CLINICAL STUDY PROTOCOL

Protocol 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
Amendment Number:	2.0
Version Date:	08 March 2022
Supersedes:	1.1 (Dated: 07 October 2021)
Investigational Product:	^{124}I-AT-01
Study Phase:	2
Study Acronym/Name:	N/A
Brief Protocol Title:	An Open-label, Phase 2 Study to Evaluate Organ Level Uptake Quantitation Repeatability of ^{124}I-AT-01 in Subjects with Systemic Amyloidosis
Sponsor Name and Address:	Attralus, Inc. 50 Francisco Street, Suite 450 San Francisco, CA 94133
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IND Number:	132282
EudraCT Number:	N/A

CONFIDENTIAL

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SPONSOR SIGNATORY

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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Protocol Accepted and Approved by:

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Greg Bell
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3/8/2022
Date

PRINCIPAL INVESTIGATOR SIGNATORY

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
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I have read the protocol described above, concur that it contains all information necessary to conduct the study, and agree to abide by all provisions set forth therein. I agree to conduct this study in accordance with the International Council on Harmonisation Tripartite Guideline on Good Clinical Practice (ICH E6 GCPs) and applicable local regulations. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board (IRB) and have complied with all financial and administrative requirements of the governing body of the clinical institution and the Sponsor. I will obtain written informed consent from each study subject prior to performing any study specific procedures that are NOT my routine standard of care. I understand that my signature on a case report form indicates that the data therein has been reviewed and accepted by me. I understand that this document and related information is subject to confidentiality terms found in my signed Confidentiality or Clinical Services Agreement. I agree to protect the confidentiality of my patients when allowing the Sponsor of this clinical investigation, and/or relevant regulatory authorities and IRBs, direct access to my medical records for study subjects.

_____ _____

Signature Date

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LIST OF ABBREVIATIONS AND ACRONYMS

Term	Definition
ADA	Anti-drug antibodies
AE	Adverse event
AL	Amyloid light chain
ATTR	Amyloid transthyretin
ALECT2	Amyloid leukocyte cell-derived chemotaxin-2
AUC_{0-t}	Area under the whole blood radioactivity-time curve from time 0 to the last quantifiable drug concentration
BMI	Body mass index
BNP	Brain natriuretic peptide
BP	Blood pressure
CBC	Complete blood count
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL	Apparent systemic clearance
C_{max}	Maximum observed whole blood radioactivity
CMR	Cardiac magnetic resonance
CNR	Contrast to noise ratio
COVID-19	Coronavirus-19
CR	Complete response
CRF	Case report form
CRO	Contract or Clinical Research Organization
CT	Computerized tomography
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data collection
EOS	End of study
ET	Early termination
FSH	Follicle stimulating hormone
GCPs	Good clinical practices
HIPPA	Health Insurance Portability and Accountability Act
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational new drug
iOSAT	Potassium iodide (KI) 130 mg
IRB	Institutional review board
IRR	Infusion-related reaction

IV	Intravenous
λz	Terminal elimination rate constant
LAR	Legally authorized representative
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NOAEL	No-observed-adverse-effect level
NSAIDs	Nonsteroidal anti-inflammatory drugs
NT-proBNP	N-terminal prohormone of brain natriuretic peptide
NYHA	New York Heart Association
OTC	Over the counter
PBS	Phosphate-buffered saline
PET	Positron emission tomography
PK	Pharmacokinetics
PT	Preferred term
RBC	Red blood cell
ROI	Region(s) of interest
SAE	Serious adverse event
SAP	Serum amyloid P-component; statistical analysis plan
SBP	Systolic blood pressure
scFc	Single chain Fc
SD	Standard deviation
SNR	Signal to noise ratio
SoA	Schedule of Activities
SOC	System organ class
SOP	Standard operating procedure
SPECT	Single-photon emission computerized tomography
SpO_2	Peripheral blood oxygen saturation level
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standardized uptake value
$t_{1/2}$	Apparent terminal elimination half-life
TEAE	Treatment-emergent adverse event
T_{max}	Time of maximum observed whole blood radioactivity
TnI	Troponin I
UACR	Urine albumin creatinine ratio
UPT	Urine pregnancy test
UTARP	UT Amyloidosis Research Program
VGPR	Very good partial response
Vss	Apparent volume of distribution at steady state
WBC	White blood cell
WOCBP	Women of childbearing potential

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Number: AT01-001	**Version:** 1.0	**For National Authority Use Only**
IND Number: 132282	**EudraCT Number:** N/A	
Sponsor: Attralus, Inc		
Investigational Product: ^{124}I-AT-01		

Title of Study: 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

Brief Title: An Open-label, Phase 2 Study to Evaluate Organ Level Uptake Quantitation Repeatability of ^{124}I-AT-01 in Subjects with Systemic Amyloidosis

Brief Study Rationale:

There currently are no approved imaging agents that specifically detect and quantify amyloid deposits in patients. 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 patients 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 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 patients with systemic amyloidosis.

Type of Study and Development Phase:	**Countries/Regions:**
Human pharmacology, Phase 2	United States

Study Period: Approximately nine (9) months.

Objectives and Key Endpoints:

Objectives	Key Endpoints
Primary	
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.	• Repeatability coefficient (Bland-Altman plots) and intraclass correlation coefficient (ICC) associated with the quantification of radioactivity associated with organ level ^{124}IAT01 uptake measurements.
Secondary	
• To characterize the safety and tolerability of repeat doses of ^{124}I-AT-01 administered by IV infusion or slow IV bolus.	• Incidence of treatment-emergent AEs[1] 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 administration of ^{124}I-AT-01). • Change from Baseline in vital signs. • Change from Baseline in ADA.

Design/Methodology:

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.

Number of Subjects Planned:	**Gender:**	**Age:**
Approximately 20	Male or female	≥18 years of age

Protocol Number: AT01-001	**Version:** 1.0	**For National Authority Use Only**
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Diagnosis and Key Criteria for Eligibility:

Eligible subjects will have:

- Has a history of AL or ATTR systemic amyloidosis with at least one organ with clinically demonstrable amyloid involvement.
- Able to undergo 2 PET/CT scans as part of the study, including ability to lie supine for up to 1 hour.

Total Subject Duration: Approximately 14 weeks.	**Treatment Duration:** Approximately 6 weeks
Investigational Product, Dose, and Route of Administration: ^{124}I-AT-01, 1 mCi ±10% (≤2 mg AT-01) via IV infusion or slow IV bolus at 1 mL/5 seconds	**Control, Dose, and Route of Administration:** N/A

Organ Uptake Quantitation Evaluation:

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.

The signal to noise ratio (SNR) and contrast to noise ratio (CNR) will be plotted against standardized uptake value (SUV) based metrics. Repeatability will be assessed using Bland-Altman plots. Intraclass correlation coefficient (ICC) and its associated 95% confidence interval will be presented.

Safety Evaluation:

All AEs and SAEs will be recorded from the time of informed consent until the final EOS telephone follow-up (~Week 10). AEs will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 5. All adverse events occurring during the study will be recorded and classified based on Medical Dictionary for Regulatory Activities (MedDRA) terminology. The number and percentage of subjects experiencing TEAEs and SAEs will be tabulated for the safety population by system organ class (SOC) and preferred term (PT). TEAEs and SAEs will be tabulated by severity and relationship to study medication. Each subject will be counted only once within a SOC or a PT by using the AE with the highest severity or greatest relationship, respectively, within each category.

TEAEs or SAEs leading to early discontinuation will be summarized as described above.

Listings for all reported adverse events, including SAEs, will be provided. In addition, separate listing for SAEs, AEs leading to premature withdrawal from the study, and all deaths will be generated.

Vital signs will include blood pressure (mmHg) and heart rate (beats per minute). Vital signs will be summarized at Baseline and for each study visit when vital signs were obtained. Changes from Baseline in vital sign measurements will also be summarized. Baseline is defined as the last vital signs obtained prior to the initiation of study drug.

Protocol Number: AT01-001	**Version:** 1.0	**For National Authority Use Only**
IND Number: 132282	**EudraCT Number:** N/A	
Sponsor: Attralus, Inc		
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Title of Study: 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

Statistical Considerations:

This is an open-label, single arm study. In general, for continuous variables, the mean, standard deviation (SD), median, and range will be presented. Categorical variables will be summarized by frequency counts and percentages.

Subject disposition will be summarized for all subjects who signed the ICF and will include the number of subjects who received study treatment and the number and percentage of subjects who completed or prematurely discontinued the study, classified by reasons for premature discontinuation.

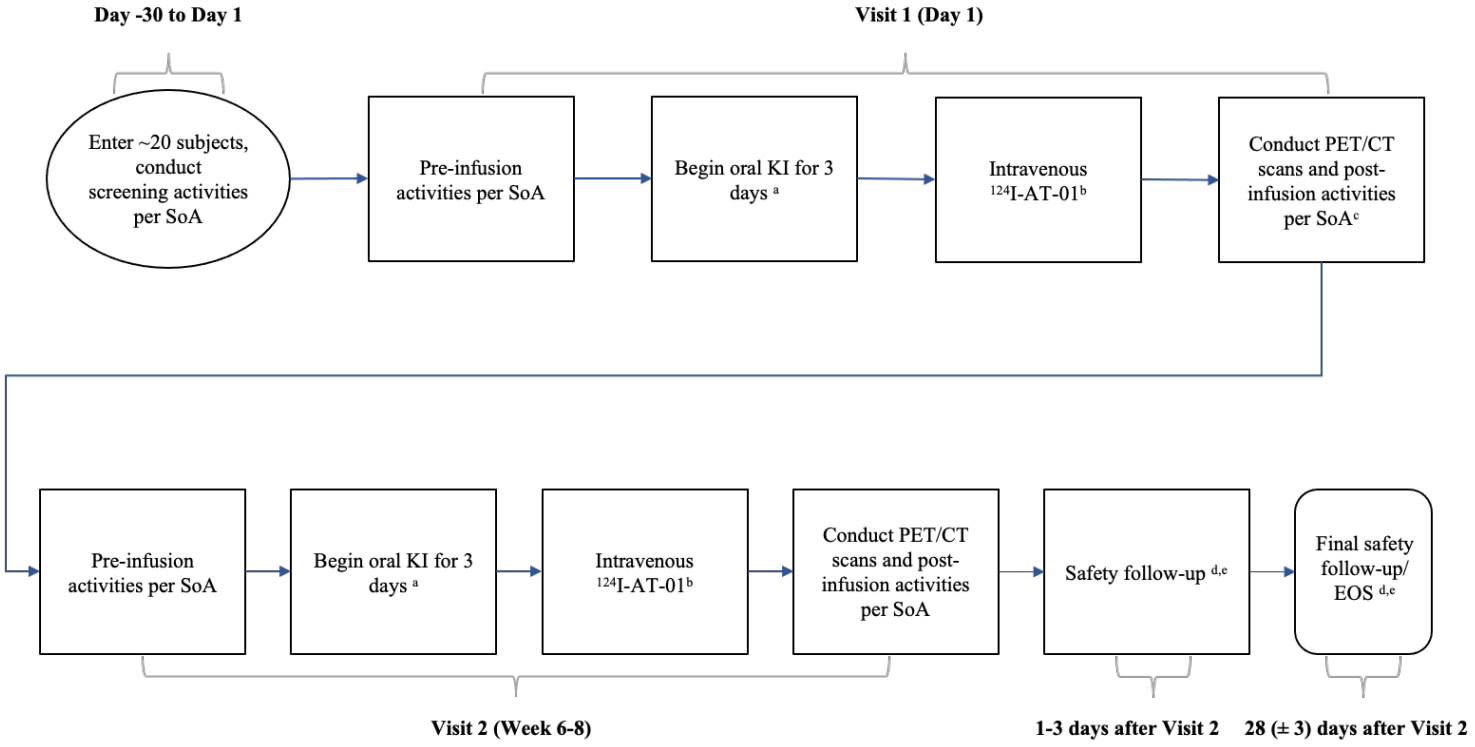
Description of Data Monitoring:

Study conduct and subject safety will be monitored on an ongoing basis by the study Sponsor.

Version Date: 08 March 2022

1.2 Study Schema

Figure 1: Protocol AT01-001: Schema



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.

1.3 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

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.

2.0 INTRODUCTION

^{124}I-AT-01 is an amyloid-reactive synthetic peptide (p5+14 or APi1832) radiolabeled with iodine-124. There currently are no approved imaging agents that specifically detect and quantify amyloid deposits in patients with systemic amyloidosis. As a positron emission tomography (PET)/X-ray computed tomography (CT) imaging agent that binds many forms of human and murine amyloid, it may fulfill this unmet clinical need by enabling detection of amyloid in abdominothoracic organs or tissues of patients with systemic amyloidosis.

2.1 Study Rationale

Systemic amyloidosis is an incurable disease, and about 20% of patients with cardiac or advanced kidney involvement experience early deaths (<1 year). Recent progress in the treatment of AL amyloidosis with proteasome inhibitors, chemotherapies, and immunotherapies that target plasma cells has greatly improved patient prognosis; however, median survival remains low at approximately five years (Milani 2018; Palladini 2020). Earlier quantitative detection of amyloid in abdominothoracic organs or tissues and assessment of response to treatment may improve the prognosis of these patients. However, there currently are no approved imaging agents that specifically detect and quantify amyloid deposits in patients.

As a PET/X-ray 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 patients 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 AT-01 in subjects with amyloid light chain (AL) or amyloid transthyretin (ATTR) systemic amyloidosis. This will help to determine whether AT-01 can be used to monitor disease progression and treatment response in patients with systemic amyloidosis.

2.2 Background

2.2.1 Systemic Amyloidosis

Systemic amyloidosis is a rare protein misfolding and deposition disorder that results in tissue amyloid deposits and progressive organ failure. The amyloid deposits are composed of highly organized proteinaceous (amyloid) fibrils in association with proteoglycans (hypersulfated proteoglycans) and serum derived proteins, serum amyloid P, apolipoprotein E, and apolipoprotein A-IV (Muchtar 2021). Amyloid is insoluble and resistant to degradation. The resistance to catabolism results in progressive tissue amyloid accumulation and organ dysfunction.

Amyloidosis can be acquired or hereditary and can affect various organs, including the liver, spleen, heart, kidneys, peripheral and autonomic nervous systems, gastrointestinal tract, lungs and pleura, skin, and soft tissues. Symptoms are usually nonspecific and slowly progressive, resulting in delays in diagnosis. Approximately 37 different proteins have been identified as

amyloidogenic; at least 17 of them can cause systemic disease, in which the amyloidogenic protein is produced in one site (e.g., bone marrow, liver) and is deposited at distant site(s) (e.g., heart, kidneys) (Wechalekar 2016).

The most common forms in the United States (US) are derived from immunoglobulin light chains (AL-associated amyloidosis), wild type or mutant transthyretin (wtATTR- and ATTR-associated amyloid, respectively), leukocyte chemotactic factor 2 (ALECT2), or serum amyloid protein A (AA). The incidence of visceral amyloidosis is estimated to be ~8 patients per 1 million persons per year, with ~4,500 new cases diagnosed every year in the US (Wechalekar 2016).

Current Imaging Diagnostics

Currently, there are no approved methods to document the extent of whole-body amyloid deposition or its response to treatment. Thus, there is a critical need to develop a method for objective, quantitative visualization of a patient's amyloid burden.

Routine anatomic imaging techniques (i.e., CT, magnetic resonance imaging (MRI), ultrasound) are not "amyloid-specific". Furthermore, organ-specific amyloid deposits are rarely visualized with current approved nuclear medicine agents. Although European investigators have imaged cardiac amyloid distribution in patients with ATTR amyloidosis using planar gamma scintigraphy or single-photon emission computerized tomography (SPECT) imaging with ^{123}I-labeled serum amyloid P-component (SAP) (Hazenberg 2007), ^{99m}Tc-aprotinin or ^{99m}Tc- 3,3-diphosphono-1,2 propanodicarboxylic acid (DPD) (Rapezzi 2011), these agents are not approved in the US, nor do they detect amyloid in all affected organ sites. The FDA-approved Aβ amyloid imaging agents, ^{18}F-Florbetapir (Amyvid), ^{18}F-Flutemetamol (Vizamyl), and ^{18}F-Florbetaben (Neuraceq), are only approved for use in very specific populations of suspected Alzheimer's disease patients and have not been shown to be effective at imaging systemic amyloid in organs other than the heart in some patients; therefore, they are not suitable for providing non-invasive detection of whole-body amyloid load (Dorbala 2014).

2.2.2 Description of ^{124}I-AT-01

^{124}I-AT-01 is an amyloid-reactive synthetic peptide (p5+14 or APi1832) radiolabeled with ^{124}I under development for use as a PET/CT imaging agent for the detection of amyloid in abdominothoracic organs or tissues of patients with systemic amyloid disease. AT-01 (p5+14 or APi1832) is a synthetic, all natural, 45 amino acid peptide (MW = 4763.46 Da) with a net +12 positive charge that has been shown to specifically bind to amyloid *in vitro* and *in vivo* (Wall 2015).

Clinical experience with ^{124}I-AT-01 is derived from Study AMY1001 (NCT: NCT03678259), a single-center, open-label, exploratory, Phase 1/2 PET/CT imaging study to detect amyloidosis in 57 subjects, 50 of which had systemic amyloidosis, two (2) of which were asymptomatic ATTR carriers, and five (5) of which were healthy volunteers. The primary outcome measure was

localization of AT-01 using PET/CT imaging following a single dose via intravenous (IV) infusion. Overall, ^{124}I-AT-01 was well tolerated, with no deaths or drug-related serious adverse events. The gender-averaged, whole-body, effective dose for ^{124}I-AT-01 in the first three subjects was estimated to be 0.24 ± 0.02 mSv/MBq (8.7 mSv/mCi). The whole blood radioactivity half-life was 21.9 hours. ^{124}I-AT-01 was detected in one or more organs in >90% of patients with systemic amyloidosis, including detection in the heart, kidney, liver, and spleen. ^{124}I-AT-01 was detected in the liver and kidney in one (1) of five (5) healthy volunteers (both organs were identified in the same subject).

A detailed description of the chemistry, mechanism of action, and nonclinical pharmacology of ^{124}I-AT-01 is provided in the Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

2.3.1 Potential Benefits

Based on the initial study of ^{124}I-AT-01 in patients with known systemic amyloidosis, ^{124}I-AT-01 has been shown to detect amyloid in the heart, kidney, liver, spleen, and pancreas but does not bind to these organs in healthy volunteers, indicating that ^{124}I-AT-01 may enable a comprehensive assessment of the extent and severity of amyloid deposition in patients with systemic amyloidosis. This information may benefit patients by supporting a diagnosis, providing information on amyloid organ deposition and severity/extent of disease, and enabling monitoring of disease progression and response to therapies.

2.3.2 Potential Risks

Clinically significant potential risks and their mitigation strategies are summarized in Table 1. As with all imaging studies involving radiopharmaceuticals, the greatest risks to subjects in this study are associated with reactions to the radiotracer and the radiation dose associated with the injected radionuclide and external x-rays associated with the CT component of the PET/CT scan. These risks are described in Sections 2.3.2.1 and 2.3.2.2.

Table 1: Protocol AT01-001: Risk Assessment

Potential Risk	Rationale for Risk	Risk Mitigation Strategy
Study Intervention(s)		
Infusion-related reactions	As with all protein/peptide infusions, there is a potential for an infusion-related reaction (IRR) in subjects administered ^{124}I-AT-01 (Doessegger 2015).	Subjects will be monitored during and following the administration of ^{124}I-AT-01 and instructed to report any symptoms indicative of an IRR without delay (Section 7.1.1.1).
Immunogenicity	As with all therapeutic proteins, there is a potential for an immune response in subjects administered ^{124}I-AT-01.	Subjects will be monitored during and following the administration of ^{124}I-AT-01and instructed to report any symptoms indicative of an immune response without delay.
Radiation exposure	^{124}I-AT-01 contains radioactive iodine.	Subjects exposed to ^{124}I-AT-01 will be pretreated with nonradioactive elemental iodine (^{127}I), administered as potassium iodide (KI) at recommended doses prior to and for 3 days after dosing (Section 2.3.2.1). Subjects must agree to prevent pregnancy during the study and for at least 90 days afterwards (Section 5.1).
Study Procedures		
Exposure to SARS-CoV-2 virus	International guidelines (e.g., FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency) on the conduct of clinical trials during the COVID-19 pandemic.	Section 2.3.2.2.

Abbreviations: CT = computed tomography; ECG = electrocardiogram; FDA = United States Food and Drug Administration; PET = positron emission tomography; SpO_2 = peripheral blood oxygen saturation.

2.3.2.1 Risks Associated with Radiation Exposure

^{124}I is one of several radioactive isotopes of iodine commonly used in human research and medical care with a radioactive half-life of 4.2 days. The clinically important risk of exposure to ^{124}I derives from the potential sequestration of iodine in the thyroid gland and the concentration of radiation exposure in that gland. Subjects exposed to ^{124}I as ^{124}I-AT-01 will be treated with three daily doses of nonradioactive elemental iodine (^{127}I), administered as potassium iodide (KI), at recommended doses beginning >30 minutes and within 24 hours prior to dosing. No other clinically important untoward effects of this well-characterized iodine isotope are expected at the doses planned in this study.

From Study AMY1001, the gender-averaged mean whole-body effective radiation dose associated with ^{124}I-AT-01 was 0.24 ± 0.02 mSv/MBq. Therefore, the 1 mCi dose used for each dose in this study will result in an estimated whole-body effective dose of ~8.7 mSv associated with the radiotracer. The whole blood radioactivity half-life was 21.9 hours. Whole blood

radioactivity levels were <100 Bq/mL at 48 hrs following a single 1 mCi dose of ^{124}I-AT-01 (Wall 2021).

Subjects will also be exposed to radiation from the PET/CT imaging. To reduce radiation dose from the PET/CT protocol, image acquisition will use a low-dose CT for attenuation correction.

Women of childbearing potential must also agree to remain as abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 90 days after the last dose of study intervention. Men with female partners of childbearing potential must also agree to remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 30 days plus 90 days (a spermatogenesis cycle) after the last dose of study intervention. Men must also agree to refrain from donating sperm during this same time period. Additional details are provided in Section 5.1.

2.3.2.2 Risks Associated with Exposure to the Virus SARS-CoV-2

In consideration of the Coronavirus disease (COVID-19) pandemic caused by the virus SARSCoV-2 and the impact it may have on clinical trials, COVID-19 related risks to subjects are carefully considered and will be documented on an ongoing basis. Measures that prioritize trial subject safety and data integrity have been developed in consideration of local guidelines. To minimize risk of exposure associated with trial participation, the Schedule of Activities (SoA) (Section 1.3) has been optimized to allow for an adequate follow-up and assessment of the safety of ^{124}I-AT-01, without unnecessarily increasing subject exposure.

As the pandemic situation evolves, the Sponsor will reassess risks, which will be documented as part of the Sponsor's trial master file. If escalation of the pandemic during this trial and local circumstances lead to a local change in risk assessment, additional measures may be implemented. In this case, an Investigator-driven risk assessment will be conducted and documented in the Investigator’s site master file and communicated to the Sponsor.

2.3.3 Benefit/Risk Conclusion

The potential benefits of having a comprehensive assessment of the extent of amyloid deposits in subjects with systemic amyloidosis have been considered against the risks associated with (i) ^{124}I-AT-01, (ii) the study procedures, (iii) the method of administration, and (iv) the COVID-19 pandemic. Subjects in this study will be closely monitored for potential risks. Eligibility criteria excludes subjects with higher risk, including those with significant co-morbidity such as Eastern Cooperative Oncology Group (ECOG) score of 3 or greater, New York Heart Association (NYHA) Class IV heart failure, or other ongoing serious illness.

For patients with systemic amyloidosis, there is a substantial medical need for amyloid-specific imaging diagnostics. Therefore, the Sponsor considers that the value of the information to be gained outweighs the risks associated with participating in this study.

3.0 OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
• 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.	• Repeatability coefficient (Bland-Altman plots) and ICC associated with the quantification of radioactivity associated with organ level ^{124}I-AT-01 uptake measurements.
Secondary	
• To characterize the safety and tolerability of repeat doses of ^{124}I-AT-01 administered by IV infusion or slow IV bolus.	• Incidence of treatment-emergent AEs[1] from Day 1 to EOS. • Change from Baseline in clinical laboratory values[2] at Visits 2 and Safety Follow-up 1 (1-3 days after the second administration of ^{124}I-AT-01). • Change from Baseline in vital signs. • Change from Baseline in ADA.

Abbreviations: ADA = anti-drug antibodies; AEs = adverse events; AL = amyloid light chain; ATTR = amyloid transthyretin; CT = computerized tomography; EOS = end of study; ICC = intraclass correlation coefficient; IV = intravenous; PET = positron emission tomography.

1. Adverse events will be graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.
2. Clinical laboratory tests are described in Section 10.2 and include hematology and serum chemistry.

4.0 STUDY DESIGN

4.1 Overall 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.

Adverse events will be monitored and recorded from Screening through the final safety follow-up/EOS. The schedule for all screening, treatment, and follow-up period activities is provided in the SoA (Section 1.3).

4.1.1 Screening Period

The screening period is up to 30 days. Eligibility criteria (Section 5.0) will be confirmed and informed consent, as specified in Section 10.1.3, will be obtained. Blood and urine tests as outlined in the SoA (Section 1.3) will be obtained during the screening period.

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

4.1.2 Pre-Administration Period

Subjects will begin therapy with KI 130 mg (e.g., iOSAT, Potassium Iodide Oral Solution USP, 65 mg/mL) orally once every day for 3 days beginning at least 30 minutes and within 24 hours prior to dosing with ^{124}I-AT-01 on the Day 1 and Week 6 visits to block radioactive iodine uptake in the thyroid gland.

4.1.3 Administration Period

Administration of ^{124}I-AT-01 and the associated study procedures occur at the Day 1 and Week 6 (+ 2 week) visits. Administration of ^{124}I-AT-01 and the associated study procedures are described in Section 4.1.3.1.

4.1.3.1 Administration of Study Intervention(s) and Associated Procedures

Day 1 and Week 6 (+ 2 week) Visits

The schedule for administration of ^{124}I-AT-01 is provided in the SoA (Section 1.3). Administration of ^{124}I-AT-01 occurs at the Day 1 and Week 6 to Week 8 visits, as follows:

Prior to Administration of ^{124}I-AT-01

1) Clinical laboratory tests and biomarker analysis (including serum pregnancy test in WOCBP) will be obtained within 7 days prior to the second administration of ^{124}I-AT-01, as described in the SoA (Section 1.3). The results of the pregnancy test must be available and be negative prior to ^{124}I-AT-01 administration in all WOCBP.
2) Instruct subject to take oral KI daily for 3 days, as described in Section 4.1.2.
3) Record concomitant medications and monitor and record AEs throughout the study visit.

Administration of ^{124}I-AT-01

4) Subjects enrolled under protocol Version 2.0 will receive a single dose of 1 mCi (± 10%) ^{124}I-AT-01 by slow IV bolus at a rate of 1 mL/ 5 seconds. During ^{124}I-AT-01 administration, monitor subjects for infusion-related reactions (IRRs), as described in Section 7.1.1. 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.

After Completion of Administration of ^{124}I-AT-01

5) Blood pressure and heart rate will be measured 5-10 minutes after administration of ^{124}I-AT-01.
6) Subjects will undergo a PET/CT scan 5 hours (± 30 minutes) after the start of administration of ^{124}I-AT-01 to quantify ^{124}I-AT-01 uptake in organs. ^{124}I-AT-01 whole-body scans will be acquired by study-designated PET/CT scanners, as described in Section 8.1.4.

   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 (i.e., they will not receive a second administration of ^{124}I-AT-01 or undergo a second scan) and will undergo early termination (ET) activities, as provided in the SoA (Section 1.3) and as described in Section 4.1.5.
7) Any adverse events will be recorded; patient can be discharged after completing the scan and deemed stable by study staff.

4.1.4 Follow-up Period

As shown in the SoA (Section 1.3), the follow-up period is 28 +/- 3 days after the second administration of ^{124}I-AT-01. It consists of the following:

- Safety Follow-up 1: a safety follow-up phone call 1-3 days after the second administration of ^{124}I-AT-01 and a safety laboratory draw 1-3 days after the second administration of ^{124}I-AT-01; and
- Safety Follow-up 2: a final safety follow-up phone call 28 ± 3 days after the second administration of ^{124}IAT-01 for collection of AEs and concomitant medication, and a blood draw 28 ± 3 days after the second administration of ^{124}I-AT-01 for anti-drug antibodies (ADA).

Blood draws for laboratory and ADA will be collected locally by visiting nurse/phlebotomist.

Both Safety Follow-up 1 and Safety Follow-up 2 activities will be conducted for subjects who discontinue for IRRs, as described in Section 7.1.1.1, at either the first or second administration of ^{124}I-AT-01.

4.1.5 Early Termination Visit

Subjects that are withdrawn or discontinued per the criteria provided in Section 7.1 will undergo the ET activities provided in the SoA (Section 1.3) within 7 days from the early termination decision. Blood draw for ADA should be obtained if ET is ≥4 weeks after the first administration of ^{124}I-AT-01 of ^{124}I-AT-01 and will be collected locally by visiting nurse/phlebotomist.

ET activities do not apply to subjects discontinued for IRRs. Safety Follow-up 1 and Safety Follow-up 2 activities (Section 4.1.4) will be conducted for subjects who discontinue for IRRs at either the first or second administration of ^{124}I-AT-01.

4.2 Scientific Rationale for Study Design

This is a multicenter, open-label, single arm study in subjects with systemic amyloidosis 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.

4.2.1 Choice of 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.

4.2.2 Choice of Primary Endpoint and Analysis

The primary endpoint is to evaluate the repeatability of organ-specific quantitation of radiotracer uptake using PET/CT imaging of ^{124}I-AT-01 in subjects with AL or ATTR systemic amyloidosis. To evaluate organ uptake of ^{124}I-AT-01 using PET/CT as a quantitative imaging biomarker, quantitative readings must be repeatable and reproducible (Meikle 2021).

4.2.3 Choice of Duration of Treatment and Follow-up

^{124}I-AT-01 is eliminated by radioactive decay (half-life ~ 4.2 days), cell-mediated protein clearance, and catabolism. Ten radioactive half-lives will assure complete clearance of radioactivity after the first PET/CT imaging visit and before the second PET/CT imaging visit. Ten half-lives is ~ 6 weeks. Thus, the two doses of ^{124}I-AT-01 will be separated by at least 6 weeks. A final safety follow-up 28 days after the second dose of ^{124}I-AT-01 represents more than five half-lives, a routinely recommended post-treatment safety assessment period (CIOMS 2005).

4.3 Justification for Dose(s) and Posology

In the AMY1001 trial, doses of 0.3, 1, and 2 mCi of ^{124}I-AT-01 were evaluated. All but the first five subjects in the AMY1001 study received a 2 mCi dose of ^{124}I-AT-01. However, review of the experience in the AMY1001 study indicated that the 1mCi dose of ^{124}I-AT-01provides sufficient exposure to characterize amyloid deposits. The 1mCi dose is being used in a study conducted under a separate IND at Brigham and Women's Hospital and will be used in this study. This dose is associated with ≤2 mg of p5+14 peptide (AT-01). The nonclinical safety of AT-01 was evaluated in a single IV dose toxicity study in Sprague Dawley rats. A maximum tolerated dose was not determined, and the no-observed-adverse-effect-level (NOAEL) was considered to be at least 17.6 mg/kg (105.8 mg/m^2) for a single IV dose administration in rats. This dose is approximately 100-fold greater than the maximum 2 mg dose (~0.03 mg/kg) intended for administration to patients. Additional details are provided in the IB.

4.4 End of Treatment Definition

Subjects may withdraw from this study at any time and for any reason and shall not be subject to prejudice to further medical care by the Investigator or study site. Reasons for end of treatment and/or ET are provided in Section 7.0.

4.5 End of Study Definitions

If, during the study, it becomes evident to the Sponsor that the study should be stopped prematurely, the study will be terminated and appropriate notification will be given to the Investigator(s) and IRB(s), as applicable. The Sponsor, or designee, will instruct the Investigators to stop dispensing study materials/treatment and to arrange for study closeout at each site.

The end of the study is defined as whichever of the following comes first:

- The last safety follow-up of the last enrolled subject; or
- The Sponsor's decision to terminate the study.

The Sponsor, or designee, will notify the Investigator when to contact the IRB to inform them that the study is complete.

4.6 Subject Completion Definition

Subjects have completed the study when they have received both administrations of ^{124}I-AT-01 and both PET/CT scans and have completed the EOS activities, including the final safety follow-up telephone call and blood draw. Subjects who require further follow-up for an adverse event (AE) will be followed according to Section 8.3.

5.0 STUDY POPULATION

Subjects will be enrolled and will receive study treatment only if they meet all inclusion criteria (Section 5.1) and none of the exclusion criteria (Section 5.2).

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all the following criteria apply:

1) Understands the study procedures and is capable of giving signed informed consent, as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2) Male or female ≥18 years of age.
3) Has a history of AL or ATTR systemic amyloidosis with at least one organ with clinically demonstrable amyloid involvement defined by:
    a) For AL systemic amyloidosis:
        i) Positive tissue (e.g., fat-pad, gastrointestinal tract, etc.) biopsy for AL amyloid, and
        ii) Achieved a hematologic very good partial response (VGPR) or complete response (CR) based on their most recent assessment and within 12 months of screening, and
        iii) At least one of the following:
            (1) Cardiac, renal, or liver biopsy positive for amyloid, or
            (2) NT-proBNP ≥650 pg/mL, or
            (3) Left ventricle septal wall thickness ≥12 mm by echocardiogram or cardiac magnetic resonance (CMR), or
            (4) 24-hour urine protein >500 mg, or
            (5) Urine albumin-to-creatinine ratio (UACR) >300 mg/g.
    b) For ATTR (wild type or variant) systemic amyloidosis:
        i) Positive cardiac biopsy for ATTR amyloid, or
        ii) At least two of the following:
            (1) Positive extracardiac tissue (e.g., fat-pad, GI tract, etc.) biopsy for ATTR amyloid or positive transthyretin gene mutation associated with amyloid (obtained at any time), or
            (2) Left ventricle septal wall thickness ≥12 mm by echocardiogram or CMR (in the absence of alternative causes), or
            (3) Pyrophosphate (PYP) scintigraphy with myocardial uptake ≥grade 2 (or heart/contralateral chest ratio >1.5) using SPECT/CT scan if AL amyloidosis is excluded.

4) Able to undergo two PET/CT scans as part of the study, including ability to lie supine for up to 1 hour.
5) For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 90 days after the last dose of ^{124}I-AT-01.
    a) A woman is considered of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.
    b) Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
    c) Contraception methods that do not result in a failure rate of <1% per year such as cap, diaphragm, or sponge with spermicide, or male or female condom with or without spermicide, are not acceptable.
    d) The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
6) For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
    a) With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 120 days (a spermatogenesis cycle) after the last dose of study intervention. Men must refrain from donating sperm during this same time period.

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1) Is pregnant or breast-feeding.
2) Is mentally or legally incapacitated, has significant emotional problems at the time of the study, or has a history of psychosis.
3) Has received in the last 6 months or are currently receiving treatment with anti-amyloid monoclonal antibody therapy (i.e., CAEL101, NEOD001, PRX-004, or NI006) or are expected to begin treatment prior to completing this study.

4) Has received heparin or heparin analogs (e.g., enoxaparin, dalteparin, fondaparinux) within 7 days of Day 1 (first administration of ^{124}I-AT-01).
5) Has a significant co-morbidity (e.g., ECOG score of 3 or greater), NYHA Class IV heart failure, uncontrolled infection, or other ongoing serious illness.
6) Has a known allergy to potassium iodine treatment.
7) Has end-stage renal disease and is receiving hemodialysis or peritoneal dialysis.
8) Has severe claustrophobia that would prevent completion of the PET/CT imaging protocol.
9) Has received an investigational agent within five half-lives of the agent or 30 days, whichever is longer, prior to Screening.
10) Has any illness that, in the opinion of the Investigator, might confound the results of the study or pose additional risk to the subject.

5.3 Lifestyle Considerations

Specific lifestyle considerations are not required.

5.4 Screen Failures

Subjects that fail screening will be recorded as screen failures in the source documentation.

Subjects that terminate the study early may be replaced, as described in Section 5.5.

5.5 Subject Replacement

Subjects that are withdrawn (except for an AE) or are lost to follow-up during the study may be replaced to ensure an appropriate number of subjects complete the study. The decision to replace a subject will be made in agreement between the Sponsor and Investigator. Subjects who do not receive a second dose of ^{124}I-AT-01 or have a PET/CT scan following the second dose of ^{124}I-AT-01 will be replaced.

6.0 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

6.1 Study Intervention(s)

The study intervention is described in Table 2. For complete information regarding the administration of study intervention, refer to the Study Manual.

Table 2: Protocol AT01-001: Study Intervention

Arm Name	^{124}I-AT-01
Intervention Name	^{124}I-AT-01
Type	Radiopharmaceutical
Dosage Form	Solution for Injection
Unit Dose Strength(s)	0.004-0.037 GBq (0.1-1 mCi)/mL; NMT 2 mg AT-01
Dosage Level(s)	1 mCi (± 10%) ^{124}I-AT-01 Half-life is 4.2 days. Calculate the correct dosage from date and time of calibration.
Route of Administration	IV infusion (2-5 minutes) or slow IV bolus at 1 mL/5 seconds. Additional details are provided in the Pharmacy Manual.
Use	Experimental
IMP or NIMP	IMP
Sourcing	^{124}I-AT-01 will be manufactured for each subject and will be supplied to the investigative site by the Sponsor.
Storage	Store upright in a shielded container at room temperature. The expiration time of ^{124}I-AT-01 is 96 hours after its end of synthesis.
Packaging and Labeling	Multidose 10 mL vial. Contains: [^{124}I]p5+14, 1.3-1.8 mg in phosphate-buffered saline (PBS) for injection. >90% radiochemical purity (remainder iodide), >99% radionuclidic purity. The product is sterile and non-pyrogenic. May be diluted with sodium chloride for injection (USP). DO NOT USE if cloudy or contains particulate matter.
Handling	Aseptically withdraw and handle doses. The empty syringe and IV administration sets shall be disposed of in accordance with appropriate local radioactive waste management guidance.

Abbreviations: IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; NMT = no more than.

6.2 Preparation/Handling/Storage/Accountability

^{124}I-AT-01 will be manufactured by 3D Bioimaging, LLC (Little Rock, AR) and will be supplied to the investigative site in a multidose 10 mL vial. It will be delivered in a container with appropriate radioactive shielding. Any damage to the vial should be reported immediately to both

the Sponsor and 3D Imaging using the contact information provided in the Pharmacy Manual. Store upright in a shielded container.

Aseptically withdraw and handle doses. The half-life of ^{124}I is 4.2 days. Calculate the correct dosage from date and time of calibration. The expiration time of ^{124}I-AT-01 is 96 hours after its preparation.

The empty syringe and IV administration sets will be disposed of in accordance with appropriate local radioactive waste management guidance.

The Investigator (or designee) will be responsible for keeping current and accurate records of the dose of ^{124}I-AT-01 dispensed and its disposition.

6.3 Measures to Minimize Bias

Because this study is an exploratory, single arm, open-label human pharmacology study, measures to minimize bias are not applicable.

6.4 Study Intervention Compliance

Only subjects enrolled in this study may receive treatment with ^{124}I-AT-01. All study drug during the study will be administered by qualified clinical site staff. The date and time for each dose will be recorded in the CRFs. The date of and reason for any deviations in protocol-specified dosing will be documented in the case report forms.

6.5 Dose Modifications/Interruptions and Retreatment Criteria

Subjects may only receive the specified dose of ^{124}I-AT-01. Modifications of the dosage and retreatment are not allowed, except as provided in Section 7.1.1.

6.6 Access to Study Intervention After End of Study

Administration of ^{124}I-AT-01 under this protocol will be completed at Visit 2 (Week 6 to Week 8). No further treatment with ^{124}I-AT-01 will occur under this protocol, and ^{124}I-AT-01 will not be made available to subjects by the Sponsor after completion of the study.

6.7 Treatment of Overdose

For this study, any dose of ^{124}I-AT-01 greater than 1.1 mCi or >2 mg AT-01 is considered overdose. There are no specific treatments for overdose. In the event of an accidental overdose, the Investigator should do the following:

- Contact the Sponsor/Medical Monitor immediately;
- In consultation with the Sponsor/Medical Monitor, determine, whether additional steps should be taken;

- Closely monitor the subject for any AEs or serious AEs (SAEs); and
- Document the quantity of the excess dose.

6.8 Concomitant Medications and Procedures

A concomitant medication is any drug or substance administered between signing the ICF and the EOS Visit. A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy) performed between obtaining informed consent and the EOS Visit that is not otherwise specified in the protocol.

6.8.1 Allowed Concomitant Medications and Procedures

There are no restrictions on concomitant medications, unless specified as prohibited (Section 6.8.2).

6.8.2 Prohibited Concomitant Medications and Procedures

Concurrent enrollment in any other drug, biologic, or device clinical study; or treatment with an unapproved investigational drug under development is prohibited.

If a participant is scheduled for an elective procedure during the study, they should postpone the procedure until their participation in the study is complete.

Heparin or heparin analogs are prohibited within 7 days of a planned administration of ^{124}I-AT-01. Additional details are provided in Section 7.1.1.2.

6.8.3 Rescue Medication or Supportive Therapy for Adverse Events

Not applicable.

7.0 DISCONTINUATION OF STUDY INTERVENTION AND/OR SUBJECT DISCONTINUATION OR WITHDRAWAL

7.1 Discontinuation of Study Intervention

All subjects are free to withdraw from participating in this study at any time for any reason, specified or unspecified, and without prejudice. No constraints will be placed on ordinary subject management.

Subjects will be withdrawn for any of the following reasons:

- The subject withdraws consent.
- The subject does not have amyloid deposits in the heart, liver, spleen or kidney on the Day 1 PET/CT scan, as described in Section 8.1.4.
- The subject begins treatment with heparin or a heparin analog within 7 days of a planned administration of ^{124}I-AT-01, as described in Section 7.1.1.2.
- The subject experiences an intolerable AE or serious AE (SAE).
- The subject enrolls into another clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 8.3.5.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator or Sponsor.
- Investigator decision that it is not in the best medical interest of the subject to continue participation in the investigation.
- The Sponsor prematurely terminates the study.

Prior to discontinuing a subject, every effort should be made to obtain as much follow-up data as possible. Withdrawn or discontinued subjects will undergo ET activities per the SoA (Section 1.3). Subject withdrawals will be documented clearly on the source documents and applicable case report forms (CRFs). Subject withdrawals will be documented clearly on the source documents and applicable CRFs.

Discontinued subjects will be assessed for adverse events via a telephone call 24-48 hours after decision to discontinue.

Notification of subject withdrawals will be made to the Sponsor, or designee.

7.1.1 Specific Stopping Criteria

7.1.1.1 Infusion-related Reactions

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 (Doessegger 2015). IRRs have been reported, among other terms, as anaphylaxis, anaphylactoid reactions, cytokine release syndrome, hypersensitivity reaction, etc. Symptoms suggestive of an IRR include but not limited to the following: tachypnea with respiratory distress, new onset rash or pruritus, chills, stridor, wheezing, swollen or itchy lips or tongue, onset of abdominal cramping, or hypotension.

Treatment-emergent adverse events starting on the day of ^{124}I-AT-01 administration will be summarized to evaluate potential infusion-related reactions.

Subjects will be monitored for IRRs and managed as follows:

- During administration of ^{124}I-AT-01: if an IRR occurs during administration, the administration will be immediately discontinued and the subject will be treated for their symptoms and discontinued from the study. Activities for Safety Follow-up 1 (1-3 days after the second administration) and Safety Follow-up 2/EOS (28 (± 3) days after the second administration) will be conducted, per the SoA (Section 1.3).
- After administration of ^{124}I-AT-01: if an IRR occurs in a subject after completion of the administration, the subject will be treated for their symptoms, managed in accordance with standard of care, and the IRR will be recorded as an AE. If the symptoms respond promptly to minimal intervention (e.g., responds promptly to symptomatic treatment with antihistamines, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs)) then, at the discretion of the Investigator, the subject may continue in the study. If the symptoms are prolonged (e.g., not rapidly responsive to symptomatic medication), require IV fluids or treatments, or require hospitalization, the subject will be discontinued from the study. Activities for Safety Follow-up 1 (1-3 days after the second administration) and Safety Follow-up 2/EOS (28 (± 3) days after the second administration) will be conducted, per the SoA (Section 1.3).

7.1.1.2 Heparin or Heparin Analogs

Concomitant use of heparin or heparin analogs within 7 days of a planned administration of ^{124}I-AT-01 is prohibited (Section 6.8.2), as follows:

- Subjects who have received heparin or a heparin analog within 7 days of Day 1 (first administration of ^{124}I-AT-01) are excluded from the study (Section 5.2).

- If a subject receives heparin or a heparin analog within 7 days of the planned Week 6 administration of ^{124}I-AT-01 and PET/CT scan, they will be discontinued from the study (i.e., they will not receive a second administration of ^{124}I-AT-01 or undergo a second scan) and will undergo ET activities, as provided in the SoA (Section 1.3) and as described in Section 4.1.5.

If a subject begins treatment with heparin or a heparin analog after the Week 6 administration of ^{124}I-AT-01 and PET/CT scan, they may continue the study, as described in the SoA (Section 1.3).

7.2 Missed Visits

If a subject misses any of the scheduled visits, the visit is considered missed and recorded as such in the source documents and CRFs.

7.3 Lost to Follow-up

Subjects who do not return for a scheduled visit (missed visit) and cannot be contacted, may be considered lost to follow-up. The site will attempt to contact the subject through a minimum of two telephone calls. If the subject still cannot be contacted, the site will send a certified letter to the last known address of the subject. If no contact is made by the subject, the site will consider the subject lost to follow-up. All follow-up attempts will be documented and kept with the subject's source documentation, and the applicable CRFs will be completed.

8.0 STUDY ASSESSMENTS AND PROCEDURES

8.1 ^{124}I-AT-01 Organ Uptake Assessments

8.1.1 Medical History and Demographics

Medical history includes clinically significant diseases, organ or stem cell transplants, and reproductive status. All prescription medications used by the subject regularly or within 30 days preceding Day -1 must be recorded. Prior or concurrent treatment regimens for systemic amyloidosis should be recorded. Demographic data will include age, sex, body mass index (BMI), amyloid subtype, time since diagnosis of systemic amyloidosis, and ethnic origin (also referred to as self-reported race and ethnicity in some regions of the world).

8.1.2 Biomarkers

Biomarkers including NT-proBNP, brain natriuretic peptide (BNP), serum free light chains (only subjects with AL amyloidosis), and UACR (only subjects with AL amyloidosis) will be obtained at Screening and Week 6 (Visit 2), as specified in the SoA (Section 1.3).

8.1.3 Administration of ^{124}I-AT-01

^{124}I-AT-01 will be administered while the subject is at the clinical site. ^{124}I-AT-01 will be administered as described in Section 4.1.3.

During ^{124}I-AT-01 administration, monitor subjects for IRRs, as described in Section 7.1.1.

8.1.4 ^{124}I-AT-01 PET/CT Imaging

Planned time points for all PET/CT imaging are provided in the SoA (Section 1.3). Subjects will undergo a PET/CT scan 5 hours (± 30 minutes) after the start of administration of ^{124}I-AT-01 to quantify ^{124}I-AT-01 uptake in organs. ^{124}I-AT-01 whole-body scans will be acquired using study-designated PET/CT scanners (see Imaging Manual for further information).

Subjects without evidence of amyloid in at least one of the following organs on the Day 1 scan: heart, liver, kidneys, or spleen, will be discontinued from the study (i.e., not receive a second administration of ^{124}I-AT-01 or undergo a second scan) and will undergo ET activities provided in the SoA (Section 1.3) and as described in Section 4.1.5.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Vital Signs, Body Weight, and Height

Planned time points for vital signs, body weight, and height are provided in the SoA (Section 1.3). Additional vital signs may be taken at any other times, if deemed necessary.

Heart rate and blood pressure measurements will be performed with subjects in a supine position for at least 5 minutes, except when they are seated or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness), or if deemed necessary by the Investigator or designee. Blood pressure measurements should be measured on the same arm throughout the study.

8.2.2 Clinical Laboratory Testing

A list of clinical laboratory tests to be performed is provided in Appendix 2.

The clinical safety laboratory tests will be performed at a central laboratory. Samples for complete blood count (CBC) and chemistry should be obtained and analyzed based on central lab requirements. Laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator or designee.

8.2.3 Pregnancy Testing

Subject samples for pregnancy testing will be acquired pre-administration at the Screening and Week 6 visits in women of childbearing potential, as specified in the SoA (Section 1.3). All women of childbearing potential (defined in Appendix 4) must have a negative pregnancy test prior to administration of ^{124}I-AT-01 at the Day 1 and Week 6 visits to participate in the study. Samples for serum pregnancy tests must be drawn within 7 days prior to ^{124}I-AT-01 administration for all women of childbearing potential.

Prior to enrollment in the study, female subjects of childbearing potential and male subjects must be advised of the importance of avoiding pregnancy or partner pregnancy, respectively, during the trial, and the potential risks associated with an unintentional pregnancy. Contraceptive and barrier guidance and collection of pregnancy information is described in Appendix 4.

8.2.4 Unscheduled Safety Visits

Additional visits may be scheduled, as necessary, to ensure the safety and well-being of subjects. All additional exams should be fully documented in the source documents and on Unscheduled Visit CRFs, as appropriate.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs; the methods of recording, evaluating, and assessing causality of AEs and SAEs; and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Adverse events will be graded for seriousness, severity, and relationship to study drug treatment.

After obtaining informed consent, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be recorded from the time of informed consent until the final EOS telephone follow-up (~Week 10).

Throughout the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

8.3.2 Method of Detecting AEs and SAEs

Adverse events may be spontaneously reported by the subject, obtained through non-leading questioning, or noted during examination of a subject.

When recording an AE, a diagnosis is always preferable; however, in the absence of a diagnosis, the Investigator should record each sign and symptom as an individual AE.

Medical or surgical procedures (e.g., cardiac ablation) should not be recorded as AEs. Rather, the condition for which the procedure was performed should be recorded.

Adverse events will be recorded from the time informed consent (Section 10.1.3) is obtained through the end of the study. The data will be recorded on the appropriate CRF, regardless of whether they are thought to be associated with the study or treatment with study drug.

Investigators are not obligated to actively seek SAE information from subjects that complete the study but are encouraged to notify the Sponsor or designee of any SAE occurring at any time after a subject has discontinued or completed the study that they judge may be reasonably related to treatment with study drug or study participation.

8.3.3 Follow-up of AEs and SAEs

All related SAEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, relevant hospital records (i.e., discharge summary), or consultation with other health care professionals. The Investigator must ensure that all subject identifiers are redacted from supportive documentation prior to submission.

The Sponsor or designee may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, the Sponsor or designee should be provided with a copy of any postmortem findings, including histopathology.

New or updated information obtained during SAE follow-up should be recorded in the original/existing form(s); updates should be made to the relevant data in the EDC. If EDC is not available, then new or updated information should be recorded on a new paper SAE form; the original or prior paper SAE forms must not be re-used or altered. By signing the SAE form, the Investigator or designee attests to the accuracy and completeness of the data and that he/she has reviewed the report being submitted and approves it. If a paper form is used, the same information is to be captured in the EDC when EDC becomes available.

8.3.4 Regulatory Reporting Requirements for SAEs

Any SAE experienced by the subject between the time of the signing of the ICF and up to the EOS telephone call (approximately Week 10) must be recorded on an SAE form, regardless of the severity of the event or its relationship to treatment with study drug. Once the Investigator determines that the event meets the protocol definition of an SAE, the SAE must be reported to the Sponsor, or designee, within 24 hours.

Prompt notification of an SAE by the Investigator to the Sponsor is essential to meet the legal obligations and ethical responsibilities regarding the safety of subjects and the safety of a study intervention under clinical investigation.

Reporting of a SAE requires the following:

- Completion of the SAE Report Form details in the EDC, or if the EDC is not available, transmission of the paper SAE Report Form to the Sponsor or designee, via email as noted in the Study Manual. The SAE event is to be reported within 24 hours of the Investigator's knowledge of the event. If paper submission is used, the same information is to be entered into the EDC when EDC becomes available.
- Reporting of additional, follow-up information for previously reported SAEs should follow the same reporting timeframe and procedures as initial reports. New or updated information should be made to the relevant data in the EDC. If EDC is not available, new or updated information should be recorded on a new paper SAE form; the original or prior paper SAE forms must not be re-used or altered.
- Accompanying documentation, such as laboratory data, concomitant medication records, hospital records etc., should be redacted and transmitted to the Sponsor or designee as outlined in the Study Manual. In addition, the corresponding AE in the AE CRF (as applicable) should be updated to ensure all data points documented in the AE CRF are aligned with the matching data points on the SAE Report Form.

The Sponsor has a legal responsibility to notify health authorities about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the local regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, as appropriate according to local requirements.

Investigator Safety Reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.5 Pregnancy

The Investigator must report a pregnancy occurring in a female subject to the Sponsor or designee within 24 hours of the study site staff becoming aware of the pregnancy. In addition, if a female subject becomes pregnant within 12 weeks after last dose of study drug, the pregnancy must also be reported within 24 hours of the study site becoming aware of the pregnancy. The Investigator or study site staff must also follow the pregnancy until the outcome is known and submit the outcome as follow-up within 24 hours of notification of outcome. Follow-up Pregnancy Forms may be submitted as required as additional information is obtained. Although pregnancy occurring in a clinical study is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy, for medical reasons, will be recorded as an AE or SAE and followed as such. Pregnancies in partners of male study subjects will similarly be monitored for the full duration of the pregnancy and/or followed through a definitive outcome (i.e., birth, or spontaneous or elective abortion). Pregnancy reporting must be submitted via email as noted in the Study Manual.

8.3.6 Death Events

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the Sponsor or designee. If cause of death is not available within the 24-hour reporting period, “death” must be reported as the SAE term to meet timelines, and the cause of death must be actively queried and submitted as a follow-up report.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Hypothesis

Not applicable.

9.2 Definition of Enrollment

"Enrolled" means a subject, or their legally authorized representative, has provided agreement to participate in this clinical study following completion of the screening and informed consent processes. Potential subjects who are screened for the purpose of determining eligibility for the study, but who do not participate in the study, are considered screening failures and are not considered enrolled.

9.3 Sample Size Determination

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.

9.4 Analysis Sets

Safety analyses will be performed on the All-enrolled Population, consisting of all subjects who undergo at least one PET/CT scan or receive any amount of ^{124}I-AT-01.

Analyses of repeatability will be performed on the Image Evaluable Population, consisting of 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.

9.5 Statistical Analyses

The study statistical analysis plan (SAP) will specify the statistical methodology and reporting for all aspects of the planned analyses. Additional unplanned analyses may be required. All unplanned analyses will be clearly identified in the clinical study report.

9.5.1 General Considerations

This is an open-label, single arm study. In general, for continuous variables, the mean, standard deviation (SD), median, and range will be presented. Categorical variables will be summarized by frequency counts and percentages.

Subject disposition will be summarized for all subjects who signed the ICF and will include the number of subjects who received study treatment and the number and percentage of subjects who completed or prematurely discontinued the study, classified by reasons for premature discontinuation.

Discontinuations

The reason for study discontinuation and the number of days post-study drug treatment on which the subject discontinued will be summarized.

Protocol Deviations

Protocol deviations will be provided in a listing with reasons for the deviation and the date of occurrence. Any exclusion of subjects from exploratory analysis populations, and how these exclusions impact data analysis, will be addressed in the clinical study report.

Missing Data

There will be no imputation for missing safety or whole blood radioactivity data.

9.5.2 Primary Endpoint(s)

The primary objective of this study is to evaluate the repeatability of organ-specific quantitation of radiotracer uptake following PET/CT imaging of AT-01 in subjects with AL or ATTR systemic amyloidosis. The corresponding primary endpoint is:

- Repeatability coefficient (Bland-Altman plots) and intraclass correlation coefficient (ICC) associated with the quantification of radioactivity associated with organ level ^{124}I-AT-01 uptake measurements.

The signal to noise ratio (SNR) and contrast to noise ratio (CNR) will be plotted against standardized uptake value (SUV) based metrics. Repeatability will be assessed using Bland-Altman plots. ICC and its associated 95% confidence interval will be presented. Quantitative organ uptake analyzed by an automated method will be summarized. Between-reader agreement in visual determination of AT-01 uptake will be evaluated by Cohen's kappa.

9.5.3 Secondary Endpoint(s)

The secondary objective of this study is to characterize the safety and tolerability of repeat doses of ^{124}I-AT-01 administered by IV infusion or slow IV bolus. The corresponding secondary endpoints are as follows:

- Incidence of treatment-emergent AEs from Day 1 to EOS. AEs will be graded using Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.
- Change from Baseline in clinical laboratory values at Visits 2 and Safety Follow-up 1 (1-3 days after the second administration of ^{124}I-AT-01). Clinical laboratory tests are described in Section 10.2 and include hematology and serum chemistry.
- Change from Baseline in vital signs.
- Change from Baseline in ADA.

Exploratory analyses may be performed to examine the relationship between images and biomarkers including, but not limited to, NT-proBNP, free light chains (AL subjects only), and UACR (AL subjects only).

9.5.4 Safety Analysis

Safety will be assessed through reported adverse events (graded using NCI CTCAE version 5) and changes in laboratory parameters.

Adverse Events

All adverse events occurring during the study will be recorded and classified based on Medical Dictionary for Regulatory Activities (MedDRA) terminology. Only treatment-emergent adverse events (TEAEs), which are adverse events that occur after the start of study drug, will be summarized.

The number and percentage of subjects experiencing TEAEs and SAEs will be tabulated for the safety population by system organ class (SOC) and preferred term (PT). TEAEs and SAEs will be tabulated by severity and relationship to study medication. Each subject will be counted only once within a SOC or a PT by using the AE with the highest severity or greatest relationship, respectively, within each category.

TEAEs or SAEs leading to early discontinuation will be summarized as described above. Treatment-emergent adverse events starting on the day of dosing at each dosing visit will be summarized by SOC and PT to evaluate potential infusion-related reactions.

Listings for all reported adverse events, including SAEs, will be provided. In addition, separate listing for SAEs, AEs leading to premature withdrawal from the study, and all deaths will be generated.

Vital signs will include blood pressure (mmHg) and heart rate (beats per minute). Vital signs will be summarized at Baseline and for each study visit when vital signs were obtained. Changes from Baseline in vital sign measurements will also be summarized. Baseline is defined as the last vital signs obtained prior to the initiation of study drug.

Clinical Laboratory Analyses

Baseline for clinical chemistry parameters is defined as the most recent laboratory measurement obtained prior to the initiation of study drug. Clinical laboratory parameters from the tests itemized in Section 10.2, will be summarized as both absolute value and change from Baseline for each visit per the SoA (Section 1.3).

Laboratory parameters with quantitative abnormalities will be listed as ‘flagged’ based on the Sponsor’s internal guidelines. Flagged laboratory parameters will be presented by incidence and frequency.

Clinical safety laboratory tests performed during the study will be analyzed by a central clinical laboratory.

9.6 Interim Analyses

Not applicable.

10.0 APPENDICES WITH SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

Appendix 2: Clinical Laboratory Tests

Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Appendix 4: Contraceptive and Barrier Guidance

Appendix 5: Protocol Amendment History

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- 21CFR Parts 50, 54, 56 and 312;
- Applicable ICH Good Clinical Practice (GCP) Guidelines;
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS); and
- Applicable local laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator is responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC at least annually, in accordance with the requirements, policies, and procedures established by the IRB/IEC;
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures; and
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators must provide financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements to the appropriate regulatory authorities. In addition, Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor their Contract or Clinical Research Organization (CRO) partner is financially responsible for additional testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor their CRO are financially responsible for further treatment of the subject's disease.

10.1.3 Informed Consent

A signed and dated IRB approved ICF will be obtained prior to any protocol-specified screening procedures being performed. Each subject will be provided with oral and written information describing the nature, purpose, and duration of the study; participation/termination conditions; and risks and benefits. The subject will also sign and date an authorization form required under the Health Insurance Portability and Accountability Act (HIPPA), if applicable, that authorizes the use and disclosure of the subject's protected health information. The original signed ICF will be retained in the subject records, and a copy will be provided to the subject.

Subjects unable to sign the ICF may participate in the study if a legal representative or witness provides the consent (in accordance with ICH-GCP and local regulations) and the subject confirms his/her interest in study participation. The subject will be informed that they can freely withdraw consent and stop participation in the study at any time with no prejudice post-study care.

Subjects who are re-screened are required to sign a new ICF if it has been more than 30 days from the initial consent date.

10.1.4 Data Protection

Subjects will be sequentially assigned a study number at Screening that will be used throughout the study. All subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or other identifiable information will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject during the informed consent process (Section 10.1.3).

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by health authority inspectors.

All information provided by the Sponsor, verbally and in writing, is confidential. The Investigator agrees not to disclose any such information without prior written permission of the Sponsor. This document may be disclosed to study personnel under the Investigator's supervision and to the IRB under the condition that they also agree to maintain its confidentiality. Any supplemental information (e.g., protocol amendment) that may be added to

this document is confidential and must also be handled accordingly. The information obtained from the Sponsor may be disclosed to obtain informed consent from subjects who wish to participate in the study.

Study documents provided by the Sponsor (protocols, IB, etc.) will be stored appropriately to ensure their confidentiality.

The Investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.1.5 Data Quality Assurance

All subject data relating to the study will be recorded on printed or eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 10 years after study 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. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6 Source Documents

All medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real time as it is collected. Source documentation consists of original subject documents, as well as data and records with information relevant to the subject and his/her participation in the study.

Source documents consist of, but are not limited to, subject hospital charts, clinic notes, subject medical records, original test results, laboratory data, worksheets, drug accountability records, consent forms, telephone records, etc. Source documents must be available for review and inspection during on-site monitoring of the study by the Sponsor, their designees, the IRB, and/or appropriate regulatory authorities.

Subject-completed forms are also considered source data. Only subjects are to record information in subject diaries and questionnaires, if used. In no instance should an Investigator or study site personnel record any data or make changes to subject-completed forms. The Investigator or designee should review subject-completed forms during study visits. If an entry is found to be illegible or a mistake is found (e.g., incorrect year was recorded), the subject may be instructed to edit the entry

10.1.7 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of subjects.

Study/Site Termination Due to Adverse Events

Study stopping criteria due to adverse events are provided in Section 7.1.1.

Study/Site Termination Due to Other Reasons

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines; and/or

Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the Investigator. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up

10.1.8 Publication Policy

- All study data generated from this study will be regarded as confidential, until appropriate analysis and review by the Sponsor or its designee and the Investigator(s) are completed. The results of the study may be published or presented at scientific meetings by the Investigator(s) after the review by, and in consultation and agreement with the Sponsor, such that confidential or proprietary information is not disclosed.
- Prior to publication or presentation, a copy of the final text should be forwarded by the Investigator(s) to the Sponsor or its designee, for comment. Such comments shall aim to ensure the scientific integrity of the proposed publications and/or presentations and ensure that the data and material referring to Attralus, Inc products and activities receive fair, accurate, and reasonable presentation.
- The Sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical Laboratory Tests

Laboratory Tests	Parameters		
Hematology	Complete blood count (CBC) with differential		WBC differential: • Bands/stabs • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes
	White blood cell (WBC) count		
	Red blood cell (RBC) count		
	Hemoglobin (Hgb)		
	Hematocrit (Hct)		
	Platelet count (Plt)		
Serum Chemistry	Sodium (Na)	Creatinine (Cr)	Alanine aminotransferase (ALT, SGPT)
	Potassium (K)	Uric acid	Aspartate aminotransferase (AST, SGOT)
	Chloride (Cl)	Albumin	Calcium (Ca)
	Bicarbonate (HCO_3)/CO_2	Total protein	Phosphate (PO_4)
	Glucose	Total bilirubin	Lactate dehydrogenase (LDH)
	Blood urea nitrogen (BUN)	Alkaline phosphatase	
Biomarker Assays	N-terminal prohormone of brain natriuretic peptide (NT-proBNP)	Serum free light chain[1]	
	Brain natriuretic peptide (BNP)	Urine albumin creatinine ratio (UACR)[1]	
Pregnancy Testing	Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2]		

1. Subjects with AL systemic amyloidosis only.
2. Serum pregnancy and laboratory tests must be drawn within 7 days prior to ^{124}I-AT-01 administration 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.

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10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE
• An unsolicited AE is an AE that was not solicited using a Subject Diary and that is communicated by a subject or subject's parent(s)/ legally authorized representative (LAR) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The subjects or subject's parent(s)/LAR will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of subject or parental/LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the subject's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the subject or subject's parent(s)/LAR(s) will be collected during interview with the subject or subject's parent(s)/LAR(s) and by review of available medical records at the next visit. • Solicited AEs are predefined local (at the infusion site) and systemic events for which the subject is specifically questioned, and which are noted by the subject in their diary.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
• Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any serious AE that, at any dose:
• **Results in death**
• **Is life-threatening** The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• **Requires inpatient hospitalization or prolongation of existing hospitalization** - In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. - Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
• **Results in persistent or significant disability/incapacity** - The term disability means a substantial disruption of a person's ability to conduct normal life functions. - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• **Is a congenital anomaly/birth defect**
• **Other situations:** - Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information. • It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor or designee in lieu of completion of SAE/AE required form. • There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor or designee. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Attralus, Inc. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Attralus, Inc. • The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Attralus, Inc to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide Attralus, Inc with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The Investigator will submit any updated SAE data to Attralus, Inc within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting to Attralus, Inc. via the Electronic Data Collection (EDC) System
• The primary mechanism for reporting an SAE to Attralus, Inc. will be the EDC system. • If the EDC system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • The site will enter the SAE data into the EDC system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the EDC system has been taken off-line, then the site can report this information as noted in the Study Manual. • Contacts for SAE reporting can be found in the Study Manual.

SAE Reporting to Attralus, Inc. via Paper Data Collection Tool
• It is the responsibility of the Investigator to report SAEs to the Sponsor within 24 hours of awareness of the event or safety information, whether initial or follow-up. Do not delay in the reporting of suspected SAE in order to obtain additional information. Any additional information, if collected, can be reported to the Sponsor as a follow-up to the initial report. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the Study Manual.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal; or
- Premenopausal female with one of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

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

Postmenopausal Female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required. The Screening Visit FSH will be processed using the chemistry tube and the Day 1 FSH will need to be collected separately and sent to the central lab for analysis. A pregnancy test is required until both FSH measurements have been collected and results have been received that verify the postmenopausal state of the female subject.

Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT

during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

For Women of Childbearing Potential

Agreement to remain as abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year during the treatment period and for at least 90 days after the last dose of study intervention.

a. A woman is considered of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

b. Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

c. Contraception methods that do not result in a failure rate of <1% per year such as cap, diaphragm, or sponge with spermicide, or male or female condom with or without spermicide, are not acceptable.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

For Men:

Agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

a. With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 30 days plus 90 days (a spermatogenesis cycle) after the last dose of study intervention. Men must refrain from donating sperm during this same time period

10.4.3 Collection of Pregnancy Information

Female Subjects Who Become Pregnant

- The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor, as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

Male Subjects with Partners Who Become Pregnant

- The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive any study intervention.

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5 Appendix 5: Protocol Amendment History

The amendment history for Protocol AT01-001 is provided in Table 3.

Table 3: Protocol AT01-001: Amendment History

Version	Version Date	Brief Description
2.0	08 March 2022	Revisions from Version 1.1 include the following: • Addition of slow IV bolus at 1 mL/5 seconds as a method of administration. • Updated clinical experience to reflect final results from Study AMY1001. • Minor administrative and editorial revisions.
1.1	07 October 2021	Revisions from Version 1.0 include the following: • Addition of heparin/heparin analogs as a prohibited concomitant medication within 7 days of infusion of ^{124}I-AT-01. • Minor administrative and editorial revisions.
1.0	27 September 2021	• Original protocol; used for pre-submission activities. This version was not submitted to any health authorities or IRBs/ECs, nor was it implemented.

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