February 14, 2023

To Whom It May Concern:

This is the statistical analysis plan (SAP) for the below mentioned study.

Study Title: A Phase 1-2, dose-escalating, 6-part study to evaluate the safety and pharmacokinetics and pharmacodynamics of single and multiple doses of AT-007 in healthy adult subjects and adult subjects with Classic Galactosemia (CG) or GALK Deficient Galactosemia

NCT: NCT04117711

Document Date of SAP: 20 July 2021

Please contact me with any questions.

Respectfully,

Evan Bailey, MD
Exective Clinical Director

STATISTICAL ANALYSIS PLAN

A PHASE 1-2, DOSE-ESCALATING, 6-PART STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF SINGLE AND MULTIPLE DOSES OF AT-007 IN HEALTHY ADULT SUBJECTS AND ADULT SUBJECTS WITH CLASSIC GALACTOSEMIA (CG) OR GALK-DEFICIENT GALACTOSEMIA

SAP Version 3.0
FINAL
Date: 20 July 2021

for

Protocol No. AT-007-1001

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REVISION HISTORY

Version	Date	Author	Comments
Final V1.0	03DEC2019	Shekar Sunkoju	Initial document
Final V2.0	14JULY2020	Shekar Sunkoju	Added Part D Extension and E.
Final V3.0	20JUL2021	Dipayan Maity	• Addressed client comments on 25May2021: o Updated Enzyme activity categories. o Added forest plot for Subgorup analysis of blood Galactitol. • Update Biomarker section 7.11 and LOT for biomarker related tables.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	adverse event
Ae_{t1-t2}	amount of unchanged drug excreted though urine
ALT	alanine transaminase
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration-time curve
AUC_{inf}	Area under the concentration time curve from time zero extrapolated to infinity
AUC_{last}	Area under the concentration time curve from time zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUC_{tau}	area under the concentration-time curve within the dosing interval
AUC_{Extrap} (%)	percentage of AUCinf based on extrapolation
BLQ	below the quantifiable limit
BUN	blood urea nitrogen
CI	confidence interval
CL/F	Clearance after extravascular administration
CG	classic galactosemia
C_{last}	last quantifiable concentration determined directly from individual concentration time data
C_{max}	maximum concentration, determined directly from individual concentration time data
CL_R	renal clearance
CRA	clinical research associate
CRU	clinical research unit
CSF	cerebrospinal fluid
CSR	clinical study report

Abbreviation or Specialist Term	Explanation
C_{trough}	trough or predose concentration
CV	coefficient of variation
DLT	dose limiting toxicity
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	electronic case report form(s)
EOE	end of extension
EOS	end-of-study
fe_{t1-t2}	fraction of the administered dose excreted in urine over the interval from time t1 to time t2
FSH	follicle-stimulating hormone
fu/f	fraction of orally administered drug excreted into urine
GALK	Galactokinase
GALT	galactose-1-phosphate uridylyltransferase
HIV	human immunodeficiency viruses
HR	heart rate
ICH	international council for harmonisation
IEC	Independent Ethics Committees
IRB	institutional review board
LLQ	lower limit of quantitation
MAD	multiple ascending dose
MRS	magnetic resonance spectroscopy
MTD	maximum tolerated dose
OTC	over the counter
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily
QT	ECG interval between the start of the Q wave and the end of the T wave

Abbreviation or Specialist Term	Explanation
QTcF	ECG interval between the start of the Q wave and the end of the T wave corrected for heart rate using Fridericia's formula
R_{ac}	accumulation ratio
RBC	red blood cell
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SP	safety population
SRC	safety review committee
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{last}	time of the last quantifiable concentration
T_{max}	time of the maximum concentration
V_z/F	apparent volume of distribution during terminal phase
λz	The observed terminal rate constant; estimated by linear regression through at least 3 data points in the terminal phase of the log concentration time profile

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1 INTRODUCTION

This statistical analysis plan (SAP) is consistent with the statistical methods section of the final study protocol (Version 6.0, dated 05 May 2020) and includes additional detail of pharmacokinetic (PK) and safety summaries to be included in the clinical study report (CSR).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

- To evaluate the safety of single and multiple ascending doses of orally administered AT-007 in healthy adult subjects and adult subjects with CG or GALK-deficient Galactosemia

2.2 Secondary Objectives

- To evaluate the pharmacokinetic (PK) parameters of single and multiple doses of orally administered AT-007 in healthy adult subjects and adult subjects with CG or GALK-deficient Galactosemia
- To evaluate the effect of single and multiple doses of orally administered AT-007 on the level of galactitol, a biomarker of aldose reductase (AR) activity, in adult subjects with CG or GALK-deficient Galactosemia
- To evaluate the effect of single and multiple doses of orally administered AT-007 on the levels of galactose and its other metabolites in adult subjects with CG or GALK-deficient Galactosemia

2.3 Exploratory Objectives

- To measure the levels of AT-007 in the cerebrospinal fluid (CSF) of healthy adult subjects

2.4 Primary Endpoints

The primary endpoints of this study are overall safety and adverse events (AEs). Safety will be assessed by the following endpoints:

- AEs
- Clinical safety laboratory tests (hematology, chemistry, urinalysis)
- Physical examinations
- Vital signs
- Electrocardiograms (ECGs)

2.5 Secondary Endpoints

The secondary endpoints are the following:

- PK parameters in healthy subjects, subjects with CG, and subjects with GALK-deficient Galactosemia
- Galactitol galactose and its other metabolites in the blood of subjects with CG and subjects with GALK-deficient Galactosemia
- Urine galactitol for subjects with CG and subjects with GALK-deficient Galactosemia

2.6 Exploratory Endpoints

The exploratory endpoints are the following:

- AT-007 level in the CSF of healthy subjects (Part C only)

3 STUDY DESIGN

3.1 General

This study is a first-in-human, randomized, placebo-controlled, 6-Part, single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy adult subjects, adult subjects with CG, and adult subjects with GALK-deficient Galactosemia. The study is designed to assess the safety and PK (including metabolites) of AT-007 in these subjects as well as the effect of AT-007 on biomarkers of galactose metabolism (galactose, and galactose metabolites) in subjects with galactosemia. The study is being conducted in multiple centers in the US and Europe.

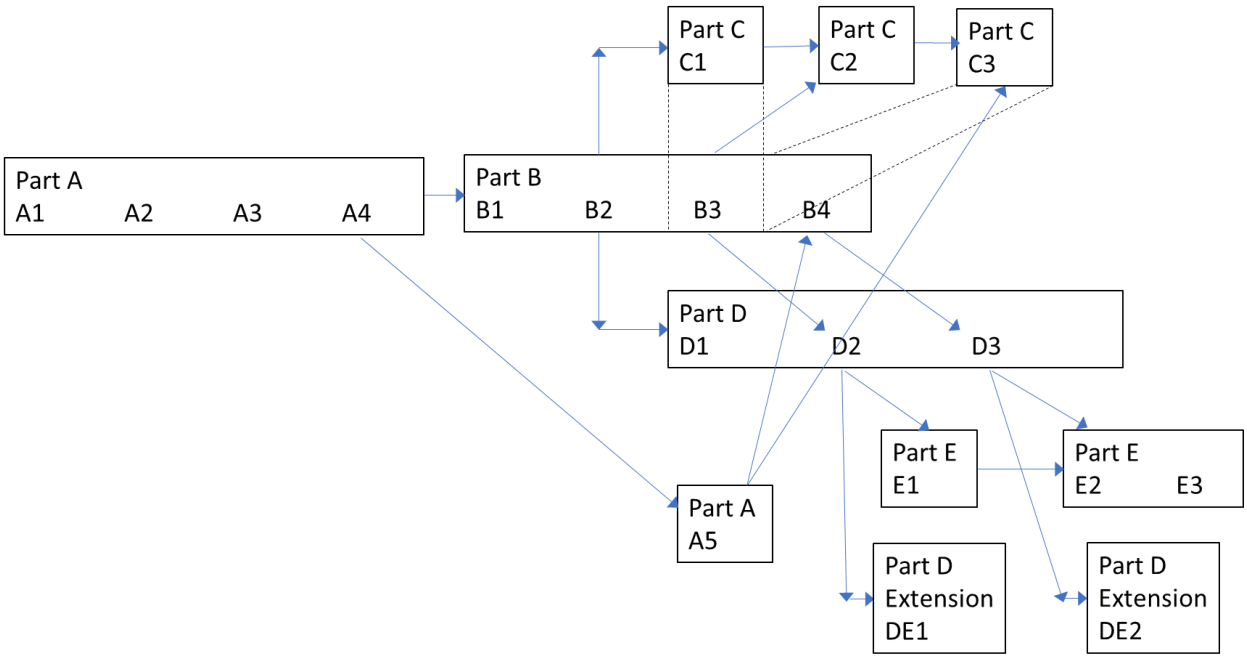
This study consists of 6 parts with the timing of the parts (shown in Table 3-1 and Figure 1):

Table 3-1: Study Design

Study Part	Study Population	Design	Planned Number of Cohorts	Subjects Per Cohort	Total # of Subjects
Part A	Healthy Adult Subjects	SAD	5	8	40
Part B	Healthy Adult Subjects	MAD (QD for 7 days)	4	6 in 2 cohorts & 8 in 2 cohorts	28
Part C	Healthy Adult Subjects	MAD (QD for 7 days)	3	4	12
Part D	Adult Subjects with CG	SAD, 5-day washout, MAD (QD for 27 days)	3	6	18
Part E	Adult Subjects with GALK-deficient Galactosemia	SAD, 5-day washout, MAD (QD for 27 days)	1 to 3	6	18
Part D Extension	Adult Subjects with CG	MAD (QD for 90 Days)	1 to 2	8 to 16	16

CG = Classic Galactosemia; MAD = multiple ascending dose; QD = once daily (dosing); SAD = single ascending dose.

Figure 1: Study Schematic



Within each Part, the Cohorts are sequential. Solid lines with arrows indicate that data from the part or cohort at the non-arrow end are required before the part or cohort at the arrow end can start. Dotted lines indicate cohorts (C1 and B3; C3 and B4) that will be conducted simultaneously. Parts D, E, and D Extension are not dependent on Part C results, and no temporal relationship between Parts D, E, and D Extension and Part C is implied. Also, with the exception of Cohorts B4, C3, D3, E2, E3, and DE2 being directly or indirectly dependent on Cohort A5 results, no temporal relationship between Cohort A5 and any other part/cohort is implied. Cohort DE2 (start and dose level) are not dependent on results from Cohort DE1.

For all cohorts in all parts (A, B, C, D, E, and D Extension), the study consists of a Screening Period (28 days [Day -28 to Day -1] in Parts A, B, and C and 40 days [Day -40 to Day -1] in Part D and E [and D Extension for de novo subjects who did not participate in Part D and subjects whose last visit in Part D was >40 days before Day 1 in the Part D Extension]), a period of study treatment and associated assessments, and an End-of-Study (EOS) Visit (28 days after the last dose of study drug) (for Part D Extension, the visit at 28 days after the last dose is called the end of extension [EOE] Visit). Subjects will be randomized and receive the first dose of study drug on Day 1. At a minimum, subjects will remain at the clinical research unit (CRU) through 24 hours after the first dose. Subjects in Part A have one in-clinic stay during the Treatment Period and will receive the single dose in the CRU. Subjects in Parts B and C have 1 in-clinic stay with all 7 doses taken in the CRU. Subjects in Part D and E have 3 in-clinic stays with most doses taken at home. Subjects in Part D Extension will have 2 in-clinic stays and monthly out-patient

visits with most doses taken at home. Subjects who withdraw or are withdrawn from the study after taking study drug will not be replaced.

Safety will be monitored and blood samples will be collected for PK in all parts of the study. Also, subjects in the selected dose cohorts of Parts A (SAD) and D (SAD portion only) will have urine collected for PK. In addition, subjects in Part C will have 1 lumbar puncture for CSF collection. Also, subjects in Part D and E will have blood samples and urine collected for biomarkers of galactose metabolism.

The starting dose in Part A was 0.5 mg/kg as a single dose. Subsequent doses in Part A and all doses in Parts B, C, D, and E are based on the results of previous cohorts and/or previous parts of the study. Part A of the study started first. Part A Cohort 5 (40 mg/kg single dose) was recently added to the protocol (version 4.0) and results showed the dose was safe and well tolerated. Part B started after all subjects in Cohorts A1 through A4 completed the study (minus the EOS Visit). Given that the results for 40 mg/kg in Cohort A5 were acceptable, Part B Cohort 4 (40 mg/kg) will start with this version of the protocol (version 5.0). The first cohort in Part C (C1) started after both safety and PK data from Cohorts B1 and B2 were reviewed. Cohort C1 was conducted simultaneously with Cohort B3 and used the same dose as Cohort B2 (10 mg/kg). The second cohort in Part C (C2) started after safety and PK data from Cohort B3 were reviewed and used the same dose as Cohort B3 (20 mg/kg); safety and PK results for Cohort C1 were also considered before starting Cohort C2. The third cohort in Part C (C3) will start with this version of the protocol (version 5.0) and use the same dose as Cohort B4 (given the results from Cohort A5); safety and PK results for Cohort C2 were also considered before starting Cohort C3. The first cohort in Part D (D1) started after all subjects in Cohorts A1 through A4 completed the study including the EOS Visit and all subjects in Cohorts B1 and B2 completed the study (minus the EOS Visit). The dose for Cohort D1 (5 mg/kg) was not higher than the dose for Cohort B2 (10 mg/kg). The second cohort in Part D (D2) started after all subjects in Cohort B3 completed the study (minus the EOS Visit) and the dose level (20 mg/kg) was the same as that for Cohort B3. The third cohort in Part D (D3) will start after all subjects in Cohort B4 complete the study (minus the EOS Visit) and the dose level will not be higher than the 40 mg/kg dose used for Cohort B4. The starting dose for Part E (Cohort E1) will be the most clinically appropriate dose as determined by the evaluation of available safety, tolerability, and PD (reduction in galactitol level) in Part D and the dose will not be higher than the highest acceptable dose in Part D at the time of starting Part E (after all subjects complete Cohorts D1 and D2 but may be before, during, or after Cohort D3). The Safety Review Committee (SRC) reviewed/will review safety data before each dose escalation and before the start of Parts B, C, D, and E. Also, the Sponsor reviewed/will review all PK and galactitol data as they become available.

The dose for the first cohort of the Part D Extension (DE1) will be 20 mg/kg/day based on acceptable SAD and MAD safety and PK data from Cohort D2. After SRC review of all SAD and MAD data and Sponsor review of PK and galactitol data for Cohorts D1 through D3, a second cohort of the Part D Extension (DE2) may be initiated to evaluate a dose higher than 20 mg/kg/day if this dose was well tolerated in the SAD and MAD portions of the study in both healthy volunteers and subjects with CG.

The review of the PK data from Cohorts A1 through A4 and the first 2 cohorts of Part B confirmed that once daily (QD) dosing is adequate.

3.1.1 Study Population

For Parts A, B, and C - The study population will include healthy male or non-pregnant, non-lactating female adult between 18 and 65 years of age, inclusive.

For Part D and D Extension - Male and non-pregnant, non-lactating female adult between the ages of 18 and 65 years, inclusive, with a Classic Galactosemia (CG) diagnosis confirmed by evidence of absent or significantly decreased (<1%) galactose-1-phosphate uridylyltransferase (GALT) activity in red blood cells and by historical record of diagnosis of GALT deficiency (medical record or gene analysis report or written communication by health care professional), and who have no other significant health problems unrelated to CG.

For the Part D Extension, subjects who previously participated in but did not complete Part D must not have discontinued Part D because of study drug related TEAE(s).

3.1.2 Evaluations at Screening and Check-in

3.1.2.1 Screening Evaluations

The screening visit must occur within 28 days before the first dose of study drug for Parts A, B, and C and within 40 days before the first dose of study drug for Part D, E and D Extension.

The Part D Extension screening visit is only applicable to the following subjects:

- De novo subjects
- Subjects whose last visit in Part D was >40 days before Day 1 in Part D Extension

Part D Extension subjects who previously participated in Part D and had a last Part D visit within 40 days before Day 1 of the extension do not need a screening visit for the extension.

Subjects will be evaluated at the screening visit to determine their eligibility to enroll in the study. The following procedures will be done at screening:

- Obtain signed informed consent from the subject and from the subject's caregiver/LAR (if applicable)

The informed consent documents will be discussed with each potential subject and caregiver/LAR (if applicable), and each potential subject (and caregiver/LAR if applicable) will sign the informed consent form(s), as appropriate, for the study prior to any study-specific procedures being performed.

- Review inclusion/exclusion criteria
- Obtain medical history (including current medication)
- Obtain demographic data (not necessary for Part D subjects being re-screened for Part D Extension)
- Perform physical examination including height and weight
- Measure vital signs
- Conduct 12-lead ECG
- Collect fasting blood sample(s) for clinical laboratory testing (hematology, coagulation and biochemistry); serology testing (screening for HIV, hepatitis B, and hepatitis C); and, for female subjects of childbearing potential only, serum pregnancy test (also follicle-stimulating hormone (FSH) test for female subjects claiming postmenopausal status)
- Collect fasting urine sample for urinalysis and drugs of abuse screen (also cotinine screen for subjects in Parts A, B, and C only)

For Part D, E and D Extension only, the following procedures will be done in addition to the ones listed above:

- Collect blood sample for assessment of GALT activity in red blood cells and GALT or GALK gene analysis (GALT for Parts D and D Extension and GALK for Part E)
- Collect blood sample for assessment of aldose reductase activity
- MRI/MRS of the brain if the subject and caregiver/LAR have consented to the brain imaging
- Collect blood sample for analysis of biomarkers of galactose metabolism including galactose, galactitol, and galactose-1-p
- Collect urine sample (spot collection) for analysis of galactitol

Note: For Part D Extension subjects who were previously screened for Part D but had the last Part D visit >40 days before Day 1 in the extension, GALT and aldose reductase activity assessments do not need to repeated. The MRI/MRS of the brain will be done at the Part D Extension screening visit for these subjects only if they did not consent for it in Part D (hence, no baseline scan during Part D screening) but consented for it in Part D Extension. If they consented

for the brain scan in both Part D and Part D Extension, then the screening MRI/MRS was done during the Part D screening visit and does not need to be repeated.

Subjects who are taking any disallowed medication(s) but otherwise eligible for the study may washout their disallowed medications (washout of at least 5 half-lives of the disallowed medication with the longest half-life). After the washout period, they may be rescreened.

Eligible subjects will be contacted to inform them of their eligibility and schedule the start of study drug dosing for those wishing to continue in the study. Subjects (and caregivers if applicable for Part D Extension) in Parts A, B, C and D Extension will be instructed to arrive at the CRU at approximately 11 am on the day before the scheduled first dose of study drug. Subjects/Caregivers in Part D will be instructed to arrive at the CRU in the morning on the day before the scheduled first dose of study drug (ie, approximately 24 hours before the first dose).

3.1.2.2 Check-in Evaluations

Subjects will arrive at the CRU at approximately 11 am (Parts A, B, C, and D Extension) or sometime in the morning (Part D and E [approximately 24 hours before the first dose]) on the day before the scheduled first dose of study drug. The following procedures will be done:

- For Part D Extension subjects who did not have a Part D Extension screening visit only, obtain signed informed consent from the subject and from the subject's caregiver/LAR (if applicable)
- Review of inclusion/exclusion criteria
- Obtain updates, if any, for medical history
- Perform physical examination including weight
- Measure vital signs
- Conduct 12-lead ECG
- Collect fasting blood sample(s) for clinical laboratory testing (hematology, coagulation and biochemistry); and, for female subjects of childbearing potential only, serum pregnancy test (pregnancy test must be negative for the subject to receive study drug)
- Collect fasting urine sample for urinalysis and drugs of abuse screen (also cotinine screen for subjects in Parts A, B, and C only)
- Collect AE and concomitant medication data
- Feed the subject (2 meals [lunch and dinner])
- Fast the subject overnight for at least 10 hours

For Part D and E only, the following procedures will be done in addition to the ones listed above:

- Collect blood sample for analysis of biomarkers of galactose metabolism including galactose, galactitol, and galactose-1-p.
- Collect urine over 24 hours (morning of Day -1 to immediately before the first dose [Day 1]) for analysis of galactitol
- Feed the subject (2 to 3 meals depending on check-in time)

Subjects who no longer fulfill all inclusion criteria and/or now fulfill one or more exclusion criteria will be discontinued from the study and sent home. These subjects will be replaced.

Subjects who continue to fulfill all inclusion criteria and none of the exclusion criteria will continue in the study.

3.1.3 Randomization and Treatment Assignments

Subjects will be randomly assigned to either AT-007 or matching placebo in Parts A, B, D, E and D Extension. The number of subjects to be treated with AT-007 and the number of subjects to be treated with placebo in each cohort are described in Section 3.1.4. Subjects will be assigned to open-label AT-007 in Part C.

Up to 116 subjects are planned to be dosed in this study:

- Part A: 5 cohorts of 8 healthy subjects each
- Part B: 2 cohorts of 6 healthy subjects each and 2 cohorts of 8 healthy subjects each
- Part C: 3 cohorts of 4 healthy subjects each
- Part D: 3 cohorts of 6 subjects with CG each
- Part E: 1 to 3 cohorts of 6 subjects with GALK-deficient Galactosemia each
- Part D Extension: 1 to 2 cohorts with a combined total of 16 subjects with CG

The number of cohorts and total number of subjects may increase if doses above 40 mg/kg are tested in additional cohorts.

In Parts A, B, D, E and D Extension, subjects will be randomized to receive either active drug (AT-007) or placebo. Each subject will receive an assigned treatment based on the randomization schedule prepared by the study statistician.

Parts A and B will be double-blinded (the Sponsor/ CRO, clinical site staff [except for unblinded pharmacist for Parts A and B], and the subjects will not know which subjects are treated with AT-007 or placebo).

In Part C, all subjects will be assigned to receive active drug (AT-007). Part C will be open-label.

In Parts D, E and D Extension the clinical site staff [except for the unblinded pharmacist], and the subjects will be blinded to study treatment. The Sponsor/CRO will not be blinded to study treatment in Part D, as the relationship between exposure in Parts D, E and D Extension (subject with galactosemia) vs. exposure in healthy subjects will need to be evaluated on an ongoing basis to ensure that AT007 blood level remain within the limits achieved in Part B. This process will minimize the number of subjects with galactosemia potentially exposed to plasma concentrations of AT-007 not previously tested and shown to be safe in healthy subjects.

3.1.4 Study Drug Administration

Parts A, B, C, and D of the study will start more or less sequentially followed by starting Parts E and D Extension more or less concurrently. However, conduct of all study parts will overlap.

Within each part, the cohorts (dose levels) will be dosed sequentially. The SRC will review available safety data through a pre-specified timeframe (Day 3 for Part A, Day 8 for Parts B and C, and Day 12 for Part D [and E, if applicable]) and provide recommendations for the next cohort. If there is a second cohort in Part D Extension, the dose will be higher than 20 mg/kg and depend on the results for that dose in healthy subjects and subjects with CG in Part D. Additional cohorts will be enrolled if it is deemed appropriate after safety assessment by the SRC and confirmation by the Sponsor. A decision to repeat a dose level or to study another higher or lower dose level may be made. The Investigator(s) and Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs) will be notified of these decisions.

The SRC will also review data for the last cohort for each study part except that there will be no next cohort within the same part of the study.

AT-007 dose levels in Part A were between 0.5 and 40 mg/kg. Dose levels in subsequent parts of the study are based on the safety and pharmacokinetic results (and galactitol results in Parts D, E and D Extension only) of previous cohorts and/or previous parts of the study. Doses higher than 40 mg/kg may be evaluated if the human C_{max} and AUC are substantially lower than the corresponding values calculated in nonclinical experiments and no dose limiting toxicity is observed up to and including at the 40 mg/kg dose. If dose escalation above 40 mg/kg is feasible based on the above criteria, these higher doses may be investigated in additional SAD and MAD cohorts in healthy subjects and in subjects with CG or GALK-deficient Galactosemia if no AT-007 levels are detected in the CSF collected from the healthy subjects enrolled in Cohort C3.

For Parts A, B, and C, subjects will take the study drug (oral capsules of AT-007 or placebo) in the CRU under the supervision of study personnel. Study staff will conduct a hand and mouth check immediately after dose to ensure that the medication has been appropriately swallowed.

Most study drug doses in Parts D, E and D Extension subjects will be taken on an out-patient basis (ie, at home). Each subject will be provided with a diary card to record the dates/times for all doses taken at home.

All doses of study drug should be taken under fasting conditions. Subjects should take all doses of study drug in the morning (with water) after overnight fasts of at least 10 hours. Subjects may end their fast at any time ≥2 hours after taking the study drug. These conditions are mandatory for doses associated with PK sampling and recommended for all other doses regardless of whether taken at home or in the clinic.

3.1.4.1 Part A: Double-blind SAD, Healthy Subjects

Four dose levels were initially planned for the SAD group and a fifth dose level was recently added and completed (**Table 3-2**). Subjects were enrolled in 5 sequential cohorts of 8 subjects each, for a total of 40 subjects. The first cohort included a sentinel group (first 2 subjects with 1 per treatment) dosed at the same time. Dose administration for the remainder of the first cohort occurred only at least 24 hours after the 2 sentinel subjects received study drug (AT-007 or placebo) and were contingent upon acceptable safety results through 24 hours for the sentinel subjects per Investigator in consultation with the Sponsor and with explicit agreement from the Sponsor. Subjects were housed at the CRU for observation for at least 48 hours after dosing. Subjects returned for the EOS Visit at 28 days after the dose. Progression to and the dose level for the next cohort were dependent upon safety data through Day 3 from the previous cohort.

Table 3-2: SAD Dose Cohorts in Healthy Subjects (Part A)

Cohort	Dose	
A1 (sentinel group)	Single dose of AT-007 oral capsule, dose 0.5 mg/kg (n = 1)	placebo (n = 1)
A1 (remainder of cohort)	Single dose of AT-007 oral capsule, dose 0.5 mg/kg (n = 5)	placebo (n = 1)
A2	Single dose of AT-007 oral capsule, dose 5 mg/kg (n = 6)	placebo (n = 2)
A3	Single dose of AT-007 oral capsule, dose 10 mg/kg (n = 6)	placebo (n = 2)
A4	Single dose of AT-007 oral capsule, dose 20 mg/kg (n = 6)	placebo (n = 2)
A5	Single dose of AT-007 oral capsule, dose 40 mg/kg (n=6)	placebo (n = 2)

n = number of subjects; SAD = single ascending dose.
Note: The number of cohorts and total number of subjects may increase if doses above 40 mg/kg are tested in additional cohorts.

3.1.4.2 Part B: Double-blind MAD, Healthy Subjects

Four dose levels are planned for the MAD group in Part B (**Table 3-3**). Subjects will be enrolled in 4 sequential cohorts of 6 or 8 subjects each, for a total of 28 subjects. The initial dose level for

Part B (5 mg/kg) was based on the results from Part A (Cohorts A1 through A4). Subjects will receive study drug (AT-007 or placebo) QD for 7 consecutive days. Progression to and the dose level for the next cohort will be dependent upon safety data through Day 8 from the previous cohort as well as results from Part A.

Table 3-3: MAD Dose Cohorts in Healthy Subjects (Part B)

Cohort	Dose	
B1	AT-007 oral capsule QD for 7 consecutive days, dose 5 mg/kg (n = 6)	placebo (n = 2)
B2	AT-007 oral capsule QD for 7 consecutive days, dose 10 mg/kg (n = 4)	placebo (n = 2)
B3	AT-007 oral capsule QD for 7 consecutive days, dose 20 mg/kg (n = 6)	placebo (n = 2)
B4	AT-007 oral capsule QD for 7 consecutive days, dose 40 mg/kg (n = 4)	placebo (n = 2)

n = number of subjects; MAD = multiple ascending dose; QD = once daily.
Note: The number of cohorts and total number of subjects may increase if doses above 40 mg/kg are tested in additional cohorts. The numbers of subjects in the cohorts are intended to ensure at least 6 subjects on AT-007 at each well-tolerated dose level when Cohort C subjects at the same dose level are considered.

3.1.4.3 Part C: Open-label MAD, Healthy Subjects

The first cohort of Part C (i.e., Cohort C1) was conducted concurrently with Cohort B3 but at different locations with the same CRU, and the second cohort of Part C (Cohort C2) was conducted after Cohort B3. Cohort C1 used the same dose (10 mg/kg) as Cohort B2; Cohort C2 used the same dose (20 mg/kg) as Cohort B3; and Cohort C3 will use the same dose as and run concurrently with Cohort B4 (40 mg/kg) (Table 3-4). Results for prior Part C cohorts will be considered before starting the next Part C cohort. Each of the cohorts in Part C will consist of only 4 subjects and all subjects will be assigned to open-label AT-007.

Table 3-4: MAD Dose Cohorts in Healthy Subjects with CSF Collection (Part C)

Cohort	Dose
C1	AT-007 oral capsule QD for 7 consecutive days, dose 10 mg/kg (n = 4)
C2	AT-007 oral capsule QD for 7 consecutive days, dose 20 mg/kg (n = 4)
C3	AT-007 oral capsule QD for 7 consecutive days, dose 40 mg/kg (n=4)

n = number of subjects; MAD = multiple ascending dose; QD = once daily.

3.1.4.4 Part D: SAD and MAD in Subjects with CG

Three dose levels are planned for the subjects with CG (Table 3-5). Subjects will be enrolled in 3 sequential cohorts of 6 subjects each for a total of 18 subjects. The initial dose level for Part D will be based on the results from Parts A (Cohorts A1 through A4) and Cohorts B1 and B2. Subjects will receive study drug (AT-007 or placebo) on Day 1 and remain at the CRU for at

least 48 hours after the first dose. Subjects will then have a 5-day washout period (Day 1 postdose through Day 6 predose). Then, subjects who tolerated the single dose will take the same study drug QD for 27 consecutive days (Day 6 through Day 32, inclusive) for the multiple dosing portion of Part D. For each individual subject, the Investigator and the Sponsor will decide whether the subject can start the multiple dosing portion of Part D. The Investigator must consult the Sponsor. Starting the multiple dosing portion requires explicit agreement from the Sponsor. In the 27-day multiple dosing portion, subjects will take most of their doses at home (fasting conditions recommended). Progression to and the dose level for the next cohort will be dependent upon safety data through Day 12 and at least single dose PK and galactitol results from the previous cohort as well as additional Part B (and possibly Part C) results.

Table 3-5: SAD and MAD Dose Cohorts in Subjects with Classic Galactosemia (Part D)

Cohort	Dose	
D1	AT-007 oral capsule on Day 1, dose 5 mg/kg (SAD portion), followed by a 5-day-washout, and AT-007 oral capsule QD for 27 days (MAD portion), dose TBD mg/kg (n = 4)	placebo (n = 2)
D2	AT-007 oral capsule on Day 1, dose 20 mg/kg (SAD portion), followed by a 5-day-washout, and AT-007 oral capsule QD for 27 days (MAD portion), dose TBD mg/kg (n = 4)	placebo (n = 2)
D3	AT-007 oral capsule on Day 1, dose TBD mg/kg (SAD portion), followed by a 5-day-washout, and AT-007 oral capsule QD for 27 days (MAD portion), dose TBD mg/kg (n = 4)	placebo (n = 2)

n = number of subjects; MAD = multiple ascending dose; QD = once daily; SAD = single ascending dose; TBD = to be determined.

Note: The number of cohorts and total number of subjects may increase if doses above 40 mg/kg are tested in additional cohorts. The overall number of subjects per cohort may be increased up to 8 subjects to address any potential lost-to-follow-up among subjects treated with either placebo or AT-007. Subjects treated with study drug (placebo or AT-007) in a cohort may be randomized to treatment in another cohort (separate consent required) within the same Part (assuming no safety or tolerability issues in the prior cohort) as long as there is a washout period ≥5 days between the last dose in a cohort and the first dose in the next cohort.

3.1.4.5 Part E: SAD and MAD in Subjects with GALK-deficient Galactosemia

The starting dose level for subjects with GALK-deficient Galactosemia will be the most clinically appropriate dose as determined by the evaluation of safety, tolerability, and PD (reduction in galactitol level) in Part D cohorts completed at the time of starting Part E (Table 3-6**).** If needed, additional dose levels may be tested in additional cohorts. If applicable, dose levels for subsequent cohorts in Part E will be based on safety data through Day 12 and at least single dose PK and galactitol results from the previous cohort(s) in Part E and possibly additional cohorts in Part D.

Subjects will receive study drug (AT-007 or placebo) on Day 1 and remain at the CRU for at least 48 hours after the first dose. Subjects will then have a 5-day washout period (Day 1 postdose through Day 6 predose). Then, subjects who tolerated the single dose will take the same study drug QD for 27 consecutive days (Day 6 through Day 32, inclusive) for the multiple dosing portion of Part E. For each individual subject, the Investigator and the Sponsor will decide whether the subject can start the multiple dosing portion of Part E. The Investigator must consult the Sponsor. Starting the multiple dosing portion requires explicit agreement from the Sponsor. In the multiple dosing portion, subjects will take most of their doses at home. Subjects will return to the site for brief in-clinic stays after the first week of multiple dosing and at the end of multiple dosing. Subjects will return for the EOS Visit at 28 days after the last dose.

Table 3-6: Dose Cohort in Subjects with GALK-deficient Galactosemia (Part E)

Cohort	Dose	
E1	AT-007 oral capsule on Day 1, dose TBD mg/kg (SAD portion), followed by a 5-day-washout, and AT-007 oral capsule QD for 27 days (MAD portion), dose TBD mg/kg (n=4)	placebo (n=2)

n = number of subjects; MAD = multiple ascending dose; QD = once daily; SAD = single ascending dose; TBD = to be determined.

Note: There may be up to 2 additional cohorts if the decision is made to test more than 1 dose level. Also, the number of cohorts and total number of subjects may increase if doses above 40 mg/kg are tested in additional cohorts. The overall number of subjects per cohort may be increased up to 8 subjects to address any potential lost-to-follow-up among subjects treated with either placebo or AT-007. Subjects treated with study drug (placebo or AT-007) in a cohort may be randomized to treatment in another cohort (separate consent required) within the same Part (assuming no safety or tolerability issues in the prior cohort) as long as there is a washout period ≥5 days between the last dose in a cohort and the first dose in the next cohort

3.1.4.6 Part D Extension: 90-Day Dosing in Subjects with Classic Galactosemia

The Part D Extension is open to the following subjects:

- Subjects who completed Part D may start in the extension at any time after the EOS Visit in Part D.
- Subjects who participated in but discontinued Part D for reasons other than study drug related TEAE (and completed an EOS Visit at any time >14 days after the last dose) may start in the extension at any time after the EOS Visit in Part D.
- Subjects who participated in but discontinued Part D for reasons other than study drug related TEAE (and who either did not have an EOS Visit or had an EOS Visit before 14 days after the last dose) may start in the extension at any time beyond 14 days after the last dose in Part D.

- De novo subjects who did not participate in Part D may participate in the 90-day Extension after they undergo all the required screening procedures from Day -40 to Day -1, including the baseline MRI/MRS (if the necessary consents are obtained for this scan).

The dose for the first cohort of the Part D Extension (DE1) will be 20 mg/kg/day based on acceptable SAD and MAD safety and PK data from Cohort D2 (**Table 3-7**). After SRC review of all SAD and MAD data and Sponsor review of PK and galactitol data for Cohorts D1 through D3, a second cohort of the Part D Extension (DE2) may be initiated to evaluate a dose >20 mg/kg/day if this dose was well tolerated in the SAD and MAD portions of the study in both healthy volunteers and subjects with CG.

A screening visit is required for de novo subjects and subjects whose last visit in Part D was >40 days before Day 1 in the Part D Extension.

Within each cohort of up to 16 subjects, subjects will be randomly assigned in a 3:1 to AT-007 and placebo. Subjects will receive study drug (AT-007 or placebo) on Day 1 and remain at the CRU for at least 24 hours after the first dose. Subjects will receive 1 daily dose of the same study drug (AT-007 or placebo) for a total of 90 consecutive days. In the extension, subjects will take most of their doses at home. Subjects will have 1 in-clinic stay associated with the first dose, a second in-clinic stay with the last dose, and out-patient visits at Months 1 and 2. Subjects will return for the EOE Visit at 28 days after the last dose.

Maximum duration of study participation (Screening through EOE Visit) for an individual subject will be approximately 158 days for a de novo subject and approximately 218 days for a subject who was screened for Part D, completed Part D, and completed Part D Extension without requiring a screening visit for the Part D Extension and without counting any washout period between Part D and Part D Extension.

Table 3-7: 90-Day Dose Cohort in Subjects with Classic Galactosemia (Part D Extension)

Cohort	Dose	
DE1	AT-007 oral capsule on Day 1, dose 20 mg/kg (SAD portion), followed by AT-007 oral capsule QD for a total of 90 days, dose 20 mg/kg (n=up to 12)	placebo (n=up to 4)

n = number of subjects; MAD = multiple ascending dose; QD = once daily; SAD = single ascending dose.
Note: There may be up to 1 additional cohort if the decision is made to test more than 1 dose level. Regardless of whether there is 1 or 2 cohorts, the maximum number of subjects is 16. However, the number of cohorts and total number of subjects may increase if doses above 40 mg/kg are tested in additional cohorts. The overall number of subjects per cohort may be increased to address any potential lost-to-follow-up among subjects treated with either placebo or AT-007.

3.1.4.7 Dose Escalation and Dose De-escalation

The SRC will make recommendations to the Sponsor regarding dose escalation or de-escalation for each cohort based on the results from the previous cohort. The Sponsor will act upon this recommendation and inform the Investigator(s) and the IRB(s)/IEC(s).

The SRC will pay particular attention to dose limiting toxicities (DLTs) defined as any AT-007-related AE or clinically relevant finding on laboratory tests, ECGs, vital signs, or physical examinations that, in the opinion of the Investigator and/or the SRC, precludes administering the dose to any subject and/or continuing to administer daily doses to the subject who experienced the event. For DLTs, as well as fatal serious adverse events (SAEs) and life-threatening SAEs, breaking the blind will be considered and initiated (as needed) per SRC discussion and agreement.

Dose-escalation will be stopped and de-escalation initiated if

- ≥ 2 subjects on AT-007 (B and C cohorts of the same dose level considered together) experience a DLT at any time through 24 hours after the last dose of study treatment
- Any subject on AT-007 has a fatal SAE or life-threatening SAE requiring urgent intervention at any time through 24 hours of the last dose of study treatment

Dose escalation within each part of the study will be continued until the MTD is identified per the rules above or the SRC and/or Sponsor decide to stop dose escalation. Dose de-escalation, if initiated within any part of the study, will continue until the MTD is identified or the SRC and/or Sponsor decide to stop.

If the events outlined in the above MTD definition do not occur at any dose level in a study part, then the MTD will be the highest dose level in that study part.

If the events outlined in the above MTD definition occur at any given dose level, the Sponsor may decide to investigate a dose higher that the previously well-tolerated dose but lower than the dose at which one of the events outlined in the above MTD definition occurred.

3.1.5 Concomitant Medications

Subjects must not take any over the counter (OTC) medication (including nutritional or dietary supplements, herbal preparations, or vitamins) ≤ 7 days prior to the first dose of study drug until the EOS (or end of extension (EOE)) Visit without evaluation and approval by the Investigator. For subjects with CG or GALK-deficient Galactosemia, use of medications to treat Galactosemia complications will be permitted by approval of the Investigator.

Subjects must not take any prescription medication, except that allowed per protocol in this section, from 14 days prior to the first dose of study drug until the EOS (or EOE) Visit without

evaluation and approval by the Investigator. For subjects with CG or GALK-deficient Galactosemia, use of medications to treat galactosemia complications will be permitted by approval of the Investigator.

In addition, use or consumption of the following are not permitted:

- Tobacco- or nicotine-containing products within 6 months prior to the first dose of study drug (including negative cotinine test at screening) through the EOS Visit (subjects in Parts A, B, and C only)
- Drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates) from a negative drug test at screening through the EOS (or EOE) Visit (Exception: Subjects with CG or GALK-deficient Galactosemia may take such drugs or drugs that produce positive drug screening results if clinically indicated and on a stable dose for ≥ 1 month prior to screening and throughout the study.)
- Any strong inhibitor/inducer of CYP2C19 and/or CYP3A4 (eg, barbiturates, phenothiazines, cimetidine, carbamazepine) within 30 days prior to the first dose of study drug through the visit before the EOS (or EOE) Visit
- Beverages or foods that contain alcohol, high levels of sorbitol, grapefruit, poppy seeds, broccoli, Brussels sprouts, pomegranate, star fruit, char-grilled meat, or caffeine/xanthine from 48 hours prior to the first dose of study drug through the visit before the EOS (or EOE) Visit (allowance for an isolated single incidental consumption may be evaluated and approved by the Investigator based on the potential for interaction with the study drug)

Permitted concomitant medications in this study are the following:

- Female hormonal contraceptives or hormone replacement therapy (Parts A, B, C, D, E and D Extension)
- Concomitant medications and dietary supplements with stable doses maintained for ≥ 1 month prior to screening and through the EOS (or EOE) Visit (Part D, E and D Extension)

3.1.6 Treatment Compliance

Treatment compliance is assured during Parts A, B, and C and for in-clinic doses during Part D, E and D Extension because subjects will take the study drug in the CRU under supervision by the study center staff.

During Part D, E and D Extension, study drug will be dispensed and collected periodically because subjects will be taking most doses at home. Treatment compliance will be determined by counting the capsules dispensed and collected at each of these visits and by reviewing subjects' study drug diary cards.

For Part D, E and D Extension, treatment compliance is defined by the percentage of planned dose administered and is calculated as:

(Actual Number of Dose Taken / Planned Number of Doses) x 100

3.1.7 Pharmacokinetic Sampling Schedule

In Part A, blood samples for plasma AT-007 PK will be collected predose (within 60 min before the dose) and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours (±5 minutes for all time points) after the dose.

For Part A, Cohort A4 and A5, urine samples for AT-007 PK will be collected predose (spot collection within 60 min before the dose) and in 4-hour intervals (0 to 4, > 4 to 8, > 8 to 12, > 12 to 16, > 16 to 20, and > 20 to 24) through the first 24 hours after the dose followed by 12-hour intervals (> 24 to 36, > 36 to 48, > 48 to 60, and > 60 to 72) from 24 hours postdose to 72 hours postdose. Allowable windows for urine collection container changes will be ± 30 minutes through the first 24 hours and ± 1 hour thereafter.

In Part B, on Day 1, blood samples for plasma AT-007 PK will be collected predose (within 60 minutes before the dose) and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (± 5 minutes for all time points) after the dose. On Day 2, blood samples for plasma AT-007 PK will be collected predose (ie, at 24 hours ± 5 minutes after the Day 1 dose and before the Day 2 dose). On Day 7, blood samples for plasma AT-007 PK will be collected predose (within 60 minutes before the dose) and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (± 5 minutes for all time points) after the dose. Also, blood samples for plasma AT-007 PK will be collected at 24, 36, and 48 hours (± 5 minutes for all time points) after the Day 7 dose; these collections will be taken on Day 8 and Day 9.

In Part C, on Day 1, blood samples for plasma AT-007 PK will be collected predose (within 60 minutes before the dose) and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (± 5 minutes for all time points) after the dose. On Day 2, blood samples for plasma AT-007 PK will be collected predose (ie, at 24 hours ± 5 minutes after the Day 1 dose and before the Day 2 dose). On Day 7, blood samples for PK will be collected predose (within 60 minutes before the dose) and at 0.5, 1, 1.5,

2, 4, 6, 8, and 12 hours (± 5 minutes for all time points) after the dose. Also, blood samples for plasma AT-007 PK will be collected at 24, 36, and 48 hours (± 5 minutes for all time points) after the Day 7 dose; these collections will be taken on Day 8 and Day 9. A lumbar puncture will be done after the Day 7 dose to collect CSF for analysis of AT-007. For Cohort C1, the timing (hours after the dose) of the lumbar puncture will be based on plasma AT-007 PK results from Cohorts B1 and B2. For Cohort C2, the timing of the lumbar puncture was based on PK results from Cohorts B1, B2, and B3. For Cohort C3, the timing of the lumbar puncture will be based on PK results from Cohorts B1, B2, B3, and B4. The intent is to perform the lumbar puncture at the time of maximum observed concentration (T_{max}) after the Day 7 dose.

In Part D, for the Day 1 dose, blood samples for plasma AT-007 PK will be collected predose (within 60 minutes before the dose) and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours (± 5 minutes for all time points) after the dose. On Days 12 and 32, blood samples for plasma AT-007 PK will be collected predose (within 60 minutes before the dose) and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (± 5 minutes for all time points) after the dose. On Day 13, a blood sample for plasma AT-007 PK will be collected predose (ie, at 24 hours ± 5 minutes after the Day 12 dose). On Day 33, blood samples for plasma AT-007 PK will be collected at 24 and 36 hours (± 5 minutes for both time points) after the Day 32 dose. On Day 34, a blood sample for plasma AT-007 PK will be collected at 48 hours (± 5 minutes) after the Day 32 dose.

For Cohort D3 only, urine for PK will be collected predose (spot collection within 60 minutes before the Day 1 dose) and in 4-hour intervals (0 to 4, > 4 to 8, > 8 to 12, > 12 to 16, > 16 to 20, and > 20 to 24) through the first 24 hours after the Day 1 dose followed by 12-hour intervals (> 24 to 36, > 36 to 48, > 48 to 60, and > 60 to 72) from 24 to 72 hours after the Day 1 dose. Allowable windows for urine collection container changes will be ± 30 minutes through the first 24 hours and ± 1 hour thereafter.

In Part E, on Day 1 dose, blood samples for PK will be collected predose (within 60 minutes before the dose) and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, and 48 hours (±5 minutes for all time points) after the dose. On Days 12 and 32, blood samples for PK will be collected predose (within 60 minutes before the dose) and at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours (±5 minutes for all time points) after the dose. On Day 13, a blood sample for PK will be collected predose (i.e., at 24 hours ±5 minutes after the Day 12 dose). On Day 33, blood samples for PK will be collected at 24 and 36 hours (±5 minutes for both time points) after the Day 32 dose. On Day 34, a blood sample for PK will be collected at 48 hours (±5 minutes) after the Day 32 dose.

For Part E, Urine for galactitol measurement will be collected over the 24 hours immediately before and the 24 hours immediately after the dose on Day 1. Urine for galactitol measurement will be collected over the 24 hours immediately after the dose on Days 12 and 32. For each collection of urine for galactitol measurement, an aliquot of the total urine collected will be

analyzed for creatinine. Also, a spot collection for urine galactitol measurement will be taken at screening.

For Part D Extension, blood samples for PK will be collected on Day 1, a predose (within 60 minutes before the dose) blood sample for PK will be collected. On Days 30, 60, and 90, blood samples for PK will be collected predose (24 hours [± 15 minutes] after the dose taken the day before and within 60 minutes before the dose administered on that day) and at 2, 4, 8, and 12 hours (±5 minutes for all time points) after the dose.

For Part D Extension, Urine spot collection for galactitol analysis to check the study entry criterion based on urine galactitol (applicable only to subjects requiring a screening visit because it is assumed that urine galactitol for subjects not requiring the screening visit remain in the study eligible range).

3.1.8 Evaluation of Biomarkers

In Part D, E and D Extension, blood samples for the analysis of galactose, galactitol, and galactose-1-phosphate and urine samples for the analysis of galactitol will be collected. With the exception of the blood samples for biomarkers taken at Screening and Day -1, the time points and allowable windows for the blood samples for biomarkers will match those for the blood samples for PK.

3.2 Evaluation of Treatment Safety

3.2.1 Adverse Events

Adverse events will be monitored from the time the subject signs the informed consent throughout the study. AEs will be collected for each subject from the time of informed consent through the EOS (or EOE) Visit. The following details will be collected: description of the AE, start date and time, stop date and time, action taken with study treatment (dose not changed, dose reduced, drug interrupted, drug withdrawn, dose increased, not applicable), outcome (recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, fatal, unknown), severity (mild, moderate, severe), seriousness (yes, no), relationship to study drug (not related, unlikely related, possibly related, probably related). An AE is considered “unexpected” if the AE is not listed in the Investigator Brochure or is not listed with the observed specificity or severity.

3.2.2 Clinical Laboratory Assessments

A Clinical Laboratory Improvement Amendments certified laboratory will perform the following clinical laboratory tests:

- Hematology: hemoglobin, hematocrit, total and differential leukocyte count, RBC, and platelet count
- Serum chemistry: albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), sodium (Na+), potassium (K+), chloride (Cl-), lactate dehydrogenase (LDH), calcium (Ca), uric acid, glucose, direct bilirubin (DB), and gamma-glutamyl transferase (GGT)
- Coagulation: prothrombin time (PT) and international normalized ratio (INR)
- Serology: blood tests for hepatitis B surface antigen, hepatitis C antibody, and HIV.
- Urinalysis by an automated or manual urine "dipstick" method: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, leukocyte esterase, and urobilinogen. If protein, occult blood, nitrite, or leukocyte esterase values are out of range, a microscopic examination will be performed.
- Urine drug screen: drugs of abuse (amphetamines, benzodiazepines, barbiturates, cannabinoids, cocaine, opiates)
- Urine cotinine screen (subjects in Parts A, B, and C only)
- Pregnancy test (all female subjects of childbearing potential)
- FSH (for female subjects claiming postmenopausal status)

For Parts D, E and D Extension only, the following tests will be done in addition to the ones listed above:

- GALT (Part D and Part D Extension but only done once for subjects participating in both Parts) or GALK (Part E) activity in red blood cells
- GALT (Part D and Part D Extension but only done once for subjects participating in both Parts) or GALK (Part E) gene analysis
- Aldose Reductase activity (only done once for subjects participating in both Parts D and D Extension)

Fasted samples for hematology, coagulation, chemistry, and urinalysis assessments will be collected at the following time points:

- Part A: Screening, Day -1, Day 3, EOS
- Part B: Screening, Day -1, Day 6, EOS
- Part C: Screening, Day -1, Day 6, EOS
- Part D: Screening, Days -1, 6, 12, 20, 32, EOS

- Part E: Screening, Days -1, 6, 12, 20, 32, EOS
- Part D Extension: Screening, Days -1, 30, 60, 90, EOE

3.2.3 Vital Signs

Vital signs (blood pressure, pulse rate, respiration rate, and temperature) will be measured as follows:

- Part A: Screening, Day -1 check-in, predose (within 60 min before the dose) on Day 1, at 4 hours (±10 minutes) after the dose on Day 1, once daily on Days 2 and 3, and EOS
- Part B: Screening, check-in on Days -1 and 6, predose (within 60 min before the dose) on Days 1 and 7, at 4 hours (±10 minutes) after the dose on Days 1 and 7, once daily on Days 2, 8, and 9, and EOS
- Part C: Screening, check-in on Days -1 and 6, predose (within 60 min before the dose) on Days 1 and 7, at 4 hours (±10 minutes) after the dose on Days 1 and 7, once daily on Days 2, 8, and 9, and EOS
- Part D: Screening, every check-in, every check-out, predose (within 60 min before the dose) and 4 hours (±10 minutes) after the dose on Days 1, 6, 12, 20, and 32, once daily on all other in-clinic days, and EOS
- Part E: Screening, every check-in, every check-out, predose (within 60 min before the dose) and 4 hours (±10 minutes) after the dose on Days 1, 6, 12, 20, and 32, once daily on all other in-clinic days, and EOS
- Part D Extension: Screening (if applicable), every check-in, every check-out, predose (within 60 min before the dose) and 4 hours (±10 minutes) after the dose on Days 1, 30, 60, and 90, once daily on all other visits, and at the EOE visit.

Additional vital signs measurements may be taken as deemed medically necessary by the Investigator/designee. For purposes of qualifying any given subject for study participation, out of range vital signs may be repeated once.

All vital signs measurements will be taken with the subject in a seated position and after the subject has been resting in that seated position for at least 5 minutes. Any time during the study after the first dose of study drug, abnormal vital sign measurements considered to be clinically significant by the Investigator/designee will be reported as AEs.

3.2.4 Electrocardiograms

The ECGs will be performed as follows:

- Part A: Screening, Day -1 check-in, predose (within 60 min before the dose) on Day 1, at 2 hours (±10 minutes) after the dose on Day 1, on Day 3, and EOS
- Part B: Screening, Day -1 check-in, predose (within 60 min before the dose) on Days 1 and 7, at 2 hours (±10 minutes) after the dose on Days 1 and 7, and EOS
- Part C: Screening, Day -1 check-in, predose (within 60 min before the dose) on Days 1 and 7, at 2 hours (±10 minutes) after the dose on Days 1 and 7, and EOS
- Part D: Screening, Day -1 check-in, predose (within 60 min before the dose) and 2 hours (±10 minutes) after the dose on Days 1, 6, 12, 20, and 32, and EOS
- Part E: Screening, Day -1 check-in, predose (within 60 min before the dose) and 2 hours (±10 minutes) after the dose on Days 1, 6, 12, 20, and 32, and EOS
- Part D Extension: Screening, Day -1 check-in, predose (within 60 min before the dose) and 2 hours (±10 minutes) after the dose on Days 1, 30, 60, and 90, and EOE

All ECGs will be done with the subject in a supine position and after the subject has been resting in that supine position for at least 5 minutes.

3.2.5 Physical Examinations

Physical examinations will be performed as follows:

- Part A: Screening; Days -1 and 3; and EOS
- Part B: Screening; Days -1, 6, and 9; and EOS
- Part C: Screening; Days -1, 6, and 9; and EOS
- Part D: Screening; Days -1, 6, 12, 20, 32, and 34; and EOS
- Part E: Screening; Days -1, 6, 12, 20, 32, and 34; and EOS
- Part D Extension: Screening; Days -1, 30, 60 and 90; and EOE

Height will be measured at screening. Weight will be measured as part of all physical examinations. Any time during the study after the first dose of study drug, abnormal findings considered to be clinically significant by the Investigator/designee will be reported as AEs.

3.2.6 Other Safety Assessments

In Parts D and E, brain MRI/MRS will be performed during the Screening Period and toward the end of the MAD treatment (i.e., either on Day 30, Day 31, or Day 32). MRI/MRS will only be performed in a subset of subjects who specifically consent to the brain imaging.

In Part D Extension, brain MRI/MRS will be performed during the Screening Period (unless the subject previously participated in Part D and had a brain MRI/MRS performed during the Screening Period for Part D) and toward the end of the treatment period (i.e., either on Day 88, Day 89, or Day 90). MRI/MRS will only be performed in subjects who specifically consent to the brain imaging.

3.2.7 Protocol Deviation Reporting

Procedural deviations found by the clinical research associate (CRA) during monitoring visits and data deviations captured on the electronic case report form (eCRF) and found through programming and examining the database will be listed by subject.

4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

There are a few changes in the study conduct or analysis plans relative to the study protocol:

- The objective "To evaluate the effect of single and multiple doses of orally administered AT-007 on the levels of galactose and its other metabolites in adult subjects with CG or GALK-deficient Galactosemia" is a secondary objective according to the study protocol, but it should be an exploratory objective only.
- The secondary endpoint "Galactose, galactitol, and other galactose metabolites in the blood of subjects with CG and subjects with GALK-deficient Galactosemia" was replaced by "Galactitol in the blood of subjects with CG and subjects with GALK-deficient Galactosemia" and the exploratory endpoint "Galactose and galactose metabolites in the blood of subjects with CG and subjects with GALK-deficient Galactosemia" was added.
- Additional subgroup analysis performed for Part D blood and urine Galactitol will be performed if data permit.
- Urine galactitol concentrations for each collection interval will also be presented normalized to urine creatinine.
- The DBL will be carried out after the completion of Part D and CSR will be written for Part A to D. This will lead to unblinding of Part A and Part B subjects to the study team. Part D- Extension will be carried out as CSR addendum.

5 QUALITY CONTROL AND QUALITY ASSURANCE METHODS FOR DATA ANALYSIS

Case report forms will be monitored and collected by ICON. All monitored eCRFs will be sent to the Data Management group at ICON and processed according to the ICON Study Specific Procedure SSP DM-48480001.01 Data Management Plan (DMP). The DMP describes eCRF data processing, edit checks, data query management, medical dictionary coding, SAE reconciliation, data transfers, and data quality review through database lock or any necessary reopening of the database. After database lock, the data will be retrieved from the database using SAS® version 9.4 or higher.

6 PHARMACOKINETIC ASSESSMENTS

6.1 Pharmacokinetic Assessments

6.1.1 Pharmacokinetic Analysis

Pharmacokinetic parameters will be calculated from the plasma concentration-time data using noncompartmental techniques (Phoenix WinNonlin®, Build 8.0.0.3176 or higher, Certara L.P. (Pharsight), St. Louis, MO) and actual sampling times. PK parameters will also be determined using the urine concentration data collected over 48 hours after dosing (Cohort A4 and A5).

For subjects in Part C, a Day 7 lumbar puncture will be done to collect CSF for AT-007 measurement using a qualified assay.

The PK parameters in Table 6-1will be determined for the SAD parts of the study (i.e. Part A the single dose period of Part D and E).

Table 6-1: Pharmacokinetic Parameters of AT-007 After a Single Dose in Healthy Subjects (Part A) and Subjects with Classic Galactosemia (Single Ascending Dose Period of Part D and E)

Parameter	Definition
C_{max}	Maximum concentration, determined directly from individual concentration time data
T_{max}	Time of the maximum concentration
λ_z	The observed terminal rate constant; estimated by linear regression through at least 3 data points in the terminal phase of the log concentration-time profile
$T_{1/2}$	The observed terminal half-life, calculated as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$
AUC_{last}	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity; calculated as: $AUC_{\inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$
AUC_{Extrap} (%)	The percentage of AUC_{inf} based on extrapolation
C_{last}	The last quantifiable concentration determined directly from individual concentration-time data
T_{last}	Time of the last quantifiable concentration
CL/F	Clearance after extravascular administration, calculated as: $CL/F = Dose/AUC_{inf}$
Vz/F	Volume of distribution in the terminal phase, calculated as: $Vz/F = (CL/F)/\lambda_z$

The PK parameters in Table 6-2will be determined for the MAD parts of the study (ie, Parts B, C, and multiple dosing period in Parts D and E, and Part D Extension).

Table 6-2: Pharmacokinetic Parameters of AT-007 During Multiple Dosing in Healthy Subjects (Parts B and C) and Subjects with Galactosemia (Multiple Ascending Dose Period of Parts D and E and Part D Extension)

PK Parameter	Definition
C_{max}	Maximum concentration, determined directly from individual concentration time data (Day 1 and Day of Last Dose)
T_{max}	Time of the maximum concentration (Day 1 and Day of Last Dose)
λ_z	The observed terminal rate constant; estimated by linear regression through at least 3 data points in the terminal phase of the log concentration-time profile (Day of Last Dose only)
$T_{1/2}$	The observed terminal half-life, calculated as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$ (Day of Last Dose only)
AUC_{tau}	Area under the concentration-time curve during the 24-hour dosing interval; calculated using the linear trapezoidal rule (Day 1 and Day of Last Dose) Note: If quantifiable data are not observed through 24 h postdose, AUC_{tau} will be estimated using extrapolation (from the time of the last reported concentration to 24 h) and AUC_{last} will also be reported.
AUC_{last}	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule (Day of Last Dose; Day 1 if quantifiable data are not observed through 24 h postdose)
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity; calculated as: $AUC_{inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$ (Day of Last Dose only)
AUC_{Extrap} (%)	The percentage of AUC_{inf} based on extrapolation (Day of Last Dose only)
C_{last}	The last quantifiable concentration determined directly from individual concentration-time data (Day 1 and Day of Last Dose)
T_{last}	Time of the last quantifiable concentration (Day 1 and Day of Last Dose)
CL/F	Clearance after extravascular administration, calculated as: $CL/F = Dose/AUC_{tau\ (Day\ X)}$, where Day X = Day of Last Dose and Dose is the actual dose administered (mg/kg x kg). (Day of Last Dose only) Note: CL/F/kg may also be reported
Vz/F	Volume of distribution in the terminal phase, calculated as: $Vz/F = (CL/F)/\lambda_z$ (Day of Last Dose only) Note: Vz/F/kg may also be reported
Rac	The accumulation ratio during multiple dose administration, based on C_{max} and AUC_{tau}; calculated as: Rac (AUC_{tau}) = AUC_{tau} (Day X) / AUC_{tau} (Day 1) Rac (C_{max}) = C_{max} (Day X) / AUC_{tau} (Day 1) Note: Rac will be tabulated with the pharmacokinetic parameters on Day X. Note: Day X = Day of Last Dose

Note: Day of Last Dose is Day 7 in Parts B and C, Day 32 in in the MAD portion of Part D and E, and Day 90 in Part D Extension

Urine concentration data from Part A4, A5 and Part D3 will be used to determine the following parameters:

Ae	Amount excreted into urine, calculated over 72 hours
Fe%	Fraction of drug excreted in urine over 72 hours, calculated as Ae/dose X 100%

Only data points that describe the terminal elimination log-linear decline will be used in the regression equation for calculation of terminal elimination phase rate constant; C_{max} and any data point in the distribution phase are not included in the calculation. A minimum of 3 points will be used for determination of the terminal elimination phase rate constant. A general rule of adjusted R^2 >0.80 will be considered as acceptable for calculation of the terminal elimination phase rate constant. If the adjusted R^2 falls below 0.80, then the terminal elimination phase rate constant will be reported as not determined (ND) and that subject's λ_z, $t_{1/2}$, AUC_{inf}, CL/F, and Vz/F will be reported as ND in the appropriate listings. If the extrapolated AUC_{inf} is more than 20%, then AUC_{inf}, CL/F and Vz/F will be listed but excluded from descriptive summaries and statistical analysis.

6.1.2 Treatment of Outliers

Individual concentration-time points, if considered anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of the available documentation. Any such exclusion will be discussed with the sponsor and clearly outlined in the study report.

Entire individual treatment profiles for a subject may be excluded following review of the available documentation and discussion with the sponsor. However, results of analysis with and without the excluded profiles may be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

Any anomalous concentration values observed at predose will be identified and discussed in the CSR. Pharmacokinetic parameters will be computed if the predose concentration value is not greater than 5% of C_{max} for a given subject. If the predose concentration value is greater than 5% of C_{max} concentration on Day 1, then the PK parameter data for the given subject will be listed but excluded from the PK summaries and statistical analysis. Subjects who experience emesis during the course of the study will be excluded from the PK summaries and statistical analysis if vomiting occurs at or before 2 times median T_{max}.

6.1.3 Non-Quantifiable Concentrations

All concentration values reported as no results (not collected or not determined) values will be treated as missing. For the calculation of concentration summaries, all concentrations below the quantifiable limit (BLQ) will be treated as 0. For the purpose of calculating PK parameters and plotting mean and individual concentration-time profiles, concentrations below the lower limit of quantitation (BLQ) will be treated as zero prior to the the first quantifiable concentration; subsequent values BLQ concentrations will be treated as “missing.”

7 STATISTICAL METHODS

7.1 General

The statistical analysis will be conducted following the principles specified in the International Council for Harmonization (ICH), formerly the International Conference of Harmonization, Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

All statistical tabulations and analyses will be done using SAS®, Version 9.4 or higher.

Unless otherwise noted, for continuous outcomes, descriptive statistics will include the number of subjects, mean, 95% confidence interval (CI) for the mean, standard deviation (SD), median, minimum (Min), maximum (Max), 25th percentile, and 75th percentile. For categorical outcomes, the number and percentage of subjects will be presented. Descriptive statistics will generally be presented by AT-007 group. For summaries of continuous AT-007 PK concentration and parameter data, the coefficient of variation will also be presented.

In the data listings, study day relative to first dose of study drug may be presented. Study day relative to first dose will be calculated as: event date - first dose date (+ 1 if event day ≥ first dose date).

For analyses of change from baseline, baseline will generally be defined as the predose assessment on Day 1 or Day -1, as scheduled. If this value is unavailable, the last non-missing value prior to dosing will be used.

All data from the CRFs, as well as any derived variables, will be presented in data listings.

For safety summaries, the unscheduled and repeat assessments will not be summarized; however, all results will be included in the data listing.

Unless otherwise noted, the analyses will be done by Parts and actual treatment/dose received.

Three sets of outputs will be created: One set for Part A, B, C, and D, one set for Part D Extension and one set for Part E(as detailed below). In creating tables in 3 sets, parts already completed can be analyzed earlier than the whole study has been completed.

Study Part	Study Population	Design	Table
Part A	Healthy Adult Subjects	SAD	Parts A, B, C, and D will be summarized under 1st set
Part B	Healthy Adult Subjects	MAD (QD for 7 days)	
Part C	Healthy Adult Subjects	MAD (QD for 7 days)	
Part D	Adult Subjects with CG	SAD, 5-day washout, MAD (QD for 27 days)	
Part D Extension	Adult Subjects with CG	MAD (QD for 90 Days)	Part D Extension will be summarized under 2nd set
Part E	Adult Subjects with GALK-deficient Galactosemia	SAD, 5-day washout, MAD (QD for 27 days)	Part E will be summarized under 3rd set

7.2 Handling of Dropouts or Missing Data

Missing observations will be treated as missing at random, and Missing data will not be imputed.

7.3 Multicenter Studies

For Part A, B and C, this is a monocenter study. For Part D, E and D Extension, this is a multicenter study. For the purpose of PK and safety analysis data across sites will be pooled together and presented per dose group.

7.4 Examination of Subgroups

For Parts D, E and D Extension, blood galactitol changes will be analyzed based on below subgroup categories if data permit:

- Gender: Male / Female
- Age: < 21 years / >= 21 years and < 30 years / >= 30 years
- BMI: <22 kg/m^2 / 22-25 kg/m^2 / >25 kg/m^2
- Enzyme activity: ≤0.1%, 0.1-0.4%, >0.4%

Additionally forest plot will be displayed for Part D and E at Day 32 and for Part D extension at Day 90/EOT for blood galactitol results.

7.5 Analysis Populations

Two analysis populations will be defined:

- Screened Population (SP): The screened population will consist of all subjects who are screened independent if they were eligible or not.

- Randomized Population: The randomized population will consist of all subjects who are randomized to any cohort.
- Safety Population: The safety population will consist of all subjects who are randomized and receive at least 1 dose of study drug. All analyses will be performed according to treatment received. This population will be used for all analyses of safety data and biomarker data.
- Pharmacokinetic Population: The PK population will consist of all subjects who receive at least 1 dose of AT-007 and have sufficient concentration-time data to estimate at least one of the planned PK parameters, as determined by the study Pharmacokineticist. This population will be used for all analyses of PK.

For Parts D and E, the safety and PK population may be defined separately for the SAD and MAD periods.

7.6 Subject Accountability

Summaries of analysis populations and subject disposition will be presented by parts and will contain the following information:

- Number and percentage of subjects screened and screened failure
- Number and percentage of subjects enrolled
- Number and percentage of subjects randomized
- Number and percent of subjects who are dosed
- Number and percent of subjects who completed the study
- Number and percent of subjects who discontinued from study early and reason for early discontinuation
- Number and percent of subjects in each population

Subject disposition will be presented in listings using screened population.

7.7 Drug Exposure and Compliance

A data listing, by subject, containing study drug dosing and dosing errors, if any, will be provided.

For Parts D, E and D Extension, summary of compliance, including compliance categories of less than 80%, between 80% and 120%, and greater than 120%, will be reported by treatment group and study parts based on Safety Population. Compliance data will also be listed by study participants for each Part and Cohort.

7.8 Protocol Deviation Reporting

Important protocol deviations (IPD) will be identified and classified by the deviation types in the IPD document.

A listing of all IPDs identified will be presented for all subjects based on the safety population (SP) and will include the deviation type and description.

7.9 Subject Demographics and Baseline Characteristics

Demographic and baseline characteristics (including age, sex, race, ethnicity, weight, height, and body mass index) will be summarized using descriptive statistics by parts and cohorts based on safety population. Also disease characteristics will be summarized i.e. Blood Galactitol, Urine Galactitol, Blood Galactose, Blood GAL-1P, Blood Galactonate and Brain galactitol (MRS) for Part D, D extension and Part E. No formal statistical analyses will be performed.

The medical history of all subjects as well as the neurological history of subjects with CG and subjects with GALK-deficient Galactosemia will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 or higher. The number and percentage of subjects with abnormal findings in each SOC and each PT will be summarized by parts and cohorts based on safety population.

7.10 Analysis of Pharmacokinetic Data

Plasma and urine PK parameters of AT-007 (including metabolites if determined) will be summarized by dose level and part using descriptive statistics. CSF concentration of AT-007 for cohort C1, C2 and C3 will be summarized by Cohort.

The PK Population will be used for all listings, concentration summaries, PK summaries and statistical analysis. The individual sampling and subject concentration-time for plasma and CSF concentrations will be listed and displayed graphically (plasma only) on linear and semi-log scales. The plasma and CSF drug concentrations will be summarized descriptively by nominal time point, Part and Cohort in tabular and graphical (plasma only) formats (linear and semi-log scales). The amount of AT-007 in urine will be listed by subject and summarized by nominal collection interval, Part and Cohort. Summary statistics will include: n, arithmetic mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, maximum, and geometric mean (GM).

Pharmacokinetic parameters for AT-007 will be listed and summarized descriptively by Part, Cohort and Day, including n, arithmetic mean, SD, minimum, median, maximum, CV(%),GM, geometric SD, geometric CV%; geometric CV% calculated as the square root of the exponentiated SD of the natural log transformed data (SQRT(exp(sln^2)-1)), where appropriate. For t_{max}, only n, minimum, median, and maximum will be reported.

The dose proportionality of the primary PK parameters, AUC_{last}, AUC_{inf} and C_{max} after single dose (Part A, Part D and E, single dose portion) and $AUC_{tau,}$ and C_{max} for single and multiple doses, over the administered dose range will be investigated using the following power model,

log(PK parameter) = a + b * log(dose), where a is the intercept and b is the slope.

Dose proportionality will be assessed for each part of the study separately. Furthermore, pooling of data across all parts at same dose level may be used to access overall dose proportionality for the entire range of the administered doses. However, pooling will be based on either the Day 1 dose or following multiple doses.

Each log-transformed PK parameter will be fit with a power model with a fixed effect term for log-transformed dose. For each PK parameter, the slope and associated 90% CI will be presented. A minimum of 3 values per dose cohort must be available for a given parameter to estimate dose proportionality with the power model.

The following is the example SAS code can be implemented:

```
PROC MIXED DATA=PKPARM;
     BY PARAMCD;
     MODEL LOGPK= LOGDOSE / SOLUTION CL DDFM=KR;
     ESTIMATE "SLOPE" LOGDOSE 1 / ALPHA = 0.1 CL;
     ESTIMATE "INTERCEPT" INTERCEPT 1 / ALPHA = 0.1 CL;
     ODS OUTPUT SOLUTIONF =SOLNF;
     ODS OUTPUT ESTIMATES =ESTIMATE;
RUN;
```

7.11 Analysis of Biomarker Data

For Part D and E:

- Plasma Galactitol, the analysis should evaluate maximum galactitol reduction (absolute change and percent change) defined as the lowest galactitol value on any of the following days of treatment (Day 1, Day 12, Day 32) vs. Galactitol level at baseline (calculated as a mean of 2 pre-dose measurements, such as Day -1 and Time-0 on Day 1 of dosing)
- Plasma Galactose, the analysis should evaluate the pre-dose galactose level on Day 12 and Day 32 vs. Galactose level at baseline (evaluated as a mean 2 pre-dose measurement, such as Day -1 and Time-0 on Day 1 of dosing)
- Whole blood Gal-1P the analysis should evaluate the pre-dose Gal-1P on Day 12 and Day 32 vs. Gal-1P level at baseline (evaluated as a mean 2 pre-dose measurement, such as Day -1 and Time-0 on Day 1 of dosing)

In addition, plasma galactitol changes will be analyzed based on below subgroup categories if data permit:

- Gender: Male / Female
- Age: < 21 years / >= 21 years and < 30 years / >= 30 years
- BMI: <22 kg/m^2 / 22-25 kg/m^2 / >25 kg/m^2
- Enzyme activity: <0.1%, 0.1-0.4%, >0.4%

Urine galactitol levels will be provided as tabulated values and they will not be subjected to a formal analysis.

For genetic analysis, allele specific mutations will be reported as tabulated information

7.12 Analysis of Safety Data

7.12.1 General

The evaluation of safety will be based on the occurrence of treatment-emergent adverse events (TEAEs); discontinuations from study drug and/or the study because of AEs; clinical laboratory test results, physical examination findings, vital sign evaluations, and 12-lead ECGs results. All safety endpoints will be summarized descriptively. No statistical inference will be applied to the safety endpoints. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data.

Safety measures including the baseline data will be summarized descriptively within each part (Parts A, B, C, D, E and D Extension) of the study by each cohort (dose level of AT-007 and placebo), pooled AT-007 group, and pooled placebo group.

For analyses of change from baseline, baseline will generally be defined as the predose assessment on Day 1 or Day -1, as scheduled. If this value is unavailable, the last nonmissing value prior to dosing will be used. Otherwise, missing observations will be treated as missing at random, and no data imputation will be performed. All data from the eCRFs, as well as any derived variables, will be presented in data listings.

7.12.2 Adverse Events

All AEs will be coded to system organ class (SOC) and preferred term (PT) using MedDRA, Version 22.0 or later, and presented by subject data listings.

A treatment-emergent AE (TEAE) is defined as an AE that is not present prior to cohort with investigational product, but appeared following cohort or was present at cohort initiation but worsened during cohort. An AE that was present at cohort initiation but resolved and then

reappeared while the subject was on cohort is a TEAE (regardless of the intensity of the AE when the cohort was initiated). Programmatically, an AE will be classified as a TEAE if the start date and time occurs on or after the start date and time of first investigational product dosing.

The TEAE will be assigned to treatment based on the start date/time of occurrence.

The overall incidence of TEAEs (number and percentage of subjects) as well as the number of events will be summarized by cohort, severity grade, SAEs, causally related TEAE and SAEs, TEAEs leading to study or treatment discontinuation, life-threatening SAEs, and SAEs resulting in death.

The TEAEs will be summarized and tabulated at both the subject (number [%] of subjects) and event (number of events) level:

- By cohort, SOC, and PT
- By cohort, SOC, PT, and maximum reported severity
- By cohort, SOC, PT, and closest relationship to study drug

For the incidence at the subject level by SOC and PT, if a subject experiences more than 1 event within the same SOC and PT, only 1 occurrence will be included in the incidence.

For the incidence at the subject level by SOC, PT, and severity, if a subject experiences more than 1 event within the same SOC and PT, only the highest severity grade will be included in the incidence.

For the incidence at the subject level by SOC, PT and relationship to study drug; if a subject experiences more than 1 event within the same SOC and PT, only the most closely related occurrence will be included in the incidence.

Any SAEs, AEs with outcome of deaths, or AEs resulting in discontinuation of study or cohort will be presented.

7.12.3 Clinical Laboratory Assessments

Observed and change from baseline of continuous clinical laboratory values (serum chemistry, hematology, coagulation, and urinalysis) for each parameter will be summarized by Part and cohort at each scheduled nominal time point. The number and percentage of subjects with shift changes from baseline based on the laboratory normal ranges will be tabulated. Laboratory data will be listed by subject at each time point. Clinical laboratory values that are out of normal ranges will be presented in a separate listing. Urinalysis laboratory tests will be presented in data listings only.

7.12.4 Vital Signs

Vital signs data will be listed by subject at each nominal time point. Observed and change from baseline vital signs values will be summarized by part and cohort at each nominal time point for SP.

7.12.5 Electrocardiograms

Observed values and change form baseline of 12-lead ECG parameters (HR, RR, PR, QRS, QT, and QTcF intervals) will be summarized descriptively by Part and cohort at each scheduled time point collected for SP. Individual ECG data will be listed for SP.

7.12.6 Physical Examinations

Physical examination findings will be presented in a subject listing for SP.

7.12.7 Prior and Concomitant Medications

Prior and concomitant medications will be summarized separately by the World Health Organization Drug Dictionary (Version March 2016 or later) and classified according to ATC codes levels 2 (therapeutic sublevel) and preferred name . Prior and concomitant medication data will be listed for each part, each cohort/dose using safety population.

7.13 Sample Size

No formal sample size calculation is required. The approximate sample size (up to 40 healthy subjects in Part A, up to 40 healthy subjects in Parts B and C combined, up to 34 subjects with CG in Part D and Part D Extension combined if no subject participates in both, and up to 18 subjects with GALK-deficient Galactosemia in Part E) is not based on statistical considerations. The number of subjects is typical for Phase 1 studies of this type and is adequate to meet study objectives.

The number of cohorts and/or total number of subjects may increase if the PK data reveal an insufficient exposure at 40 mg/kg. In Parts D and E, the overall number of subjects per cohort may be increased up to 8 subjects to address any potential lost-to-follow-up among subjects treated with either placebo or AT-007. In Parts D and E, subjects treated with study drug (placebo or AT-007) in a cohort may be randomized to treatment in another cohort (separate consent required) within the same Part (assuming subject had no safety or tolerability issues in the prior cohort) as long as there is a washout period ≥5 days between the last dose in a cohort and the first dose in the next cohort. Subject to certain timing considerations, Part D subjects may also participate in Part D Extension (separate consent required).

7.14 Interim Analysis

No interim analysis will be performed.

But within each part (A, B, C, D, E and D Extension) of the study, the Safety Review Committee will review safety (including AE, laboratory, physical examination, vital signs, and ECG data) through Day 3 in Part A, Day 8 in Parts B and C, and Day 12 in Parts D and E, respectively for each cohort and provide a recommendation to proceed or not to proceed to the next cohort as well as the dose level for AT-007. The AT-007 dose level may be increased, decreased, or repeated from one cohort to the next.

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7.15 General Conventions for Tables, Listings and Figures

Tables and listings will be presented in landscape mode with minimum of 3/4" bound edge margin and 3/8" other margins on 8.5" x 11" paper.

Times new roman font size of no less than 8 point will be used for tables and listings.

A source line will be included on the bottom of each page of all tables and listings. It will contain the SAS code program name and the run date and time.

Each variable is recorded to a specific number of decimal places. If the raw data is presented with varying precision, then the least precise value will be considered as the data precision.

For summary tables, unless otherwise specified, the number of decimal places provided in the SAS output will be based on the accuracy of the least accurate value in the raw data as follows:

n	integer
Arithmetic mean	1 decimal place more than the least accurate number in the raw data
SD	2 decimal place more than the least accurate number in the raw data
CV(%)	2 decimal places
Geometric mean	1 decimal place more than the least accurate number in the raw data
Median	1 decimal place more than the least accurate number in the raw data
Percentiles	1 decimal place more than the least accurate number in the raw data
Minimum	same number of decimal places as raw data
Maximum	same number of decimal places as raw data
Confidence interval	same number of decimals as the associated statistic
Geometric mean ratio	2 decimal places

8 TABLES, FIGURES, AND LISTINGS

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