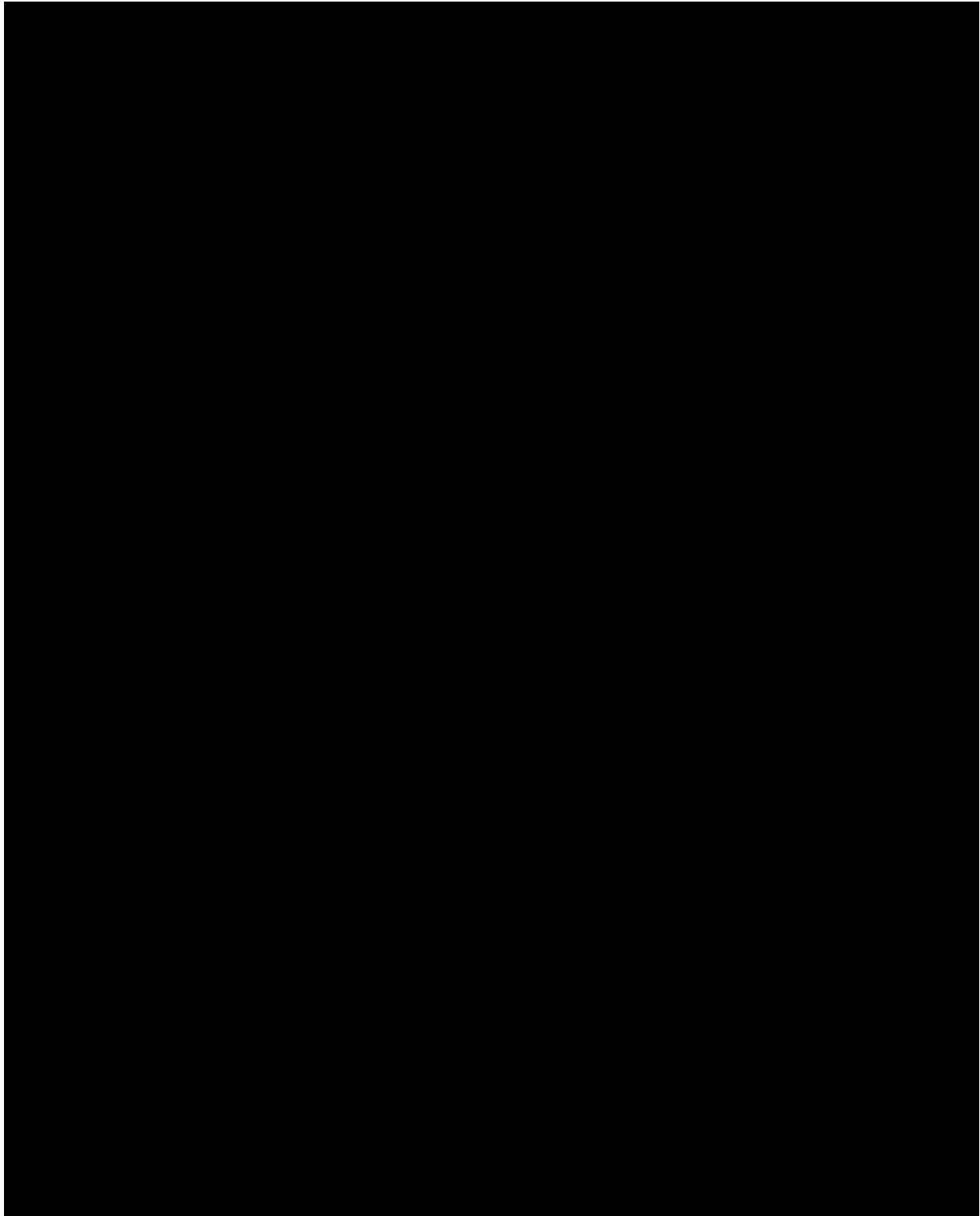




Appendix P EuroQol Five Dimensions Questionnaire (EQ-5D)

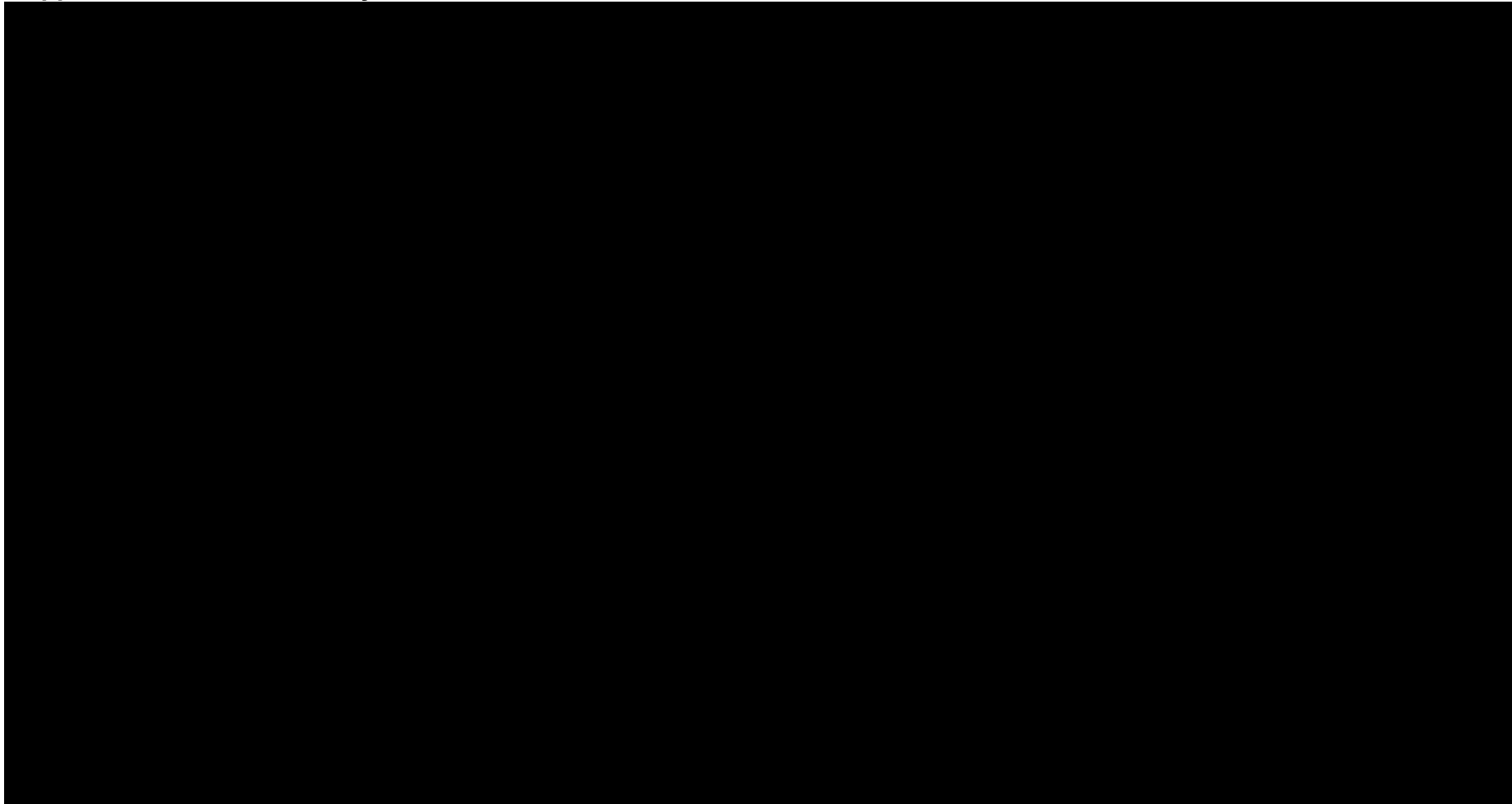


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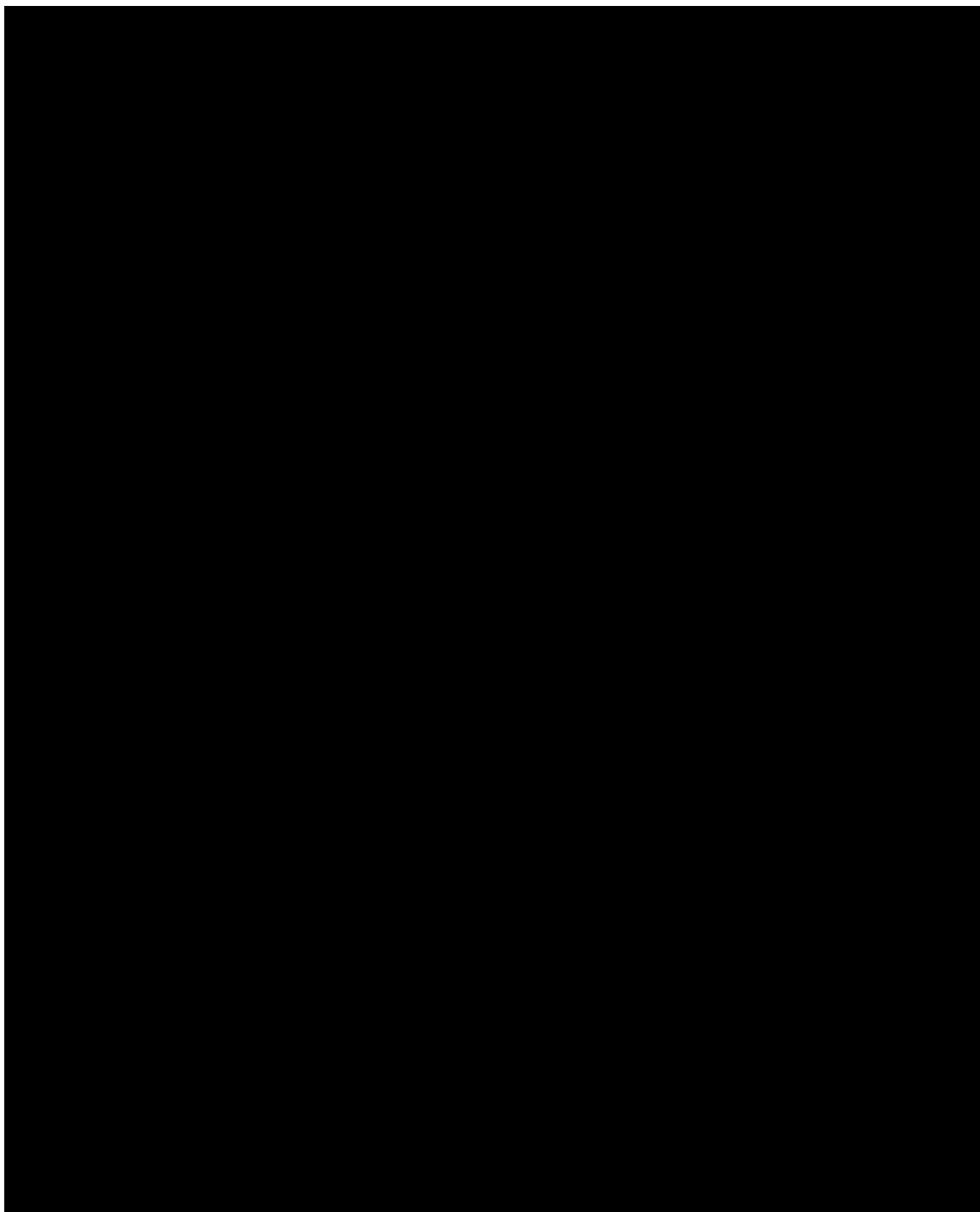
USA (English) © 2009 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

Appendix Q Falls Efficacy Scale

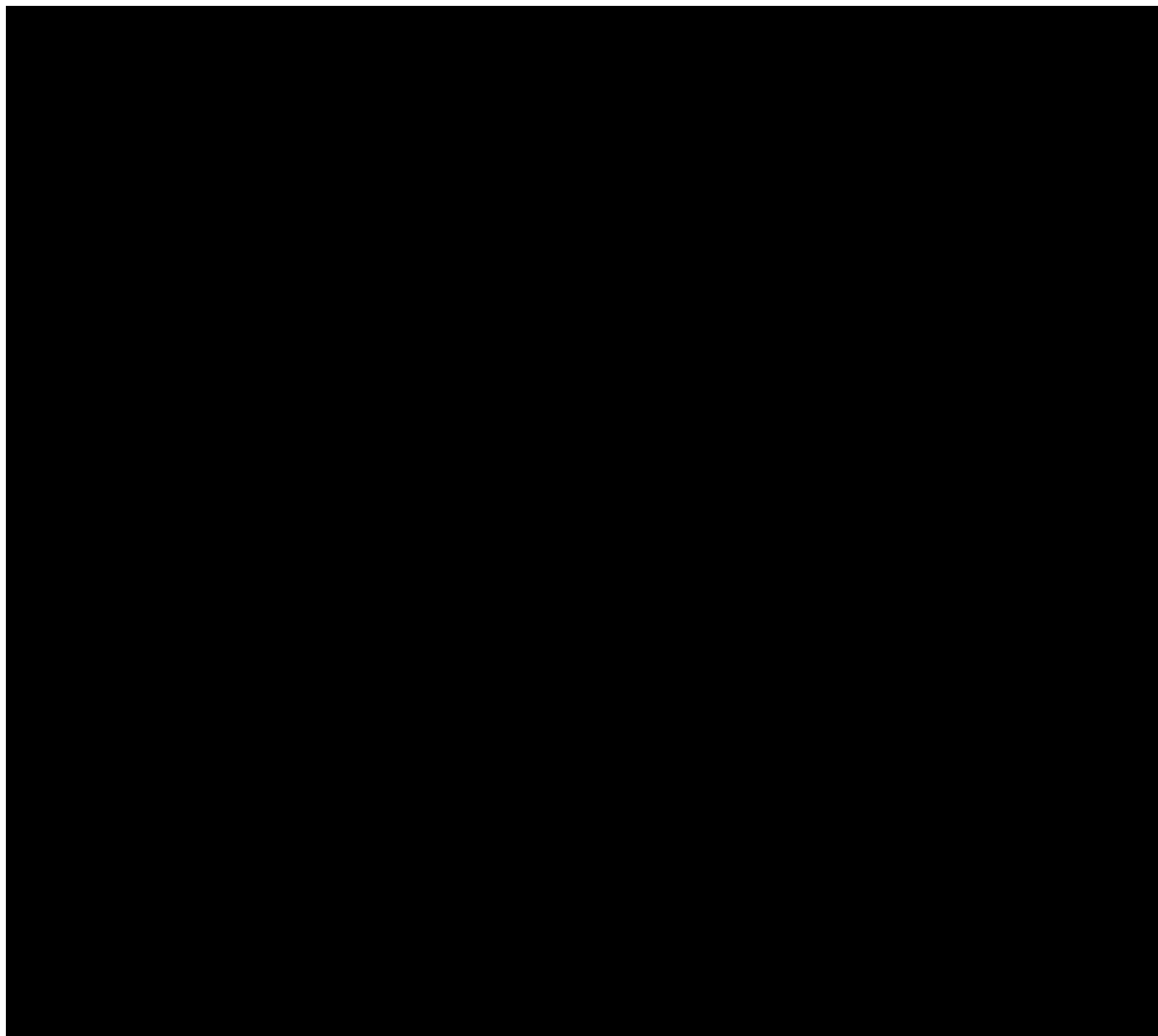


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Appendix R Health-Related Productivity Questionnaire (HRPQ)



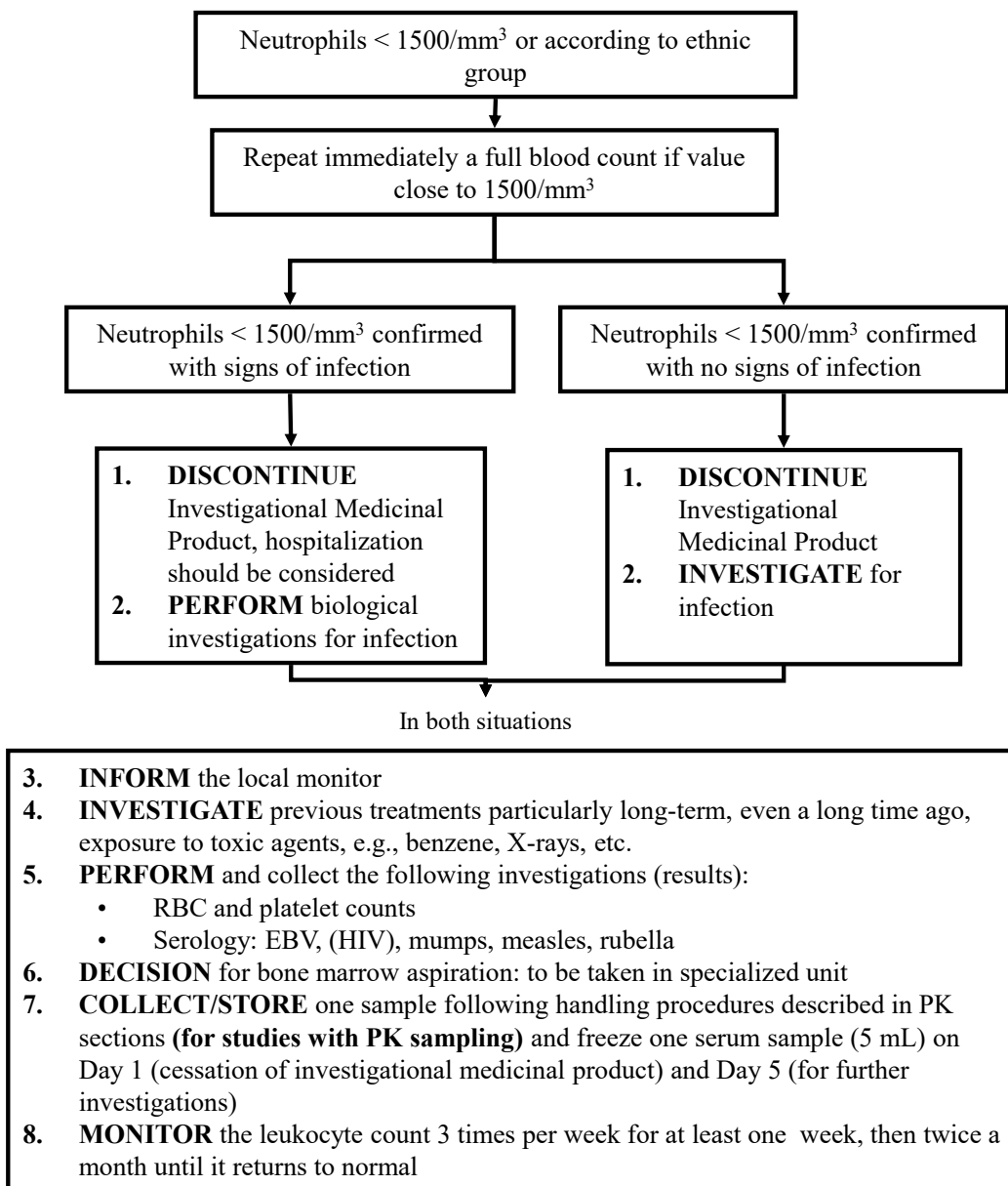
Health Related Productivity Questionnaire V2 - PD
All Rights Reserved



Health Related Productivity Questionnaire V2 - PD
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Appendix S General guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA

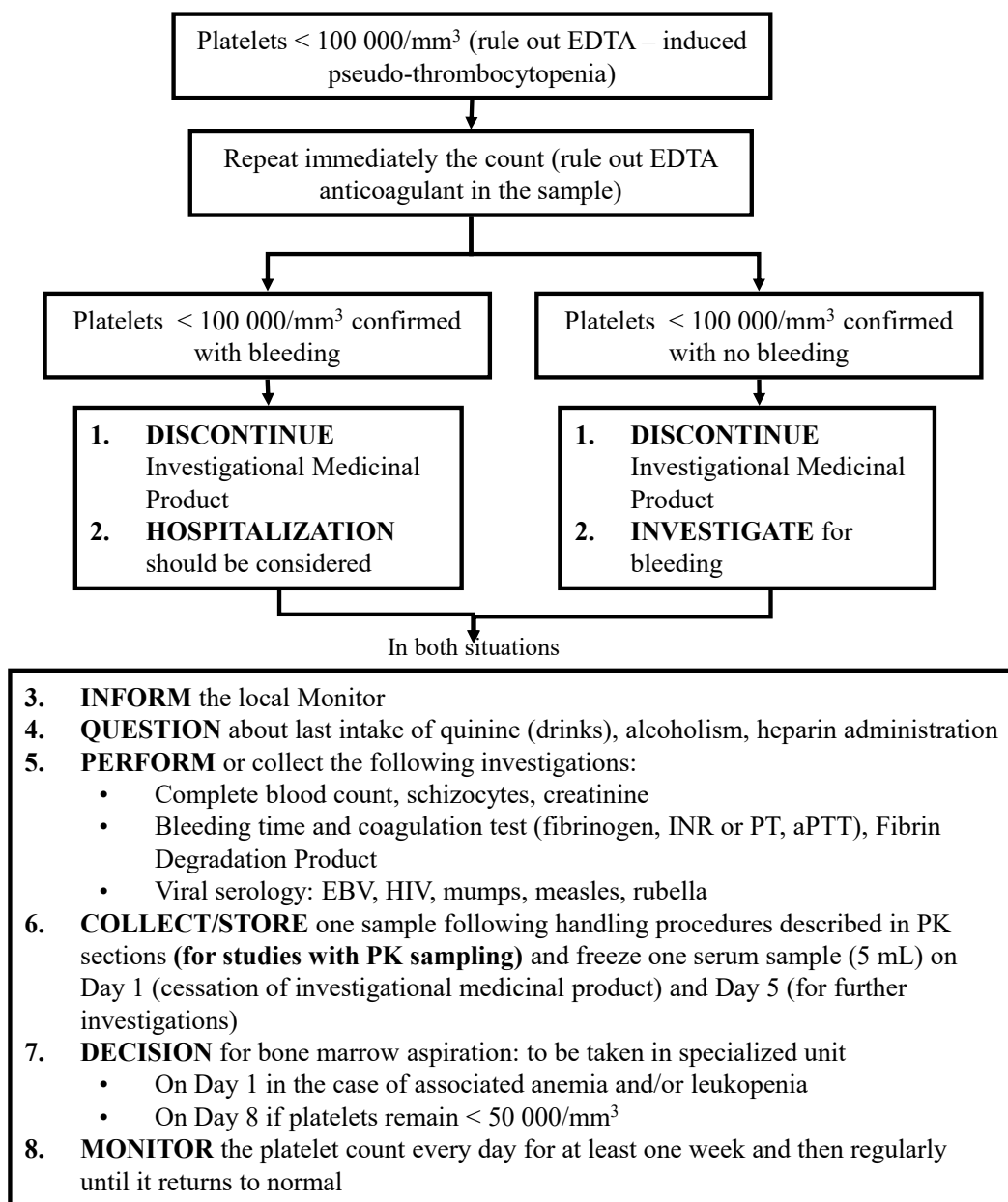


Note:

- The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
- For individuals of African descent, the relevant value of concern is <1000/mm³

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in [Section 10.4.2](#) is met.

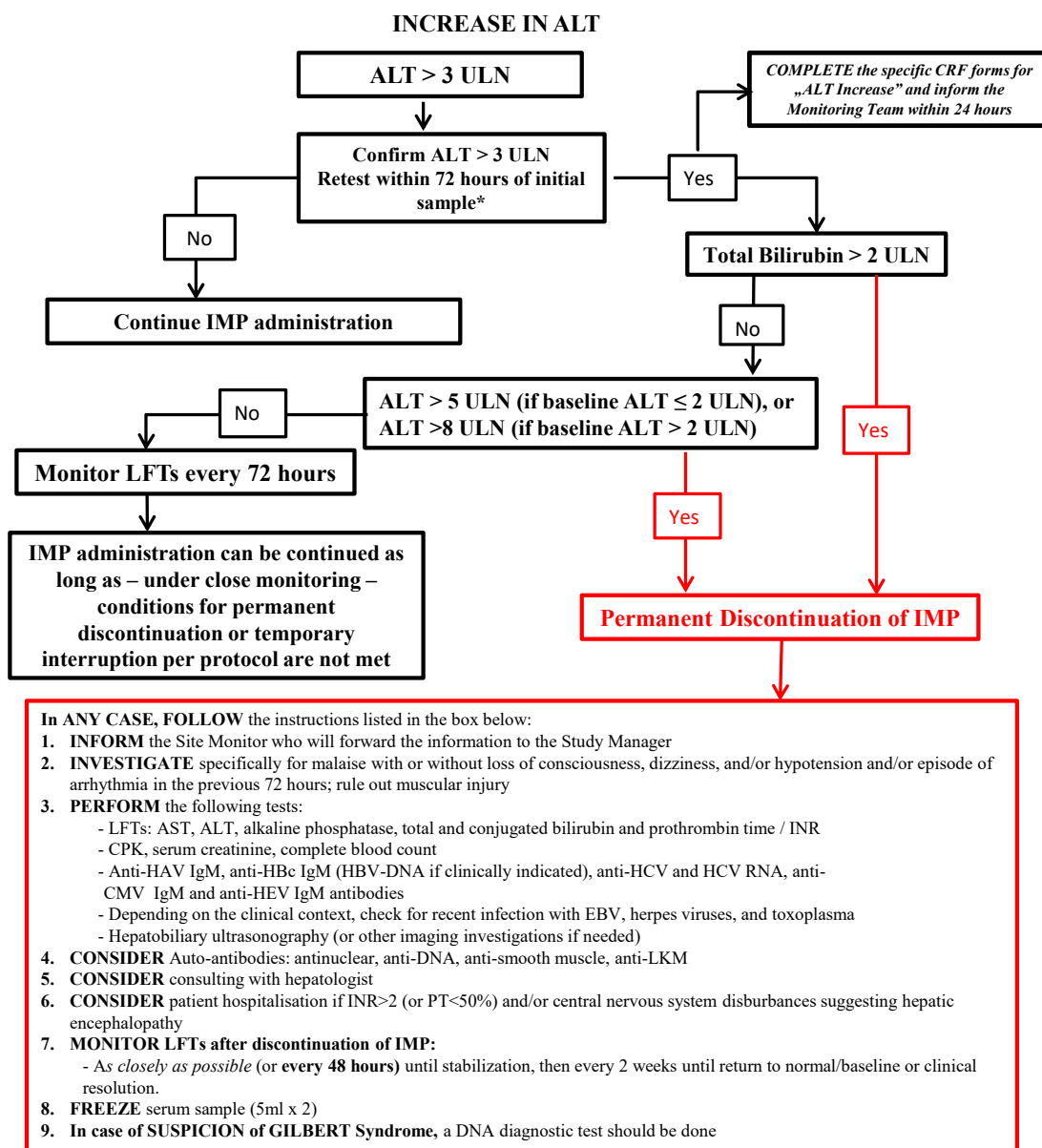
THROMBOCYTOPENIA



Note:

The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in [Section 10.4.2](#) is met.

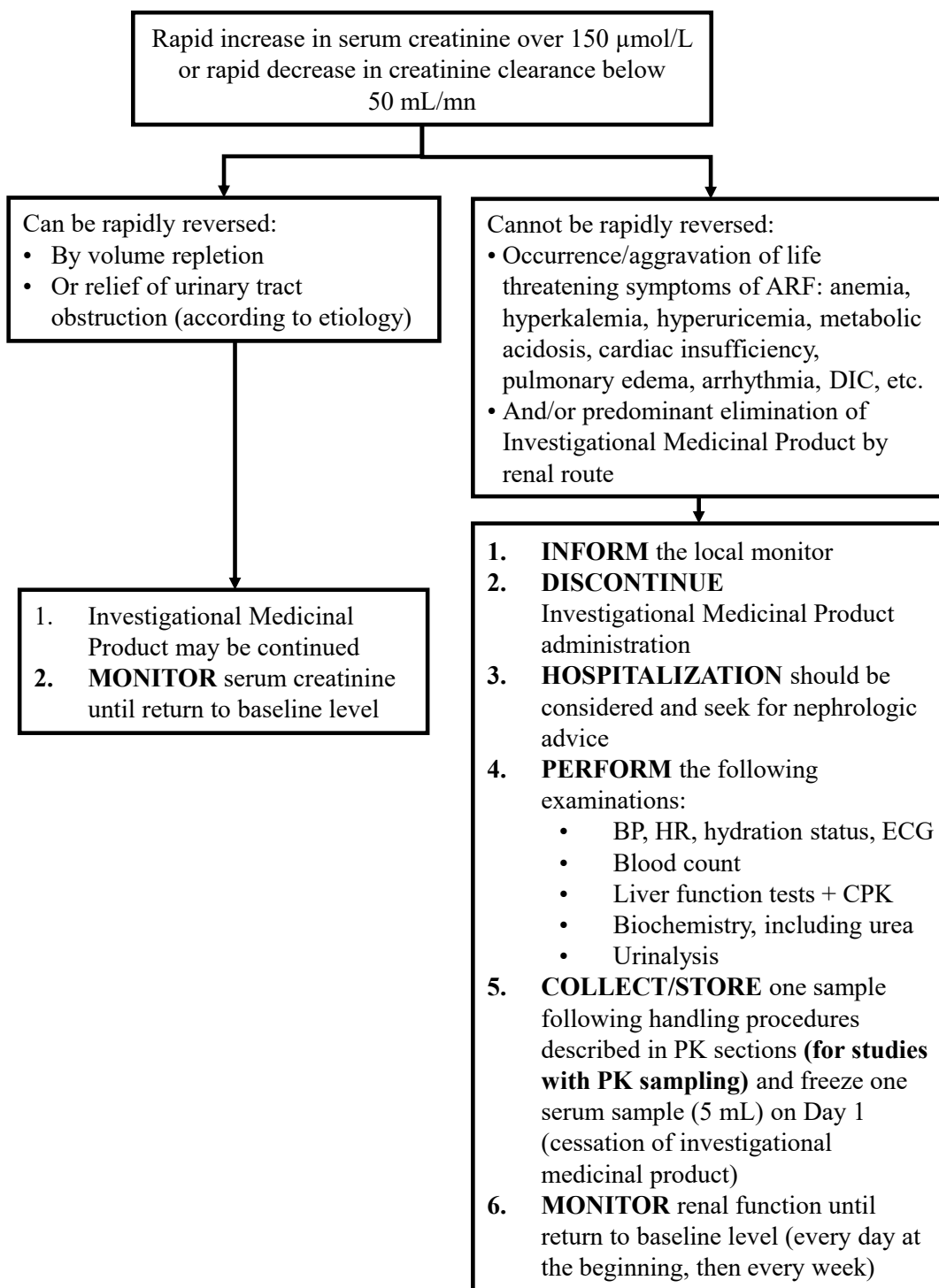


*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

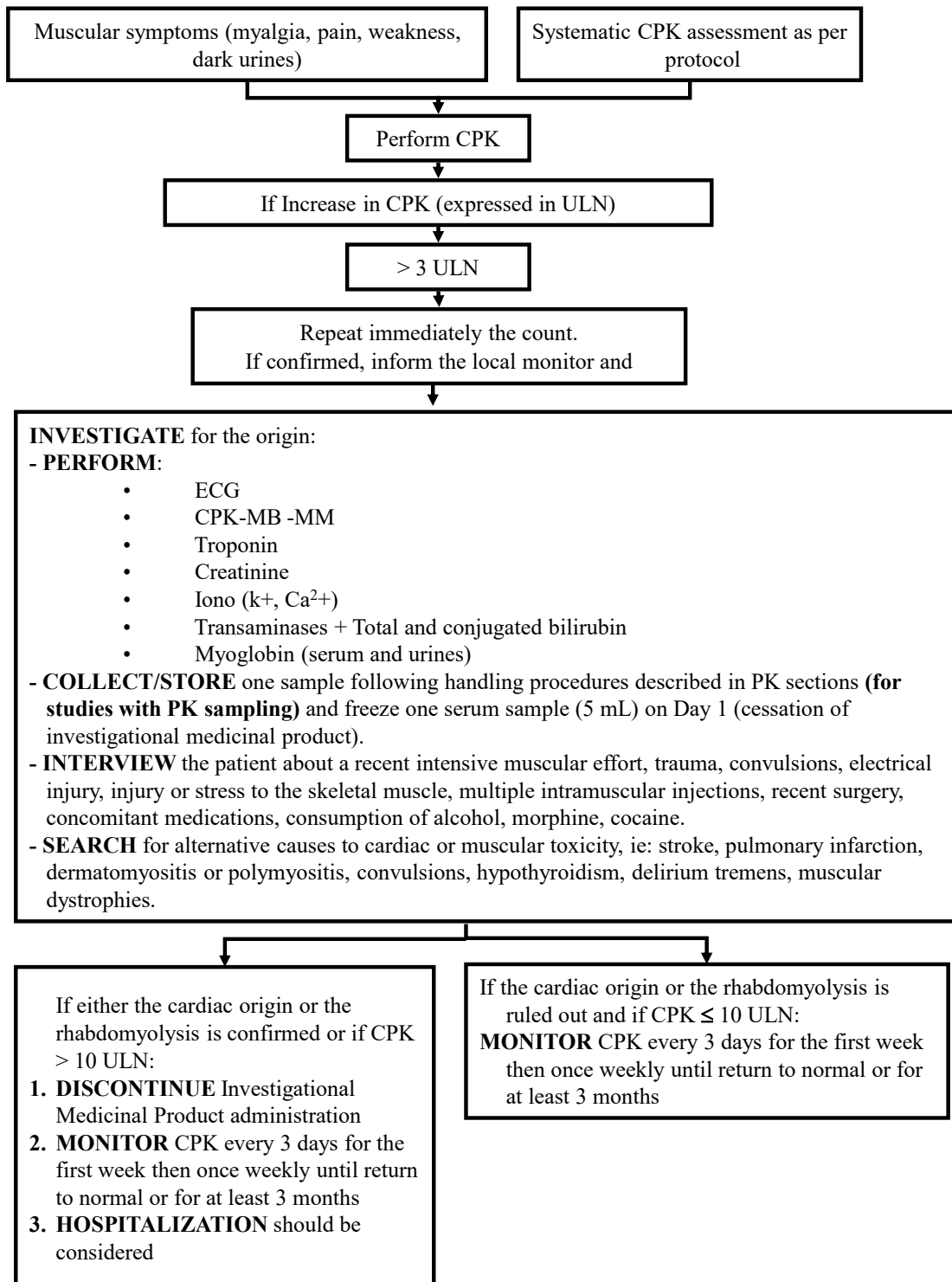
- “Baseline” refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See [Section 10.4](#) for guidance on safety reporting.
- Normalization is defined as \leq ULN or baseline value, if baseline value is $>$ ULN.

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met.
Acute renal failure is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

SUSPICION OF RHABDOMYOLYSIS



Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met.
Suspicion of rhabdomyolysis is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Section 10.4.2 is met.

Appendix T Country-specific requirements

The country-specific requirements for Japan and Israel are included in the protocol in the relevant sections, and the rationale for the amendment is included in [Appendix U](#) (Protocol amendment history).

Appendix U Protocol amendment history

The Protocol Amendment Summary of Changes for the current amendment is located directly before the Clinical Trial Summary.

Amended clinical trial protocol 05 (03 September 2020)

This amended protocol (amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The protocol is being amended to include a 1-year prolongation of the open-label long-term follow-up period (Period 3) of Part 2. This prolongation is being done to allow time for analysis of the results from the 52-week double blind period (planned for Q1 2021) to inform the potential long-term extension program.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary, Study design, Assessment schedule, Duration of study period (per patient); Section 1.2, Graphical study design for Part 2; Section 1.3.3, Part 2: study schedule of assessments (Periods 3 and 4); Section 6.1, Description of the study; Section 6.2.1, Duration of study participation for each patient; Section 6.2.2, Determination of end of clinical trial (all patients); Section 6.5, Discussion of study design; Section 8.1, Investigational medicinal product; Section 8.3.2, Randomization code breaking during Parts 1 and 2; Section 9.1.2, Part 2: Treatment phase; Section 9.2.3.1, Parkinson's disease-cognitive rating scale; Section 9.3.3.3, Vital signs; Section 9.3.3.4, Physical examination; 9.3.3.5, Neurological examination; 9.3.3.6, Ophthalmological examination; Section 9.3.3.7, Electrocardiogram (ECG); Section 9.4.3, Dopamine transporters scan assessment; Section 9.4.5.1, Montreal cognitive assessment score; Section 9.4.5.2, Oral symbol digit modalities test score; Section 9.4.5.3, Trail making test A and B score; 9.4.5.4, Beck depression inventory, second edition; Section 9.4.5.7, Parkinson's disease questionnaire – 39 score; Section 9.4.5.8, EuroQol five dimensions questionnaire; Section 9.4.5.9, Falls efficacy scale; Section 9.5, Health-related productivity questionnaire; Section 10.1.2.10, Long term follow-up period (Period 3); Section 10.1.2.11, Six-week follow-up visit (Period 4, end-of-study visit, Visit 16: Week 214 ±7 days); Section 10.3.3, List of criteria for permanent treatment discontinuation; Section 10.3.4, Handling of patients after permanent treatment discontinuation; Section 10.3.5, Procedure and consequence for patient withdrawal from study, Section 11.5.2, Two-step final analysis	Sections updated.	To add the supplementary visits and corresponding assessments related to the 1-year prolongation of the long-term follow-up period (Period 3).
Clinical trial summary, Study objectives, Endpoints; Section 5.2.3	Update of the exploratory	To clarify the objectives of the

Section # and Name	Description of Change	Brief Rationale
Exploratory objectives	study objectives.	long-term follow-up period (period 3).
Clinical trial summary, Assessment schedule; Section 1.3.3, Part 2: Study schedule of assessments (Periods 3 and 4); Section 6.2.2, Determination of end of clinical trial (all patients); Section 10.1.2.10, Long term follow-up period (Period 3)	Sections updated.	To specify that Visit 15 (Week 208) will be the last study visit for patients who will transition to a long-term study with GZ/SAR402671.
Section 6.5, Discussion of study design	Revised text regarding Parkinson's disease (PD) medications.	To clarify the PD medications allowed during the study.
Section 13.2, Responsibilities of the Sponsor	Added text stating the monitoring may include remote monitoring, and details are provided in separate documents.	Sanofi protocol template update, adapting to the changing trial environment.
Throughout	Administrative changes.	Minor, therefore not summarized.

Amended clinical trial protocol 04 (21 May 2020)

This amended protocol (amendment 04) is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The protocol is being amended to remove the interim analysis, to include guidance for Covid-19 pandemic, to incorporate feedback received from the Investigator(s), as well as other changes deemed necessary by the Sponsor.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary (Study objectives, Endpoints), Section 5.2.3, Exploratory Objectives; New Section 9.4.6, Parkinson's disease progression model	Added a new exploratory objective and endpoint.	To better characterize Parkinson's disease (PD) progression in early stage PD patients carrying a β -glucocerebrosidase gene (GBA) mutation.
Clinical Trial Summary (Statistical considerations), Section 6.3, Interim Analysis; Section 11.5.1, Interim Efficacy Analysis	Removed interim analysis.	Interim analysis planned for administrative purposes that are no longer required by the Sponsor.
Section 1.3.2, Part 2: Study schedule of assessments (Periods 1 and 2),	Added text to address Covid-19 pandemic.	To provide guidance during Covid-19 pandemic.

Section # and Name	Description of Change	Brief Rationale
footnote "u"; Section 1.3.3, Part 2: Study schedule of assessments (Periods 3 and 4), footnote "f"; Section 8.8.1.1, Temporary use of strong or moderate CYP3A4 inducers or inhibitors; Section 10.1.2, Part 2: Treatment phase; New Section 10.1.2.12, Contact for IMP dispensing during Covid-19 outbreak		
Section 4.2.2, Risk assessment	Updated section.	Last information regarding gastrointestinal, liver and central nervous system safety data were added.
Section 8.7, Responsibilities	Added text regarding Direct-to-Patient investigational medicinal product (IMP) delivery.	To avoid treatment discontinuation in exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic diseases (eg, Covid-19 pandemic), terrorist attack).
Clinical Trial Summary (Assessment schedule); Section 1.3.2, Part 2: Study schedules of assessments (Periods 1 and 2); Section 1.4.2, Part 2: Treatment phase; Section 10.1.2, Part 2: Treatment Phase (Visit Window); Section 10.1.2.9, Visit 9: Week 52 (± 14 days)	Week 52 visit window increased.	To facilitate site organization.
Section 8.8, Concomitant medication; Section 8.8.5, Medications that can prolong the QT interval	Specified the forbidden concomitant treatment during the study.	Protocol clarification.
Section 10.3.3, List of criteria for permanent treatment discontinuation; Section 10.3.4, Handling of patients after permanent treatment discontinuation; Section 10.3.5, Procedure and Consequence for Patient Withdrawal From Study	Specified the patient management in case of study/treatment discontinuation	Protocol clarification.
Section 8.8.3, Medications with risk for dopamine transporters scan imaging	Revised the paragraph to match E 26 criterion.	Correction.
Section 9.6.1, Optional stored DNA sample (not applicable in Israel); Section 1.3.2, Part 2: Study schedule of assessments (Periods 1 and 2); Section 10.1.2.9, Visit 9: Week 52 (± 14 days)	Second optional sample added.	To better characterize drug response.
Section 9.4.2.1.1, Lumbar puncture	Deleted reference to an Operations Manual.	There is no Operations Manual for this study.
Section 1.3.2, Part 2: Study schedule of assessments (Periods 1 and 2);	Clinical global impression scale (CGI) removed from Weeks 13, 26, and 39 in Part	Correction.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.3, Part 2: Study schedule of assessments (Periods 3 and 4); Section 10.1.2.6, Visit 6: Week 13 (± 3 days); Section 10.1.2.7, Visit 7: Week 26 (± 3 days); Section 10.1.2.8, Visit 8: Week 39 (± 3 days); Section 10.1.2.10, Long term follow-up period (Period 3)	2 Period 2, and from all visits in Part 2 Periods 3 and 4.	
Section 7.2.3, Exclusion criteria related to current knowledge of GZ/SAR402671 IMP	Updated section.	Medical/surgical history and previous/concomitant medication data not required for screen failures.
Section 9.3.3.6, Ophthalmological Examination	Week 39 added as an intermediate time point.	Protocol clarification.
Section 10.1.2.2, Visit 2: Randomization/baseline at Week 0/Day 1; Section 10.1.2.9, Visit 9: Week 52 (± 14 days);	"Should" replaced by "must" for the order of assessments.	Protocol clarification.
Section 10.1.2.9, Visit 9: Week 52 (± 14 days)	Added text to provide more guidance on transition to long-term follow-up.	Protocol clarification.
Section 10.4.5, Guidelines for management of specific laboratory abnormalities	Table 5: Updated table for Symptomatic overdose with IMP for which a specific form is to be completed.	Correction.
Section 10.4.3, Instructions for reporting serious adverse events	Copies of medical records only sent upon request by the Sponsor.	Administrative change.
Section 17, Appendices: Appendix A, List of common GBA mutations	Revised to include new GBA mutations.	Updated with the last known mutations.
Throughout	Administrative changes.	Minor, therefore not summarized.

Amended clinical trial protocol 03 (Global) (20 July 2018)

This amended protocol is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The protocol is being amended to incorporate feedback received from the Investigator(s), as well as other changes deemed necessary by the Sponsor.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Names and addresses	Updated address of Sponsor.	Editorial correction.
Synopsis (study design, assessment	Extended screening period duration from 45	Up to 30 days is required to obtain the

Section # and Name	Description of Change	Brief Rationale
schedule, duration of study period)	to 60 days.	genetic laboratory results, and the screening is split in 2 steps. The objective to increase the final 2 weeks to 4 weeks to give more time to the sites to perform all remaining examinations including MRI and DAT scan. This will facilitate the logistics of the screening period and may prevent protocol deviation.
Sections 1.1 and 1.2 Graphical study design Part 1 and Part 2		
Sections 1.3.1 and 1.3.2 Study schedule of assessment Part 1 and Part 2		
Section 6 Study design		
Section 1.3.1 Part 1: Study schedule of assessment	Ophthalmologic examination added at the early withdrawal Visit 8 (Week 8).	Aligned flowchart footnote description with visit assessment.
Section 1.3.2 Part 2: Study schedule of assessment	Footnote "c" updated and added following details 'genetic screening will not need to be repeated to confirm eligibility of patients from Part 1 to enroll in Part 2'.	Provided clarification that the genetic screening does not need to be repeated for patients from Part 1 being screened for Part 2.
Synopsis (exclusion criteria)	Updated the exclusion criteria 26 (E 26) and revised the list of the drugs that have the potential to interfere with DATSCAN imaging based on the DATSCAN USPI.	List of drugs updated to follow DATSCAN label.
Section 7.2.3 Exclusion criteria related to current knowledge of GZ/SAR402671 IMP		
Section 9.3.3.6 Ophthalmological examination	"baseline visit" replaced by "screening visit".	Clarify that in both study parts, the first ophthalmological examination must be performed during screening (and not "at baseline", which corresponds to the randomization visit on Week 0/Day1).
Section 10.1.1.9 Visit 9 (safety follow-up completion visit; ±3 days)	Text in section 10.1.1.9 is aligned with the corresponding flowchart footnote	Flowchart footnote was updated in the last amendment, corresponding text in other sections aligned with updated footnote.
Synopsis (assessment schedule)	Added following additional details: If the following examinations including lumbar puncture, DAT scan, and PK analyses on plasma and CSF have been performed recently, then the Investigator can discuss with Sponsor the need to repeat these examinations. Repeat examination(s) will be done on a patient by patient basis.	Provided more clarification on examinations to be performed at early end of treatment or withdrawal from Part 2.
Section 10.3.5 Procedure and consequence for patient withdrawal from study		
Appendix A	Deleted the reference to an operation manual. Updated the mutation table and added T369M variant where history of RBD is required.	There is no such operational manual in the study.

Section # and Name	Description of Change	Brief Rationale
Section 17 Appendix	Added 2 new appendix, Appendix T Country specific requirements and Appendix U Protocol amendment history.	To add country specific requirements and prior amendment history.
Throughout	Minor editorial, typographical error corrections and document formatting revisions	Minor, therefore have not been summarized.

Amended protocol 05: 06-Jun-2017

This amended protocol (Amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The protocol is being amended mainly to incorporate feedback received from Investigators to facilitate enrollment and clarify some sections.

Major changes specific to this global amendment include the following:

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary (Study population, Inclusion Criteria); Section 4.2.1 Study rationale Section 7.1 Inclusion criteria	Inclusion criteria I 03 updated: Increase the patient upper age limit from 70 to 80 years old.	Given the acceptable safety and tolerability profile of venglustat seen in healthy volunteers and other patient populations at doses used in the current study, the average age of a Parkinson's disease patient, and Parkinson's disease guidelines within certain countries, it is appropriate to increase the upper age limit from 70 to 80 years in this trial.
Clinical Trial Summary (Study population, Exclusion Criteria); Section 7.2.2 Exclusion criteria Section 7.2.3 Exclusion criteria	Revise exclusion criterion E 20 to specify the prohibited duration of medication use. Revise exclusion criterion E 25 to delete the words "of screening."	Specify the prohibited duration of the medication's use, ie, within 30 days or 5 half-lives, whichever is longer, prior to randomization Delete "of screening" which was written by error in this exclusion criteria.
Section 6.1 Description of the study	Clarify that the internal review committee can comprise individuals involved in the conduct of the study	Because the data reviewed by this internal review committee will be blinded, they will be reviewed by individuals from the clinical trial team involved in the study conduct.
Throughout	<ul style="list-style-type: none"> Minor editorial changes to punctuation, grammar, and syntax. Table of contents were updated. Flow charts were updated to reflect the study procedures in Section 10. Sections, table footnotes and citations, and references were renumbered. Tables were reformatted. Abbreviations were updated in text, Section 3 (Abbreviations), and table footnotes. References were updated. 	Minor, therefore have not been summarized.

Amended protocol 04 (local for Japan): 01-Feb-2017

This amended protocol (Amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The protocol is being amended primarily to incorporate feedback received from Health Authorities on the clinical trial notification in Japan.

Major changes specific to Japan sites include the following:

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary (Assessment Schedule); Section 1.2 Graphical study design; Section 1.3.3 Part 2: Study schedule of assessment (Period 3 and 4); Section 9.3.3.3 Vital signs; Section 10.1.2.10 Long-term follow-up period (Period 3)	Change the visit interval, as every 3 months in the long-term follow up period in Part 2 is only for Japanese patients.	Additional visits (W65, W91, W117, and W143), for Japanese patients only, between the 6 month follow-up visits in the LTFU (Period 3) of Part 2 are added so Japanese patient safety can be monitored by a healthcare professional every 3 months.
Section 1.3.1 Part 1 Study schedule of assessments; Section 10.1.1.2 Visit 2: Randomization/baseline at Week 0/Day 1	Changes in description of hospitalization from Visit 2 through Visit 4 in Part 1 for Japanese patients.	To ensure Japanese patients' safety in the beginning of the treatment period in Part 1 (dose escalation phase).
Section 4.2.2 Risk assessment	Addition of the new information to the risk assessment.	The delayed development of fetus and related findings in the skeletal system in the non-clinical toxicology study on embryo-fetal development were added as the information to be shared.
Section 8.8.1.1 Temporary use of strong or moderate CYP3A4 inducers or inhibitors; Section 10.3.3 List of criteria for permanent treatment discontinuation	Specified the patient management in terms of study drug administration rules when a temporary use of a strong or moderate CYP3A4 inducer or inhibitor is required.	Description of the impact on study drug administration in case such concomitant medication is required was added to specify the patient management in terms of study drug administration rules.
Appendix C	Guidance on contraceptive methods and collection of pregnancy information updated.	To provide some additional information on the reproductive potential of bilateral tubal ligation, a definition of post-menopausal state, some clarifications on contraceptive methods to be followed in both male and female during the study, and the non-approval status of the

		drugs and medical device in Japan.
Throughout	<ul style="list-style-type: none"> Administrative changes. Minor editorial changes to punctuation, grammar, and syntax. Sections, table footnotes and citations, and references were renumbered. Tables of contents were updated. Abbreviations were updated and were listed in revised Section 3, Abbreviations. 	Minor, therefore have not been summarized.

Amended protocol 03: 08-Dec-2016

This amended protocol (Amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The protocol is being amended to primarily incorporate feedback received from Health Authorities in the United States and Japan, as well as other changes deemed necessary by the Sponsor. Please note a separate local amendment was previously issued for patients enrolled in Japan and several changes from the Japan amendment are being incorporated into this global amendment, as applicable.

Major changes specific to this global amendment include the following:

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary (study population); Section 7.1 Inclusion criteria Section 7.2 Exclusion criteria	Inclusion criteria I 01, I 02, I 03, I 05 and exclusion criteria E 14 updated.	I 01. and I 02. were clarified, indicating that both do not need to be met in order to qualify (just one or the other). I 03. was clarified in order to appropriately define the Japanese adult patient population age range. I 05. was clarified to state that patients on stable PD medication need to be on 'ON' state when scoring the Hoehn and Yahr scale at baseline. E 14. was clarified to state forms and duration of contraception.
Throughout	<ul style="list-style-type: none"> Administrative change. Minor editorial changes to punctuation, grammar, formatting, abbreviations, and syntax. Sections and table footnote 	Minor, therefore have not been summarized.

annotations renumbered.

- In Part 2 Treatment Phase, site Visit 4 at Week 0, Day 3 has been removed from Section 1.3.2 Part 2: Study schedule of assessments (Periods 1 and 2) flowchart for consistency (it was added to original protocol in error). Therefore, visit numbers throughout the protocol have been renumbered; Section 10.1.2.4 has been removed.

Amended protocol 02 (local for Israel): 15-Aug-2016

This amended protocol (Amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Due to local regulatory approval in Israel for DNA material collection, and since there will be sufficient DNA samples collected in other countries for this study, it is the Sponsor's proposal to not to collect DNA samples from patients enrolled in any Israeli site.

Major changes specific to this global amendment include the following:

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Study flow chart Section 9.6.1 Optional DNA stored sample, Section 10.1.1.2, Section 10.1.2.2, Section 10.1.2.4, Section 12.2 Informed consent	Remove DNA sample collection for patients in Israel.	Due to local regulatory approval in Israel for DNA material collection, and since there will be sufficient DNA samples collected in other countries for this study, it is the Sponsor's proposal to not to collect DNA samples from patients enrolled in any Israeli site.

Amended protocol 01 (local for Japan): 15-Nov-2016

This amended protocol (Amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The Sponsor proposed to include Japanese Parkinson's disease patients carrying a GBA mutation (GBA-PD) in the planned global Phase 2 clinical study since, based on preliminary data, the probability of differences in PK and drug response between Japanese and non-Japanese

populations was expected to be low. In addition, the characterization of GZ/SAR402671 safety, tolerability, PK, and pharmacodynamics profile in Japanese GBA-PD patients may be more informative than in healthy Japanese subjects.

It was not feasible for Japan to participate in Part 1 of the global Phase 2 clinical study as too few Japanese patients would be enrolled, given there were only 5 patients per dose cohort planned in Part 1 of the global study. Sanofi/Genzyme has considered it scientifically appropriate to include Japan in the multiple-country study with embedding Japanese dose escalation scheme instead of Phase 1 study in Japanese patients.

Accordingly, the following modifications were proposed to the global study to optimize GZ/SAR402671 for characterization in Japanese GBA-PD patients since the number of diagnosed Japanese GBA-PD was very limited. The dose escalation phase (Part 1) in Japanese GBA-PD patients was conducted exactly as the dose escalation phase outside of Japan, except for a 3:1 randomization ratio as opposed to a 4:1 randomization ratio outside of Japan. In major movement disorder centers, both within and outside of Japan, the majority of such centers had ≤ 10 patients with a known mutation that would be eligible for this. Other changes allow for clarifications of the original intent of the protocol.

Major changes specific to this global amendment include the following:

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary (study design); Section 6.1 Description of the study	The study design was updated in order to describe the study duration, sample size and randomization ratio being used for Japanese GBA-PD patients in each part of this trial.	It is not feasible for Japan to participate in Part 1 of the global Phase 2 clinical study as too few Japanese patients would be enrolled, given there are only 5 patients per dose cohort planned in Part 1 of the global study.
Clinical trial summary (study population); Section 7.1 Inclusion criteria	I03 was clarified in order to appropriately define the Japanese adult patient population age range.	Sanofi/Genzyme has considered it scientifically appropriate to include Japan in the multiple-country study with embedding Japanese dose escalation scheme instead of Phase 1 study in Japanese patients.
Throughout	<ul style="list-style-type: none"> Administrative change. Minor editorial changes to punctuation, grammar, formatting, abbreviations, and syntax. Sections and table footnote annotations renumbered. In Part 2 Treatment Phase, site Visit 4 at Week 0, Day 3 has been removed from Section 1.3.2 Part 2: Study schedule of assessments (periods 1 and 2) flowchart for consistency (it was added to original protocol in error). Therefore, visit numbers throughout the protocol have been renumbered; Section 10.1.2.4 has been removed. 	Minor, therefore have not been summarized.