STATISTICAL ANALYSIS PLAN

STUDY TITLE:

A MULTICENTER, OPEN-LABEL, SINGLE-ARM, PHASE 2 STUDY TO EVALUATE SAFETY AND ORGAN UPTAKE QUANTITATION REPEATABILITY OF ^{124}I-AT-01 USING POSITRON EMISSION TOMOGRAPHY/X-RAY COMPUTED TOMOGRAPHY (PET/CT) IN SUBJECTS WITH SYSTEMIC AMYLOIDOSIS

PROTOCOL NUMBER:

AT01-001

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VERSION HISTORY

SAP Version	Version Date	Change(s)	Rationale
1.0	01APR2022	NA	Initial Draft
2.0	16DEC2022	Added repeatability analyses, updated units for clinically significant change in laboratory values and vital signs table, update analysis day to 43 for visit 2/week 6	Add analyses for interpretability, increase clarity

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1 LIST OF ABBREVIATIONS

Table 1-1: List of Abbreviations

Abbreviation	Term
ADA	Anti-drug antibodies
AL	Amyloid light chain
ATC	Anatomical Therapeutic Chemical
ATTR	Amyloid transthyretin
ATTRv	Hereditary Amyloid transthyretin
ATTRwt	Wild type Amyloid transthyretin
BMI	Body mass index
BNP	Brain natriuretic peptide
CI	Confidence interval
CNR	Contrast to noise ratio
CRF	Case report form
CT	Computed tomography
dFLC	Difference in involved and uninvolved free light chains
eGFR	Estimated glomerular filtration rate
EOS	End of study
FLC	Free light chains
ICC	Intraclass Correlation Coefficient
ICF	Informed consent form
ICH	International Conference on Harmonisation
IES	Image evaluable set
IRR	Infusion-related reaction
IV	Intravenous
KI	Potassium iodide
MedDRA	Medical Dictionary for Regulatory Activities Terminology
PET	Positron emission tomography
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation

SGOT	Serum glutamic-oxaloacetic transaminase (replaced by AST)
SGPT	Serum glutamic-pyruvic transaminase (replaced by ALT)
SMQ	Standardized MedDRA Query
SNR	Signal to noise ratio
SOA	Schedule of activities
SUV	Standardized uptake value
TEAE	Treatment-emergent adverse event
UACR	Urine albumin-to-creatinine ratio
WBC	White blood count
WHO	World Health Organization

2 PURPOSE OF THE ANALYSES

The purpose of this statistical analysis plan (SAP) is to provide detailed information to aid in the implementation of the statistical analysis of the study data. It briefly summarizes the protocol, describes the analysis sets that will be analyzed, and describes the analyses to be performed. The details of the specific statistical methods that will be used are provided. Table, figure, and listing specifications are in separate documents. This analysis plan is meant to supplement the study protocol. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy.

This SAP is written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports and will be finalized prior to database lock.

3 PROTOCOL SUMMARY

3.1 Study Rationale

There currently are no approved imaging agents that specifically detect and quantify amyloid deposits in subjects.

As a positron emission tomography (PET)/X-ray computed tomography (CT) imaging agent that binds many forms of human and murine amyloid, ^{124}I-AT-01 may fulfill this unmet clinical need by enabling detection of amyloid in abdominothoracic organs or tissues of subjects with systemic amyloidosis. Thus, this study has been designed to assess the repeatability of organ-specific quantitation of radiotracer uptake following PET/CT imaging of ^{124}I-AT-01 in subjects with amyloid light chain (AL) or amyloid transthyretin (ATTR) systemic amyloidosis. This will help to determine whether ^{124}I-AT-01 can be used to monitor disease progression and treatment response in subjects with systemic amyloidosis.

3.2 Study Objectives

The primary study objective is to evaluate the repeatability of organ-specific quantitation of radiotracer uptake following PET/CT imaging of ^{124}I-AT-01 in subjects with AL or ATTR systemic amyloidosis.

The secondary study objective is to characterize the safety and tolerability of repeat doses of ^{124}I-AT-01 administered by intravenous (IV) infusion or slow IV bolus.

3.3 Study Design

This is a multicenter, open-label, single arm study in subjects with AL or ATTR systemic amyloidosis. ^{124}I-AT-01 is the only study intervention; neither reference therapy nor placebo will be administered.

This study consists of a screening period of up to 30 days; two, one-day treatment periods (Day 1 and Week 6); a safety follow-up 1-3 days after the second administration of ^{124}I-AT-01, and a final safety follow-up 28 ± 3 days after the second administration of ^{124}I-AT-01. Thus, the total subject duration is approximately 14 weeks. A study flow chart is provided in appendix 14.1 and a schedule of events is provided in appendix 14.2.

A formal sample size calculation is not provided for this study. The sample size of up to 20 subjects was estimated based on systematic literature review analysis sets.

3.4 Study Population

^{124}I-AT-01 is designed to selectively bind to amyloid; therefore, the objectives of this study can only be met by including subjects with documented systemic amyloidosis and known visceral organ amyloid deposits. Subjects with AL or ATTR systemic amyloidosis were selected for this study because these are the most common forms of systemic amyloidosis at the study sites.

4 GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following general analysis and reporting conventions will be used:

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form n (%). If a count is 0, no percentage will be shown. To ensure completeness, summaries for categorical variables will include all categories, even if no subjects had a response in a particular category. Denominators will include subjects with non-missing data, unless otherwise specified. The number of subjects with missing data for categorical variables will be summarized without a percentage.
- Continuous variables will be summarized using mean, standard deviation (SD), minimum, maximum, median, and number of subjects. The mean, median, and confidence intervals (CI) will be rounded and reported to 1 more level of precision than the original observations, and the SD will be rounded and reported to 2 more levels of precision than the original observations. The minimum and maximum will be the same precision as the original data.
- Following SAS default rules, the median will be reported as the rounded average of the two middle numbers if the dataset contains even numbers.
- P-values, if any are provided, will be rounded and reported to 3 decimal places if greater than 0.001. If the rounded p-value is less than 0.001, '<0.001' will be reported. If the rounded p-value is >0.999, '>0.999' will be reported.
- Unless otherwise specified, the baseline value for all measures is the last non-missing value prior to the first dose, obtained on or before the date of the first dose of study drug. For measurements that occur on the date of the first dose of study drug with time collected, the measurement will be considered the baseline value if the measurement time is prior to the time of the first dose.
- No preliminary rounding will be performed; rounding will only occur after analysis. To round, consider digit to right of last significant digit: if < 5 then round down, if ≥ 5 then round up.
- All listings will be sorted in order of subject, parameter (when applicable), and time of assessment (e.g., visit, time, and/or event).
- Dates in listings will be displayed as yyyy-mm-dd (e.g., 2021-10-14).
- Age (in years) will be calculated as [(date of informed consent – date of birth)] /365.25 and will be reported as the integer part of the derived age, with no rounding, in the analysis datasets, tables, and listings.
- All analyses will be performed using the SAS System version 9.4.

5 ANALYSIS SETS

The analysis sets for the planned analyses are defined as follows:

- Enrolled Set

  The Enrolled Set is defined as all subjects who signed the informed consent form (ICF) and met eligibility criteria.

- Safety Set

  The Safety Set is defined as all subjects who receive any amount of ^{124}I-AT-01. The Safety Set will be used for safety analyses.

- Image Evaluable Set

  The Image Evaluable Set (IES) is defined as all subjects who undergo PET/CT scans on both Day 1 and 6 to 8 weeks after Day 1 and who have evaluable images at both time points. The IES will be used for analyses of repeatability.

6 STUDY SUBJECTS

6.1 Disposition of Subjects

The following disposition information will be summarized for all subjects who signed the ICF:

- The number of subjects screened
- The number of subjects who screen failed (subjects who fail screening once, are re-screened, and are treated in the study are counted as screen failures and as enrolled subjects. Subjects who fail screening twice are counted only once as screen failures.)
- The number of subjects who received any study treatment
- The number of subjects who received two doses of AT-01
- The number of subjects in each analysis set
- The number and percentage of subjects who completed the study
- The number and percentage of subjects who discontinued the study and the reason for premature study discontinuation
- The number and percentage of subjects who discontinued the study due to COVID-19
- The distribution of the number of days relative to first dose of study drug (i.e., date of discontinuation – date of first dose + 1) for subjects who prematurely discontinue from the study

A data listing of subject disposition for all subjects who signed the ICF will also be provided.

6.2 Demographic and Other Baseline Characteristics

Subject demographics and other baseline characteristics will be summarized for the Safety Set.

The table will include age, sex, race, ethnicity, height, weight, body mass index (BMI), estimated glomerular filtration rate (eGFR), time since diagnosis of systemic amyloidosis, organ involvement, amyloid subtype, ATTRwt, mutation type for ATTRv subjects, free light chains (FLC) type for AL subjects, normal FLC ratio (kappa/lambda; between 0.26 and 1.65, inclusive for subjects with eGFR >= 30 mL/min/1.73m^2, between 0.37 to 3.17 for subjects with eGFR <30 mL/min/1.73m^2), difference between involved and uninvolved serum free light chains (dFLC), NT-proBNP, BNP, and UACR.

If age is missing, age (years) will be calculated relative to the date of informed consent, as described in Section 4.

Years since diagnosis of systemic amyloidosis will be calculated as year of diagnosis date relative to the year of informed consent (i.e., year of informed consent – year of diagnosis).

eGFR will be calculated via the CKD-EPI equation and have a unit of mL/min/1.73m^2:

eGFR = 141 x $\min(SCr/\kappa, 1)^{\alpha}$ x $\max(SCr/\kappa, 1)^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if Black], where SCr (standardized serum creatinine) = mg/dL, κ = 0.7 (females) or 0.9 (males), α = -0.329 (females) or -0.411 (males).

Demographic and baseline characteristics will be presented in data listings for all enrolled subjects.

A listing of baseline disease characteristics will also be provided.

6.3 Medical, Surgical, and Procedural History

Medical history includes clinically significant diseases, organ or stem cell transplants, and reproductive status. Medical history will be coded using Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 24.1 and will be summarized as counts and percentages for the Safety Set by system organ class and preferred term. A subject will be counted only once for each condition. A listing of medical history data will be provided.

A by-subject listing of surgical and procedural history will be provided.

6.4 Prior and Concomitant Medications

The prior and concomitant medications will be coded using the latest version of World Health Organization Drug Dictionary (WHO Drug), Global version (2021-SEP) to identify the drug class and preferred drug name.

Concomitant medications will include all medications that started on or after day of first dose of the study drug or that stopped on or after day of first dose of study drug, including medications that are classified as ongoing. Prior medications will include all medications that started and stopped prior to the day of first dose of the study drug. Any medication with a partially missing start date or stop date which allows the possibility that the medication is both prior and concomitant will be classified as both. Any medication with a completely missing stop date (i.e., day, month, and year are missing) will be classified as ongoing. For a medication with a completely missing start date, the medication will be classified as both a prior and concomitant medication unless the stop date is prior the date of first dose of study drug, in which case the medication will be classified as a prior medication.

The number and percentage of subjects using prior medications, and separately concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) level 3 term, and preferred drug name for all subjects in the Safety Set. A subject will be counted at most once within each ATC level 3 term, and preferred drug name combination. All percentages will use the number of subjects in the Safety Set as the denominator. The tabular summaries will be sorted by descending overall frequency by ATC level 3 term, and preferred drug name.

Prior and concomitant medication data will also be presented in a data listing for subjects in the Safety Set.

The above tabulations will be repeated for prior and concomitant medications reported on the amyloid medication case report form (CRF) for the treatment for systemic amyloidosis.

7 STUDY OPERATIONS

7.1 Protocol Deviations

Protocol deviations will be summarized by severity (i.e., major or minor) and category and provided in a listing. Any exclusion of subjects from exploratory analysis populations, and how these exclusions impact data analysis, will be addressed in the clinical study report.

7.2 Measures of Treatment Compliance

Treatment compliance is summarized in section 9.2.

8 ENDPOINT EVALUATION

8.1 Overview of Efficacy Analysis Methods

8.1.1 Multicenter Studies

Study subjects will be enrolled from multiple study sites in the United States. For all analyses, study data will be analyzed and summarized as a whole, and no formal accommodation for site-to-site variation will be made. Site identifiers will be included in by-subject listings.

8.1.2 Assessment Time Windows

The following study visits are scheduled:

Table 8-1: Assessment Time Windows

Visit	Analysis Visit Number	Window	Target Day
Screening	0	Day -30 to Day 1	N/A
Visit 1/Day 1	1	Day 1	1
Visit 2 /Week 6	2	After Day 1 to Week 8	43
Safety Follow-up 1	3	1-3 days after second infusion	1 day after second infusion date
Safety Follow-up 2/EOS/ET	4	28 (25-31) days after second infusion	28 days after second infusion date

All scheduled visits including assessments performed outside the target window, will be included in summary tables, figures, and listings. Scheduled visit data will be presented according to the nominal CRF recorded visit. Early termination visit and unscheduled visit data will be mapped to scheduled visits using the windows in Table 8-1. Early termination visit and unscheduled visit data will be included in tables and figures if no scheduled visit data is available for the nominal CRF recorded visit. If more than one unscheduled assessment (early termination or unscheduled) is performed within an analysis window for a visit without a nominal CRF record, the assessment performed closest to the target day will be used, if there is a tie, the earlier assessment will be used.

For clinical laboratory evaluation tables, early termination visits and unscheduled safety data will be mapped to scheduled visits using analysis windows. For all other safety tables and figures, early termination visits and unscheduled safety data will not be mapped to scheduled visits using analysis windows. All data, scheduled and unscheduled, will be included in listings.

8.1.3 Timing of Analyses

All final analyses will be performed after the study is completed and the database is locked.

8.1.4 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons will be made. Any p-values will be considered descriptive.

8.2 Primary Endpoint

The repeatability of organ-specific quantitation of radiotracer uptake will be assessed using PET/CT imaging of ^{124}I-AT-01 in subjects with AL or ATTR systemic amyloidosis and will be presented using multiple methods by organ (heart, liver, spleen, and kidney) to explain the relationship and describe the variability between assessments. The quantitative methods that will be used are (1) repeatability coefficients, (2) Bland-Altman plots, (3) Intraclass Correlation Coefficients (ICC), and (4) Signal-to-Noise Ratio and Contrast-to-Noise Ratio vs SUV-based metrics plots. There are 3 readers at each time point and 2 reads per scan per reader for quantitative reads. The above quantitative methods will be deployed to measure multiple types of repeatability.

These methods are described in more detail in sections 8.2.1, 8.2.2, 8.2.3, and 8.2.4.

The SUV-based metrics are peak SUV (denoted SUVpeak, collected as suv_peak_organ from the imaging dataset), and max SUV (denoted SUVmax, collected as suv_max_organ from the imaging dataset).

In addition to the above quantitative methods, AT-01 uptake will be visually determined by three expert radiologists for each scan of each organ. Agreement among the three reads will be evaluated by scan using Fleiss' kappa. Agreement between each reader's two scans will be evaluated using Cohen's kappa. Details are described in section 8.2.5.

The quality of imaging results will be taken into consideration such that any images with a "Not Readable" indication of scan image quality will be excluded from primary analyses.

All imaging results will be listed.

8.2.1 Repeatability Coefficient

8.2.1.1 Repeatability coefficients using observed values

- *Computation of the Endpoint*

The repeatability coefficient is the value under which the difference between any two repeat measurements of the same measurand acquired under repeatability conditions should fall within 95% probability.

If we assume normality of the repeated measurements, we have:

$$Repeatability\ Coefficient = 1.96 \times \sqrt{\frac{\sum(m_2 - m_1)^2}{n}}$$

where m_1 and m_2 are the two measurements performed on each of the n subjects.

- *Analysis of the Endpoint*

Summary tables with the repeatability coefficients for SUVpeak and SUVmax by organ will be produced 2 different ways:

1. Within Reader by Reader and Visit: where m_1 and m_2 are the 2 reads for a specific reader and visit.
2. Between Visit by Reader: where m_1 is the average of the 2 reads for a specific reader at Visit 1 and m_2 is the average of the 2 reads for the same reader at Visit 2.

8.2.1.2 Repeatability coefficients and within-subject coefficient of variation using log-transformed data

- *Computation of the Endpoint*

For the following calculations, $d_{ln} = \ln(m_2) - \ln(m_1)$.and m_1 and m_2 are the two measurements performed on each of the n subjects:

The repeatability coefficient is estimated as RC = (exp(±1.96SD(d_{ln}))-1) x 100.

The within-subject coefficient of variation is wCV% = (exp($SD_{d\ ln}$ / $\sqrt{2}$))-1) x 100.

- *Analysis of the Endpoint*

A summary table with the 95% repeatability coefficient and within-subject coefficient of variation for SUVpeak and SUVmax by organ will summarize repeatability in 2 different ways:

1. Within Reader by Reader and Visit: where m_1 and m_2 are the 2 reads for a specific reader and visit.
2. Between Visit by Reader: where m_1 is the average of the 2 reads for a specific reader at Visit 1 and m_2 is the average of the 2 reads for the same reader at Visit 2.

In addition to the above statistics, descriptive statistics of the average of and difference of m_1 and m_2 will be presented.

All of these analyses will be conducted on the image evaluable population for subjects with organs/visits where positive AT-01 uptake is detected by all three expert radiologists.

8.2.2 Bland-Altman Plots

- *Computation of the Endpoint*

Each of the n subjects will be represented on the graph by assigning the mean of two measurements as the x-value and the difference between the two measurements as the y-value:

$$\left(\frac{m_1 + m_2}{2}, m_2 - m_1\right)$$

where m_1 is the first measurement and m_2 is the second measurement taken for each of the n subjects. The x-axis will be labeled "Average of the two measurements" and the y-axis will be labeled "Difference between two measurements". A horizontal solid line will be plotted at the mean difference between the values (i.e. $y = \bar{x}$). Horizontal dashed lines will be plotted at the limits of agreement given by: $= \bar{x} \pm 1.96 \times \sqrt{\frac{\sum((m_2-m_1)-\bar{x})^2}{n}}$, where $\bar{x} = \frac{\sum(m_2-m_1)}{n}$. The values of all 3 horizontal lines will be displayed on each plot.

- *Analysis of the Endpoint*

Plots will be produced for SUVpeak and SUVmax by organ for the Image Evaluable Set in 2 different ways:

1. Between Reader by Visit: where m_1 is the average of the 2 reads for a specific reader and visit and m_2 is the average of the 2 reads for a different reader for the same visit.
2. Between Visit by Reader: where m_1 is the average of the 2 reads for a specific reader at Visit 1 and m_2 is the average of the 2 reads for the same reader at Visit 2.

8.2.3 Intraclass Correlation Coefficient (ICC)

- *Computation of the Endpoint*

A two-way mixed effects model with absolute agreement type for a single rater/measurement will be used to calculate the intraclass correlation coefficient. SAS Proc Mixed with subject as a random effect will be used to produce covariance parameter estimates.

ICC will be calculated as the covariance parameter estimate for subject divided by the sum of the covariance parameter estimates for subject and residuals.

Fisher's z-transformation will be used to calculate a 95% CI of ICC (r) where

$z' = \frac{1}{2}\ln\frac{1+r}{1-r}$, and $SE_{z'} = \frac{1}{\sqrt{N-3}}$, making the 95% CI = z' ± 1.96 $SE_{z'}$

To transform the endpoints of the CI back to correlation coefficients, the following formula will be used: $= \frac{\exp(2z)-1}{\exp(2z)+1}$.

- *Analysis of the Endpoint*

A summary table with the ICC for SUVpeak and SUVmax by organ will be produced "Among Reader by Visit": where m_1 is the average of the 2 reads for a specific reader and visit, m_2 is the average of the 2 reads for the second reader and m_3 is the average of the 2 reads for the third reader for the same visit.

8.2.4 Signal to Noise and Contrast to Noise Ratios

- *Computation of the Endpoint*

SNR is calculated as (suv_peak_organ / suv_peak_organ_std_dev) for each read.

CNR is calculated as ([suv_peak_organ]-[suv_peak_aorta_cylinder]) / (suv_peak_aorta_std_dev_cylinder) for each read.

All variables come from the imaging dataset.

- *Analysis of the Endpoint*

Signal to Noise ratios (SNR) and Contrast to Noise ratios (CNR) will each be plotted against SUVpeak and SUVmax by organ for the Image Evaluable Set by reader (taking the averages of the two reads) and visit.

8.2.5 Inter-rater and Intra-rater Agreement

AT-01 uptake is determined by three expert radiologists determination of AT-01 uptake for each region, it is one evaluation per expert per organ per visit. The number and % of subjects with positive AT-01 uptake will be described by expert by visit and organ. The inter-rater agreement in positive AT-01 uptake between the three expert radiologist's determination by visit will be presented using Fleiss' kappa. The intra-rater agreement in positive AT-01 uptake between Scan 1 and Scan 2 in each expert radiologist's determination by expert will be presented using Cohen's kappa and its 95% confidence interval.

8.2.6 Coefficient of Variation

- *Computation of the Endpoint*

The coefficient of variation is a measure of relative variability, calculated as:

- $Coefficient\ of\ Variation = \frac{\sqrt{\frac{\sum(m_i-\bar{x})^2}{n-1}}}{\bar{x}}$, where $\bar{x} = \frac{\sum m_i}{n}$, and m_i is the i^{th} measurement per organ per subject. There are expected to be i=6 measurements for each visit per organ per subject.*Analysis of the Endpoints*

Summary tables with descriptive statistics for the coefficients of variation for SUVmax and SUVpeak by organ will be produced by visit.

8.3 Examination of Subgroups

The repeatability coefficients, Bland-Altman plots, and intraclass correlation coefficients described in section 8.2 will be repeated by amyloid type: (AL versus ATTR).

9 SAFETY EVALUATION

The secondary study objective is to characterize the safety and tolerability of repeat doses of ^{124}I-AT-01 administered by IV infusion or slow IV bolus. The key secondary endpoints are incidence of treatment-emergent AEs from Day 1 to EOS, change from baseline in clinical laboratory values at Visits 2 and Safety Follow-up 1 (1-3 days after the second infusion), change from baseline in vital signs, and change from baseline in anti-drug antibodies (ADA).

Change from baseline in ADA is outside the scope of this SAP.

9.1 Overview of Safety Analysis Methods

The safety analyses will be performed for the Safety Set and will include treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), vital signs, biomarkers, and concomitant medications. Tabular summaries of descriptive statistics will be presented for all subjects included in the Safety Set.

For all safety endpoints, baseline will b

e the last non-missing value before administration of ^{124}I-AT-01.

Safety data will not be imputed, except for partial and missing dates, which will be imputed only for defining TEAEs and concomitant medications. Imputed dates will not be presented in data listings.

Partial dates will be imputed for the purposes of defining TEAEs as follows:

- For a missing start day where the month and year are present, the start day will be set to the first day of the month, unless 1) the first day of the month is before the most-recent date of administration of ^{124}I-AT-01 and the month and year are the same as the month and year of the most-recent date of administration of ^{124}I-AT-01, and 2) the end date is on or after the most-recent date of administration of ^{124}I-AT-01or the end date is completely missing, in which case the start day will be set to the most-recent date of administration of ^{124}I-AT-01.
- For a missing start day and month where the year is present, the start day and month will be set to January 1st, unless 1) January 1st is before the most-recent date of administration of ^{124}I-AT-01 and the year is the same as the year of the most-recent date of administration of ^{124}I-AT-01, and 2) the end date is on or after the most-recent date of administration of ^{124}I-AT-01 or the end date is completely missing, in which case the start day and month will be set to that of the most-recent date of administration of ^{124}I-AT-01.
- For a missing end day where the month and year are present, the end day will be set to the last day of the month, unless the month and year are the same as the month and year of the last contact date for the subject, in which case the end day will be set to that of the subject's last contact date.
- For a missing end day and month where the year is present, the end day and month will be set to the subject's last contact date, unless the year of the subject's last contact date is

greater than the end year, in which case the end day and month will be set to December 31st.

9.2 Extent of Exposure

Only subjects enrolled in this study may be treated with ^{124}I-AT-01. During the study, qualified clinical site staff will administer all study drug. The date and time for each dose will be recorded in the CRFs.

The actual dose of ^{124}I-AT-01 will be summarized in mCi and mg by study visit. The administration type (infusion, IV bolus), duration of administration (for infusions) and number of subjects experiencing an administration interruption and associated reason for interruption will be summarized by study visit.

^{124}AT-01 compliance is defined as receiving 1 mCi (+/- 10%) (<= 2mg ^{124}AT-01). KI compliance is defined as receiving KI orally for 3 days in the specified time periods. The number of and percent of compliant subjects for ^{124}AT-01 and for KI will be summarized by visit.

A listing of all administrations of ^{124}I-AT-01 will be provided by subject and visit.

A listing of all administrations of potassium iodide (KI) will be provided by subject and visit.

9.3 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1 to identify the system organ class and preferred term. All AEs and SAEs will be recorded from the time of informed consent until the final EOS telephone follow-up (~Week 10).

Treatment-emergent AEs are defined as events that are newly reported or reported to worsen in severity after the start of treatment. Adverse events that occur after the treatment start date, occur on the treatment start date with a time that is equal to or after treatment start time, or that have a missing AE start date will be categorized as treatment-emergent. Treatment-emergent AEs will be summarized for the Safety Set.

9.3.1 Overall Summary of AEs

An overall summary of AEs will be presented and will reflect a count of TEAEs, TEAEs by CTCAE grade, TEAEs by relationship to investigational product, and treatment-emergent serious adverse events (SAEs). Additionally, the table will reflect the count and percentage of subjects experiencing the following: any TEAEs, SAEs, TEAEs classified by relationship to investigational product, and TEAEs by CTCAE grade. All percentages will use the number of subjects in the Safety Set as the denominator.

9.3.2 Subject-level and Event-level Summary of AEs

A summary table will be presented to reflect a count and percentage of subjects experiencing at least 1 TEAE in each system organ class and preferred term and a count of TEAEs occurring in subjects in the Safety Set within each system organ class and preferred term. All percentages will use the number of subjects in the Safety Set as the denominator. A subject

will be counted only once for a category. For the event-level summaries, subjects experiencing more than 1 AE within a category be counted more than once. Tabular summaries will be sorted by descending frequency in subject counts by system organ class and preferred term.

TEAEs and SAEs will also be tabulated by CTCAE grade, relationship to AT-01 administration, and relationship to KI. Each subject will be counted only once within a SOC or PT by using the AE with the highest severity or greatest relationship within each category.

Records with missing CTCAE grade will be counted as severe.

Records with missing relationship to AT-01 or KI will be counted as related.

Listings for all reported adverse events will be provided.

9.4 Deaths, Serious Adverse Events, and Other Significant Adverse Events

Treatment-emergent SAEs, TEAEs leading to study withdrawal, and TEAEs resulting in death will be summarized separately for all subjects in the Safety Set. All percentages will use the number of subjects in the Safety Set as the denominator. Summary tables will reflect a count and percentage of subjects experiencing at least 1 TEAE in each system organ class and preferred term within each AE subset (serious, leading to study withdrawal, leading to death). The tabular summary will be sorted by descending frequency of system organ class and preferred term based on the overall incidence.

Records with missing SAE flags will be counted as SAEs.

Separate listing for SAEs, AEs leading to premature withdrawal from the study, and all deaths will be generated.

9.4.1 TEAEs on Day of Dosing

Infusion-related reactions (IRRs) can be any signs or symptoms experienced by subjects during the infusion of pharmacologic or biologic agents or any event occurring on the first day of the infusion. Treatment-emergent adverse events starting on the day of dosing at each dosing visit will be summarized by SOC and PT in order to evaluate potential IRRs.

A data listing of TEAEs starting on the day of dosing at each dosing visit will be provided.

IRRs which occur during administration will be captured on the AT01 Infusion CRF as any non-blank answer for “If discontinued, provide reason” or “If interrupted, reason for interruption” and will be provided in a listing.

9.4.2 TEAEs by Visit

TEAEs by CTCAE grade, treatment-emergent SAEs by CTCAE grade, and TEAEs leading to study withdrawal will be categorized by their start date. The two time categories will be (1) after Visit 1 and prior to the Visit 2 date and (2) after the Visit 2 date.

9.4.3 Hypersensitivity AEs

Hypersensitivity TEAEs will also be summarized by SOC and preferred term. Hypersensitivity TEAEs are all the preferred terms in the Standardized MedDRA Queries (SMQs) of Hypersensitivity (narrow scope).

9.5 Clinical Laboratory Evaluation

Baseline for clinical chemistry parameters is defined as the most recent laboratory measurement obtained prior to the initiation of study drug. The post-baseline visits are Visit 2 / Week 6 and Safety Follow-up 1 (1-3 days after the second infusion).

Baseline and all post-baseline visit values and change from baseline to post-baseline in laboratory parameters for clinical labs will be summarized for the Safety Set using descriptive statistics, as described in Section 4. Unscheduled visits will be mapped to scheduled visits using analysis windows according to Section 8.1.2.

Biomarkers include NT-proBNP, brain natriuretic peptide (BNP), serum free light chains (only subjects with AL amyloidosis), UACR (only subjects with AL amyloidosis), FLC ratio (Kappa/Lambda) (only subjects with AL amyloidosis), and dFLC (only subjects with AL amyloidosis).

Serum chemistry, Hematology, and biomarker assays will also be presented in data listings for subjects in the Safety Set. The listing will include the reference range (if applicable), classification of high, low, critical, or exclusion, and an abnormal flag. Classification of laboratory values and reference ranges in the data listings will be based on the global laboratory reference ranges used across all sites.

Laboratory parameters with clinically significant changes will be summarized and listed as 'flagged' based on the Sponsor's internal guidelines based on Appendix 14.3.

Additional categorizations of biomarker results for the Image Evaluable Set will be produced including the number and percentage of subjects with:

- Screening and Visit 2 NT-proBNP < 650 ng/L
- Screening or Visit 2 NT-proBNP >= 650 ng/L
- Screening or Visit 2 NT-proBNP >= 650 ng/L and change in NT-proBNP of >= 30% and >= 300 ng/L from Screening to Visit 2
- Screening or Visit 2 NT-proBNP missing
- AL subjects with a normal FLC ratio at Screening and Visit 2

This summary will also include descriptive statistics for dFLC in AL subjects with an abnormal FLC ratio at Screening or Visit 2. NT-proBNP will be displayed in ng/L using the conversion: 1 ng/L = 8.457 pmol/L.Pregnancy test results will also be presented in a data listing for the Safety Set.

9.6 Vital Signs

Baseline and all post-baseline visit values and change from baseline to post-baseline values in systolic blood pressure, diastolic blood pressure, heart rate, weight, and body mass index (BMI) will be summarized for the Safety Set using descriptive statistics, as described in Section 4. Height at baseline will be summarized using descriptive statistics, as described in Section 4, and will be used in the calculation of BMI at post-baseline visits.

Vital sign results by visit will be presented in a data listing for subjects in the Safety Set.

Vital signs with clinically significant changes will be summarized and listed as 'flagged' based on the Sponsor's internal guidelines based on Appendix 14.3.

10 PHARMACOKINETIC EVALUATION

Not applicable.

11 INTERIM ANALYSES AND DATA MONITORING

The data will be continuously monitored for safety throughout the study. No interim analysis is planned.

12 CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

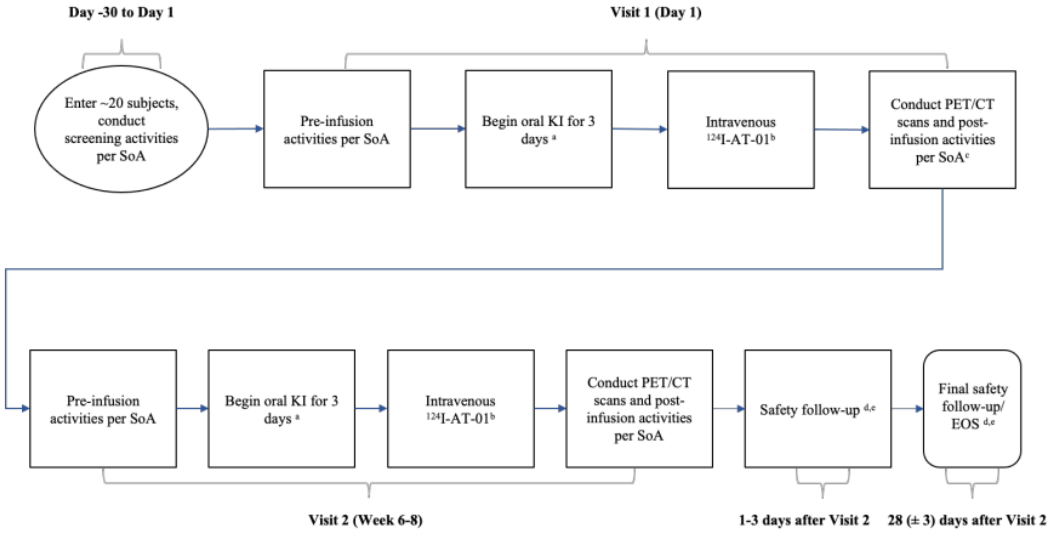
Not applicable.

13 REFERENCES

1. Quantitative Imaging Biomarkers Alliance (QIBA). Indices of Repeatability, Reproducibility, and Agreement. 2013. http://qibawiki.rsna.org/images/8/8c/FMRITechnicalPerformanceIndices041613.pdf
2. PET/CT Standardized Uptake Values (SUVs) in Clinical Practice and Assessing Response to Therapy. (2011). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3026294/

14 APPENDIX

14.1 Study Flow Chart



Abbreviations: CT = computerized tomography; IV = intravenous; PET = positron emission tomography; SoA = schedule of activities.

a. Begin oral KI for 3 days, beginning >30 minutes and <24 hr prior to dosing.
b. ^{124}I-AT-01 will be administered by IV infusion over 2-5 minutes (subjects enrolled under protocol Version 1.1) or slow IV bolus at 1 mL/5 seconds (subjects enrolled under protocol Version 2.0). For all subjects, ^{124}I-AT-01 will be administered by the same route (IV infusion over 2-5 minutes or slow IV bolus at 1 mL/5 seconds) at the Week 6 visit as on the Day 1 visit.
c. Subjects will be discontinued if amyloid deposits are not identified in the Day 1 PET/CT scan in at least one of the following organs: heart, liver, spleen or kidney.
d. Record concomitant medications and conduct biomarker/safety assessments per SoA.
e. Safety follow-ups will be done via telephone call for all subjects.

14.2 Schedule of Activities

Visit	Screening	Visit 1/ Day 1		Visit 2/ Week 6		Safety Follow-up 1 [j]	Safety Follow-up 2 (EOS) [j]	Early Termination (ET) [k,l]
Window	**Day –30 to Day 1**	**± 0 days**		**Week 6 to Week 8**		**1-3 Days After Visit 2**	**28 (± 3) Days After Visit 2**	**<7 days from ET Decision**
Timing of Activity(ies)		**Prior to ^{124}I-AT-01**	**^{124}I-AT-01 and Scan**	**Prior to ^{124}I-AT-01**	**^{124}I-AT-01 and Scan**			
Assessment/Procedures								
Informed Consent [a]	X							
Medical history and Demographics	X							
Inclusion and Exclusion criteria	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Oral Potassium Iodide (KI) [b]		X		X				
^{124}I-AT-01 Administration [c]			X		X			
Biomarker and Safety Assessments								
Vital Signs (HR and BP) [d]		X	X	X	X			
Body Weight		X		X				
Height		X						
Pregnancy Test (WOCBP) [e,f]	X			X				
PET/CT Scan			X		X			
Adverse events [g]	X	X	X	X	X	X	X	X
Laboratory [h,i]	X			X		X		
Biomarkers [h,i]	X			X				
Urine UACR (AL subjects only) [i]	X			X				
Serum ADA [i]	X			X			X	X

All sections in blue refer to protocol sections:

Abbreviations: ADA = anti-drug antibodies; AL = amyloid light chain amyloidosis; BP = blood pressure; CBC = complete blood count; EOS = end of study; ET = early termination; HR = heart rate; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; UACR = urine albumin-to-creatinine ratio; WOCBP = women of childbearing potential.

a. Informed consent, as described in Section 10.1.3.

b. KI is self-administered by the subject daily for 3 days, beginning >30 minutes and <24 hr prior to dosing, as described in Section 4.1.2.

c. ^{124}I-AT-01 will be administered by IV infusion over 2-5 minutes (protocol Version 1.1) or slow IV bolus at 1 mL/5 seconds (protocol Version 2.0), as described in Section 4.1.3. For all subjects, ^{124}I-AT-01 will be administered by the same route (IV infusion over 2-5 minutes or slow IV bolus at 1 mL/5 seconds) at the Week 6 visit as on the Day 1 visit.

d. Subjects must remain semi-recumbent for at least 5 minutes prior to blood pressure measurements. Blood pressure and heart rate will be measured within an hour prior to dosing and 5-10 minutes after administration of ^{124}I-AT-01.

e. Serum pregnancy test, as indicated in Section 10.2, will be obtained in all women of childbearing potential.

f. Serum pregnancy and all other laboratory samples must be drawn within 7 days prior to administration of ^{124}I-AT-01 in all WOCBP. The results of the pregnancy test must be available and be negative prior to ^{124}I-AT-01 administration in all WOCBP.

g. Adverse events will be monitored from Screening through the EOS Visit. For Safety Follow-up 1 and 2, adverse events and concomitant medications can be obtained by phone call.

h. Clinical laboratory tests and biomarker analysis, as described in Section 10.2. Baseline sample will be collected within 30 days prior to the first administration of ^{124}I-AT-01; second sample within 7 days prior to the second administration of ^{124}I-AT-01; third sample at Safety Follow-up 1 after the second administration of ^{124}I-AT-01.

i. Urine and blood may be collected locally by visiting nurse/phlebotomist. An additional serum ADA sample will be obtained at Screening for subjects who provided consent for the extra ADA sample.

j. Safety follow-ups for concomitant medications and adverse events will be done via telephone call for all subjects. Both Safety Follow-up 1 and Safety Follow-up 2 activities will be conducted for subjects who discontinue for IRRs at either the first or second administration of ^{124}I-AT-01.

k. Blood draw for ADA should be obtained if ET is ≥4 weeks after first administration of ^{124}I-AT-01.

l. Early Termination activities do not apply to subjects discontinued for IRRs. Please follow Safety Follow-up 1 and Safety Follow-up 2 activities for subjects experiencing IRR with either the first or second administration of ^{124}I-AT-01.

14.3 Clinically Significant Change in Laboratory Values and Vital Signs

Category	Measurement	Criteria for Clinically Significant Change
Laboratory	Hematocrit (%)	Decrease > 20% and < LLN Increase > 20% and > ULN
Laboratory	Hemoglobin (g/dL)	Decrease > 20% and < LLN Increase > 20% and > ULN
Laboratory	Leukocytes ($x10^9$/L)	Decrease > 20% and < LLN Increase > 50% and > ULN
Laboratory	Lymphocyte count ($x10^9$/L)	Decrease > 20% and < LLN Increase > 50% and > ULN
Laboratory	Neutrophils ($x10^9$/L)	Decrease > 20% and < LLN Increase > 50% and > ULN
Laboratory	Platelets ($x10^9$/L)	Decrease > 20% and < LLN Increase > 50% and > ULN
Laboratory	Glucose (mmol/L)	Value < 2.775 mmol/L Increase > 50% and > ULN
Laboratory	Bilirubin (umol/L)	Increase > 50% and > ULN
Laboratory	Alkaline phosphatase (IU/L)	Increase > 50% and > ULN
Laboratory	Aspartate Aminotransferase (IU/L)	Increase > 100% and > ULN
Laboratory	Alanine Aminotransferase (IU/L)	Increase > 100% and > ULN
Laboratory	Potassium (mmol/L)	Absolute decrease > 0.8 mmol/L and < LLN Absolute increase > 0.8 mmol/L and > ULN
Laboratory	Sodium (mmol/L)	Absolute decrease > 0.8 mmol/L and < LLN Absolute increase > 0.8 mmol/L and > ULN
Vital Signs	Systolic Blood Pressure (mmHg)	Decrease > 20 mmHg and SBP < 90 mmHg
Vital Signs	Diastolic Blood Pressure (mmHg)	Increase > 10 mmHg and DBP < 50 mmHg

15 ATTACHMENTS

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