Official Title: A Phase 1, Open-Label, Positron Emission Tomography Study in Healthy Adult Subjects to Determine the Relationship Between Plasma Concentration and Brain Target Occupancy of ASN51 Following a Single Oral Dose

NCT ID: NCT06390098

Document Date: Protocol Version 2.0: 19 May 2021

CLINICAL TRIAL PROTOCOL

A Phase 1, Open-Label, Positron Emission Tomography Study in Healthy Adult Subjects to Determine the Relationship Between Plasma Concentration and Brain Target Occupancy of ASN51 Following a Single Oral Dose

Protocol Number: ASN51-102

Original Protocol: Version 2.0, 19 May 2021

Investigational Product: ASN51 (O-linked-β-N-acetylglucosaminidase inhibitor)

Indication: Alzheimer's Disease

IND Number: TBD

Trial Registration: ClinicalTrials.gov: *not yet assigned*
EudraCT: 2021-001918-10

Sponsor: Asceneuron S.A.
EPFL Innovation Park
Bâtiment B, CH-1015 Lausanne, SWITZERLAND

Primary Medical Officer (EU):
Name: [redacted] M.D., M.Sc., Ph.D.
Title: [redacted] Early Clinical Development
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Name: [redacted] M.D.
Title: [redacted] Clinical Development and Translational Medicine
Email: [redacted]
Phone (U.S. Cell): [redacted]

Emergency On-Call Physician:

[redacted]

Compliance Statement:

This clinical trial is to be performed in compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements.

Confidentiality Statement:

SPONSOR SIGNATURE PAGE

Protocol Title: A Phase 1, Open-Label, Positron Emission Tomography Study in Healthy Adult Subjects to Determine the Relationship Between Plasma Concentration and Brain Target Occupancy of ASN51 Following a Single Oral Dose

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As the Sponsor representative, I confirm that the Sponsor will comply with all Sponsor obligations as detailed in all applicable regulations and guidelines. I will ensure the Investigator is informed of all relevant information that becomes available during the conduct of this trial.

[redacted]

Date May 20, 2021

INVESTIGATOR AGREEMENT

Protocol Title: A Phase 1, Open-Label, Positron Emission Tomography Study in Healthy Adult Subjects to Determine the Relationship Between Plasma Concentration and Brain Target Occupancy of ASN51 Following a Single Oral Dose

Protocol Number: ASN51-102

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As an Investigator, I agree to comply with all protocol specifications and ensure the safety of subjects enrolled at my site. I agree to conduct the trial in accordance with applicable regulations, Research Ethics Committee (REC)/Medicines Healthcare and products Regulatory Agency (MHRA)specifications, and ICH GCP guidance. I will ensure site personnel understand their obligations in the conduct of this trial and will provide site personnel with all relevant information that becomes available during the conduct of this trial.

Principal Investigator Name: [redacted] MBBS

[redacted]

Principal Investigator Signature: [redacted] _____

Date: 20-May-2021

INVESTIGATOR AGREEMENT

Protocol Title: A Phase 1, Open-Label, Positron Emission Tomography Study in Healthy Adult Subjects to Determine the Relationship Between Plasma Concentration and Brain Target Occupancy of ASN51 Following a Single Oral Dose

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Principal Investigator Name: [redacted]

Institution Address: [redacted]

Principal Investigator Signature: _ [redacted] _____

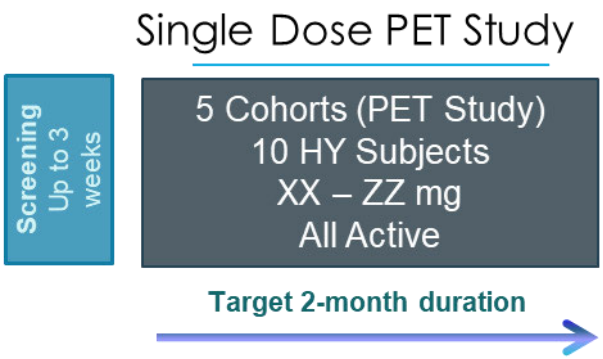
Date: 21 May 2021

2.0 STUDY SYNOPSIS

Title	A Phase 1, Open-Label, Positron Emission Tomography Study in Healthy Adult Subjects to Determine the Relationship Between Plasma Concentration and Brain Target Occupancy of ASN51 Following a Single Oral Dose
Development Phase	Phase 1
Sites	Single center
Indication	ASN51 is indicated for the treatment of adults with Alzheimer's Disease (AD)
Investigational Drug and Dosage Form	Investigational drug: ASN51 ([redacted] ASN51)
Route of Administration	Oral

Study Design

ASN51-102 is an open phase 1 safety, tolerability, pharmacokinetics and pharmacodynamics study of oral ASN51 in healthy adult subjects.



Open-label single oral doses of ASN51 will be administered to up to 10 (aged 25-55 years, inclusive) healthy adult male or female subjects to investigate the target brain occupancy of O-GlcNAcase by ASN51.

Each subject will have up to 3 imaging sessions, with one scan in each session. In the first imaging session, subjects will have a baseline PET scan. In the second and third imaging sessions, subjects will receive a single oral dose of ASN51, followed by an on-treatment PET scan. Subjects will receive an intravenous dose of the radiolabeled tracer, [^{18}F]-IMA601, at the start of each PET scan.

Selection of the dose levels to be administered and the timing of the PET scans relative to the time of study drug administration will be made by the safety review committee (SRC) depending on the results of the single ascending dose tolerability study ASN51-101 in healthy young adult subjects and the results of the previous study drug administrations in study ASN51-102.

Study Objectives

Primary Objective:

- To assess the brain O-GlcNAcase occupancy using [^{18}F] IMA601 PET, following a single oral dose of ASN51

Secondary Objectives:

- To assess the relationship between the plasma concentration of ASN51, and the time-course of brain O-GlcNAcase occupancy using [^{18}F]-IMA601 PET, following a single oral dose of ASN51
- To assess the single dose safety and tolerability of ASN51 in healthy adult subjects under fasted conditions

Study Population

Inclusion Criteria:

Individuals meeting all the following **inclusion criteria** and none of the **exclusion criteria** will be eligible to participate None of the inclusion criteria are eligible for re-screening. No waivers will be granted and any deviation from below will get recorded as a major protocol deviation. An exception can apply for subjects who meet the inclusion and exclusion criteria, but then miss a cohort that is filled and so they are no longer eligible due to lapse of the 3-week screening window; these subjects may be rescreened. Screening period duration is 3 weeks.

1. Healthy as determined by the Investigator, based on a medical evaluation including medical history physical examination, neurological examination, laboratory tests and cardiac monitoring.
2. Men or women aged 25-55 years, inclusive (age range was selected on grounds of radiation burden).
3. Women of child-bearing potential with partners of child-bearing potential (see Section 9.10.7 for definitions) must agree to use highly effective contraception (per CTFG 2020; bilateral tubal occlusion, hormonal contraception associated with inhibition of ovulation except oral contraception, intra-uterine device with or without intrauterine hormone-releasing system, sexual abstinence in relation to the preferred and usual lifestyle of the subject) from at least 28 days before first tracer dosing through 30 days after last dose of IMP. All women of child-bearing potential must have a negative pregnancy test result before administration of test article. Vasectomized partner is also an accepted a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomized partner has received medical assessment of the surgical success.
4. Women of non-childbearing potential must be postmenopausal [the last menstrual period was at least 12 months ago, and FSH at screening confirms postmenopausal status, or have no uterus, ovaries, or fallopian tubes). Women who are surgically sterile must provide documentation of the procedure by an operative report or by ultrasound.
5. Non-sterilized male subjects who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from 1 day prior to the first tracer administration throughout the total duration of the treatment period and 90 days

after the last dose of IMP. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period.

6. Body weight > 50.0 kg for men and > 45.0 kg for women and Body Mass Index within the range 18.5-30.0 kg/m2 (inclusive).
7. Subjects must understand the nature of the study and must provide signed and dated written informed consent in accordance with local regulations before the conduct of any study-related procedures.
8. Subjects must be, in the opinion of the Investigator, able to participate in all scheduled evaluations, likely to complete all required tests, and likely to be compliant.
9. Subjects must be fluent in the local language.
10. Subjects must agree not to post any personal medical data related to the study or information related to the study on any website or social media site (e.g., Facebook, Twitter, etc.) until the trial has completed.

Individuals who meet any of the following **exclusion criteria** will not be eligible to participate:

1. A positive urine drug screen/alcohol test at Screening or Day -1.
2. Any history of psychiatric disorders, including substance use disorders, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria.
3. A diagnosis of intellectual disability (intellectual developmental disorder) or mental retardation.
4. Significant suicide risk as assessed by C-SSRS.
5. A positive Hepatitis B surface antigen or positive Hepatitis C antibody result at Screening.
6. A positive test for human immunodeficiency virus (HIV) antibody at Screening.
7. Alanine aminotransferase or aspartate aminotransferase levels greater than 1.5 times the upper limit of normal (ULN) at Screening or between Screening and first dose of tracer.
8. Frequently used any tobacco-containing (e.g., cigar, cigarette, or snuff) or nicotine-containing product (e.g., nicotine chewing gum, nicotine plasters, or other product used for smoking cessation) within 3 months prior to first dose of tracer. Frequent use is defined as 3 or more days per week. Use of any tobacco- or nicotine-containing product is prohibited within 1 week of first dose of tracer.
9. History of regular alcohol consumption within 12 months of the study defined as an average weekly intake of >21 alcoholic units/week for men or >14 alcoholic units/week for women.
10. Regularly consumed (e.g., more days than not) excessive quantities of xanthine-containing beverages (e.g., more than five cups of coffee or the equivalent per day) within 30 days prior to Screening or between Screening and first dose of tracer.
11. Received or used an investigational product (including placebo) or device within the following time period prior to the first tracer dosing day in the current study: 90 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
12. Other than exceptions outlined in Section 9.10, use of prescription or non-prescription drugs, vitamins, herbal, and dietary supplements (including St John's Wort) within 7 days (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study tracer medication.

13. History of clinically significant sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
14. Loss of more than 400 mL of blood within 3 months prior to first dose of tracer, i.e., blood donor.
15. A positive serum pregnancy test or lactation.
16. A history or presence of any disease, condition, or surgery likely to affect drug absorption, distribution, metabolism, or excretion. Subjects with a history of cholecystectomy should be excluded.
17. A history or presence of a clinically significant hepatic, renal, gastrointestinal, cardiovascular, endocrine, pulmonary, ophthalmologic, immunologic, hematologic, dermatologic, or neurologic abnormality.
18. A clinically significant abnormality on physical examination, neurological examination, ECG, or laboratory evaluations at screen or between screen and first tracer dose administration.
19. A corrected QT interval measurement corrected according to the Fridericia rule (QTcF) > 450 msec for males and 470 msec for females during controlled rest at screen or between screen and first tracer dose administration, or family history of long QT syndrome.
20. Any clinically significant abnormalities in rhythm, conduction, or morphology of the resting ECG and any abnormalities in the 12-lead ECG that, in the judgement of the Investigator or Medical Monitor, may interfere with the interpretation of QTc interval changes, including abnormal ST-T-wave morphology or left ventricular hypertrophy.
21. PR (PQ) interval shortening < 120 msec (PR < 120 msec but > 110 msec is acceptable if there is no evidence of ventricular pre-excitation).
22. PR (PQ) interval prolongation (>220 msec), intermittent second- (Wenckebach block while asleep or in deep rest is not exclusionary) or third-degree AV block.
23. Persistent or intermittent complete bundle branch block (BBB), incomplete bundle branch block (IBBB), or intraventricular conduction delay (IVCD) with QRS > 120 msec.
24. A clinically significant vital signs abnormality at screening This includes, but is not limited to, 3 measurements (each 5 minutes apart) in the seated position: (a) systolic blood pressure < 90 or >140 mmHg, (b) diastolic blood pressure <50 or > 95 mmHg, or (c) heart rate < 45 or >100 beats per minute. The average of the 3 measurements should be used to assess eligibility at screening.
25. Significant (> 10%) weight loss or gain within 30 days prior to Screening and first tracer dose administration.
26. A history of seizure. History of a single benign febrile convulsion of childhood is permitted.
27. A history of head trauma, including closed head injury with loss of consciousness.
28. A history of symptomatic orthostatic hypotension (i.e., postural syncope).
29. A history of neuroleptic malignant syndrome.
30. A history of chronic urinary tract infections.
31. The subject is, in the opinion of the Investigator or Medical Monitor, unlikely to comply with the protocol or is unsuitable for any reason.

32. Currently employed by Asceneuron SA or by a clinical trial site participating in this study, or a first-degree relative of an Asceneuron SA employee or of an employee at a participating clinical trial site.
33. Unsatisfactory venous access
34. Significant exposure to ionizing radiation as part of research (defined as ICRP category IIb or above: no more than 10 mSv in addition to natural background radiation including this trial), within the previous 12 months prior to first tracer dose administration.
35. Unsuitable or unwilling to undergo the imaging procedures, as determined by an MRI safety questionnaire. Reasons for exclusion include but are not limited to presence of a cardiac pacemaker or other implanted electronic device; ferromagnetic metal foreign bodies, intracranial aneurysm clips or other metallic objects; non-MRI compatible heart valves; inner ear implants; or a history of claustrophobia.
36. Significant structural brain abnormality, as determined by MRI.
37. Contraindication for arterial cannulation: Allen's test indicating potential risk in placement of the arterial cannula.
38. Subjects with a COVID-19 vaccination within two weeks of screening or due to receive second dose of COVID-19 vaccine while participating in the study.

Trial Procedures and Assessments

After assessing eligibility during a 3-week screening period, up to 10 healthy male subjects or female subjects will participate in the study. Subjects will be admitted to the study center on Day -1, the day before (first) tracer administration for baseline assessments and to (re-)confirm eligibility. Subjects will stay in the clinical unit for 5 days (4 nights) for imaging sessions 2 and 3. For the baseline PET scan, subjects may leave the unit in the evening. Blood samples for PK analysis will be collected pre-dose and at specified time points up to Day 4 post-dose (sessions 2 and 3). Physical examinations, vital signs, ECG, will be performed at specified times. Adverse events will be recorded throughout the study. A follow-up visit will take place 7 days (±3 days) after receiving the last tracer dose. For details regarding the timing of specific procedures, see Table 1.

Safety Review Committee (SRC):

The study will be monitored by an SRC. The SRC is intended to ensure the treatment does not pose undue risk to subjects. Safety and pharmacokinetic data will be assessed by the SRC prior to start of the study to determine the first dose level to be administered. For details regarding study safety oversight and SRC, see Section 7.5. The SRC will be composed of the following core individuals:

- Principal Investigator (PI) or delegate
- Asceneuron SA medical monitor or delegate (must be a physician).

Endpoints

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Primary Outcome Measures

- Pharmacodynamic (PD): [^{18}F]-IMA601 regional total volume of distribution (VT) at each brain scan.

<table>
<tr><td colspan="2">Secondary Outcome Measures
• Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) up to follow-up
• Serious Adverse Events (SAEs) up to 4 weeks after last administration
• Laboratory tests
• Vital signs
• ECG
• Physical examination
• Pharmacokinetic (PK): plasma concentration of ASN51at the time of each post-dose PET scan.
• PK/PD: relationship between ASN51 exposure and receptor occupancy.</td></tr>
<tr><td>Statistical Considerations</td><td>A full description of the statistical evaluations, general considerations, and procedures for handling missing data will be provided in the Statistical Analysis Plan (SAP) and, if applicable, in the data management plan (DMP). The SAP will provide full details of the analyses, the data displays and the algorithms to be used for data derivations.
In general, trial data will be reported using summary tables, figures, and data listings. Descriptive statistics will be used to summarize the data. For continuous variables, the mean, standard deviation, median, minimum, and maximum will be provided. For discrete data, incidence and percentages will be provided. Statistical tests will be 2-sided at the alpha level of 0.05, unless stated otherwise.
For the analysis of the PET data, O-GlcNAcase occupancy will be quantified for each post-dose PET scan as the fractional change from the subject's baseline PET scan. Decreases in regional total volume of distribution (V_T) from baseline to post-dose scans will be interpreted as an effect of O-GlcNAcase occupancy by ASN51. The Lassen plot will be used to estimate the target occupancy by calculating the changes of V_T between baseline and post-dose against baseline V_T for 14 brain regions of interest. The non-displaceable volume of distribution (V_{ND}) will be constrained to be equal for all scans within a subject.
Occupancy estimates will be plotted against plasma concentrations of ASN51, corresponding to the start of each post-dose PET scan. The following model will be fitted to the occupancy data set.
$RO = 100 \times (C_p / (Cp + EC_{50}))$
Where RO is the estimated receptor/target occupancy (%), C_p is the measured plasma concentration of ASN51 (ng/mL) and EC_{50} is the plasma concentration of ASN51 that corresponds to 50% receptor/target occupancy.
Treatment-emergent AEs will be tabulated and summarized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). The number and percentage of patients who experienced AEs coded with the same PT and SOC will be summarized by treatment group (in descending order according to the incidence in the investigational study drug</td></tr>
</table>

	group). Adverse events will also be tabulated by severity and by relationship to study drug. Summary tables will be accompanied by individual subject listings broken down by treatment group, including pre-dose events. SAEs will be listed and summarized similarly to AEs. Reasons for death will only be listed. Reasons for premature discontinuation of study drug will be listed and summarized by frequency tables. ECG variables, vital sign measurements and laboratory measurements will be summarized at each time point using mean, median, standard deviation, min, max, number of available observations, and change from baseline. Individual patient listings of ECG data, vital signs data and laboratory measurements will be provided. For PK and PD secondary endpoints, individual subject listings will be provided. Mean and individual plasma concentration-time profiles for ASN51 will be presented graphically for each group. PK variables will be summarized using arithmetic mean, STD, geometric mean, median, minimum, maximum, and %CV. Exploratory data-driven analyses will be performed with the caveat that any statistical inference will not have any confirmatory value. Listings of all individual subject data will be produced.
Determination of Sample Size	The trial is hypothesis generating, so no formal calculation of sample size is appropriate. The sample size of at most 10 subjects is considered adequate to allow modelling of the relationship between ASN51 plasma concentrations and the occupancy of O-GlcNAcase and is within the range generally accepted for PET studies. Enrolment of subjects into the study will be stopped as soon as the brain O-GlcNAcase occupancy versus ASN51 plasma concentrations is sufficiently characterized in opinion of the SRC.

Table 1: Visit and Assessment Schedule for Each Dose Level[20]

	Screening[0]		Imaging session 1 [Baseline PET] [0, 2]		Imaging session 2 [on-treatment] [2, 3]			Imaging session 3 [on-treatment] [2, 3]			Follow-up visit or ET [4]
	Visit 1	Visit 2 [MRI]	Visit 3 (in-patient)		Visit 4 (in-patient)			Visit 5 (in-patient)			
Day(s) (relative to PET scan)			Day –1	Day 1	Day –1 7 days post 1st PET	Day 1	Day 4	Day –1 7-14 days post 2nd PET	Day 1	Day 4	Day 8
Informed consent	X										
Inclusion/exclusion criteria	X		X		X						
Demographics	X										
Medical/surgical history	X										
Allen's test	X			X		X			X		
Admission			X		X			X			
Inpatient stay[5]			←	→	←	→		←	→		
MRI scan[6, 7]		X									
Venous cannulation[8]				X		X			X		
Arterial cannulation				X		X			X		
Administration of [^{18}F]-IMA601[9]				X		X			X		
PET scan[10]				X		X			X		
Dose of study drug [3, 11]						X			X		
Discharge[12]				X			X			X	
Safety assessments											
Physical and neurol. examination[13]	X				X[13]			X[13]			X
Pregnancy and FSH[14]	X	X	X		X			X			X
Height, weight & BMI[15]	X	X									
Vital signs[16]	X		X			X			X		X
12-lead ECG[17]	X		X			X			X		X
Serology (including HBsAg, anti-HCV)	X										

	Screening[0]		Imaging session 1 [Baseline PET] [0, 2]		Imaging session 2 [on-treatment] [2, 3]			Imaging session 3 [on-treatment] [2, 3]			Follow-up visit or ET [4]
	Visit 1	Visit 2 [MRI]	Visit 3 (in-patient)		Visit 4 (in-patient)			Visit 5 (in-patient)			
Day(s) (relative to PET scan)			Day –1	Day 1	Day –1 (7 days post 1st PET)	Day 1	Day 4	Day –1 (7-14 days post 2nd PET)	Day 1	Day 4	Day 8
Hematology, biochemistry, coagulation, and urinalysis	X		X		X		X[19]	X		X[19]	X
Urine drug and cotinine screen and Alcohol Urine Test	X		X		X			X			
C-SSRS	X										X
Blood Samples											
PK plasma sampling[18]						X	X		X	X	
Arterial Blood Sampling				X		X			X		
Ongoing Subject Review											
Concomitant Medicines	◄----------										----------►
Adverse Events	◄----------										----------►

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; ET = Early Termination; HBsAg = Hepatitis B surface antigen; HCV = Hepatitis C virus; MRI = Magnetic resonance imaging; PET = Positron emission tomography; PK = Pharmacokinetics; WOCBP = Women of childbearing potential.

1. **Screening Assessments:** Screening will be within 21 days before imaging session 1.
2. **Imaging Admissions:** Admission for imaging session 2 will be within 7 days after the baseline PET scan; and admission for imaging session 3 will be within 7–14 days after imaging session 2.
3. **PET Repeat/Reschedule:** In the case of technical failures (i.e., such as unsuccessful tracer synthesis or a PET scanner malfunction etc.) a PET scan may need to be repeated or rescheduled. In such cases, subjects may be asked to stay for up to 48 h longer in each imaging session or repeat an imaging session at a later date. If the failure affects imaging session 1 before administration of radioactivity, the baseline scan may be repeated. If the failure affects imaging session 1 after administration of radioactivity, the baseline scan may be repeated once. If the technical failure affects imaging sessions 2 or 3 (after the subject has received an ASN51 dose), a third imaging session may be required, after a 7-day washout of the last dose of ASN51. Subjects will receive no more than 3 single doses of ASN51, or 3 doses of [^{18}F]-IMA601 during the study.
4. **Follow-up Visit or ET:** A follow up visit will be 7 days (±3 days) after the last on-treatment PET scan. Additional follow-up by telephone for any potential SAEs will be 28 days (±3 days) after the last on-treatment PET scan.
5. **Inpatient Stay:** Subjects will be admitted on Day –1 of imaging sessions 1, 2 and 3. Subjects will remain inpatient for both imaging sessions 2 and 3 for up to 72 h after dosing. In session 1, subject may leave the clinical unit in the evening of Day 1.
6. **MRI Questionnaire:** Subjects will complete an MRI questionnaire before the MRI scan, to exclude unsuitable subjects.

7. **MRI Scan:** Screening MRI will occur once all other screening results are available. If a subject is being re-screened (i.e. missed cohort) and there is already a recent MRI scan available within 3 months from their first screening period (ie if subjects were a reserve subject for a previous group but were not dosed and are no longer within the screening window) they do not need to have a repeat MRI scan.
8. **Venous cannulation:** One for administration of [^{18}F]-IMA601 (all imaging sessions) and one PK sampling (imaging sessions 2 and 3) (two venous cannulae be used).
9. **[^{18}F]-IMA601 Administration:** At the start of each PET scan.
10. **PET Scan:** Subjects will have one baseline PET scan during imaging session 1, and two on-treatment PET scans during imaging sessions 2 and 3. For session 1, subjects will receive dosing water after a minimum of 10 hours fast (no food or drink except water) and will fast for a further 4 h after their dose with the PET scan done approximately 2 h after taking the dosing water. Other than the dosing water, water is not allowed from 2 h before until 2 h after dosing. The times of on-treatment PET scans for all subsequent groups will be selected based on review of emerging data. Subjects will have no more than 3 PET scans in total during the study.
11. **ASN51 Administration:** Subjects will receive an oral dose of ASN51 following a minimum 10 h fast (no food or drink except water) and will fast for a further 4 h after their dose. Other than the water required to take the study medicine, water is not allowed from 2 h before until 2 h after dosing.
12. **Inpatient Discharge:** Subjects will be inpatient until after their baseline PET in imaging session 1, and until at least 72 h after their dose of study drug in imaging sessions 2 and 3.
13. **Physical Examination:** A full physical and neurological examination will be done at screening visit 1 and at the follow-up visit (or Early Termination visit). All other indicated physical examinations (Day -1 for sessions 2 and 3) should be symptom-directed, and include neurological assessment of cranial nerves, motor, sensation, coordination, reflexes, and gait.
14. **Pregnancy and FSH:** Pregnancy tests in WOCBP only: serum at all timepoints except urine pregnancy test at the MRI visit. FSH at screening only in post-menopausal women. Urine pregnancy test at MRI screening visit to be done at PET site.
15. **Height, Weight, BMI:** BMI and height will be measured at screening visit 1 only.
16. **Vital Signs:** Vital signs consist of systolic and diastolic blood pressure, heart rate, tympanic temperature, and respiratory rate. Assessments will be done at screening, on Day –1 at imaging session 1, pre-dose on Day 1 in imaging sessions 2 and 3, and at follow-up. Single measurements will be made at all time points except screening. At screening, 3 measurements will be made, each 5 minutes apart. Measurements should begin with subjects in a seated position, after they have rested for 5 min. Additional unscheduled assessments may be done at the discretion of the Investigator.
17. **12-Lead ECG:** During the period of residence, ECGs will be recorded at the timepoints indicated. Assessments will be done at screening visit 1, Day -1 of imaging session 1, and pre-dose on Day 1 in imaging sessions 2 and 3, and at the follow-up visit. Single recordings will be done at all time points. Recordings should be made with subjects in a supine position, after resting for 10 min. Additional unscheduled assessments may be done at the discretion of the Investigator.
18. **PK Sampling:** Plasma samples for assay of the ASN51 will be collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h post-dose. Samples scheduled immediately before the PET scan should be taken as close as possible to the planned start of the PET scan samples scheduled for the end of the PET scan should be taken as soon as possible after the PET scan is finished; and samples scheduled during the PET scan should be taken either before or after the PET scan, as close to the scheduled timepoint as possible.
19. Hematology, biochemistry, coagulation, and urinalysis to be taken 72 h post-dose in sessions 2 and 3.
20. T**iming of Assessments:** If more than one assessment is foreseen for a timepoint, PET procedures prevail. All assessments should be staggered in the same order throughout the study with the PK sampling point closest to the scheduled timepoint.

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LIST OF TABLES

4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Definition/Explanation
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease (AD) Assessment Scale-Cognitive Subscale
AE	Adverse Event
Ae	Amount excreted
ALT (SGPT)	Alanine aminotransferase (Serum Glutamic Pyruvic Transaminase)
ALP	Alkaline phosphatase
ANOVA	Analysis of Variance
AST (SGOT)	Aspartate aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under the Curve
$AUC_{0-\infty}$	Area under the curve from time zero to infinity
AUC_{0-t}	Area under the curve from time zero to last concentration above LOQ
BID	Bis in die, twice a day dosing (or QD [once daily]
BLQ	Below Limit of Quantification
BMI	Body mass index
BUN	Blood Urea Nitrogen
C	Celsius
CDR	Clinical Dementia Rating: numeric scale used to quantify the severity of symptoms of dementia
C_{max}	Maximum concentration
CRF	Case Report Form
CNS	Central nervous system
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
dL	Deciliter
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ERP	Event related potential

Abbreviation or Term	Definition/Explanation
EudraCT	European Union Drug Regulating Authorities Clinical Trials is the European Clinical Trials Database of all clinical trials of investigational medicinal products
FDA	Food and Drug Administration
Fe	Fraction (%) of amount excreted
FSH	Follicle stimulating hormone
g	Gram
GFR	Glomerular Filtration Rate
GlcNAc	β-D-N-acetylglucosamine
Hct	Hematocrit
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
IB	Investigator Brochure
HIPAA	Health Information Portability and Accountability Act of 1996
ICH	International Conference on Harmonization
IEC	Institutional ethics committee
IMP	Investigational Medical Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IU	International unit
IV	Intravenous
IWRS	Interactive Web Response System,
kg	Kilogram
L	Liter
LLOQ	Lower limit of quantification
λ_Z	Rate elimination constant
µg	Microgram
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mmHg	Millimeters of Mercury

Abbreviation or Term	Definition/Explanation
MMSE	Mini-Mental State Examination
MOA	Mode of action
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
N	Normal
ng	Nanogram
NFTs	Neurofibrillary tangles
NOAEL	Non observable adverse effect level
OGA	O-linked-β-N-acetylglucosaminidase
O-GlcNAcase	O-linked-N-acetylglucosaminyltransferase or OGA
OGT	O-linked-N-acetylglucosaminyltransferase
PBMC	Peripheral blood mononuclear cell
PD	Parkinson's disease
PET	Positron emission tomography
pH	Hydrogen ion concentration
PHF	Paired helical filament
PR	ECG: time from the beginning of the P wave to the beginning of the QRS complex
Pre	Before
QD	Quaque die, once daily
QRS	ECG: The QRS complex represents the electrical impulse as it spreads through the heart ventricles
PSP	Progressive Supranuclear Palsy
PT	Preferred Term
QT	measurement that represents the total time interval from ventricular depolarization to complete repolarization
QTcB	heart rate-corrected QT interval according to Bazett's formula
QTcF	heart rate-corrected QT interval according to Fridericia's formula
RBC	Red Blood Cell
ROI	Region of interest
SAD	Single ascending dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous

Abbreviation or Term	Definition/Explanation
SD	Standard Deviation
SF	Straight filament
SGOT (AST)	Serum Glutamic Oxaloacetic Transaminase
SGPT (ALT)	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
SRC	Safety Review Committee
$t½$	Terminal elimination phase half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum concentration
ULN	Upper limit of normal
ULOQ	Upper limit of quantification
US	United States
WBC	White Blood Cell
V_{ND}	Non-displaceable volume of distribution
V_T	Regional total volume of distribution

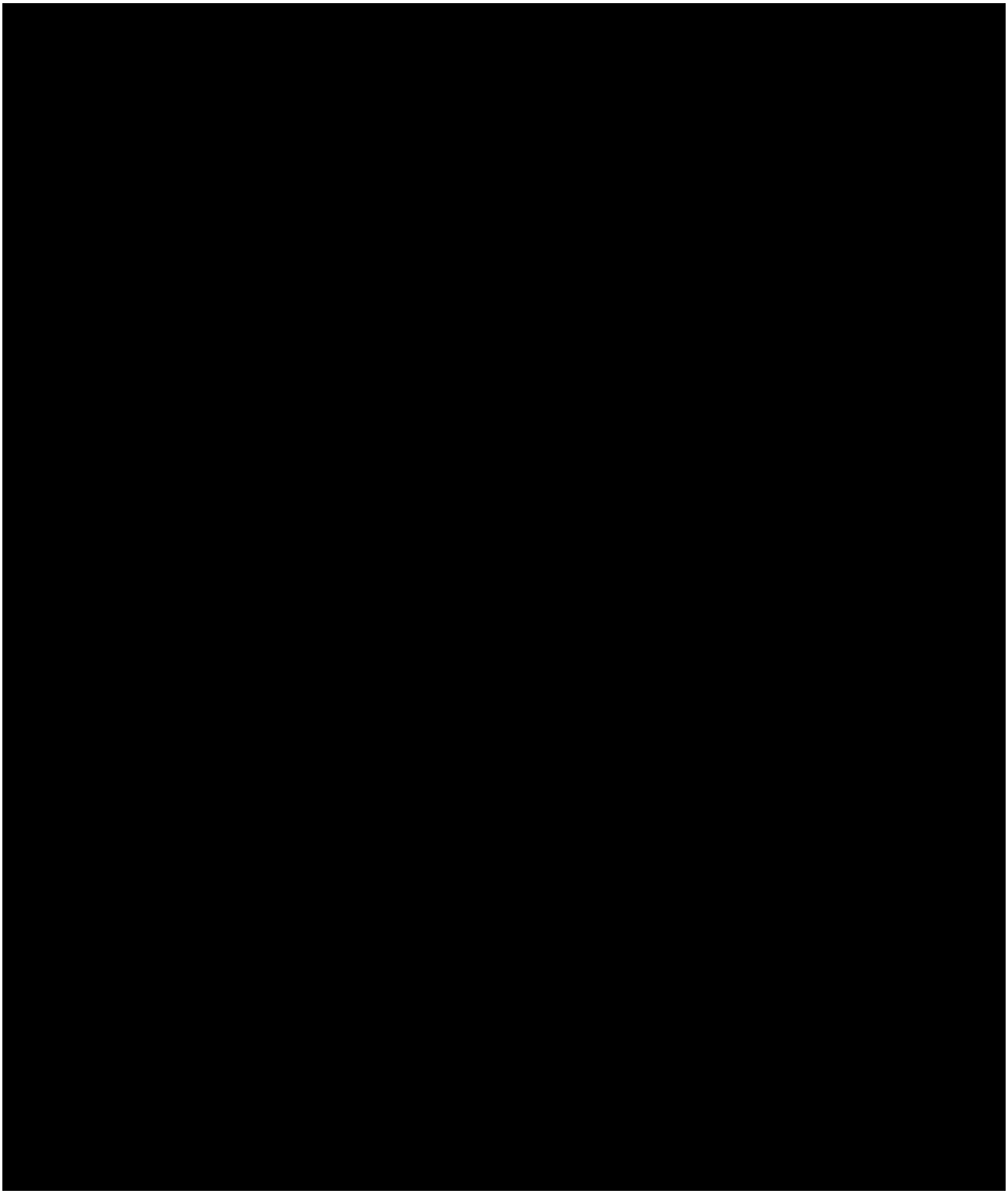
5.0 INTRODUCTION AND RATIONALE

ASN51 [redacted] is under development for the treatment of neurodegenerative diseases caused by intracellular protein aggregates (proteinopathies) in the brain. ASN51 is indicated for the treatment of adults with Alzheimer's Disease (AD).

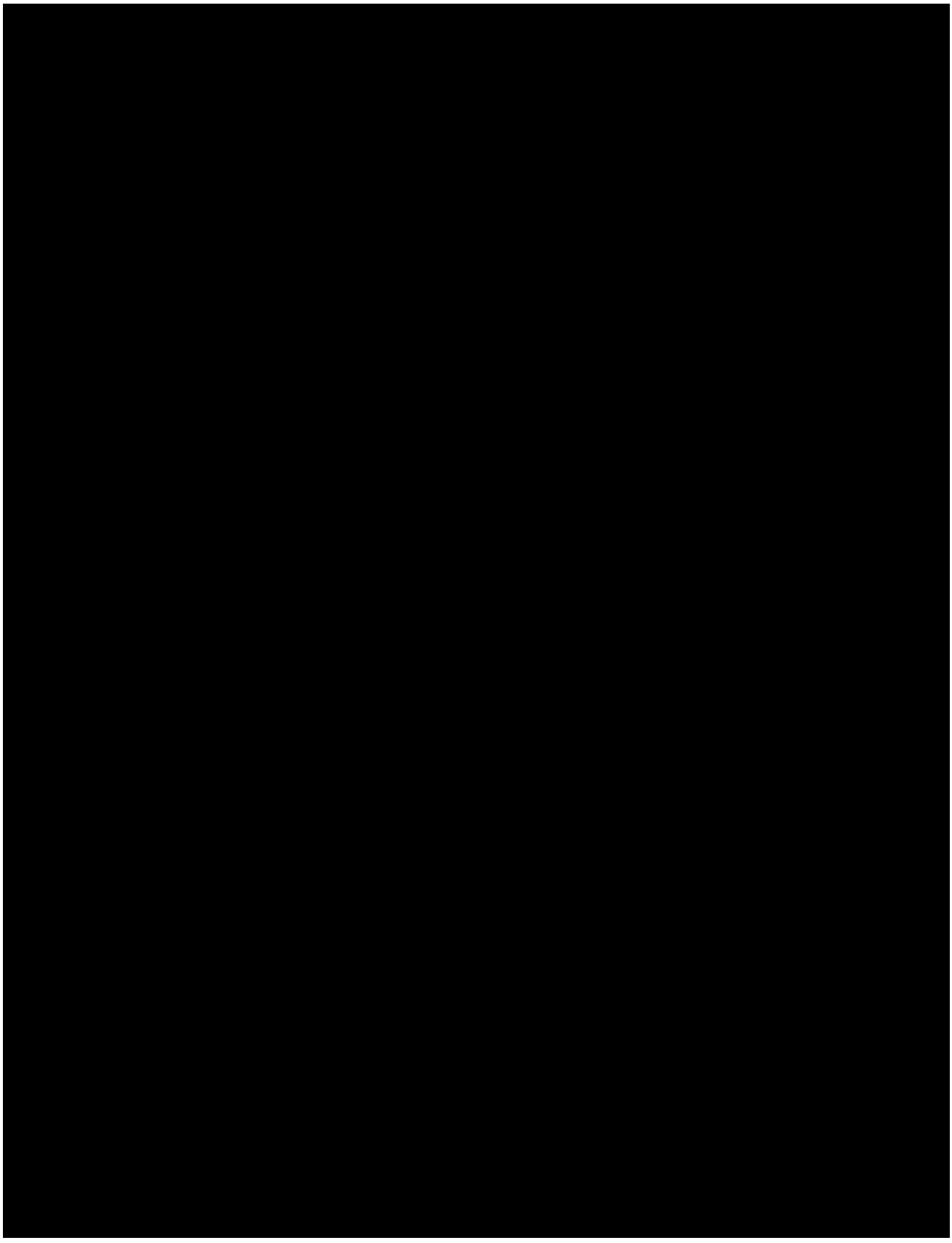
[redacted]

This single dose open study is a human Phase 1 trial in healthy adult (HA) subjects investigating the target receptor brain occupancy of ASN51 by means of PET scans. Establishing the target brain occupancy is important for dose selection because it has been shown [redacted] These data will serve as a basis for the dosing and dosing regimen in further clinical studies. The safety of ASN51 has been evaluated and there were no findings in non-clinical studies to date which would preclude the initiation of the planned Phase 1 study.

5.1 Background: O-GlcNAcylation and Protein Aggregation in Neurodegenerative Disease



5.2 ASN51 Mechanism of Action and Rationale in Alzheimer's Disease



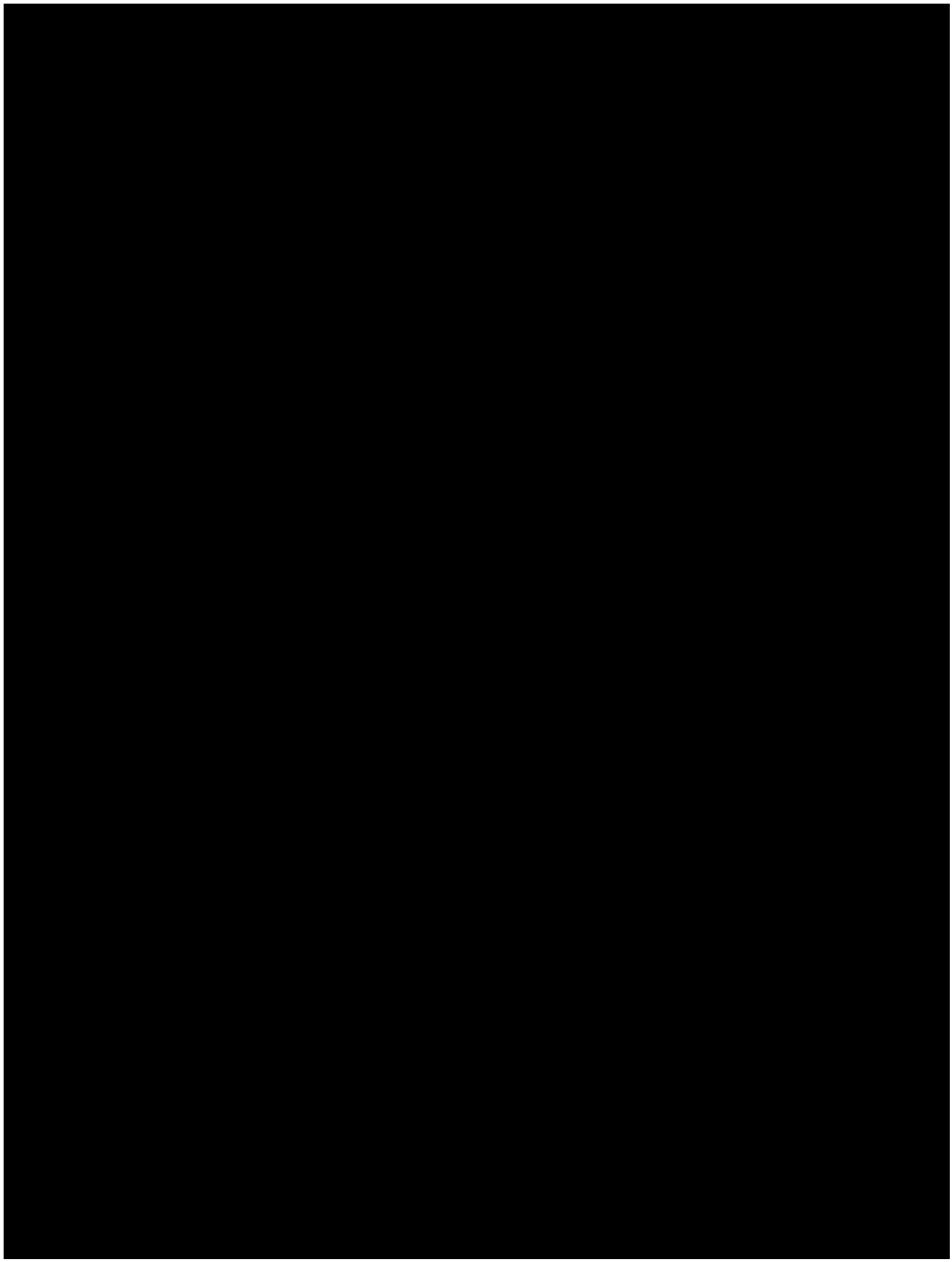
[redacted]

[redacted]

5.3 Nonclinical Studies

Nonclinical findings of potential clinical significance and relevance to this protocol are summarized briefly below; additional information is provided in the IB.

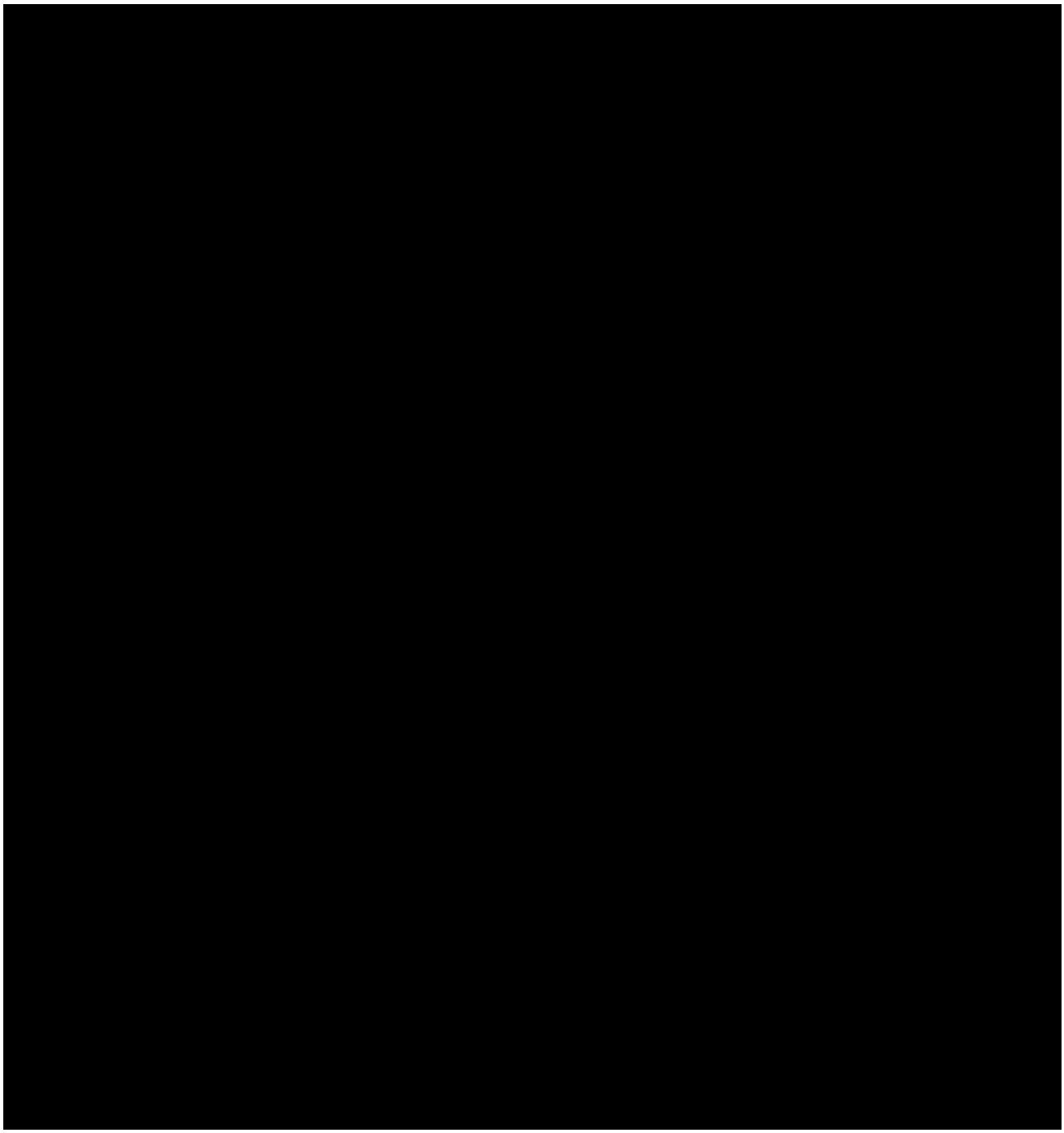
[redacted]



5.4 Clinical Experience

This study will be conducted in parallel to a separate Phase 1 single ascending dose (SAD) tolerability study in healthy young adult subjects (ASN51-101). Safety and pharmacokinetic data for each SAD cohort will be determined in ASN51-101 and will be reviewed by the safety review committee (SRC) prior to dosing in ASN51-102 at each respective dose level (Section 7.5.1). Safety, pharmacokinetic and pharmacodynamic PET data will be assessed by the SRC prior to any further dosing in this study to determine the next dose level to be administered as well as the timing of the next PET scan in relation to the time of the study drug administration. Any dose level set by the SRC will not exceed 85% of the highest well-tolerated dose level in the single rising dose tolerability study ASN51-101.

5.5 Summary of Overall Risks and Potential Benefits



Risks attributable to the COVID-19 pandemic: To address these specific risks, a risk mitigation plan for staff, volunteers, and visitors will be followed throughout the study see also Section 13.4.

6.0 OBJECTIVES

Primary Objective

- To assess the brain O-GlcNAcase occupancy using [^{18}F] IMA601 PET, following a single oral dose of ASN51

Secondary Objectives

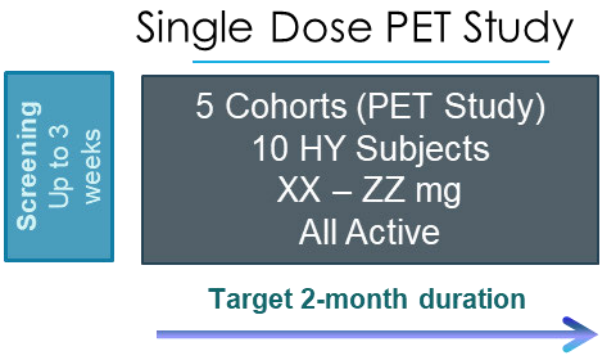
- To assess the relationship between the plasma concentration of ASN51, and the time-course of brain O-GlcNAcase occupancy using [^{18}F]-IMA601 PET, following a single oral dose of ASN51
- To assess the single dose safety and tolerability of ASN51 in healthy adult subjects under fasted conditions

7.0 INVESTIGATIONAL PLAN

7.1 Study Design

This is an open-label, adaptive-design PET study to investigate the occupancy of O-GlcNAcase by ASN51 after single oral doses in healthy adult male and female subjects (aged 25-55 years, inclusive). The study schema is depicted in Figure 2.

Figure 2: Phase 1a ASN51-102 Study Schema



Up to 10 subjects will be enrolled. Each subject will have up to 3 imaging sessions, with one scan in each session. In the first imaging session, subjects will have 240 ml of water followed by a baseline PET scan approximately 2 h later. In the second and third imaging sessions, subjects will receive a single oral dose of ASN51 with 240 ml of water, followed by an on-treatment PET scan. Safety and pharmacokinetic data of the SAD study ASN51-101 will be assessed by the SRC prior to the dosing of the first subject(s) to determine the first dose level to be administered in session 2 after the baseline session 1 and the timing of the PET scans in relation to the study drug administration time. At most 2 subjects will be dosed on the same study day. For subsequent sessions, the dose level and the time of the PET scan in all imaging session 2 and 3 will be determined after review of the results from the first on-treatment PET scan, including the PK data. Subjects will receive an intravenous dose of the radiolabelled tracer, [^{18}F]-IMA601, at the start of each PET scan.

This study will have an adaptive design: to adequately evaluate the exposure versus receptor occupancy (RO) relationship, various doses of ASN51 of up to 85% of the highest well-tolerated dose level in the preceding SAD study ASN51-101, and the timing of on-treatment PET scans may

be altered based on emerging data or study logistical requirements. On-treatment PET scans may be scheduled up to 48 h post-dose.

After each on-treatment PET scan, the SRC will review available RO, PK, safety and tolerability data, before selecting the dose and PET scan timings for imaging session 3. Arterial blood sampling will be done during each PET scan to quantify the parent tracer related radioactivity over the course of the PET scan, and to establish a tracer metabolite corrected plasma input function. The total arterial blood volume required for each tracer injection will not exceed 145 mL. Arterial cannulation and arterial blood sampling may be reduced or removed if analysis of PET data from previous subjects indicates that noninvasive analysis of the PET scan data can be done. If a non-invasive analysis is not possible, the use of an arterial cannula with each PET scan will continue through the study.

Subjects will be screened within 21 days before their baseline PET scan. Their on-treatment PET scans will be within 7 days of their baseline scan with an interval of 7–14 days between imaging sessions 2 and 3. Subjects will be confined for 72 h after the study drug administration in sessions 2 and 3. After the baseline scan in session 1 without study drug administration, subjects may leave the unit in the evening. In the case of a technical failure (such as unsuccessful tracer synthesis), subjects may be asked to attend an additional on-treatment imaging session, in which they will receive a third oral dose of ASN51. There will be at least 7 days between each dose of ASN51. Subjects will not have more than 3 PET scans or 3 doses of ASN51 during the study. Subjects will have a follow-up visit at the research unit 7 days (± 3 days) after imaging session 3 (Day 8).

7.2 Treatment Assignment and Blinding

7.2.1 Number of Subjects

Up to 10 healthy adult subjects will be enrolled. All subjects will receive ASN51.

Subjects who withdraw or are removed from the trial after receiving investigational medicinal product (IMP) and prior to completion of the Treatment Period may be replaced on a case-by-case basis, at the discretion of the Sponsor.

7.2.2 Method of Assigning Subject Numbers to Treatment Groups

Subjects will be sequentially assigned a screening identification number upon signing of informed consent. Once eligibility is confirmed (Day 1 of imaging session 1), subjects will receive a 4-digit number on Day 1 before the start of the day's study procedures. Subjects who replace discontinuing subjects who have started procedures/assessments on Day 1 will receive the number of this subject +1000, e.g., subject 2411 will replace subject 1411, subject 2211 will replace subject 1211, etc. The substitute subject will receive the treatment assigned to the withdrawn subject. The following subject numbers are assigned:

Subject numbers 1411 – 1420, replacement subject numbers 2411 – 2420

7.2.3 Blinding

Not applicable

7.2.4 Unblinding

Not applicable

7.3 Sites

ASN51-102 is a single-center study.

7.4 Study Duration

The estimated duration of subject participation for the four parts of the study is as follows:

From Screening (3 weeks) to study conduct to follow-up (3 weeks) to telephone follow-up for potential SAEs (6 weeks): approximately 12 weeks for each subject.

7.5 Study Safety Oversight

7.5.1 Safety Review Committee

The study will be monitored by an SRC. The SRC is intended to ensure that treatment does not pose undue risk to subjects and to determine the individual dose levels to be administered in the study as well as the timing of the PET scans in relation to the time point of the study drug administration. The SRC will review RO data (ASN51-102 study only) and all available PK, safety, and tolerability data at each dose level from the planned, parallel Phase 1 SAD/MAD study ASN51-101 prior to initiating dosing in ASN51-102 and prior to each dose within this study (ASN51-102).

The SRC will be composed of the following core individuals:

- Principal Investigator (PI) or delegate
- Asceneuron SA medical monitor or delegate (must be a physician)

7.5.2 Stopping Criteria Based on Urgent Safety Events

The study (including dose escalation) will be halted if any of the following occur:

- One (1) serious adverse event (SAE) that is considered to be at least possibly related to study treatment; or
- Two (2) or more severe non-serious or clinically significant AEs that are considered to be at least possibly related to study treatment irrespective of whether they occur in the same system organ class (SOC) or not.

If following an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to the MHRA and REC. The trial will not restart until the amendment has been approved by the MHRA and REC.

7.5.3 Criteria for Dose Level Selection

Safety and pharmacokinetic data will be assessed by the SRC prior to

a) The first study drug administration

b) All subsequent study drug administrations

After each on-treatment PET scan, the SRC will review available RO, PK, safety and tolerability data, before selecting the dose and PET scan timings for the next imaging session.

The SRC may stop dosing at any time if the SRC determines that the next dose would pose an undue risk to subjects.

The safety and PK data will be reviewed by the SRC in an unblinded manner (e.g., with subject identifiers). For each meeting, the Investigator will prepare a report outlining a summary analysis of the safety data of the previous cohort.

7.6 Subject Discontinuation

In accordance with the Declaration of Helsinki, subjects have the right to withdraw from the trial at any time for any reason. The Sponsor must be notified of all subject withdrawals as soon as possible.

7.6.1 Removal of Subjects

The Investigator and Sponsor also have the right to remove subjects from the trial. The Sponsor also reserves the right to discontinue participation of an individual subject.

Subjects may be removed from the trial for the following reasons:

- Occurrence of an AE or SAE that precludes further participation
- Serious adverse event (SAE) considered related to study treatment.

- Any condition that, in the judgment of the Investigator or Sponsor, might place the subject at risk or invalidate the trial
- Pregnancy in subject
- At the request of the subject, Investigator, or Sponsor, for administrative or other reasons
- Protocol deviation or noncompliance
- One or more study drug administrations are missed
- Alanine aminotransferase (ALT) ≥ 5 x upper limit of normal (ULN).
    - ALT ≥ 3 x ULN and total bilirubin ≥ 2 x ULN or international normalised ratio (INR) > 1.5. (If a subject meets that withdrawal criterion, serum bilirubin fractionation should be performed.)
    - ALT ≥ 3 x ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia). Subjects who have -ALT ≥ 3 x ULN and < 5 x ULN, total bilirubin < 2 x ULN or INR < 1.5, who do not exhibit hepatitis symptoms or rash, can continue in the study (and continue receiving trial medication) as long as they can be monitored at least weekly until abnormal results are within the reference range or close to pre-treatment values.

Subjects that experience an AE or SAE as defined above will be followed-up by the Investigator until the AE/SAE has resolved. If a subject discontinues from the trial prematurely, reasonable efforts should be made to perform the Early Termination Visit procedures, within four weeks of discontinuation.

7.6.2 Early Termination Procedure

The early termination procedures are noted in the Schedule of Events, in any case the procedures foreseen for the follow-up visit must be completed (Table 1).

7.6.3 Replacement of Subjects

Subjects who withdraw or are removed from the trial after receiving IMP and prior to completion of the Treatment Period may be replaced on a case-by-case basis, at the discretion of the Sponsor.

7.7 Study Completion

The end of the trial is defined as the date of protocol-specified visit/assessment for the last subject participating in the trial. If the trial ends before all subjects are enrolled because the study objectives have been met, it will not be considered an early study termination.

7.8 Scientific Rationale for Study Design

ASN51 is a reversible and substrate competitive inhibitor of O-GlcNAcase that is currently being developed by Asceneuron S.A for the treatment of AD.

The primary objective of this study is to investigate the occupancy of O-GlcNAcase using PET and the O-GlcNAcase ligand [^{18}F]-IMA601, and to characterize the relationship between plasma concentration of ASN51 and the occupancy of O-GlcNAcase. These data will serve as a basis for the planning of the dosing and dosing regimen in further clinical studies.

8.0 POPULATION

8.1 Use of Healthy Young Volunteers

The ASN51-102 study will dose healthy young volunteers (HYV) for following reasons. HYVs have no confounding pathology or medication use that could interfere with this early phase study, are not expected to have vascular disease that would interfere with arterial cannulation, are unlikely to be taking concomitant medications (e.g., aspirin) that would contraindicate arterial cannulation, are better able to tolerate arterial cannulation, are better suited for obtaining a total of about 600mL of blood for full PK analysis and are better able to tolerate repeated PET scans.

8.2 Inclusion/Exclusion Criteria

Inclusion Criteria:

Individuals meeting all the following **inclusion criteria** and none of the **exclusion criteria** will be eligible to participate. None of the inclusion criteria are eligible for re-screening. No waivers will be granted and any deviation from below will get recorded as a major protocol deviation. An exception can apply for subjects who meet the inclusion and exclusion criteria, but then miss a cohort that is filled and so they are no longer eligible due to lapse of the 3-week screening window; these subjects may be rescreened.

1. Healthy as determined by the Investigator, based on a medical evaluation including medical history physical examination, neurological examination, laboratory tests and cardiac monitoring.
2. Men or women aged 25-55 years, inclusive (age range was selected on grounds of radiation burden).
3. Women of child-bearing potential with partners of child-bearing potential (see Section 9.10.7 for definitions) must agree to use highly effective contraception (per CTFG 2020; bilateral tubal occlusion, hormonal contraception associated with inhibition of ovulation except oral contraception, intra-uterine device with or without intrauterine hormone-releasing system, sexual abstinence in relation to the preferred and usual lifestyle of the subject,) from at least 28 days before first tracer dosing through 30 days after last dose of IMP. All women of child-bearing potential must have a negative pregnancy test result before administration of test article. Vasectomised partner is also an accepted a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
4. Women of non-childbearing potential must be postmenopausal [the last menstrual period was at least 12 months ago, and FSH at screening confirms postmenopausal status], or have no uterus, ovaries, or fallopian tubes). Women who are surgically sterile must provide documentation of the procedure by an operative report or by ultrasound.

5. Non-sterilized male subjects who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from 1 day prior to the first tracer administration throughout the total duration of the treatment period and 90 days after the last dose of IMP. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period.
6. Body weight > 50.0 kg for men and >45.0 kg for women and Body Mass Index within the range 18.5-30.0 kg/m2 (inclusive).
7. Subjects must understand the nature of the study and must provide signed and dated written informed consent in accordance with local regulations before the conduct of any study-related procedures.
8. Subjects must be, in the opinion of the Investigator, able to participate in all scheduled evaluations, likely to complete all required tests, and likely to be compliant.
9. Subjects must be fluent in the local language.
10. Subjects must agree not to post any personal medical data related to the study or information related to the study on any website or social media site (e.g., Facebook, Twitter, etc.) until the trial has completed.

Exclusion Criteria:

Individuals who meet any of the following **exclusion criteria** will not be eligible to participate.

1. A positive urine drug screen/alcohol test at Screening or Day -1.
2. Any history of psychiatric disorders, including substance use disorders, according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria.
3. A diagnosis of intellectual disability (intellectual developmental disorder) or mental retardation.
4. Significant suicide risk as assessed by C-SSRS.
5. A positive Hepatitis B surface antigen or positive Hepatitis C antibody result at Screening.
6. A positive test for human immunodeficiency virus (HIV) antibody at Screening.
7. Alanine aminotransferase or aspartate aminotransferase levels greater than 1.5 times the upper limit of normal (ULN) at Screening or between Screening and first dose of tracer administration.
8. Frequently used any tobacco-containing (e.g., cigar, cigarette, or snuff) or nicotine-containing product (e.g., nicotine chewing gum, nicotine plasters, or other product used for smoking cessation) within 3 months prior to first dose of tracer. Frequent use is defined as 3 or more days per week. Use of any tobacco- or nicotine-containing product is prohibited within 1 week of first dose of tracer.
9. History of regular alcohol consumption within 12 months of the study defined as an average weekly intake of >21 alcoholic units/week for men or >14 alcoholic units/week for women.

10. Regularly consumed (e.g., more days than not) excessive quantities of xanthine-containing beverages (e.g., more than five cups of coffee or the equivalent per day) within 30 days prior to Screening or between Screening and first dose of tracer.
11. Received or used an investigational product (including placebo) or device within the following time period prior to the first tracer dosing day in the current study: 90 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
12. Other than exceptions outlined in Section 9.10, use of prescription or non-prescription drugs, vitamins, herbal, and dietary supplements (including St John's Wort) within 7 days (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study tracer medication.
13. History of clinically significant sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.
14. Loss of more than 400 mL of blood within 3 months prior to first dose of tracer, i.e., blood donor.
15. A positive serum pregnancy test or lactation.
16. A history or presence of any disease, condition, or surgery likely to affect drug absorption, distribution, metabolism, or excretion. Subjects with a history of cholecystectomy should be excluded.
17. A history or presence of a clinically significant hepatic, renal, gastrointestinal, cardiovascular, endocrine, pulmonary, ophthalmologic, immunologic, hematologic, dermatologic, or neurologic abnormality.
18. A clinically significant abnormality on physical examination, neurological examination, ECG, or laboratory evaluations at screen or between screen and first tracer dose administration.
19. A corrected QT interval measurement corrected according to the Fridericia rule (QTcF) > 450 msec for males, 470 msec for females during controlled rest at screen or between screen and first tracer dose administration, or family history of long QT syndrome.
20. Any clinically significant abnormalities in rhythm, conduction, or morphology of the resting ECG and any abnormalities in the 12-lead ECG that, in the judgement of the Investigator or Medical Monitor, may interfere with the interpretation of QTc interval changes, including abnormal ST-T-wave morphology or left ventricular hypertrophy.
21. PR (PQ) interval shortening < 120 msec (PR < 120 msec but > 110 msec is acceptable if there is no evidence of ventricular pre-excitation).
22. PR (PQ) interval prolongation (>220 msec), intermittent second- (Wenckebach block while asleep or in deep rest is not exclusionary) or third-degree AV block.
23. Persistent or intermittent complete bundle branch block (BBB), incomplete bundle branch block (IBBB), or intraventricular conduction delay (IVCD) with QRS > 120 msec.

24. A clinically significant vital signs abnormality at screening or between screening and first tracer dose administration. This includes, but is not limited to, 3 measurements (each 5 minutes apart) in the seated position: (a) systolic blood pressure < 90 or >140 mmHg, (b) diastolic blood pressure <50 or > 95 mmHg, or (c) heart rate < 45 or >100 beats per minute. The average of the 3 measurements should be used to assess eligibility.
25. Significant (> 10%) weight loss or gain within 30 days prior to Screening and first tracer dose administration.
26. A history of seizure. History of a single benign febrile convulsion of childhood is permitted.
27. A history of head trauma, including closed head injury with loss of consciousness.
28. A history of symptomatic orthostatic hypotension (i.e., postural syncope)
29. A history of neuroleptic malignant syndrome.
30. A history of chronic urinary tract infections.
31. The subject is, in the opinion of the Investigator or Medical Monitor, unlikely to comply with the protocol or is unsuitable for any reason.
32. Currently employed by Asceneuron SA or by a clinical trial site participating in this study, or a first-degree relative of an Asceneuron SA employee or of an employee at a participating clinical trial site.
33. Unsatisfactory venous access
34. Significant exposure to ionising radiation as part of research (defined as ICRP category IIb or above: no more than 10 mSv in addition to natural background radiation including this trial), within the previous 12 months prior to first tracer dose administration.
35. Unsuitable or unwilling to undergo the imaging procedures, as determined by an MRI safety questionnaire. Reasons for exclusion include but are not limited to presence of a cardiac pacemaker or other implanted electronic device; ferromagnetic metal foreign bodies, intracranial aneurysm clips or other metallic objects; non-MRI compatible heart valves; inner ear implants; or a history of claustrophobia.
36. Significant structural brain abnormality, as determined by MRI.
37. Contraindication for arterial cannulation: Allen's test indicating potential risk in placement of the arterial cannula.
38. Subjects with a COVID-19 vaccination within two weeks of screening or due to receive second dose of COVID-19 vaccine while participating in the study.

8.3 Subject Withdrawal

Please see Section 7.6.1.

9.0 STUDY DRUGS

9.1 Investigational Drug

Asceneuron SA will provide ASN51 for clinical trial use in the form of [redacted]. ASN51 is provided in an immediate release [redacted] supplied in [redacted] dosage strengths. Investigational Medicinal Product (IMP) will be administered under the supervision of the Investigator or designee under fasted conditions. Each dose incl. date, time, witness will be recorded.

9.2 Study Drug Preparation

All study drugs will be prepared (i.e., packaged and labeled in individual doses) by a pharmacist, or his/her designee. All study drugs will be dispensed by the Investigator or a person under his/her supervision together with another witness.

9.3 Study Drug Packaging

Asceneuron SA will be responsible for the supply of the following drugs:

- [redacted] containing [redacted] of ASN51

The study drug will be packed and dispatched in containers. A batch release certificate will be provided, stating that the batches have been manufactured according to GMP. Study drugs are provided as [redacted] and supplied to the study center as a bulk shipment. Under the supervision of the pharmacist, the study drug will be packed per subject for each dosing occasion, according to the dosing specifications of the SRC.

9.4 Study Drug Labeling

The trial medication will be packaged and labelled by the [redacted] Pharmacy, in accordance with The Rules Governing Medicinal Products in the EU (European Union), Volume 4: Good Manufacturing Practice (GMP), and with [redacted]'s Manufacturing Authorisation for IMPs (MIA(IMP)). The IMP labels will include all the information required by Annex 13 to GMP

9.5 Study Drug Administration

While in the study clinic, subjects are not allowed to consume any food and beverages not provided by the institution. Standardized meals will be provided. An extra amount of tap water will be given if it is required for the intake of the study drug, that will be recorded.

The study drug will be administered together with 240 ml of tap water in fasted state following a minimum 10 h fast (no food or drink except water) and will fast for a further 4 h after their dose. Other than the water required to take the study medicine, water is not allowed from 2 h before until 2 h after dosing. These restrictions also apply to the session 1 baseline PET scan such that all PET scans are carried out under the same conditions.

9.6 Concomitant Medications and Therapy

Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. All concomitant medications taken during the trial will be recorded with indication, dose information, and dates of administration.

9.7 Treatment Compliance

Site personnel will maintain a record of all IMP dispensed to each subject.

For this trial, treatment compliance is defined as completion of 100% of scheduled doses, because the study drug administration is under direct control of the Investigator or designee.

9.8 Non-Investigational Medicinal Product (non-IMP)

The radioligand [^{18}F]-IMA601 (non-IMP) will be prepared by the PET site.

Product name: [^{18}F]-IMA601 (also known as [^{18}F]OGA1)

Dosage form: Solution

Effective dose: maximum 2.46 mSv each PET scan, as it includes components from PET (2.1 mSv) and CT scans (0.36 mSv)

Injected activity: Will not exceed 100 MBq for each PET scan

Route of administration: intravenous bolus

Manufacturer/source of procurement: PET site[§]

§ cGMP grade precursor will be procured from an external commercial source

9.9 Storage and Return of Study Drug

Upon receipt of the study drugs, the responsible pharmacist will inspect all study drugs for completeness. Subsequently, he/she must immediately return the enclosed acknowledgement of receipt form; duly completed and signed (the date of receipt must be noted).

The pharmacist is responsible for storage of the study drug at the study site in an appropriate lockable room at refrigerated temperature (2-8 °C). The drug will be stored according to the instructions provided by Asceneuron SA. Only the pharmacist or his/her assistant, who are otherwise not involved in the study, will handle the study drug.

A dispensing record (or similar document) as well as a Drug Accountability Record must be kept current and should contain the following information:

- Subject number for whom the drug was prepared

- Initials and date of the person who prepared the study drug
- Dates on which drug was prepared and quantity of the drug prepared
- The inventory must be available for inspection by the monitor

After sponsor confirmation, all unused investigational material (drugs and packaging) must be destroyed by the site on termination of the study and after a drug accountability check by the monitor, listing the following:

- All ASN51 administered
- All unused ASN51
- All ASN51 destructed by the site

Alternatively, upon request of Asceneuron SA, the pharmacist may send back the unused investigational drug. The pharmacist will be responsible for the inventory and accountability of all Clinical Trial Material, exercising accepted pharmaceutical practices. An accurate, timely record of the Clinical Trial Material will be maintained. Only after completion of the study, the Clinical Trial Material and the inventory will be available for inspection by the designated representatives of Asceneuron SA upon request. The original dispensing records and Drug Accountability Record are considered as source data and will be archived at the site.

9.10 Diet, Activities, and Other Restrictions

9.10.1 Concomitant Medications

Use of prescription or non-prescription drugs, vitamins, herbal, and dietary supplements (including St John's Wort) within 7 days (or 28 days if the drug is a potential hepatic enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study tracer medication and until the Follow-up visit.

The use of other types of concomitant medication is not allowed from 1 week prior to the first dose of study tracer medication until the Follow-up, except for paracetamol (at most 2g /day) or medication that is required for the treatment of AEs. If concomitant medication is needed during the study, this medication must be recorded on the eCRF, stating its generic name, time of administration, dose, route and duration, as well as the reason for administration.

Subjects who received a COVID-19 vaccination within two weeks of screening will be excluded from the study. Concomitant administration of a COVID-19 vaccination during the course of study participation will not be permitted.

An exception applies to the use of hormonal contraceptives as follows:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - intravaginal

  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - injectable
  - implantable
- intrauterine hormone-releasing system (IUS)

9.10.2 Caffeine

Subjects will abstain from ingesting caffeine- or xanthine- containing products (e.g. coffee, tea, cola drinks and chocolate) from 24 hours prior to first tracer dose administration until 72 hours after each study drug administration.

9.10.3 Alcohol

Subjects will abstain from alcohol for 48 hours prior to first tracer dose administration until the follow up visit.

9.10.4 Physical Activities

Subjects will abstain from strenuous exercise from 7 days prior to first tracer dose administration until the last follow up visit. Subjects may participate in light recreational activities during the study.

9.10.5 Dietary Aspects

Consumption of Seville oranges or grapefruit (or their juices) is not allowed from 7 days prior to the first dose of the tracer medication until 72 hours after the last study drug administration.

9.10.6 Smoking

Use of any tobacco- or nicotine-containing product is prohibited from 1 week prior to first tracer administration until 72 hours after the last study drug administration.

9.10.7 Definitions of Women of child-bearing potential

A woman is considered of childbearing potential (WOCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

10.0 STUDY PROCEDURES AND ASSESSMENTS

The Schedule of Events, including allowed visit windows, assessments, and procedures to be conducted at each visit are detailed in Table 1. Guidelines for study procedures and assessments are discussed briefly in the following sections.

10.1 Structural MRI

Structural MRI acquisition will be performed at [redacted] and will consist of a structural scanning protocol. MRI scans will be evaluated by a radiologist to exclude any subjects with major pathology or abnormalities. A radiologist's report will be provided for each MRI scan to the Investigator at [redacted]

10.2 PET scan

Dynamic PET scans will be performed at [redacted] using a Siemens Biograph 6 PET/computed tomography (CT) scanner (Siemens Healthcare, Erlangen, Germany). The subjects will be placed in the PET scanner during the scan. A low dose CT scan will be performed to correct for the attenuation of emitted radiation. Subjects will then receive an intravenous bolus injection of up to 100 MBq of the [^{18}F]-IMA601 radioligand. Dynamic emission data will be recorded for up to about 90 min after injection of the radioligand.

10.3 Clinical Safety Assessments

Assessments to characterize safety and tolerability of ASN51 are described below; associated planned analyses are described Section 12.7.

10.3.1 Informed Consent

Informed consent will be obtained as outlined in Section 13.1.2.

10.3.2 Medical History and Demographics

Medical history includes active conditions, and any medical illnesses, diagnoses, and surgeries considered clinically relevant by the Investigator.

Demographic information (year of birth, sex, race, ethnicity) will be recorded at Screening (as allowed by local regulations).

10.3.3 FSH tests

Serum FSH tests will be done using a chemiluminescent immunoassay method.

10.3.4 Drugs of abuse, urine alcohol and cotinine tests

Urine will be tested for drugs of abuse, urine alcohol and cotinine according to the laboratory's SOP. Tests will include: amphetamines, cocaine, opiates, cannabis, barbiturates, benzodiazepines, and cotinine

10.3.5 Weight and Height

Weight (measured in kilograms) and height (in meters) will be measured and recorded as noted in the Schedule of Events. Subjects may remain in clothes (without shoes). A standing height will be measured and recorded using a stadiometer at the Screening Visit only.

10.3.6 Physical and Neurological Examination

Complete physical examinations will be performed by a licensed professional at Screening, at follow-up, and at early termination, when applicable. A complete physical examination includes general appearance; head, eyes, ears, nose, and throat; and cardiovascular, dermatologic, respiratory, gastrointestinal, musculoskeletal, and neurologic systems.

All other indicated physical examinations should be symptom-directed, and include neurological assessment of cranial nerves, motor, sensation, coordination, reflexes, and gait.

Findings will be recorded as normal/abnormal for each parameter with additional description as indicated.

10.3.7 Vital Signs

Vital signs include systolic and diastolic blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature (°C; tympanic). Measurements will be obtained as noted in the Schedule of Events. At screening, obtain triplicate blood pressure measurements (5-minute intervals) while the subject is seated; use the average to assess eligibility. During the study, blood pressure may be assessed as single recording in seated position after a rest of 5 minutes.

10.3.8 Electrocardiogram

Routine single 12-lead ECGs will be performed after the subject has rested for a minimum of 10 minutes. All ECGs will be stored digitally. ECGs may be repeated once to rule out a technical error with new lead placement; only the values of the second recording will be entered into the data base. Perform additional assessments as clinically indicated.

10.3.8.1 ECG Parameters

ECG Parameters include PR interval, QRS duration, QT interval, QTcB, and QTc-Fredericia's correction (QTcF). ECGs will be interpreted as normal, abnormal clinically not significant (ncs), or abnormal-clinically significant (cs).

10.3.9 Prior and Concomitant Medications

Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care.

All concomitant medication and concurrent therapies will be documented at Screening and at all subsequent visits. Medications (investigational, prescription, over-the-counter, and herbal) and nutritional supplements taken during the 30 days prior to Day 1 of imaging session 1 will be reviewed and recorded as prior medications. Change in concomitant medication since the previous visit will be recorded. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

If subject is taking high dose biotin supplements (found in multivitamins, biotin supplements, and supplements for hair, skin, and nail growth), site personnel is to advise on the potential for laboratory test interference with certain safety labs.

10.3.10 Adverse Events

All events meeting the definition for AE, SAE, and pregnancy will be assessed and reported following guidelines provided in Section 11.0. At Day -1, during the confinement period at regular intervals, and at follow-up, subjects will be asked about any new or ongoing AEs since the previous inquiry. Four weeks after last dose of tracer administration, an inquiry via phone will be done for the identification of potential SAEs.

Clinically significant changes from baseline in any safety or clinical laboratory parameter will be recorded as AEs or SAEs, if deemed appropriate by the Investigator.

Subjects who discontinue due to a treatment-emergent SAE will be followed-up by the Investigator until the SAE has resolved (Section 7.6.1).

10.4 Clinical Laboratory Assessments

Laboratory assessments will be used routinely to assess IMP safety in all subjects. After first administration of IMP, clinically significant abnormal laboratory findings must be documented as an AE. Samples will be collected as noted in the Schedule of Events (Table 1). Clinical laboratory parameters to be assessed for safety are listed in Appendix A.

Fasting for a minimum of 4 hours prior to each blood draw is required and fasting status will be recorded. All clinical laboratory assessments will be conducted by the local laboratory unless otherwise specified. Communicate to the laboratory if the subject is receiving biotin supplements as high-dose biotin may interfere with certain laboratory assessments.

10.4.1 Serum Chemistry

Blood samples will be obtained for serum chemistry (Appendix A).

10.4.2 Hematology

Blood sample will be obtained for hematology (complete blood count with differential; Appendix A).

10.4.3 Urinalysis

A urinalysis panel (dipstick with microscopic examination on positives; Appendix A) will be obtained.

10.4.4 Coagulation Panel/(s)

A coagulation panel will be obtained (Appendix A).

10.4.5 Pregnancy Testing

A negative serum pregnancy test is required from WOCBP within 24 hours before the first dose of IMP. Additional serum pregnancy tests (or urine pregnancy tests for MRI visit at [redacted]) will be obtained from females (WOCBP) at all subsequent clinic visits as noted in the Schedule of Events (Table 1).

All pregnancy tests will be performed at the site's local laboratory [redacted]. Pregnancy in subject or partner must be reported (Section 11.6); pregnant subjects will be discontinued from the trial.

10.4.6 Serum Hormone Markers

See Appendix A

10.5 Pharmacokinetic Assessments

10.5.1 Timing for Sampling

See Table 1.

10.5.2 Procedures for PK Blood Sampling

About 2.0 mL blood for the PK samples will be collected via vena puncture or via an intravenous (i.v.) cannula placed following the local standard procedures. Information on equipment and further details on the procedures on the sampling are documented in a separate instruction manual.

10.5.3 Shipping and Labeling

Labeling and shipping instructions are provided in the Study Laboratory Manual.

10.5.4 Bioanalysis

The concentrations of ASN51 in plasma will be determined using a validated LC-MS/MS assay. In addition, urine samples may be analyzed for occurrence of metabolites of ASN51 with an exploratory method if warranted.

10.5.5 Pharmacokinetic Parameters

The plasma PK parameters for ASN51 will be derived by non-compartmental analysis of the plasma concentration-time profiles at the end of study only.

The following pharmacokinetic parameters are defined:

- The area under the plasma concentration-time curve from time zero to time t of the last measured concentration above the limit of quantification (AUC_{0-t}).
- The area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$).
- The maximum plasma concentration (C_{max}).
- The time to reach maximum plasma concentration (t_{max}).
- The terminal elimination rate constant (λ_Z) with the respective half-life ($t_{½}$)
- The percentage of the extrapolated AUC.

AUC_{0-t} will be calculated according to the linear up/log down trapezoidal method using the measured concentration-time values above the limit of quantification (LOQ). $AUC_{0-\infty}$ will be calculated by combining AUC_{0-t} and AUC_{extra}. AUC_{extra} represents an extrapolated value obtained by C_t/λ_Z, where C_t is the last plasma concentration measured above the LOQ and λ_Z represents the terminal elimination rate constant determined by log-linear regression analysis of the measured plasma concentrations of the terminal elimination phase. The half-life will be calculated as follows: $t_{½} = \ln 2 / \lambda_Z$.

The C_{max}, and time to peak concentration (t_{max}) will be directly determined from the observed plasma concentrations data. AUC_{0-t} will be calculated using linear up/log down trapezoidal method using the measured concentration-time values above the limit of quantification (LOQ).

All PK parameters will be based on actual blood sampling times [h] (relative to the corresponding administration time) rounded to two digits and negative pre-dose times will be set to zero.

10.6 Total volume of blood removed

Hematology: 7 x 2mL = 14 mL
Clinical Chemistry: 7 x 3.5mL = 24.5 mL
Coagulation: 7 x 3mL = 21 mL
FSH, Serology: 1 x 3.5 mL = 3.5 mL
Pregnancy Test*: 4 x 3.5 mL =14mL
PK: 32 x 2 mL = 64 mL
Arterial blood: 3 x 145 mL = 435mL
Total: 576 mL within about 4-6 weeks
**included in serology sample at screening*

If a study session is repeated because of a PET scan failure, an extra 53 mL of blood may be taken during the whole study.

No more than an extra 50 mL of blood will be taken from any subject.

10.7 Instructions for PET Scans

10.7.1 General Procedures

If arterial cannulation will be used, the patency of subjects' ulnar and radial arteries in both wrists will be checked, at screening and before insertion of the arterial cannula on scanning days (Allen's test). Up to 10 subjects will be enrolled. At most 2 subjects will be dosed in parallel. Each subject will have up to 3 imaging sessions, with one scan in each session. In the first imaging session, subjects will have 240 ml of water followed by a baseline PET scan approximately 2 h later. In the second and third imaging sessions, subjects will receive a single oral dose of ASN51 with 240 ml of water, followed by an on-treatment PET scan.
The study will have an adaptive design: to adequately evaluate the exposure versus RO relationship, various doses of ASN51 up to 85% of the highest well-tolerated dose in the SAD study ASN51-101 may be tested, and the timing of on-treatment PET scans may be altered based on emerging data or study logistical requirements. On-treatment PET scans may be scheduled up to 48 h post-dose. Before each on-treatment PET scan, the SRC will review available RO, PK, safety and tolerability data, before selecting the dose and PET scan timings for all on-treatment imaging sessions. Subjects will receive an intravenous dose of the radiolabelled tracer, [^{18}F]-IMA601, at the start of each PET scan.
Arterial blood sampling will be done during each PET scan to quantify the parent tracer related radioactivity over the course of the PET scan, and to establish a tracer metabolite corrected plasma input function. The total arterial blood volume required for each tracer injection will not exceed 145 mL. Arterial cannulation and arterial blood sampling may be reduced or removed if analysis of PET data from previous subjects indicates that noninvasive analysis of the PET scan data can be done. If a non-invasive analysis is not possible, the use of an arterial cannula with each PET scan will continue through the study.
Subjects will be screened within 21 days before their baseline PET scan. Their on-treatment PET scans will be within 28 days of their baseline scan with an interval of 7–14 days between imaging sessions 2 and 3. Subjects will be confined from Day -1 until about 72 h after drug intake in on-treatment sessions 2 and 3. In session 1, subjects will be confined from day -1 and may leave the clinical unit in the evening of the PET scan on Day 1. In the case of a technical failure (such as unsuccessful tracer synthesis), subjects may be asked to attend an additional on-treatment imaging session, in which they will receive a third oral dose of ASN51. There will be at least 7 days between each dose of ASN51. Subjects will not have more than 3 PET scans or no more than 3 doses of ASN51 during the study.

10.7.2 Assessment and management of risk

<u>Risk associated with the imaging techniques</u>

Subjects in this study will be exposed to an additional dose of ionising radiation as a result of their participation. The majority of the radiation dose comes from the administered radioligand, while a smaller portion comes from a low dose computed tomography (CT) scan performed to estimate tissue attenuation. To mitigate this risk, the study will exclude subjects who have had previous exposure to ionising radiation such that, their exposure would be > 10mSv for the previous year. A maximum of 100 MBq of [^{18}F]-IMA601 will be injected for each PET scan and the maximal effective dose from ionising radiation for an individual will not exceed 7.4 mSv from the PET and low-dose CT scans. The maximal radiation exposure for each subject over the whole study is presented in Table 2.

Table 2: Expected maximal radioactive exposure of each subject

Assessment	Number of scans	Effective dose per injected activity (mSv/MBq)	PET tracer Activity (MBq)	Effective dose per scan (mSv)	Total exposure (mSv)
PET emission scan	3	0.021	100	2.1	6.3
Low-dose CT scan	3			0.36	1.08
TOTAL					7.4

A maximal study exposure of 7.4 mSv for a participant, places this study towards the top of Category IIb (< 10 mSv) of the guidance published by the International Commission for Radiation Protection (ICRP). Following the ICRP 62 guidance that provides a guideline of ≤10 mSv per study where research subjects are not expected to benefit personally.

Magnetic resonance images delineating brain anatomy will be acquired in this study to aid PET image analysis. There are no known risks to subjects associated with MRI scanning, provided that they have no contraindications to MRI as listed in the exclusion criteria. Potential risks associated with metallic implants will be mitigated by administration of a questionnaire and careful screening. At all times while subjects are on the ward, registered nurses will provide care and supervision.

Risk associated with arterial cannulation

Before the PET-CT scan, subjects will have a cannula inserted into the radial artery by qualified staff using aseptic technique under local anaesthesia. That insertion may be uncomfortable, cause minor local bleeding and bruising, and can rarely lead to complications (e.g., a blood clot could form around the cannula). Most people have no after-effects of cannulation. However, very occasionally, it may cause a small scar. Very rarely, more serious complications can occur, although these usually occur when the radial artery is cannulated in sick people for therapeutic purposes, rather than in healthy subjects for research purposes.

11.0 ADVERSE EVENT DEFINITIONS, REPORTING, AND FOLLOW-UP

All AEs, SAEs, SARs, and pregnancies occurring during the protocol-specified timeframes (Table 1) will be assessed and reported per guidelines provided in the following sections.

11.1 Definitions

11.1.1 Adverse Event Associated with Study Procedures

A procedure-related AE is an AE considered by the Investigator to be related to a procedure required by the protocol (i.e., temporally associated or known risk of the procedure).

11.1.2 Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. The term "adverse event" could include any of the following events that develop or increase in severity during the course of the trial. Examples include:

- Any sign, symptom, or physical examination finding that worsens in nature, severity, or frequency compared to baseline irrespective of association with the condition under study
- Any clinically significant laboratory abnormality or laboratory abnormality that requires medication or hospitalization
- Reactions to study drug(s) including those occurring as a result of an overdose, abuse, withdrawal phenomena, sensitivity, or toxicity
- Concurrent illness
- Injury or accident

Conditions present prior to enrollment are considered Medical History. Pre-existing conditions should be reported as a TEAE if there is a change in the frequency, intensity, or the character of the condition.

11.1.3 Serious Adverse Event

A SAE is an AE that:

- results in death
- is considered life threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent/significant disability/incapacity
- results in a congenital anomaly/birth defect; or
- other medially important serious medical event

11.2 Assessment of Adverse Events

For each AE, the Investigator will assess the severity, causality, and outcome.

11.2.1 Severity

AEs should be graded as mild, moderate, severe, life-threatening, or death using the following definitions:

- Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention generally not indicated
- Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Severe: interrupts normal daily activities and generally requires systemic drug therapy or other treatment; usually incapacitating.
- Life-threatening: urgent intervention indicated
- Death: events that results in death

Severity is not considered a guide for defining regulatory reporting obligations.

11.2.2 Causality

The Investigator should consult the IB when assessing relationship to study drug and consider all possible etiologies for the AE. The Investigator will assess the causality of the AE to study procedure or study drug as follows:

1) Attributions for “Unrelated” events:

- ***Unrelated:*** the AE ***is clearly not related*** to the study drug/procedure, beyond a reasonable doubt
- ***Unlikely Related:*** the AE ***is doubtfully related*** to the study drug/procedure

2) Attributions for “Related” events:

- ***Possibly Related***: the AE ***may be related*** to the study drug/procedure
- ***Probably Related***: the AE ***is likely related*** to the study drug/procedure
- ***Definitely Related***: the AE ***is clearly related*** to the study drug/procedure

For the purposes of reporting to regulatory agencies, AEs deemed as Definitely, Probably or Possibly Related will be considered Related and those deemed Unrelated or Unlikely Related will be considered Unrelated.

AEs listed as related are considered to have a suspected “reasonable causal relationship” to the study drug/intervention (ICH E2A). The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

11.2.3 Outcome

The outcome of an AE associated will be assessed as follows:

- Recovered/Resolved: the event has improved or recuperated
- Not recovered/Not Resolved: the event has not improved or recuperated
- Recovered/resolved with sequelae: the participant recuperated but retained pathological conditions resulting from the prior disease or injury
- Fatal: termination of life as a result of an AE
- Unknown: not known, not observed, not recorded

11.3 Adverse Event Reporting and Follow Up

All AEs (i.e., any new or worsening in severity or frequency of a preexisting condition) with onset after the subject signs consent for trial participation must be promptly documented on the AE electronic case report form (eCRF). Details of the AE must include severity, relationship to study drug, duration, and outcome. Serious Adverse Events Reporting

SAEs must be reported to the Sponsor (or designee) within 24 hours of the knowledge of the occurrence.

An SAE report will be completed as thoroughly as possible including all available details about the event and the signature of the Investigator. The SAE form will be updated when additional information is received.

A death occurring during the trial must be reported to Sponsor or its designee within 24 hours of knowledge of the death whether or not it is considered treatment-related.

The Investigator also must notify the IRB/IEC of the occurrence of the SAE, in writing, as soon as is practicable and in accordance with IRB/IEC requirements and local law. A copy of this notification must be provided to Sponsor or its designee.

Subjects will be instructed to contact the Investigator site and report any adverse events that develop after being discharged from the clinical unit. The Investigator will advise the subject on appropriate treatment, if necessary, and will follow the subject up until the adverse event resolves or the subject is lost to follow-up. If, in the investigator's opinion, the adverse event could be related to sterility issues with [^{18}F]-IMA601, the investigator will inform [redacted] In the event of a positive sterility result, [redacted] Quality Assurance department will be informed and an investigation following the process as outlined in [redacted] standard operating procedures will be initiated.

11.4 Procedures for Dealing with Severe Adverse Events

In the event of any SAE which, in the investigator's opinion, justifies termination or modification of the trial (see Section 7.5.2), dosing will be stopped and the sponsor's medical monitor will be informed immediately (within 24 h of the investigator becoming aware of the event) by telephone or email, as follows.

[redacted] MD, MSc, PhD
Tel: [redacted]

Email: [redacted]
Mobile: [redacted]

For all SAEs, the investigator will complete a SAE form and provide it to the sponsor's pharmacovigilance department immediately (within 24 h of the investigator becoming aware of the event), as follows.

[redacted] MD, MSc, PhD
Tel: [redacted]
Email: [redacted]
Mobile: [redacted]

The sponsor will also be notified by email [redacted]

The investigator will notify the REC of SAEs that occur during this trial, if applicable, in accordance with the SOPs issued by the Research Ethics Service (RES).

The sponsor is responsible for determining the expectedness of the event, using the reference safety information in the Investigator's Brochure. The sponsor will notify the MHRA of all suspected unexpected serious adverse reactions (SUSARs), and will be responsible for ensuring that the REC is notified of SUSARs, if applicable.

SUSARs that are fatal or life-threatening must be notified to the MHRA and REC within 7 days after the sponsor has learned of them. Other SUSARs must be reported to the REC and MHRA within 15 days after the sponsor has learned of them.

11.5 Procedures for Handling Withdrawals Due to Adverse Events

The investigator will assess the reason for withdrawal as far as possible and will fully record the circumstances and medical details. Provided that subjects give written informed consent, they will undergo the standard medical examination and laboratory tests at withdrawal from the trial which they would have undergone had they completed it (see also Section 7.6.1).

11.6 Procedures for Reporting Pregnancies

Subjects will be asked to follow the contraception guidance in Section 8.1.

If, during the study, the investigator becomes aware of a pregnancy in a subject, or a partner of a subject, they will inform the sponsor's pharmacovigilance department immediately (within 24 h of the investigator becoming aware of the event), as follows.

[redacted] MD, MSc, PhD
Tel: [redacted]
Email: [redacted]

Mobile: [redacted]

The investigator will follow-up the pregnancy according to [redacted] SOPs, provided the subject's partner consents to that. A pregnancy will not constitute an SAE unless it meets one of the criteria in Section 11.3.

11.7 Trial Conduct

This study will be conducted in compliance with the protocol approved by the Research Ethics Committee (REC) and the Medicines Healthcare and Products Regulatory Agency (MHRA), and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the REC/MHRA except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the REC/MHRA as soon as possible.

12.0 STATISTICAL METHODS

The completeness of the data affects the integrity and accuracy of the final trial analysis. Therefore, every reasonable effort will be made to ensure complete, accurate, and timely data collection, and to avoid missing data. In general, missing data will be treated as missing and no statistical imputation method will be used unless stated otherwise. The procedures for handling missing, unused, or spurious data will be presented in the Statistical Analysis Plan (SAP).

12.1 Statistical Analysis Plan (SAP)

A SAP (and data management plan (DMP), if appropriate) will be written and finalized before the database closure. The SAP will provide full details of the analyses, the data displays and the algorithms to be used for data derivations.

The SAP will include the definition of major and minor protocol deviations/violations and the link of major protocol deviations/violations to the analysis sets.

Any deviations from the original statistical plan will be described and justified in the final report.

12.2 Analysis Populations

Three different analysis sets are defined. Subjects who withdraw from the study, or who have missing data, will be included in the statistical analyses provided that they are eligible for inclusion in the analysis population as described below.

All-treated set: This analysis set includes all randomized subjects who received study drug (at least one dose).

Safety set: This analysis set includes subjects from the all-treated set who had at least one safety assessment post-baseline. The safety set will be employed in the analysis of tolerability and safety variables.

PET population: The PET population will consist of randomised subjects who receive study medication, have a baseline PET scan, at least one post-baseline PET scan, and a PK result immediately preceding PET scan.

PK analysis population: The PK analysis population will consist of the subjects who provide evaluable data for the comparisons of interest. These subjects should have at least one quantifiable plasma concentration, should not have violated any major entry criterion likely to confound the PK analysis, and should not have deviated significantly from the protocol between enrolment and successful study completion

In all populations, treatment will be assigned based upon the treatment subjects actually received.

The primary endpoint will be analyzed using the PET population.

12.3 Sample Size

The trial is hypothesis generating, so no formal calculation of sample size is appropriate. The sample size of at most 10 subjects is considered adequate to allow modelling of the relationship between ASN51 plasma concentrations and the occupancy of O-GlcNAcase and is within the range generally accepted for PET studies. Enrolment of subjects into the study will be stopped as soon as the brain O-GlcNAcase occupancy versus ASN51 plasma concentrations is sufficiently characterized in opinion of the SRC.

12.4 Procedure for Accounting for Missing, Unused, and Spurious Data

All analyses will be performed on data available at the time point considered. In summary tables, the number of subjects with missing data will be presented unless otherwise specified. In calculation of percentages, subjects with missing data will not be considered in numerator or denominator unless otherwise specified.

12.5 Discontinuations

The number of subjects randomized who complete the treatment period (through each interim analysis time point) and who discontinue the trial will be summarized. Reasons for discontinuation will be summarized.

12.6 Pharmacokinetic Statistical Analysis

A definition of the PK parameters is described in Section 10.5. PK parameters will be described descriptively.

The PK analysis population will be used for all PK analyses. Individual subject listings will be provided. Mean and individual plasma concentration-time profiles for ASN51 will be presented graphically for each group.

PK variables will be summarized using arithmetic mean, STD, geometric mean, median, minimum, maximum, and %CV and by means of scatterplots, dose-normalized scatterplots versus dose and means plots versus the dose.

12.7 Safety and Tolerability Parameters

Definitions of the safety and tolerability parameters are described in Section 10.3. The safety set is used to perform all safety analyses.

The medical history is coded using the most recent MedDRA version and listed. All AEs and SAEs are coded using the most recent MedDRA version.

The treatment-emergent AEs are tabulated by system organ class (SOC), and individual preferred terms within each SOC by treatment group. The number and percentage of patients who experienced AEs coded with the same preferred term and SOC will be summarized by treatment group (in descending order according to the incidence in the investigational study drug group). Adverse events will also be tabulated by severity and by relationship to study drug. Summary tables will be accompanied by individual subject listings broken down by treatment group, including pre-dose events. Separate summary tables of adverse events for related/all AEs will be provided including severity and percentages.

SAEs will be listed and summarized similarly to AEs. Reasons for death will only be listed.

Reasons for premature discontinuation of study drug will be listed and summarized by frequency tables.

ECG variables, vital sign measurements and laboratory measurements will be summarized at each time point using mean, median, standard deviation, min, max, number of available observations, and change from baseline. Individual patient listings of ECG data, and laboratory measurements will be provided.

In addition, ECG parameters will be analyzed as follows (data listings):

- 450 ms < QTcF/ QTcB <= 480 ms
- 480 ms < QTcF/ QTcB <= 500 ms
- 500 ms < QTcF/ QTcB
- 30 ms < QTcF/ QTcB change from baseline <= 60 ms
- 60 ms < QTcF/ QTcB change from baseline

The mean +/- SD and median over time for ECGs will be plotted by line graphs. An analysis will be provided for the concentration versus ECG parameters based on a linear regression model (numerical and graphical analysis). The regression model will contain the change from baseline of

QT/QTcB/QTcF as the dependent variable and include the corresponding plasma concentrations of ASN51 (i.e., the plasma concentration taken at the closest timepoint to the ECG recording) as the independent variables and the subject as a random effect. Pre-dose and follow-up ECGs will not be included in this analysis.

Abnormal ECG observations will be listed.

Listings for each laboratory, ECG and vital sign parameter out of normal range will be provided, separately for above/below normal range per time point. Standard numeric laboratory parameters are presented in the units supplied. If needed, a conversion will be made to standard units.

12.8 Exposure to Study Drug

A listing with information about the drug administration will be provided.

12.9 Baseline Parameters and Concomitant Medications

Summary statistics (mean, median, standard deviation, min, max, number of available observations) will be provided for continuous demographic variables (e.g., age, height, weight). Individual patient listings of demographic data will be provided.

Qualitative demographic characteristics (gender, race) will be summarized by counts and percentages. Other baseline patient characteristics (medical history, physical examination clinical findings, previous medications, inclusion/exclusion checklist) will only be listed.

Distributions of these parameters will be compared between the treatment groups only descriptively. No statistical inference will be performed.

Previous and concomitant medications will be coded by the sponsor according to the WHO drug code and the ATC class code.

12.10 Exploratory Analyses

Exploratory data-driven analyses can be performed with the caveat that any statistical inference will not have any confirmatory value.

12.11 PET Image Data Analysis

PET data analysis will be performed using PET site's in-house MIAKAT^{TM} software package. MIAKAT^{TM} is implemented using MATLAB (The Mathworks Inc., Natick, MA, USA), and makes use of SPM (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm) for image segmentation and registration. MIAKAT^{TM} implements a robust and consistent analysis pipeline with built-in audit trail and pre-specified QC points whereby the analyst is required to inspect results of intermediate stages (for example checking the success of automated corrections for subject motion or assessing the quality of model fits).

12.11.1 Image processing

Each subject's structural MRI image will undergo grey matter segmentation and registration to a standard reference space (MNI152, (Grabner et al. 2006). The MNI152 template brain image and associated atlas (CIC atlas, (Tziortzi et al. 2011) will be nonlinearly warped to the subject's MR image to enable automated definition of regions of interest (ROIs).

The set of ROIs to be considered and reported will be selected based on previous studies (Paul et al. 2018), and the signal observed in these human PET scans and may include (but not be limited to) the frontal, parietal and occipital lobes, insular cortex, posterior cingulate gyrus, anterior cingulate, caudate nucleus, putamen, nucleus accumbens, thalamus, amygdala, hippocampus and cerebellum.

Dynamic PET images (90-minute duration) will be generated on the PET scanners using the manufacturer's recommended reconstruction settings which include corrections for scatter, randoms and attenuation. These will then be registered to each subject's MRI scan and corrected for motion using a frame-to-frame registration process with a normalised mutual information cost function. ROIs defined on the MRI images will be applied to the dynamic PET data to derive regional time-activity curves (TACs), with activity concentrations expressed as standardised uptake values (SUV), given by:

$$SUV = \frac{Act}{IA/BW}$$

where Act is the measured radioactivity concentration (kBq/ml), IA is the injected radioactivity (MBq) and BW is the subject's bodyweight (kg).

12.11.2 Arterial blood data processing

Continuous blood data will be scaled (i.e., calibrated) to match overlapping discrete whole blood samples, and then merged with the remaining discrete whole blood data to form a whole blood activity curve covering the duration of the scan. Activity measurements from the discrete plasma samples will be divided by the corresponding whole blood data to form plasma-over-blood (POB) data. The POB data will be fitted to a simple model in order to smooth and interpolate the relationship. The POB model fit curve will be multiplied by the whole blood curve to give an estimated total plasma curve.

Parent fraction (metabolite) data will be fitted to an appropriate simple model, to be determined empirically. The resulting fitted parent fraction profile will be multiplied by the total plasma curve (calculated as described above) and then smoothed post-peak using a multi-exponential fit to give the required parent plasma input function. For each scan, a time delay will be fitted and applied to the input function to account for any delay between blood sampling measurements and tissue data from the PET tomograph. The resulting parent plasma input function will be used as input for the kinetic modelling processes described in Section 12.11.3.

12.11.3 Signal change evaluation

Decreases in V_T from baseline to post-dose scans will be interpreted as an effect of O-GlcNAcase occupancy by ASN51. Target occupancy estimates may be directly calculated from scan data via methods including a 'Lassen plot' (Cunningham et al. 2010). Alternatively, the relationship between exposure and occupancy may be explored by direct fitting of a saturation model to pooled (across subjects and scans) V_T data, to obtain for example an estimate of EC50 for occupancy by ASN51. It is anticipated that data from the first subjects will be sufficient to enable a definitive selection of an appropriate analysis method to support the fulfilment of the study objectives. Data and analysis will be explored on an ongoing basis for the first four (completing) subjects. Following analysis of data from these four subjects, the data analysed to that point will be reviewed. An updated Image Analysis Plan will then be generated if appropriate, with the intention of fixing the image analysis methodology to be used for data form subsequent subjects and the dataset as a whole.

12.11.4 PET Data Reporting

The PET site [redacted] will produce a separate Imaging Analysis Report on the PET scans and the PET scan data. A STDM dataset of the report will be generated by the PET site. The RO values will be listed in both reports for sessions 2 and 3, respectively, together with the plasma concentration of ASN51 at the time of the start of each post-dose PET scan; which will be calculated by log-linear interpolation from the two closest pk data points by subject and treatment (data will come from the sponsor).

These concentration data will be transferred to the PET site for the PK-RO analysis. Three PK-RO analyses will be done: for session 2, for session 3 and for pooled data of session 2 and session 3.

12.12 Clinical Study Report

Safety and tolerability parameters as well as PK parameters will be evaluated in a Clinical Study Report.

13.0 TRIAL CONDUCT AND OVERSIGHT

13.1 Ethics

The trial will be conducted in accordance with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki, applicable ICH Good Clinical Practice Guidelines, and applicable local laws and regulations. Should a conflict arise, the Investigator will follow whichever law or guideline affords the greater protection to the individual subject.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an REC/MHRA by the Investigator and reviewed and approved by the REC/MHRA before the trial is initiated.

Protocol amendments require REC/MHRA approval before implementation of changes to the trial design, except for changes necessary to mitigate an immediate hazard to subjects.

13.1.1 Research Ethics Committee or Medicines Healthcare and Products Regulatory Agency

The trial proposal will be reviewed by a recognised REC, and by the MHRA. The trial will not proceed unless the sponsor obtains from the MHRA a clinical trial authorisation, and the REC approves the trial. No subject will have a PET scan without approval from the Administration of Radioactive Advisory Committee (ARSAC). The protocol, any protocol amendments, and the associated ICFs must be reviewed and approved by the REC/MHRA prior to screening of any potential subject.

All subject recruitment information must be submitted to the REC and Sponsor or its designee for review and approval prior to implementation. REC/MHRA approval of any protocol amendments must be received before any of the changes outlined in the amendments are put into effect, except when the amendment has been enacted to protect subject safety. In such cases, the chair of the REC/MHRA should be notified immediately, and the amendment forwarded to the REC/MHRA for review and approval.

13.1.2 Informed Consent

Appropriate forms for documenting written informed consent will be reviewed and approved by the Sponsor or its designee prior to Investigator submission to the REC/MHRA. The Sponsor or its designee must receive a copy of the REC/MHRA approval of the ICF before the shipment of IMP to the trial site.

The method of obtaining and documenting informed consent and the contents of the ICF will comply with ICH GCP guidelines, and all other applicable regulatory requirements.

The Investigator is responsible for obtaining written informed consent from each potential trial subject prior to the conduct of any trial procedures. The signed ICF must be retained in each subject's trial file and be accessible to the trial monitor. Subjects will be given a copy of the signed ICF and will be provided any new information during the course of the trial that might affect their continued participation in the trial.

If the protocol is amended and the ICF is revised, each subject will be required to provide written informed consent again using the revised ICF as applicable.

13.2 Investigator Responsibilities

- Providing oversight of trial conduct at the site
- Adhering to 21 CFR, ICH guidelines, REC/MHRA requirements, European Clinical Trials Directive (if applicable), and all other applicable local regulations
- Promptly notifying the REC/MHRA of significant safety findings
- Providing trial status updates to the REC/MHRA as required

- Provide the Sponsor with required information to complete financial certification or disclosure statement as required by regulatory authorities

A coordinating Investigator will be selected based on level of participation in the trial, therapeutic area expertise, and ability to interpret data. The coordinating Investigator will read and approve the final clinical study report and participate in publication of trial results.

Financing and insurance for this clinical trial will be addressed in clinical trial agreements with each Investigator/trial site.

13.2.1 Investigational Product Accountability

The Investigator is responsible for ensuring IMP is stored in a secure limited access location at controlled temperature as described in the IB and according to product packaging. The storage facility must be available for inspection by the trial monitor at any time during the trial.

A drug accountability record must be maintained for all IMP received, dispensed, returned, and/or lost during the trial. This record must be kept current and made available to the trial monitor for inspection. Following the close-out of the trial, all unused IMP must be returned to Sponsor and/or its designee unless other instructions have been provided for final disposition of the IMP.

13.3 Quality and Recordkeeping

13.3.1 Quality

Monitoring and auditing procedures developed by Sponsor and/or its designee will be implemented to ensure compliance with FDA and ICH GCP guidelines. The following principles will be set forth to ensure quality of trial data:

- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations)
- The Sponsor or designee is responsible for the management of trial data including quality control
- The Sponsor (or designee) will develop a monitoring plan to detail methods, responsibilities, and requirements (including handling of noncompliance issues)
- All subject data relating to the trial will be recorded on the electronic CRF unless electronically transmitted directly to the Sponsor or designee (e.g., laboratory data)
- Any changes to the data will be made only by Sponsor-authorized users; changes will be captured in an electronic audit trail
- The Investigator is responsible for verifying the accuracy of data entered at the trial site
- The Investigator will maintain accurate documentation (source data) that supports information entered in the eCRF
- The Investigator must permit trial-related monitoring, audits, REC/MHRA review, and regulatory agency inspections, and provide direct access to source data documents

- Monitors will verify source data to confirm data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable
- Monitors will evaluate the site to assure the safety and rights of subjects are being protected; and the trial is being conducted in accordance with the current protocol, trial agreements, ICH GCP, and all applicable regulatory requirements

13.3.2 Record Retention

Records and documents pertaining to the conduct of this trial (including original signed ICFs), must be retained by the Investigator for 25 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. Written notification to the Sponsor is required prior to any transfer of records to another location or party.

13.4 Disruption Due to Coronavirus Disease 2019 Pandemic (COVID-19), Considerations for COVID-19 Vaccination, and COVID-19 Risk Mitigation

If a clinical site or Investigator experiences disruption due to COVID-19 (or other natural disaster), a shortened list of assessments may be implemented as an immediate safety measure to ensure at least safety, primary, and key secondary endpoints are captured for any dosed subject. Travel services will be provided as needed for subjects to continue participation in the trial.

Based on various guidelines (e.g., *MHRA Guidance on Coronavirus [COVID-19]*), COVID-19 vaccination should be prioritized for elderly patients and patients with underlying conditions. Subjects eligible for enrollment into this study shall be healthy adult male or female subjects (age 15 – 55 years old) (Section 8.1). Every effort should be made to vaccinate subjects prior to being considered for this study based on the Investigator's risk/benefit analysis for each subject. As with any vaccine, COVID-19 vaccines may cause side effects in some patients. The overwhelming majority of adverse effects to the vaccines relate to injection-site reactions and generalized symptoms such as 'flu-like' illness, headache, chills, fatigue, nausea, fever, dizziness, weakness, myalgia, and heart rate increased (*MHRA Guidance on Coronavirus [COVID-19]*). Generally, these occur shortly after vaccination and are not associated with more serious or lasting illness. No interactions or overlapping toxicities between the IMP and COVID-19 vaccines are anticipated. For this study, subjects who received a COVID-19 vaccination within two weeks of screening or due to receive the second dose of COVID-19 vaccine while participating in the study will be excluded (Section 8.1). Concomitant administration of a COVID-19 vaccine is not permitted during participation in the study (Section 9.10.1).

This clinical trial will be done in accordance with [redacted] COVID-19 risk mitigation plan (RMP), which documents [redacted] COVID-19 virus testing strategy for volunteers and staff, social distancing measures, and management of COVID-19-like symptoms. [redacted] RMP was first notified to the Medicines and Healthcare products Regulatory Agency (MHRA) and Health Research Authority (HRA) on 22 May 2020, and applies across all [redacted] trials. The mitigation measures specified in the [redacted] COVID-19 RMP are deemed adequate for this trial. Any deviations from the RMP will be documented in a separate COVID-19 trial-specific risk assessment, prepared by the Principal Investigator (PI). Any deviations from the protocol that result from the COVID-19 pandemic will be documented.

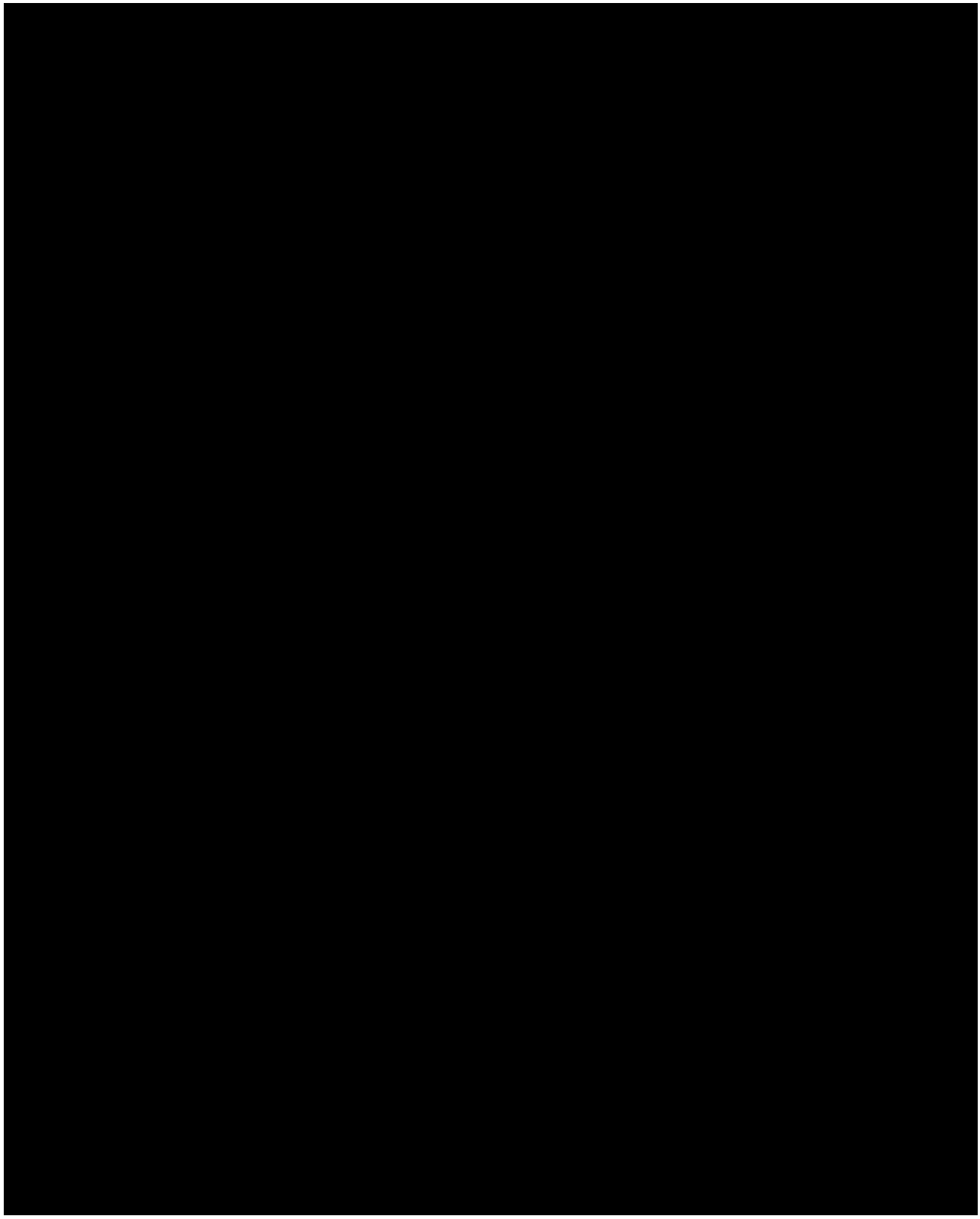
If a subject develops COVID-19, this will be reported and followed as an AE per Section 11.0. The Investigator will follow the standard operating procedures for the site as well as local, regional, and national guidelines for COVID-19. Investigators should use clinical judgement as to whether a subject should continue, temporarily stop, or permanently withdraw from the trial.

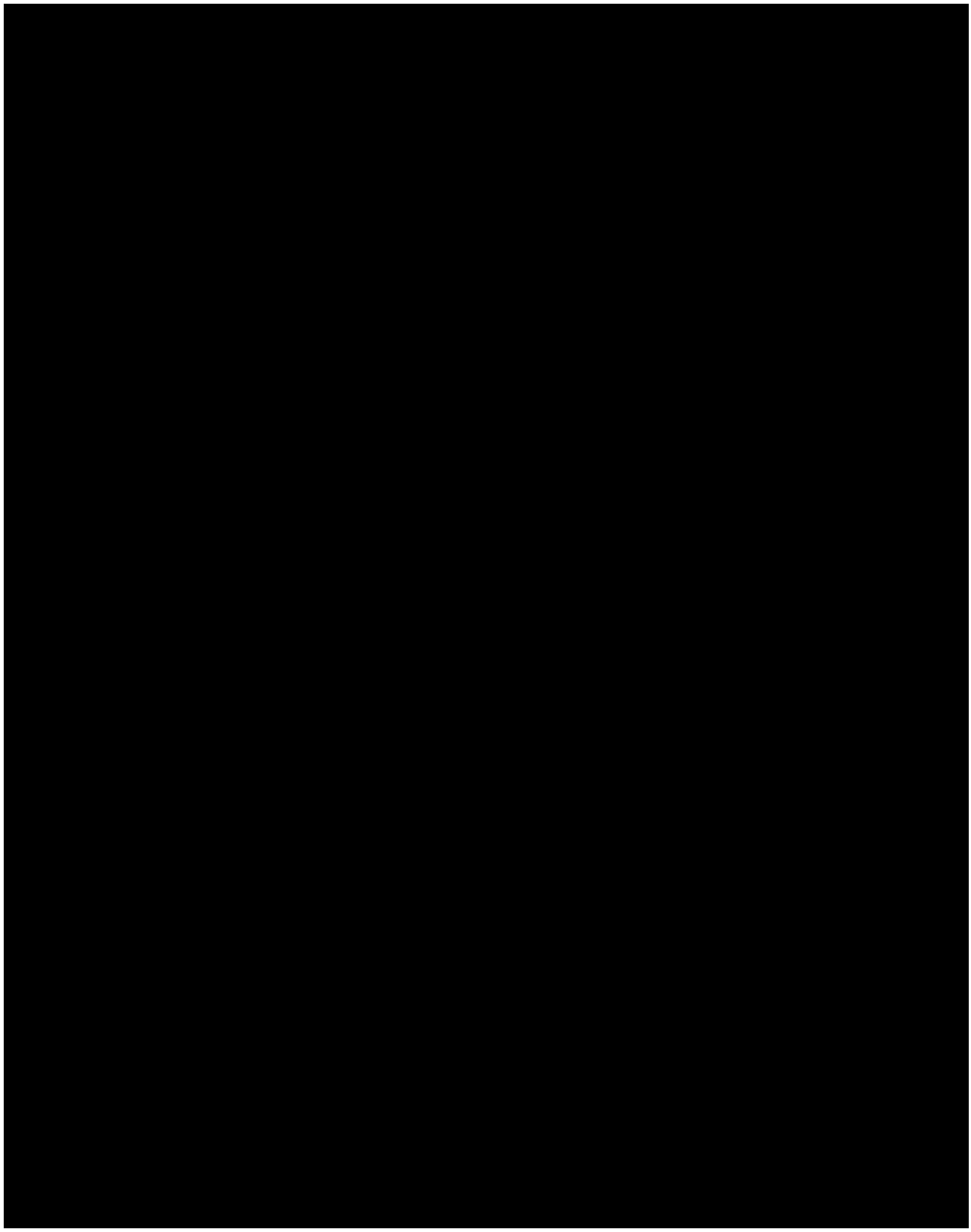
13.5 Publications

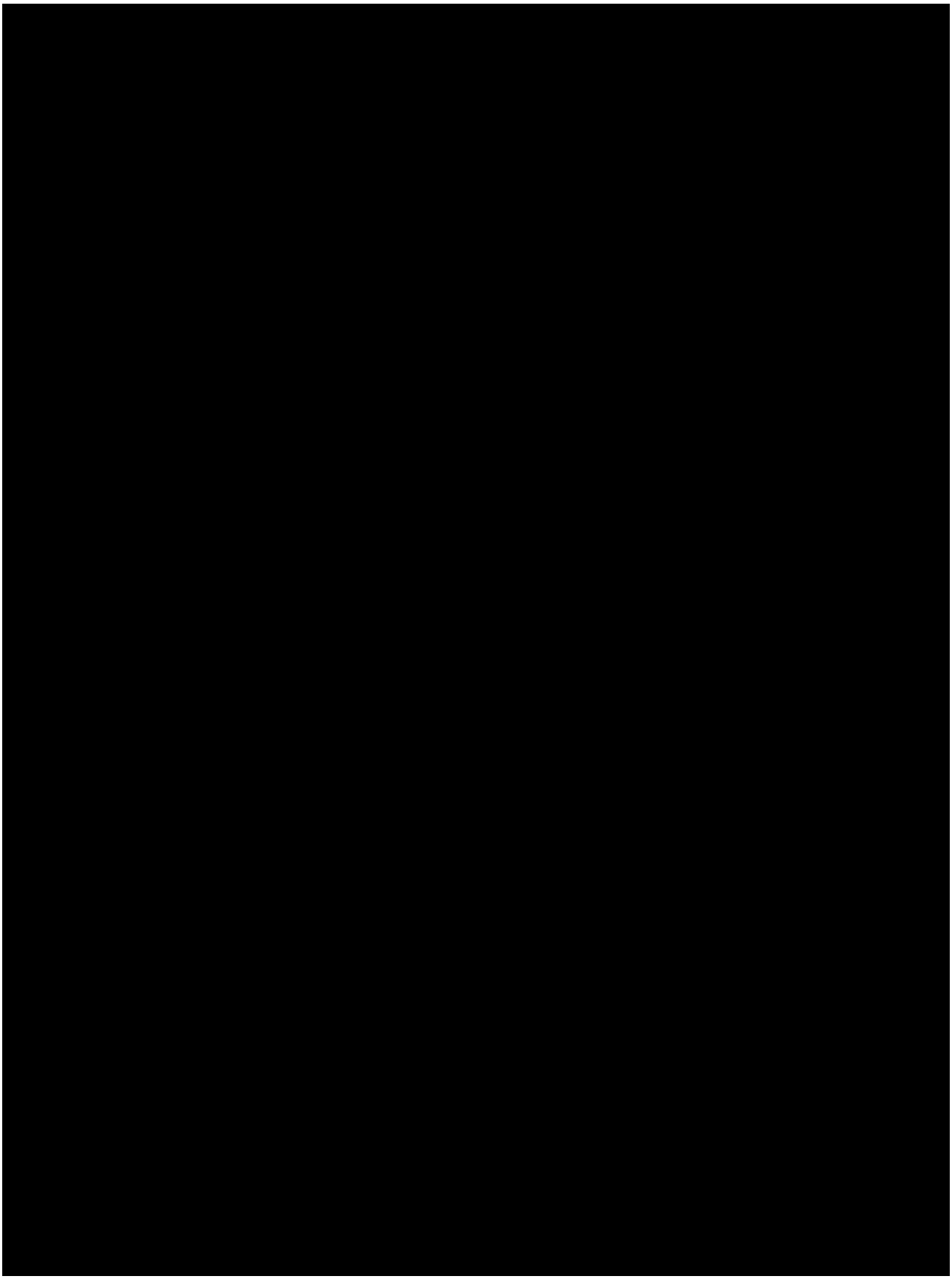
Participation as an Investigator does not confer any rights to authorship of publications. The Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and review content for accuracy.

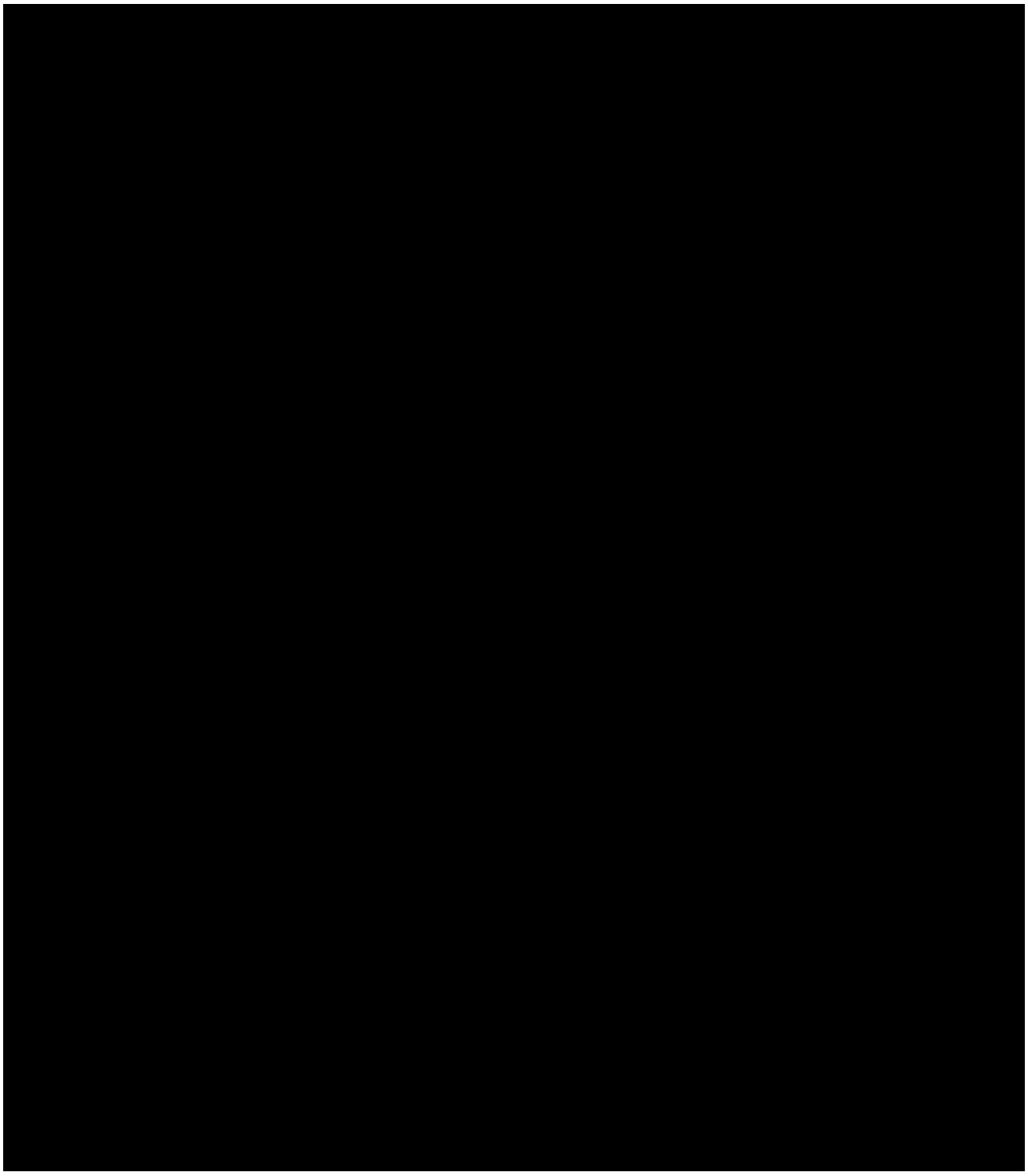
The Sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial practice, the Sponsor will generally support publication of multicenter studies in their entirety, irrespective of outcome.

14.0 REFERENCES









APPENDIX A: LABORATORY PARAMETERS

Clinical Labs for Safety [1]	Central Laboratory[2]
Serum Chemistry (basic metabolic panel-14) • alanine aminotransferase (ALT); albumin:globulin (A:G) ratio; albumin; alkaline phosphatase; aspartate aminotransferase (AST); bilirubin* (total; differentiate into direct and indirect if total > 1.5 × ULN), total; urea ; urea: creatinine ratio; calcium; carbon dioxide, total; chloride; creatinine; eGFR calculation (CKD-Epi formula); globulin, total; glucose (fasting required; note status); potassium; protein, total; sodium	Drug concentration (plasma) • ASN51
Serum Hormone Markers (for post-menopausal female subjects) • FSH	
Hematology (complete blood count with differential) • Hematocrit; hemoglobin; mean corpuscular volume (MCV); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC); red cell distribution width (RDW) • Percentage and absolute differential counts: white blood cells (WBC) • platelets; red cell counts (RBC);	
Urinalysis panel (dipstick w/microscopic examination on positives) • Color; appearance; specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen • If protein, leukocyte, occult blood, and nitrites negative, microscopic examination is not performed	
Coagulation panel • Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)	
Pregnancy testing (WOCPB only; local laboratory) • Serum (to be confirmed before Day 1 IMP) • Urine (MRI visit)	
Serology • HBsAg, HCV, HIV	
Urine drug and cotinine screen and Alcohol Tests • DOA • Cotinine • Urine Alcohol	

1 Note on laboratory forms if subject is taking high dose biotin supplements given potential for biochemical interference in certain assays.
2 Consult manual and protocol for instructions on collection, processing, and shipping to Central Laboratory

ASN51-102 Protocol_v2 - HMR signature

Final Audit Report 2021-05-20

Created:	2021-05-20
By:	[redacted]
Status:	Signed
Transaction ID:	CBJCHBCAABAAxua0VShEnsC_FL7SaqOqfL9dBcekY_0b

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