GTI1401

A Multi-Center, Open-Label, Phase I/II Study to Evaluate the Safety and Pharmacokinetics of Weekly Intravenous Infusions of Alpha-1 MP in Japanese Subjects with α_1-Antitrypsin Deficiency

Protocol Version: GTI1401 Version 1.5J (05July2016)

GTI1401-OLE

A Multi-Center, Open-Label Study to Evaluate the Long-term Safety of Weekly Intravenous Infusions of Alpha-1 MP in Japanese Subjects with α_1-Antitrypsin Deficiency

Protocol Version: GTI1401-OLE Version 1.3J (07July2016)

Statistical Analysis Plan

Version 1.0 / 21MAR2017
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Upon review of this document, including table, listing, and figure shells, the undersigned approves the statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing, and figure production can begin.

Approved by: [redacted], PhD Date: MAR/21/2017

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Date: Mar/ 23/ 2017

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Date: 3/23/2017

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LIST OF ABBREVIATIONS

AATD	$Alpha_1$-antitrypsin deficiency
ADR	Adverse drug reaction
AE	Adverse event
Alpha-1 MP	$Alpha_1$-proteinase inhibitor (human), modified process
$Alpha_1$-PI	$Alpha_1$-proteinase inhibitor
ALT	Alanine aminotransferase
AST	Aspartate transaminase
ATS	American Thoracic Society
AUC	Area under the concentration-time curve
BLQ	Below limit of quantification
C_{max}	Maximum concentration
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CV	Coefficient of variation
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
MedDRA®	Medical Dictionary for Regulatory Activities
NE	Neutrophil elastase
PFT	Pulmonary Function Test
PI*MM	Proteinase inhibitor homozygote for normal M allele
PI*(null)(null)	Proteinase inhibitor homozygote for (null) allele
PI*SZ	Proteinase inhibitor heterozygote for S and Z deficiency alleles

PI*Z	Proteinase inhibitor Z deficiency allele
PI*ZZ	Proteinase inhibitor homozygote for Z deficiency allele
pH	Potential of hydrogen; acidity/alkalinity measure
PK	Pharmacokinetics
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
t½	Terminal half-life
TEAE	Treatment-emergent adverse event
tmax	Time to reach Cmax
US	United States
WHO-DD	World health organization drug dictionary

1 Purpose of the Analysis

The purpose of this statistical analysis plan (SAP) is to outline the planned analyses to support the completion of the clinical study report (CSR) for protocol GTI1401 and GTI1401-OLE. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not identified or defined in this SAP may be performed to support the clinical development program. Any post hoc or unplanned analyses performed and not identified in this SAP will be documented in the respective CSR.

2 Introduction

Alpha$_1$-antitrypsin deficiency (AATD) is a genetic disorder in which mutations of the SERPINA1 gene (a member of the SERPIN, serine protease inhibitor gene family) lead to a reduced serum level of the serine protease inhibitor called alpha$_1$-proteinase inhibitor (alpha$_1$-PI) or, historically, alpha$_1$-antitrypsin. AATD manifests clinically as pulmonary emphysema, chronic obstructive pulmonary disease (COPD), and liver cirrhosis.

The most frequent mutation causing severe AATD is called PI*Z and was first described in a Swedish patient with emphysema. PI*MM (normal) individuals have serum alpha$_1$-PI levels in the range of 20 to 53 μM; however, PI*ZZ (homozygous abnormal) individuals with AATD have serum alpha$_1$-PI levels in the range of 2 to 10.2 μM. The estimated world-wide prevalence of PI*ZZ and PI*SZ (heterozygous abnormal) individuals is approximately 163,700 and 903,000, respectively.

Like other hereditary disorders, AATD is relatively rare (e.g., has orphan drug designation); however, it is extremely rare among Asians. In 2000, a survey supported by the Japanese Ministry of Health and Welfare identified only 16 individuals in Japan with documented AATD. AATD in Japanese patients exhibits unique features compared to AATD in Caucasians, including the lack of a PI*Z variant and a high incidence of the S_{iiyama} deficiency AATD variant. In Japanese patients homozygous for the S_{iiyama} variant, serum alpha$_1$-PI levels are in the range of 2.1 to 7.7 μM. Japanese normal individuals have serum alpha$_1$-PI levels in the range of 21 to 34 μM (94 to 150 mg/dL as measured by nephelometry, which is used as the laboratory test standard values).

Augmentation therapy with intravenous (IV) alpha$_1$-PI is administered in patients with AATD to increase the low serum concentrations in this patient population. This usage is intended to bolster the protective protease inhibitory shield against increased numbers of lung neutrophils releasing increased concentrations of NE, leading to a corrected protease: antiprotease imbalance. The restored antiprotease shield then protects the lung from elastolytic damage and slows the development of pulmonary emphysema.

Alpha$_1$-PI (human), Prolastin®, was licensed for use as augmentation therapy for AATD, at a dose of 60 mg/kg weekly, in the United States (US) in 1987 and in Germany in 1988. To date, Prolastin® has been approved in 20 countries including the United States and

European countries. Subsequently, Grifols incorporated modifications into the Prolastin manufacturing process to produce alpha$_1$-PI (human), modified process (Alpha-1 MP). This modified process results in an increased yield of alpha$_1$-PI and a product with twice the alpha$_1$-PI concentration with an improved pathogen safety profile and higher purity compared to Prolastin. Alpha-1 MP is approved for 60 mg/kg weekly IV administration in the US, Canada, Argentina, Columbia, Turkey, Chile and Australia for the treatment of patients with severe AATD and clinically evident emphysema under the trade name Prolastin®-C.

Japanese patients with AATD exhibit very different genotypes of AATD compared to the rest of the world, and the number of Japanese patients with AATD is extremely small. These subjects can exhibit symptoms of emphysema-typed COPD and therefore, will have clinically evident emphysema and along with alpha$_1$-PI deficiency. The safety and PK of augmentation therapy with Alpha-1 MP to increase serum alpha$_1$-PI levels has not been evaluated in Japanese patients with AATD. Thus, Grifols Therapeutics Inc. and Grifols Japan K.K. is conducting a study to assess the safety and PK of 60 mg/kg Alpha-1 MP administered by weekly IV infusions over 8 weeks in Japanese subjects with AATD.

3 Objectives

3.1 Primary Objectives

The primary objective of GTI1401 study is to evaluate the safety of 60 mg/kg Alpha-1 MP administered by weekly IV infusions over eight weeks in Japanese subjects with AATD.

The primary objective of GTI1401-OLE study is to evaluate the long-term safety of 60 mg/kg Alpha-1 MP administered by weekly IV infusions for approximately one year or longer (can be renewed annually with the consent of the subjects) in adult subjects with AATD in Japan.

3.2 Secondary Objectives

The secondary objective of GTI1401 study is to evaluate the trough level of total alpha$_1$-PI for weekly IV infusions of 60 mg/kg Alpha-1 MP in Japanese subjects with AATD.

The secondary objective of GTI1401-OLE study is not set up.

3.3 Exploratory Objectives

The exploratory objective of GTI1401 is to measure the following PK parameters for Alpha$_1$-PI at steady state at the end of the 8-week treatment period.

- $AUC_{0\text{-}7\ days}$
  Area under the concentration-time curve (AUC) from Day 0 to Day 7, calculated at steady state at the end of the 8-week treatment period.

- C_{max}
  Maximum concentration

- t_{max}
  The observed time to reach C_{max}

- $t_{½}$
  Terminal half-life

The exploratory objective of GTI1401-OLE is to perform CT scan (densitometry) at Ext Week 52. The CT scan data will be accumulated for the future evaluation of lung density.

- CT scan (densitometry)
  Note: Subjects will undergo CT scanning for diagnosis of clinically apparent pulmonary emphysema in GTI1401 study. This CT scan data will also serve as the baseline measurement of lung density for GTI1401-OLE study.

4 Investigational Plan

4.1 Study Design and Plan

GTI1401 study is a multi-center, open-label, trial to evaluate the safety and PK of weekly IV infusions of 60 mg/kg Alpha-1 MP in Japanese subjects with AATD. At least three adult subjects will be enrolled in the study. The study consists of an up to three-week Screening Period, and an eight-week open-label Treatment Period including a one-week PK Assessment Period after the last infusion. At the Week 9 visit when the PK evaluation period is completed, subjects will be asked whether they would like to participate in an extension trial (GTI1401-OLE). For subjects not intending to participate in the extension trial, the date of follow-up/study completion visit (30 days [4 weeks] after the last dose of the investigational drug) will be arranged. The total duration of study participation for subjects who complete the study will be up to 14 weeks.

After providing informed consent at the Screening Visit, subjects will be evaluated for study eligibility during the Screening Period (up to three weeks); for study inclusion and exclusion criteria. Eligible subjects will enter the eight-week Treatment Period to receive a total of eight weekly IV infusions of 60 mg/kg Alpha-1 MP; subjects will receive their first infusion of Alpha-1 MP at the Week 1 (Baseline) Visit. During the Treatment Period, weekly infusions of Alpha-1 MP will be performed at the study site during scheduled study visits at Weeks 1 (Baseline), 2, 3, 4, 5, 6, 7, and 8. Subjects will receive their last infusion of Alpha-1 MP at the Week 8 Visit and will then enter the one-week

PK Assessment Period. During the PK Assessment Period, subjects have a last PK blood sampling study visit at Week 9. A Follow-Up/Final Visit (30 days [4 weeks] post last study drug infusion) will occur for subjects who will not participate in Study GTI1401-OLE.

All subjects will have a blood sample collected at Weeks 1 (Baseline), 7, and 8 (prior to the infusion of Alpha-1 MP) and Week 9 which will be used for the measurement of trough $alpha_1$-PI levels.

Blood samples for PK parameters will be collected beginning at Week 8 and the collection of blood samples will extend into Week 9. The pre-infusion serial PK sample at Week 8 and the last serial PK sample (7 days after the Week 8 infusion) at Week 9 will also serve as trough blood samples for Weeks 8 and 9. The specific timing of all 10 serial blood samples includes:

- Immediately prior to infusion
- Immediately after infusion completion (after sodium chloride [NaCl] flush) (0 hour)
- 15 minutes after infusion completion
- 2 hours after infusion completion
- 4 hours after infusion completion
- 8 hours after infusion completion
- 24±4 hours (1 day after infusion completion)
- 48±4 hours (2 days after infusion completion)
- 120 hours ± 1 day (5 days after infusion completion)
- 168 hours ± 1 day (7 days after infusion completion) (Week 9 Visit)

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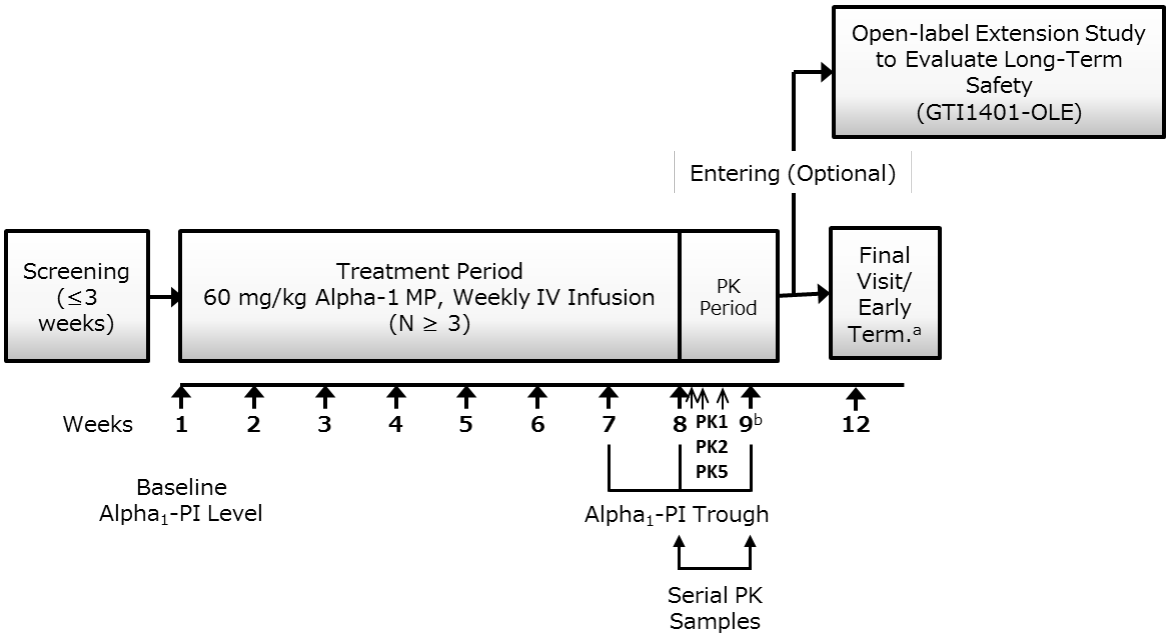
At the Week 9 visit, subjects have the option to participate in an open-label extension (OLE) study (GTI1401-OLE) in which subjects, if they opt to enroll, will continue to receive 60 mg/kg Alpha-1 MP for at least another year (with the optional subsequent annual extensions) to assess the long-term safety of Alpha-1 MP. Week 9 of the GTI1401 study is also the first week of the extension study (GTI1401-OLE). If subjects do not opt to participate in Study GTI140-OLE, they will come back to the clinic 30 days (4 weeks) after the last Alpha-1 MP infusion for the Follow-Up/End of Study Visit (Week 12).

A schematic of the overall study design is shown in Figure 1 below. The schedule of events for GTI1401 and GTI1401-OLE studies can be found in appendix 1 and appendix 2.



[a] Final Visit/Early Termination = Follow-up/Final Evaluation Visit. Subjects who discontinue early from the study will need to complete this study visit 30days (4 weeks) after the last study drug infusion.
[b] At the Week 9 Visit, subjects will be given the option to participate in the GTI1401-OLE. If they are enrolled in Study GTI1401-OLE, the Week 9 visit will be their End of Study Visit of GTI1401 study.

Figure 1 Overall Study Schema

4.2 Study Variables

No efficacy variables will be assessed for the studies. The variables to be assessed for GTI1401 and GTI1401-OLE studies are as follows:

- Adverse events, ADRs, serious AEs (SAEs), and discontinuations due to AEs or SAEs
- Vital signs (heart rate, blood pressure, respiratory rate, and temperature)
- COPD exacerbations
- Pulmonary function tests :
  - Forced Expiratory Volume in 1 second (FEV_1)
  - Forced Vital Capacity (FVC)
- Clinical laboratory parameters:
  - Chemistry
  - Hematology
  - Urinalysis
- $Alpha_1$-PI trough level
- PK parameters (GTI1401 study only):
  - $AUC_{0\text{-}7\ days}$
  - C_{max}
  - t_{max}

- $t_{½}$
- CT scan (densitometry)

5 General Statistical Considerations

All analyses will be conducted using SAS Version 9.3 or higher.

Pharmacokinetic evaluations, descriptive statistical analysis of concentrations and PK parameters according to non-compartmental standard methods, as well as graphical representation of concentrations will be performed using the computer program Pharsight Phoenix WinNonlin (Version 6.1 or higher).

Unless otherwise specified, the results from GTI1401 and GTI1401-OLE will be presented separately.

Unless otherwise noted, for continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, minimum and maximum. For categorical variables, descriptive statistics will include counts and percentages per category.

5.1 PK Data Handling

For PK parameter estimation, the actual sample time instead of nominal time will be used. For the last time point (168 hours post infusion), if the actual time deviates from the scheduled time, the interpolation or extrapolation will be used to obtain the $AUC_{0\text{-}7days}$.

When BLQ values are recorded, adopt the half value of the readable numeric value (2.5 mg/dL) for summarizing data.

5.2 Handling of Missing values

Missing values will not be imputed unless otherwise specified.

For Adverse Event
Any missing severity/relationship will be accounted as “worst case” as related in the tables.

5.3 Safety Data Handling

5.3.1 Definition of Baseline

Baseline evaluations will be those collected (non-missing) closest to and prior to the first study drug infusion, which will be conducted –within 21 days of Week 1. For both GTI1401 and GTI1401-OLE, the baseline is the baseline visit at Week 1 in GTI1401 study.
For Pulmonary Function Tests
Values collected at“PRE-BRONCHODILATOR” time-point in screening visit will be defined as baseline for “PRE-BRONCHODILATOR”. Also values collected at “POST-BRONCHODILATOR” time-point in screening visit will be defined as baseline for “POST-BRONCHODILATOR”.

5.3.2 Visit Windows for Safety Analyses

The date of all visits after the screening visit and the Week 1 (baseline) visit will be arranged within a time window of ± 1 day.

If an observation is missing at a specific scheduled visit, the value at that visit will be set to missing.

Visit recorded on CRF will be used as Analysis visit except Baseline visit.

5.3.3 Unscheduled Visit

Data collected as unscheduled visits will not be used for the tables but presented in the listing and subject data plot.

5.3.4 Follow-Up/End of Study Visit

30 days [4 weeks] after the completion of the last Alpha-1 MP infusion (Week 8) and 3 weeks after the Week 9 Visit, those subjects who do not participate in Study GTI1401-OLE will go to the clinic to complete a Follow-Up/End of Study Visit (Week 12). The Week 12 Visit should be scheduled at the protocol-specified study week relative to the date of the Week 1 (Baseline) Visit ± 1 day. The data collected during Follow-Up/End of Study Visit (Week 12) are included in Table and Listing for Safety Analysis and Concomitant Medication.

5.4 Sample Size

The targeted sample size is at least 3 subjects. Sample size was chosen based on clinical considerations and the number of available Japanese patients with AATD, not on a formal sample size calculation.

5.5 Rounding

In listings, data will be presented with the same precision as the original data; at the output creation stage, derived data will be rounded for presentation purposes.

For all summaries, the standard deviation will be presented to two decimal place greater than the original data, the mean and median will be presented to one decimal place greater than the original data and the minimum and maximum will be presented to the same number of decimal places as the original data.

For calculation of the proportion, one decimal place will be presented.

The rounding will be performed to the closest integer/first decimal using the common mid-point between the two consecutive values (e.g. 5.0 to 5.4 will be rounded to an integer of 5, and 5.5 to 5.9 will be rounded to an integer of 6)

Analysis Populations

- The All subjects screened will include all subjects during screening evaluations.
- The Safety population will include all subjects who receive any amount of Alpha-1 MP.
- The PK population (GTI1401 only) will include all subjects who receive Alpha-1 MP dose and have sufficient samples to calculate the PK parameters.

5.6 Denominator

Unless otherwise mentioned, denominator of percentage in each table will be the number of population designated in each table.

6 Subject Disposition

6.1 Summary Table of Subject Disposition		
Population	:	All subjects screened
Contents	:	• The number of all subjects screened • The number of all subjects dosed with Alpha-1 MP (Safety population) • The number and percentage of all subjects in PK population

6.2 Summary Table of Subjects Who Discontinue from the Study		
Population	:	Safety population
Contents	:	• The number and percentage of subjects who complete the study • The number and percentage of subjects who discontinue from the study by reason for discontinuation

Disposition status will be listed for all subjects. A listing will also be provided for screening failure subjects.

7 Protocol Deviations

7.1 Summary Table of Protocol Deviations		
Population	:	Safety population
Contents	:	The number and percentage of deviations by type and severity will be summarized. Deviations from the protocol will be identified during the study and discussed in the data review meeting. Protocol deviation is defined in "GTI1401 and OLE Protocol Deviation Guidance_24Oct2016_Biling_Clean.pdf" Listing of all deviation.

8 Demographics

8.1 Summary Table of Demographics		
Population	:	Safety population
Contents	:	For continuous variables, mean, standard deviation, median, and minimum/maximum will be provided. For categorical/qualitative data, frequency counts will be provided (For pregnancy status, the percentage of population is not included). Listing of following contests is provided separately. • Demographics (including alpha$_1$- Antitrypsin Deficiency history) • Smoking history • Medical history
Analysis variables	:	Contents, category and digit to be displayed are showed in the following table.

Contents	Category	Digits to be displayed
Sex	Male Female	
Age [years]		Integer
Race	Asian	
Weight [kg]		1 decimal place
Height [cm]		1 decimal place
Pregnancy status	NA (Males are included in this category) Negative Positive	
Smoking status	Never Former (>100 cigarettes or equivalent of tobacco in subject's lifetime) Current (not eligible for study)	
Total alpha$_1$-PI serum level at time of diagnosis [mg/dL]		1 decimal place
Time since First Diagnosis of alpha$_1$-Antitrypsin Deficiency [years]		1 decimal place
Best FEV_1 [L] at Baseline		2 decimal place
Best FVC [L] at Baseline		2 decimal place
FEV_1 Predicted [%]	0=< < 30 30=< < 70 70=< <100	
FEV_1 Predicted [%]		1 decimal place

15th Percentile of lung Density [g/L]		1 decimal place
Mean lung density [g/L]		1 decimal place

9 Treatments and Medications

9.1 Prior and Concomitant Medications

Definition of prior medication and concomitant medication for GTI 1401
Prior medications are defined as any medication which ended before the first infusion of study drug of GTI 1401.
Concomitant medications are defined as any medication which is started on or after the first infusion of study drug of GTI 1401 or any medication taken prior to the first infusion of study drug of GTI 1401 and continued after the first infusion of study drug of GTI 1401.

Definition concomitant medication for GTI 1401-OLE
Concomitant medications are defined as any medication which is started on or after the first infusion of study drug of GTI 1401-OLE or any medication taken prior to the first infusion of study drug of GTI 1401-OLE and continued after the first infusion of study drug of GTI 1401-OLE.

9.1.1 Summary Table of Prior and Concomitant Medication		
Population	:	Safety population
Contents	:	Summaries of all medications taken during the course of the study will be presented in tabular form and coded using ATC classification codes via the World Health Organization Drug classification Dictionary (WHO-DD). All medications will be summarized and sorted alphabetically by medication class (i.e., ATC level 2) and medication sub-class (i.e., ATC level 4). If the ATC level 4 term is missing, the ATC level 3 term will be used in the medication summary table and data listing. For the summary tables, if a subject has taken a concomitant medication more than once, the subject will be counted only once. All medications will be listed by subject. New medications starting after the first infusion will be indicated if the medication start date relative to the first study drug infusion is greater than 0 in the subject data listing.

9.2 Extent of Exposure

9.2.1 Summary Table of Drug Exposure		
Population	:	Safety population

Contents	:	Following contents regarding to exposure information are summarized. Digits to be displayed are showed in Table A • Treatment duration [Week] • Number of infusions received • Total volume infused [mL] • Volume infused per week [mL] • Infusion duration [Minute] Treatment duration in weeks is calculated as: $(\textit{The Last Dose Date} - \textit{The First Dose Date} + 7) / 7$ Volume infused per week is calculated as: *the Total Volume Infused [mL] / the Treatment Duration* [Week] Infusion Duration is calculated as: *the Infusion Stop Time [HH:MM] –* *the Infusion Start Time [HH:MM] + 1* For Infusion Duration, the summary statistics will be calculated for mean duration of each week. A list will be provided for Alpha-1 MP dose, volume prepared, and volume infused.

Table A:

Contents	Digits to be displayed
Treatment duration [week]	1 decimal place
Number of infusions received	Integer
Total volume infused [mL]	1 decimal place
Volume infused per week [mL]	1 decimal place
Infusion duration [minute]	Integer

9.2.2 Summary Table of Infusion Interruptions		
Population	:	Safety population
Contents	:	The number and percentage of infusion with interruptions will be summarized by analysis visit. Reasons for interruptions will be displayed in the listings.

9.3 Treatment Compliance

Treatment compliance will be calculated as:

$$\frac{Total\,Volume\,Infused}{Total\,Volume\ \ Prepared}\times 100\%$$

The total volume prepared is collected on the eCRF and is calculated based on the subject's weight at baseline.
The total volume prepared and dispensed by pharmacist is the intended dose volume a subject should be given based on the body weight.

Infusion compliance will be calculated as:

$$\frac{The\ Number\ of\ \ Actual\ Infusions}{The\ Number\ of\ \ Infusions\ Expected}\times 100\%$$

For subjects who drop out from the study early, the number of infusions expected will depend on the number of weeks the subjects are in the study.

9.3.1 Summary Table of Treatment Compliance		
Population	:	Safety population
Contents	:	Following contents will be displayed. • Summary of treatment compliance [%] • The number of subjects with treatment compliance >= 80% • Summary of infusion compliance [%] A listing of treatment compliance will be provided.

10 Exploratory Analysis

10.1 PK Analysis (GTI1401 only)

Alpha$_1$-Proteinase Inhibitor (alpha$_1$-PI) concentrations in serum will be measured by validated content assay. The concentration data will be presented and summarized. Time points recorded on CRF will be used as analysis time points.

Time Table for Week 8 and Week 9

Visit	Actual elapsed time (real-time)	Nominal time point (numeric version) (hours)	Scheduled time point

Visit	Actual elapsed time (real-time)	Nominal time point (numeric version) (hours)	Scheduled time point
Week 8	0	0	Immediately before the intravenous infusion
Week 8	0.30	0.25	Immediately after the intravenous infusion (after flushing the infusion line with physiological saline) (at 0 hours)
Week 8	0.55	0.5	15 minutes after completion of the intravenous infusion
Week 8	2.35	2.25	2 hours after completion of the intravenous infusion
Week 8	4.67	4.25	4 hours after completion of the intravenous infusion
Week 8	8.67	8.25	8 hours after completion of the intravenous infusion
Week 8	26.02	24.25	24 ± 4 hours (1 day after completion of the intravenous infusion)
Week 8	49.17	48.25	48 ± 4 hours (2 days after completion of the intravenous infusion)
Week 8	120.58	120.25	120 hours ± 1 day (5 days after completion of the intravenous infusion)
Week 9	169.50	168.25	168 hours ± 1 day (7 days after completion of the intravenous infusion) (Week 9)

10.1.1 Summary Table of $Alpha_1$-PI Concentrations		
Population	:	PK population
Contents	:	$Alpha_1$-PI concentrations will be summarized. The summaries will include n, mean (SD), coefficient of variation (%CV) (=SD/Arithmetic mean), median, minimum, maximum as well as geometric mean.
Digit	:	2 decimal places will be displayed for summary table of $alpha_1$-PI Concentrations.
Analysis	:	• Immediately before the intravenous infusion

visit		• Immediately after infusion completion (after sodium chloride [NaCl] flush) (0 hour) • 15 minutes after infusion completion • 2 hours after infusion completion • 4 hours after infusion completion • 8 hours after infusion completion • 24±4 hours (1 day after infusion completion) • 48±4 hours (2 days after infusion completion) • 120 hours ± 1 day (5 days after infusion completion) • 168 hours ± 1 day (7 days after infusion completion) (Week 9 Visit) Serum concentrations of alpha$_1$-PI determined by content assay will be presented in a listing by subject, study week, and scheduled or nominal time point. This data listing will provide details of all planned plasma collection time points (scheduled and nominal times as specified in Section 12.1), actual collection date and clock times and elapsed times from the start of the study drug infusion, as well as alpha$_1$-PI concentrations. Samples excluded from PK analysis will be flagged. The date/clock time for the start and completion of study drug infusion, the actual volume infused, and the actual dose infused (mg/kg) at Week 8 (PK assessment visit) will be presented in a separate listing.

10.1.2 Summary Table of Trough (pre-infusion) Levels (C_{min}) and mean C_{min}		
Population	:	PK population
Contents	:	This table include following contents. • Summary of trough (pre-infusion) levels (C_{min}) and mean C_{min} at steady state by week number (for C_{min}). Mean C_{min} calculated by the trough levels from weeks 7, 8, and 9 (exclude Week 1). • Number and Proportion with mean C_{min} of alpha$_1$-PI Concentration >= 50 mg/dL (=11.3 µM nearly equal to 11µM which is defined in ATS/ERS statement in 2003). A conversion factor of 0.226 based on the protein only molecular weight of 44.3 KDa for alpha$_1$-PI is used for converting mg/dL to µM (i.e., 1 mg/dL alpha$_1$-PI = 0.226 µM). No data imputations will be involved in the above concentration data listings, summaries, or figures. Trough (pre-infusion) levels (C_{min}) and mean C_{min} at steady state will

		be listed
Digit	:	2 decimal places will be displayed for summary table of C_{min}.
Analysis visit (only C_{min})	:	Week 1, Week 7, Week 8 and Week 9, *mean C_{min} = Average of C_{min} of each patient measured at Week 7, Week 8 and Week 9 (exclude Week 1)

10.1.3 Figures of Concentration Versus Time Curves of Individual Subjects		
Population	:	PK population
Contents	:	For concentration data, serum alpha$_1$-PI concentration versus time curves following 8 weeks of treatments in individual subjects will be presented in one figure with the actual elapsed time from the start of the study drug infusion plotted on the x-axis.

10.1.4 Figures of Concentration Versus Time Curves of All Subjects		
Population	:	PK population
Contents	:	For all subjects combined, mean or median plasma alpha$_1$-PI concentration versus time curves following 8 weeks of treatments will be presented in one figure with the nominal time plotted on the x-axis.

All serum alpha$_1$-PI concentration vs. time curves will be plotted on both linear and semi-log scales.

A spaghetti plot (on the linear scale only) will be presented for all subjects following 8 weeks of treatment for concentration values vs nominal time.

Calculation of PK Parameters

The pharmacokinetic profiles of alpha$_1$-PI following weekly administration of Alpha-1 MP will be characterized by pharmacokinetic parameters, including area under the curve (AUC) at steady state following 8 weeks of weekly infusions ($AUC_{0\text{-}7days}$), maximum concentration (C_{max}), time to first observed maximum concentration (t_{max}), and half-life ($t_{1/2}$), based on alpha$_1$-PI concentrations in serum measured using content assay.

All PK parameters will be calculated using non-compartmental methods with WinNonlin software (Pharsight Corporation, Cary NC).

The pharmacokinetic parameters of interest are determined as follows:

$AUC_{0\text{-}7days}$ area under the concentration vs. time curve at steady state over the weekly dosing interval (time 0 to 7 days), calculated by a combination of linear and logarithmic trapezoidal methods and expressed in the unit of concentration x time (mg·hr/dL). The linear trapezoidal method will be used for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations.

C_{max} the first observed peak serum alpha$_1$-PI concentration following drug infusion obtained directly from the experimental data without interpolation, expressed in concentration units (mg/dL).

t_{max} the observed time to reach peak serum alpha$_1$-PI concentration obtained directly from the experimental data without interpolation, expressed in time units (hour). If there are more than one maximum observed concentration, the t_{max} is the time to the first observed peak concentration.

$t_{1/2}$ the terminal half-life, calculated as $(\ln 2)/K_{el}$, expressed in time units (hour). The apparent terminal first-order elimination rate constant, determined by linear regression analysis of the natural log-linear segment of the plasma concentration-time curve, expressed in time^{-1} units (1/hour). At least 3 time points over 7 days following the treatment at week 8 will be included in the determination of K_{el} (Points prior to Cmax or prior to the end of infusion are not used).

C_{min} the observed serum concentrations prior to the start of infusions obtained at Weeks 7, 8 and at 7 days (168 hours) post infusion at Week 8, expressed in concentration units (mg/dL).

Mean C_{min} the average trough concentration at steady state, calculated as the mean value using the three C_{min} measurements obtained at Weeks 7, 8 and at 7 days (168 hours) post infusion at Week 9.

Analysis of PK Parameters

For PK parameters descriptive statistics and geometric mean (except t_{max}) will be calculated.

10.1.5 Summary of PK Parameters		
Population	:	PK population
Contents	:	For following PK parameters, descriptive statistics including n, mean, standard deviation (SD), %CV, median, minimum, maximum and geometric mean (except t_{max}) will be calculated. The digits to be displayed and units will be described in Table B. Data listing for PK parameter will be provided.

Table B

Contents	Digits to be displayed
$AUC_{0\text{-}7days}$ [mg･hr/dL)]	1 decimal place
C_{max} [mg/dL]	2 decimal place
t_{max} [hours]	2 decimal place
$t_{1/2}$ [hours]	2 decimal place

10.2 Lung density

Subjects will undergo CT scanning for diagnosis of clinically apparent pulmonary emphysema in GTI1401 study. This CT scan data will also serve as the baseline measurement of lung density for GTI1401-OLE study. Lung density collected by the CT scan data will be summarized in Demographics (parameter name=both).

In GTI1401-OLE study, the CT scan will be performed and summarized at Ext Week 52. The CT scan data will be accumulated for the future evaluation of lung density.

10.2.1 Summary Table of Lung Density		
Population	:	Safety population
Contents	:	For following parameters and locations, descriptive statistics including n, mean, standard deviation (SD), %CV, median, minimum and maximum will be calculated. The digits to be displayed, units and all locaion will be described in Table: Lung Density Parameter and Table: Target Location. Data listing for Lung density parameters will be provided.

Table: Lung Density Parameter

Contents	Conversion formula for analysis value	Digits to be displayed
Hu value 15 percentile [g/L]	Original value [housfield unit] + 1000	1 decimal place
Mean [g/L]	Original value [housfield unit] + 1000	1 decimal place
Standard deviation [g/L]	Original value [housfield unit] + 1000	1 decimal place
Percent below -856 hu [%]	Original value	1 decimal place
Percent below -910 hu [%]	Original value	1 decimal place
Percent below -950 hu [%]	Original value	1 decimal place
Total volume in cm3 [mL]	Original value	1 decimal place
Air volume in cm3 [mL]	Original value	1 decimal place

Table: Target Location

1	:	Lung
2	:	Lung, Left
3	:	Lung, Left Lower Lobe
4	:	Lung, Left Upper Lobe
5	:	Lung, Right
6	:	Lung, Right Lower Lobe
7	:	Lung, Right Middle Lobe
8	:	Lung, Right Upper Lobe
9	:	Lung, Thirds Left Lower
10	:	Lung, Thirds Left Middle
11	:	Lung, Thirds Left Upper
12	:	Lung, Thirds Right Lower
13	:	Lung, Thirds Right Middle
14	:	Lung, Thirds Right Upper

11 Safety Analysis

11.1 Adverse Events

Definition of Adverse Events

Adverse Event:	An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the IMP. In this protocol, non-serious COPD exacerbation will not be considered as adverse events unless SAE.
TEAE for GTI 1401	Treatment emergent adverse events (TEAE) for GTI 1401 will defined as any adverse event occurred after or on the first study drug infusion of GTI 1401 to the final visit of GTI 1401. For any subject, all AEs that occur at any time from the beginning of Alpha-1 MP administration until the final visit of the clinical trial will be considered as TEAE. All tables regarding to Adverse Events are restricted to TEAE.
TEAE for GTI1401-OLE	Treatment emergent adverse events (TEAE) for GTI 1401-OLE will defined as any adverse event occurred after or on the first study drug infusion of GTI 1401-OLE to the final visit of GTI 1401-OLE or adverse event which continue from GTI 1401 to GTI 1401-OLE. For any subject, all AEs that occur at any time from the beginning of Alpha-1 MP administration until the final visit of the clinical trial will be considered as TEAEs All tables regarding to Adverse Events are restricted to TEAE.
Adverse Drug Reaction (ADR):	The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product or study treatment and an AE is at least a reasonable possibility, that is, the relationship cannot be ruled out.

	When an AE is classified, assessing causal relationship by the Investigator, as "definitive", "probable", "possible" or "doubtful/unlikely", the event will be defined as a suspected ADR. When the causal relationship is labeled "Unrelated", then it will be considered that the AE is not imputable to the study treatment and it is not a suspected ADR.
Serious Adverse Events (SAEs):	Any event reported on the AE CRF form with the serious field ticked "Yes". A SAE is any untoward medical occurrence that at any dose: Results in death Is life-threatening Note: The term "life-threatening" in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe. Requires inpatient hospitalization or prolongation of existing hospitalization Results in persistent or significant disability/incapacity Is a congenital anomaly/birth defect
Events of Special Interest :	Events of special interest include the following: All COPD exacerbations occurring during the study will be recorded. Each subject will be assessed for signs and symptoms of exacerbations at each study visit as specified in Appendix 1 and Appendix 2. Given that COPD exacerbations are part of the natural history of AATD, COPD exacerbations will not be reported as AEs unless a COPD exacerbation meets the criteria of a SAE. If an exacerbation meets criteria for a SAE, it will be reported as such, and the standard of care should be followed. Results from standard of care should be obtained and reported.

Adverse events with incomplete start dates will be considered treatment emergent (TEAE) if:

- Day and Month are missing and the year is equal to or after the year of the first study drug dose date of each study (1401/1401-OLE);

- Day is missing, month is present and the month is equal or after the month of first dose of each study (1401/1401-OLE) and the year is equal or after the year of first dose date of each study (1401/1401-OLE);
- Day is missing and the year is equal to the year of the first infusion date of each study (1401/1401-OLE) and the month is equal to or after the month of the first infusion date of each study (1401/1401-OLE);
- Complete date is missing.

The AE tables will include the number and percentage of subjects by MedDRA primary System Organ Classes (SOC) - sorted by alphabetical order, MedDRA Preferred Terms (PT) - sorted by alphabetical order. A subject with more than one occurrence of the same adverse event in a particular system organ class/preferred term will be counted only once in the total of those experiencing adverse events in that particular system organ class/preferred term.

If a subject experiences the same adverse event at more than one severity, or with more than one relationship to study drug, the most severe rating or the stronger causal relationship to study drug will be given precedence. Any missing severity/relationship will be accounted as "worst case" as related in the tables.

All AE tables will be provided without separating AE occurred during treatment period with Follow-up period.

11.1.1 Overview of AEs		
Population	:	Safety population
Contents	:	Overview AE table will be tabulated and will present number and percentages of subjects and number of events with following items. • AEs • ADRs • AEs with fatal outcome • SAEs • AEs leading to premature discontinuation from the study • Events of special interest

11.1.2 Summary Table of AEs ADRs 11.1.3 Summary Table of ADRs		
Population	:	Safety population
Contents	:	The number and percentage of incidences of AEs and ADRs in separate table by SOC and PT

11.1.3 Summary Table of AEs by Causality

Population	:	Safety population
Contents	:	The number and percentage of incidences of AEs by causality based on SOC and PT

11.1.4 Summary Table of AEs by Severity 11.1.5 Summary Table of ADRs by Severity		
Population	:	Safety population
Contents	:	The number and percentage of incidences of AEs, and ADRs by severity based on SOC and PT will be summarized.

Following Listings regarding AEs will be provided.

- AEs
- SAEs
- Subjects with deaths
- AEs leading to premature discontinuation from the study
- AEs with Non-Serious COPD Exacerbation

11.2 Laboratory Tests

11.2.1 Summary Table of Laboratory Test		
Population	:	Safety population
Contents	:	Summary statistics for original value and change from Baseline will be provided The analysis variables are defined in appendix for laboratory parameter. For Laboratory results, a data listing will be provided.
Analysis Visit for 1401	:	Baseline, Week 5 , Week 9
Analysis Visit for 1401- OLE	:	Baseline, Ext Week 26, Ext Week 52

11.2.2 Summary Shift Table of Laboratory Test (Low, Normal and High) 11.2.3 Summary Shift Table of Laboratory Test (Normal and Abnormal)		
Population	:	Safety population
Contents	:	Shift tables for laboratory test with normal range will be provided. The analysis variables are defined in appendix for laboratory parameter..
Analysis Visit for	:	Baseline, Week 5 , Week 9

1401		
Analysis Visit for 1401- OLE	:	Baseline, Ext Week 26, Ext Week 52

11.3 Vital Signs

11.3.1 Summary Table of Vital Signs		
Population	:	Safety population
Contents	:	Summary statistics for original value and change from Baseline will be provided. The analysis variables are displayed in Table C. For vital signs results, a data listing will be provided.
Analysis Visit for 1401	:	Week 1 prior to Infusion (Baseline) and Week 1 (After completion of infusion),Week 2 ~ Week 8 (Prior to infusion / After completion of infusion)
Analysis Visit for 1401- OLE	:	Week 1 prior to Infusion (Baseline), Ext Week 1 ~ Ext Week 52 (Prior to infusion / After completion of infusion)

Table C:

Contents	Digits to be displayed
Pulse rate [BEATS/MIN]	Integer
Systolic blood pressure [mmHg] Diastolic blood pressure [mmHg]	Integer
Body temperature [C]	1 decimal place
Respiratory rate [breaths per minute]	Integer

11.4 Electrocardiogram

11.4.1 Summary Table of Electrocardiogram		
Population	:	Safety population
Contents	:	Shift tables for electrocardiogram will be provided. The analysis variables are displayed in Table D. For electrocardiogram results, a data listing will be provided.
Analysis Visit for 1401	:	Baseline, Week 9
Analysis Visit for 1401-OLE	:	Baseline, Ext Week 26, Ext Week 52

Table D:

Contents	Category
Electrocardiogram	Normal Abnormal

11.5 Urine Cotinine Test

11.5.1 Summary Table of Urine Cotinine Tests		
Population	:	Safety population
Contents	:	Shift table will be provided for Baseline value and the change from Baseline. The analysis variables are displayed in Table E.
Analysis Visit for 1401	:	Baseline, Week 5, Week 9
Analysis Visit for 1401-OLE	:	Baseline, Ext Week 26, Ext Week 52

Table E:

Contents	Category
Urine cotinine result	Negative Positive

11.6 Pulmonary Function Tests

11.6.1 Summary Table of Pulmonary Function Tests (FEV_1 and FVC)		
Population	:	Safety population
Contents	:	Summary statistics for original value and change from Baseline value will be provided for both "PRE-BRONCHODILATOR" and "POST-BRONCHODILATOR" separately. The analysis variables are displayed in Table F.
Analysis Visit for 1401	:	Screening, (Baseline), Week 5, Week 9
Analysis Visit for 1401-OLE	:	Screening (Baeline), Ext Week 26, Ext Week 52

11.6.2 Summary Table of Pulmonary Function Tests (FEV_1 % Predicted)		
Population	:	Safety population
Contents	:	Frequency counts and summary statistics will be provided for both "PRE-BRONCHODILATOR" and "POST-BRONCHODILATOR" separately. The analysis variables are displayed in Table F.
Analysis Visit for 1401	:	Screening, (Baseline), Week 5, Week 9
Analysis Visit for 1401-OLE	:	Screening (Baeline), Ext Week 26, Ext Week 52

Table F:

Contents	Digits to be displayed
Best FEV_1 [L]	2 decimal place
Best FVC [L]	2 decimal place
FEV_1 predicted [%]	Integer
FEV_1 predicted [%] category	0=< < 30 30=< < 70 70=< <100

For Pulmonary Function Tests, a data listing will be provided.

11.7 Pregnancy Tests

For pregnancy test, a data listing will be provided.

11.8 CT Scan

For CT Scan (densitometry), a data listing including lung density will be provided.

11.9 Physical Examination

For physical examination, a data listing will be provided.

12 Interim Analysis

No interim analysis is planned.

13 Changes in Planned Analysis

There are no changes in the planned analysis.

Appendix 1 Schedule of Study Procedures – GTI1401

Trial period	Screening	Treatment[a]												Follow-up
Visit[a]	Day −21 to the day before Week1	Week 1 (baseline)	Week 2	Week3	Week 4	Week 5	Week 6	Week 7	Week 8	PK1	PK2	PK5	Week 9 (Study completion)[b]	Week 12 (Study completion)[c]
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Assignment of subject number	X													
Medical history	X													
Age, sex	X													
CT Scan (densitometry)	X[d]													
Physical examination (excluding breast and urogenital examination)	X												X	X
Body height	X													
Body weight	X	X[e]				X[e]								
Blood sampling for viral safety assessment [f]		X												
Urine pregnancy test (Only in women of childbearing potential)	X					X							X	X
Urinary cotinine level	X					X							X	X
Blood and urine sampling for laboratory tests (Hematology, blood chemistry, urinalysis)	X	X [g]				X [g]							X	X
Vital signs (Pulse rate, blood pressure, respiratory rate, body temperature)[h]		X	X	X	X	X	X	X	X				X	X
12-lead ECG	X	X											(X)	
Pulmonary function tests before and after administration of a bronchodilator (FEV_1 and FVC)[i]	X [i]					X [i]							X [i]	X [i]
Blood sampling for $alpha_1$-PI concentration measurement	X [j]	X [g]						X [g]	X [k]	X [k]	X [k]	X [k]	X [k]	
Intravenous infusion of Alpha-1 MP[l]		X	X	X	X	X	X	X	X					
Observation of subjects after infusion of Alpha-1 MP[m]		X	X	X	X	X	X	X	X					
Evaluation of COPD exacerbations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a: The date of individual visits will be determined in relation to the date of the Week 1 (baseline) visit. The date of all visits after the screening visit and the Week 1 (baseline) visit will be arranged within a time window of ± 1 day. The PK evaluation period will start at the Week 8 visit and end at the Week 9 visit.

b: At the Week 9 visit, subjects will be asked whether or not they would like to enter the extension trial (GTI1401-OLE). For subjects eligible for participation in the extension trial, the Week 9 visit will be the study completion visit for this clinical trial (GTI1401).

c: Subjects not entering the extension trial (GTI1401-OLE) and subjects who receive Alpha-1 MP at any dose and discontinue this clinical trial early will be asked to return to the study center for the follow-up/study completion procedures and evaluations scheduled at the Week 12 visit. This visit should be made at the timing as close as possible to 4 weeks (i.e., 30 days) after the last dose of the investigational drug in the subject.

d: CT densitometry scan should be performed anytime from the Screening Visit to the Week 1 (Baseline) Visit; if the CT densitometry scan is performed at the Week 1 (Baseline) Visit, then it must be performed prior to the first Alpha-1 MP infusion. This CT scan will measure lung density.

e: Body weight will be used to calculate the Alpha-1 MP dose, and this recorded body weight will be used for dose calculation until the next scheduled body weight measurement.

f: Blood samples for viral safety assessment (viral NAT and viral serologic test) will be collected before the intravenous infusions of Alpha-1 MP at the Week 1 (baseline) visit. However, the collected samples will be tested only if the subject shows clinical signs or symptoms suggestive of viral infection during the trial period. Only in this case will additional blood samples for viral NAT and viral serologic test be collected. All these collected blood samples will be stored until completion of all the tests in this clinical trial (GTI1401) and the extension trial (GTI1401-OLE).

g: Sampling will be performed before each intravenous infusion of Alpha-1 MP.

h: Vital signs will be checked immediately before and after each intravenous infusion of Alpha-1 MP.

i: Pulmonary function tests after administration of a bronchodilator will be performed 15 to 30 minutes after administration of a bronchodilator. For a short-acting bronchodilator, subjects will receive 4 puffs of salbutamol given by an MDI and spacer in each pulmonary function testing. The same bronchodilator as that used at the start of the trial should be used throughout the trial period.

j: Sampling will be performed in subjects with no previously documented alpha1-PI levels as measured by nephelometry (if it is unknown whether the subject's alpha1-PI level is <50 mg/dL or not).

k: Sampling time points of PK samples: 1) Immediately before the intravenous infusion; 2) Immediately after the intravenous infusion (after flushing the infusion line with physiological saline) (at 0 hours); 3) At 15 minutes after completion of the intravenous infusion; 4) At 2 hours after completion of the intravenous infusion; 5) At 4 hours after completion of the intravenous infusion; 6) At 8 hours after completion of the intravenous infusion; 7) At 24 ± 4 hours (1 day after completion of the intravenous infusion); 8) At 48 ± 4 hours (2 days after completion of the intravenous infusion); 9) At 120 hours ± 1 day (5 days after completion of the intravenous infusion); and 10) At 168 hours ± 1 day (7 days after completion of the intravenous infusion) (Week 9).

l: Weekly intravenous infusions of 60 mg/kg of Alpha-1 MP will be given under the supervision of the investigator or a designated person at each study center.

Appendix 2 Schedule of Study Procedures – GTI1401-OLE

Procedures/Assessments / Visits	Screening/Ext Week 1 Visit		Weekly On-Site Infusion Visits (Ext Weeks 2 to 52)	Quarterly Visits (Ext Weeks 12, 24, 36, 48)	Bi-Annual Visits		End of Study Follow-Up Assessment[b] (via phone call) (Ext Week 53)
	Screening[a]	Initiation of Infusion			Ext Week 26	Ext Week 52	
Informed consent	X					X	
Inclusion/exclusion criteria	X						
Subject number confirmed	X						
Weight				X			
Collection of virus safety retain samples						X	
Physical exam (excludes breast and genitourinary)					X	X	
Urine pregnancy test (potential child-bearing females only)					X	X	
Urine cotinine					X	X	
Blood for hematology and chemistry laboratory assessments					X	X	
Blood for retains for possible future testing					X	X	
Urinalysis					X	X	
Vital signs (heart rate, blood pressure, respiratory rate, and temperature)		X	X	X	X	X	
Pre- and post-bronchodilator PFTs (FEV_1 and FVC)					X	X	
Blood for $Alpha_1$-PI level				X			
Alpha-1 MP IV infusion		X	X	X	X	X	
COPD exacerbation assessment					X	X	X
Adverse event assessment			X	X	X	X	X
Concomitant medications assessment			X	X	X	X	X

Appendix for Laboratory Parameter:

Display order	Category for Lab Test	LB parameter code	LB parameters (SI unit)	Digit to be displayed
1	HEMATOLOGY	HGB	Hemoglobin [g/L]	Integer
2	HEMATOLOGY	HCT	Hematocrit [%]	1 decimal place
3	HEMATOLOGY	PLAT	Platelets [10^9/L]	Integer
4	HEMATOLOGY	RBCH	Erythrocytes [10^12/L]	2 decimal place
5	HEMATOLOGY	WBCH	Leukocytes [10^9/L]	1 decimal place
6	HEMATOLOGY	NEUT	Neutrophils [%]	Integer
7	HEMATOLOGY	LYM	Lymphocytes [%]	1 decimal place
8	HEMATOLOGY	MONO	Monocytes [%]	1 decimal place
9	HEMATOLOGY	EOS	Eosinophils [%]	1 decimal place
10	HEMATOLOGY	BASO	Basophils [%]	1 decimal place
11	CHEMISTRY	SODIUM	Sodium [mmol/L]	Integer
12	CHEMISTRY	K	Potassium [mmol/L]	1 decimal place
13	CHEMISTRY	CREAT	Creatinine [mg/dL]	2 decimal place
14	CHEMISTRY	CA	Calcium [mg/dL]	1 decimal place
15	CHEMISTRY	UREAN	Urea Nitrogen [mg/dL]	Integer
16	CHEMISTRY	BICARB	Bicarbonate [mmol/L]	1 decimal place
17	CHEMISTRY	ALB	Albumin [g/L]	Integer
18	CHEMISTRY	AST	Aspartate Aminotransferase [IU/L]	Integer
19	CHEMISTRY	ALT	Alanine Aminotransferase [IU/L]	Integer
20	CHEMISTRY	ALP	Alkaline Phosphatase [IU/L]	Integer
21	CHEMISTRY	GLUCC	Glucose [mg/dL]	Integer
22	CHEMISTRY	PROTC	Protein [g/L]	Integer
23	CHEMISTRY	BILI	Bilirubin [mg/dL]	1 decimal place
24	URINALYSIS	PH	pH	
25	URINALYSIS	PROT	Protein	
26	URINALYSIS	GLUC	Glucose	
27	URINALYSIS	OCCBLD	Occult Blood	
28	URINALYSIS	MUCTHR	Mucous Threads	

Layout Plan

GTI1401

Protocol title: A Multi-Center, Open-Label Study to Evaluate the Safety and Pharmacokinetics of Weekly Intravenous Infusions of Alpha1-Proteinase Inhibitor (Human) in Japanese Subjects with

GTI1401-OLE

Protocol title: A Multi-Center, Open-Label Study to Evaluate the Long-term Safety of Weekly Intravenous Infusions of Alpha1-Proteinase Inhibitor (Human) in Japanese Subjects with Alpha1 Antitrypsin Deficiency

Study code: Alpha-1 MP

Sponsor: Grifols Therapeutics Inc.
79 TW Alexander Drive Research Triangle Park, NC 27709

LP status: V1.0

Date: 21MAR2017

Approval:

MAR 21, 2017
Date
[redacted], PhD

Mar 21, 2017
Date
[redacted], Pharm.D.

MAR 21, 2017
Date
[redacted], MD

Mar 23, 2017
[redacted]

Date [redacted]

Change Record

Version No.	Date	Author	Description of changes (revisions and reasons)
V0.1	2016/5/25	[redacted]	Created 1st draft
V0.2	2016/12/2	[redacted]	Incorporated client's review of 1st draft
V0.3	2016/3/1	[redacted]	Incorporated client's review of 2nd draft and MW input
V1.0	2016/3/21	[redacted]	Removed review comment

No	ID of TFLs	Tittle of TFLs	Statistical Analysis Plan		Number of Table	GTI1401	GTI1401-OLE	Remarks
1	Disp-1	6.1 Summary Table of Analysis Population	6 Subject Disposition			○	○	
2	Disp-2	6.2 Summary Table of Subjects Who Discontinue From the Study				○	○	
3	Disp-L1	6.3 Listing of Subject Disposition				○	○	"6.4 Listing of Screening Failures" will be based on this table layout.
4	Devi-1	7.1 Summary Table of Protocol Deviations	7 Protocol Deviations			○	○	
5	Devi-L1	7.2 Listing of Protocol Deviation				○	○	
6	Demog-1	8.1 Summary Table of Demographics	8 Demographics			○	○	
7	Demog-L1	8.2 Listing of Demographic Characteristics				○	○	
6	Demog-L2	8.3 Listing of Smoking History				○	○	
7	Demog-L3	8.4 Listing of Medical History				○	○	
8	Con-1	9.1.1 Summary Table of Prior Medication	9 Treatments and Medications	9.1 Prior and Concomitant Medication		○		"9.1.2 Summary Table of Concomitant Medication" will be based on this table layout
9	Con-L1	9.1.3 Listing of Medications				○	○	
10	Exp-1	9.2.1 Summary Table of Drug Exposure		9.2 Extent of Exposure		○	○	
11	Exp-2	9.2.2 Summary Table of Infusion Interruptions				○	○	
12	Exp-L1	9.2.3 Listing of Exposure Information				○	○	
13	Comp-1	9.3.1 Summary Table of Treatment Compliance		9.3 Treatment Compliance		○	○	
14	Comp-L1	9.3.2 Listing of Treatment Compliance				○	○	
15	Pk-1	10.1.1 Summary Table of Alpha1-PI Concentrations	10 Exploratory Analysis	10.1 PK Analysis (GTI1401 only)		○		
16	Pk-2	10.1.2 Summary Table of Trough (pre-infusion) Levels (Cmin) and mean Cmi				○		
17	Pk-3	10.1.3 Figures of Concentration Versus Time Curves of Individual Subjects				○		
18	Pk-4	10.1.4 Figures of Concentration Versus Time Curves of All Subjects				○		
19	Pk-5	10.1.5 Summary of PK Parameters				○		
20	Pk-L1	10.1.6 Listing of Alpha1-PI Concentrations (Week 8 and 9)				○		
21	Pk-L2	10.1.7 Listing of Alpha1-PI Concentrations				○		
22	Pk-L3	10.1.8 Listing of Trough (pre-infusion) levels (Cmin) and mean Cmin				○		
23	Pk-L4	10.1.9 Listing of PK Parameters				○		
24	Mo-1	10.2.1 Summary Table of Lung Density				○		
25	Mo-L1	10.2.2 Listing of Lung Density				○		
26	AE-1	11.1.1 Overview of AEs	11 Safety Analysis	11.1 Adverse Events		○	○	
27	AE-2	11.1.2 Summary Table of AEs				○	○	"11.1.3 Summary Table of ADRs" will be based on this table layout.
28	AE-3	11.1.4 Summary Table of AEs by Causality				○	○	
29	AE-4	11.1.5 Summary Table of AEs by Severity				○	○	"11.1.6 Summary Table of ADRs by Severity" will be based on this table layout.
30	AE-L1	11.1.7 Listing of AEs				○	○	"11.1.10 Listing of AEs leading to Premature Discontinuation from the Study" will be based on this table layout.
31	AE-L2	11.1.8 Listing of Death				○	○	
32	AE-L3	11.1.9 Listing of SAE				○	○	
33	AE-L4	11.1.11 Listing of Non-Serious COPD Exacerbation				○	○	
34	Lb-1	11.2.1 Summary Table of Laboratory Tes		11.2 Laboratory Tests		○	○	Tables for all the laboratory examination item described on SAP will be based on this table layout
35	Lb-2	11.2.2 Summary Shift Table of Laboratory Test (Low, Normal and High)				○	○	Chemistry and hematology laboratory parameter described on SAP will be based on this table layout.
36	Lb-3	11.2.3 Summary Shift Table of Laboratory Test (Normal and Abnormal				○	○	Urine laboratory parameter described on SAP will be based on this table layout.
37	Lb-L1	11.2.3 Listing of Laboratory Parameters				○	○	
38	Vs-1	11.3.1 Summary Table of Vital Signs		11.3 Vital Signs		○	○	
39	Vs-L1	11.3.2 Listing of Vital Signs				○	○	
40	Ecg-1	11.4.1 Summary Table of Electrocardiogram		11.4 Electrocardiogram		○	○	
41	Ecg-L1	11.4.2 Listing of Electrocardiogram				○	○	
42	Ur-1	11.5.1 Summary Table of Urine Cotinine Test		11.5 Urine Cotinine Test		○	○	
43	Ur-L1	11.5.2 Listing of Urine Cotinine Test				○	○	
44	Pul-1	11.6.1 Summary Table of Pulmonary Function Tests (FEV1 and FVC)		11.6 Pulmonary Function Tests		○	○	
45	Pul-2	11.6.2 Summary Table of Pulmonary Function Tests (FEV1 % Predicted)				○	○	
46	Pul-L1	11.6.3 Listing of Pulmonary Function Tests				○	○	
47	Pr-L1	11.7 Listing for Pregnancy Tests		11.7 Pregnancy Test		○	○	
48	CT-L1	11.8 Listing for CT Scan		11.8 CT Scan		○	○	
49	PE-L1	11.9 Listing for Physical Examination		11.9 Physical Examination		○	○	

General Setting

Items	Contents
Paper Size	- A4 * The documents should allow printing in A4 without changing the page setup of the documents. * Landscape orientation is preferred, portrait is allowed.
Margin	- top, bottom, left, and right: 2.54 cm (1 in)
Font type and size	- Times New Roman 9pt or larger for all * For tables, when space is an issue (i.e. in terms of the page setup), the following solutions can be used (in the following order shown below): - stacking, abbreviation; - split tables across pages; - split listings into sections.
Display	- For tables, when there is no subject to be counted, '0' will be displayed. - In the case of percentage or summary statistics can not be calculated (e.g. Denominator is 0 or there is no denominator), '-' will be displayed. If no subject to be counted and Denominator >0 then display "0" instead of "0 (0.0)".
Alignment	- The output should be left aligned on the page. - Titles and footnotes should be left aligned. - Column headers and column contents for text variables should be left justified, while column headers and column content for numeric variables should be centered. Concatenation of statistics, counts and percentages should be centered. - For variables displayed as numerical output (including dates and concatenation of statistics), and which have the same data format on all rows, the data should be aligned on the decimal point and be centered within the column.
Other	- The setting defined above in general is applicable unless otherwise specified. - A unit “μ” will be presented as “u” in tables and listings. - A unit ”temperature degree” will be presented as “C” in tables and listings. - Display Page number. - In the case there is no qualified data for the listings, express ‘No data available’.

General Setting for Title and Footnote

Title1	GTI 1401						Page 1 of x
Title2	<x title of section>						
Title3	<x x title of sub section or title of table, listing and figure>						
Title4	<x x x title of table, listing and figure>						
Title5	<target populaton>						
	column1	column2	column3	column4	column5	column6	column7
Footnote1	table footnotes (if necessary)						
….	table footnotes (if necessary)						
Footnote n	table footnotes (if necessary)						
Footnote n+1	table footnotes (if necessary)						
Footnote n+2	table footnotes (if necessary)						

In this Layout Plan, only the table footnotes will be presented in each sheet.
> For GTI1401-OLE, title 1 will be changed to "GTI1401-OLE"

GTI 1401
6 Subject Disposition
6.1 Summary Table of Analysis Population

All subjects screened

Population	n (%)
All subjects screened	xx
Safety population	xx
PK population	xx (xx x)

* Denominator of tabulation is the number of Safety Population

GTI 1401
6 Subject Disposition
6.2 Summary Table of Subjects Who Discontinue From the Study

Safety population

Reason of Study Discontinuation	N=88 n (%)
Subjects who complete the study	xx (xx x)
Subjects who discontinue from the study	xx (xx x)
Adverse Event	xx (xx x)
Withdrawal By Subject (Does not Include AEs)	xx (xx x)
• • • •	xx (xx x)

* Denominator of tabulation is the number of Safety Population

GTI 1401
6 Subject Disposition
6.3 Listing of Subject Disposition

All subjects screened

Subject Number	Safety/ PK Population	Date of Screening /Date of Last Visit (Study Day)	Complete Study	Reason for Early Discontinuation	Reason for Exclusion of Safety Population	Reason for Exclusion of PK Population
xxx	Y/N	yyyy-mm-dd / yyyy-mm-dd	N	OTHER: xxx		xxx
xxx	Y/Y	yyyy-mm-dd / yyyy-mm-dd	Y			
xxx						

>Listing for "Screening Failures" will be also provided in same format.
>Row 6 Column 3 will be changed to "Screening Failures".

>Sort order;
Subject Number

>Date of last date for who completes study is date of completion of disposition event.
Date of last date for who discontinues is date of discontinuation of disposition event.

GTI 1401
7 Protocol Deviations
7.1 Summary Table of Protocol Deviations

Safety Population

			N=88			
		Reason of Protocol Deviation	Critical n (%)	Major n (%)	Minor n (%)	Total n (%)
Protocol deviation	No		xx (xx.x)	xx (xx x)	xx (xx.x)	xx (xx x)
	Yes		xx (xx.x)	xx (xx x)	xx (xx.x)	xx (xx x)
		Entry Criteria	xx (xx.x)	xx (xx x)	xx (xx.x)	xx (xx x)
		Investigational Product	xx (xx.x)	xx (xx x)	xx (xx.x)	xx (xx x)
		Visit Schedule Criteria	xx (xx.x)	xx (xx x)	xx (xx.x)	xx (xx x)
		Informed Consent	xx (xx.x)	xx (xx x)	xx (xx.x)	xx (xx x)
		Conc. Medications	xx (xx.x)	xx (xx x)	xx (xx.x)	xx (xx x)
		Study Procedures	xx (xx.x)	xx (xx x)	xx (xx.x)	xx (xx x)
		Laboratory / PK	xx (xx.x)	xx (xx x)	xx (xx.x)	xx (xx x)
		Laboratory	xx (xx.x)	xx (xx x)	xx (xx.x)	xx (xx x)

* Denominator of tabulation is the number of Safety Population

>Only criteria which contain at least one subject will be displayed.

GTI 1401
7 Protocol Deviations
7.2 Listing of Protocol Deviation

Safety Population

Site Name	Subject Number	Category of Protocol Deviation*	Severity	Details of Protocol Deviation
xxxxxxxxxxx	xx	1	MAJOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xx	2	MINOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xx	1	MAJOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxx	xx	3	MAJOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xx	1	MAJOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxx	xx	2	MAJOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xx	4	MAJOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xx	5	MAJOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxxxxx	xx	5	MAJOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xx	6	MAJOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
	xx	7	MINOR	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

* 1. Entry Criteria 2. Investigational Product 3. Visit Schedule Criteria 4. Informed Consent 5. Conc. Medications 6. Study Procedures 7. Laboratory / PK 8. Laboratory

>Sort order;
Site, Subject Number, Category of Protocol Deviation

GTI 1401
8 Demographics
8.1 Summary Table of Demographics

Safety population

	N=xx n (%)
Sex	
Male	xx (xx x)
Female	xx (xx x)
Age [years]	
N	xx
Mean(S.D.)	xx x (xx.x)
Median	xx x
Min , Max	xx , xx
Race	
Asian	xx
Weight [kg]	
N	xx
Mean(S.D.)	xx x (xx.x)
Median	xx x
Min , Max	xx , xx
Height [cm]	
N	xx
Mean(S.D.)	xx x (xx.x)
Median	
Min , Max	xx , xx
Pregnancy status	
NA(Males are included in this category)	xx
Negative	xx
Positive	xx

GTI 1401
8 Demographics
8.1 Summary Table of Demographics

Safety population

	N=xx n (%)
Smoking status	xx
Never	xx
Former	xx
Current	
Total Alpha-1 serum level at time of diagnosis [mg/dL]	
N	xx
Mean(S.D.)	xx x (xx.x)
Median	xx x
Min , Max	xx , xx
Time since first diagnosis of Alpha-1 antitrypsin deficiency [years] *1	
N	xx
Mean(S.D.)	xx x (xx.x)
Median	xx x
Min , Max	xx , xx
Best FEV1 [L] at Baseline for "PRE-BRONCHODILATOR"	xx
N	xx x (xx.x)
Mean(S.D.)	xx x
Median	xx , xx
Min , Max	
Best FVC [L] at Baseline for "PRE-BRONCHODILATOR"	xx
N	xx x (xx.x)
Mean(S.D.)	xx x
Median	xx , xx
Min , Max	
FEV1 predicted [%] for "PRE-BRONCHODILATOR"	xx
0=< < 30	xx
30=< < 70	xx
70=< <100	

GTI 1401
8 Demographics
8.1 Summary Table of Demographics

Safety population

	N=xx n (%)
Best FEV1 [L] at Baseline for "POST-BRONCHODILATOR"	xx
N	xx x (xx.x)
Mean(S.D.)	xx x
Median	xx , xx
Min , Max	
Best FVC [L] at Baseline for "POST-BRONCHODILATOR"	xx
N	xx x (xx.x)
Mean(S.D.)	xx x
Median	xx , xx
Min , Max	
FEV1 predicted [%] for "POST-BRONCHODILATOR"	xx
0=< < 30	xx
30=< < 70	xx
70=< <100	
15th Percentile of lung density [g/L]	
N	xx
Mean(S.D.)	xx x (xx.x)
Median	xx x
Min , Max	xx , xx
Mean lung density [g/L]	
N	xx
Mean(S.D.)	xx x (xx.x)
Median	xx x
Min , Max	xx , xx

*1 Informed Consent Date - First Date of Diagnosis of Alpha-1 Antitrypsin Deficiency + 1 / 365
* Denominator of tabulation is the number of Safety Population

GTI 1401
8 Demographics
8.2 Listing of Demographic Characteristics

Safety population

Subject Number	Sex/ Age/ Race	Weight [kg]/ Height [cm]	Fertility Status/Birth Control	Smoking Status	Total Alpha-1 Serum Level at Time of Diagnosis [mg/dL]	Date of First Diagnosis	Date of Total Alpha-1 PI Serum Level	Emphysema Diagnosed by CT Scan / Date of CT scan	FEV1 [L] / Best FVC [L] at Baseline for "PRE-BRONCHODILATOR"	FEV1 [L] / Best FVC [L] at Baseline for "POST-BRONCHODILATOR"
xx	xx / xx / Asian	xx / xx	CHILDBEARING POTENTIAL /DOUBLE BARRIER METHODS	YES /CIGARS / yyyy-mm-dd	xx	yyyy-mm-dd	yyyy-mm-dd	Y / yyyy-mm-dd		xx / xx
xx	xx / xx / xx	xx/ xx	SURGICALLY STERILE	NEVER	xx	yyyy-mm-dd	yyyy-mm-dd	N		xx / xx

>Sort order;
Subject Number

GTI 1401
8 Demographics
8.3 Listing of Smoking History

Safety population

Subject Number	Smoking History	Previous Smoking Type	Date of Last Smoking
xxxx	NEVER		
xxxx	FORMER	CIGARS / PIPES	yyyy-mm-dd
xxxx	FORMER	CIGARS / CIGARETTES (xx x)	

>Sort order;
Subject Number

GTI 1401
8 Demographics
8.4 Listing of Medical History

Safety population

Subject Number	Onset Date	Resolved Date	MedDRA System Organ Class	Preferred Term	Verbatim Term
xxxx	yyyy-mm-dd	yyyy-mm-dd	xxxxxxxxxx	yyyyyyyyy	zzzzzzzzz
	yyyy-mm-dd	ONGOING	xxxxxxxxxx	yyyyyyyyy	zzzzzzzzz
xxxx	yyyy-mm-dd	yyyy-mm-dd	xxxxxxxxxx	yyyyyyyyy	zzzzzzzzz

>Sort order;
Subject Number, Onset Date, MedDRA System Organ Class, Preferred Term (Both alphabetical order)

GTI 1401
9 Treatments and Medications
9.1 Prior and Concomitant Medications
9.1.1 Summary Table of Prior Medication

Safety population

Who Drug ATC Term	N=88 n (%)
Subjects with at least one prior medication	xx (xx.x)
ATC2	xx (xx.x)
ATC4	xx (xx.x)
....	xx (xx.x)
ATC2	xx (xx.x)
ATC4	xx (xx.x)
....	xx (xx.x)

* Denominator of tabulation is the number of Safety Population

>Listing for "9.1.2 Summary Table of Concomitant Medication" will be also provided in same format.
>Row 4 column 3 will be changed to "9.1.2 Summary Table of Concomitant Medication"

>Row 10 column 3 will be changed to "Subjects with at least one concomitant medication"

>Sort order;

GTI 1401
9 Treatments and Medications
9.1 Prior and Concomitant Medications
9.1.3 Listing of Medications

Safety population

Subject Number	Start Date of Study	Concomitant Medications Start Date [1]/ End Date [2]	Route/ Dose [Units]/ Frequency	Who Drug ATC level 2 term/ Who Drug ATC level 4 term/ Preferred Term/ Reported Term	Indication
xx	yyyy-mm-dd	yyyy-mm-dd [88] *	ORAL	vvvvvvvvvvv /	
		yyyy-mm-dd [88]		xxxxxxxxxx / yyyyyyyy / zzzzzzzzzzzzz	ADVERSE EVENT (XXXXXXXXXXXX) / PFT
		yyyy-mm-dd [88]	INJECTION	vvvvvvvvvvv /	
		yyyy-mm-dd [88]		xxxxxxxxxx / yyyyyyyy / zzzzzzzzzzzzz	OTHERS (XXXXXXXXXXXX)
xx	yyyy-mm-dd	yyyy-mm-dd [88] *	OTHER (SPECIFY)	vvvvvvvvvvv /	
		yyyy-mm-dd [88]		xxxxxxxxxx / yyyyyyyy / zzzzzzzzzzzzz	ADVERSE EVENT (XXXXXXXXXXXX) /
…	…		…	…	

* New medications starting after the first infusion will be indicated if the medication start date relative to the first study drug infusion is greater than 0

[1] Study start date =< medication start date: medication start date - study start date + 1
Study start date > medication start date: medication start date - study start date

[2] Study start date =< medication end date: medication end date - Study start date + 1
Study start date > medication end date: medication end date - Study start date

>Sort order;
Subject Number, Concomitant Medications Start Date, ATC term, Preferred Term (both alphabetical order)

GTI 1401
9 Treatments and Medications
9.2 Extent of Exposure
9.2.1 Summary Table of Drug Exposure

Safety population

Parameter Statistics	
Treatment duration [week]	
N	xx
Mean(S.D.)	xx (xx x)
Median	xx x
Min , Max	xx , xx
Number of infusions received	
N	xx
Mean(S.D.)	xx (xx x)
Median	xx x
Min , Max	xx , xx
Total volume infused [mL]	
N	xx
Mean(S.D.)	xx (xx x)
Median	xx x
Min , Max	xx , xx
Volume infused per week [mL]	
N	xx
Mean(S.D.)	
Median	xx x
Min , Max	xx , xx
Infusion duration [minute]	
N	xx
Mean(S.D.)	xx (xx x)
Median	xx x
Min , Max	xx , xx

GTI 1401
9 Treatments and Medications
9.2 Extent of Exposure
9.2.2 Summary Table of Infusion Interruptions

Safety population

Visit	Number of Infusions	Number of Infusions with Interruption N (%)
Week 1	xxx	xx (xx x)
Week 2	xxx	xx (xx x)
Week 3	xxx	xx (xx x)
....	....	....

* Denominator of tabulation is the number of infusion at the visit
* A subject without infusion at the visit was excluded from analysis

GTI 1401
9 Treatments and Medications
9.2 Extent of Exposure
9.2.3 Listing of Exposure Information

Safety population

Subject Number	Visit	Study Drug Infused/ Reason for No Study Drug Infused	Infusion Start Date and Time/ Infusion Stop Date and Time (including saline flush)	Infusion Duration [Minutes]	Total Volume Prepared [mL]/ Total Volume Infused [mL]	Infusion Interrupted / Explanation for Interruption	Reason for less than 100% of IP
xx	Week 1	Y	yyyy-mm-ddThh:mm/ yyyy-mm-ddThh:mm	xx x	xxxx/ xxxx	N	
	Week 2	xxxxxxxxxxxxxx	yyyy-mm-ddThh:mm/ yyyy-mm-ddThh:mm	xx x	xxxxxxxx/ xxxx	xxxxxxxx	
xx	Week 1	Y	yyyy-mm-ddThh:mm/ yyyy-mm-ddThh:mm	xx x	xxxxxxxx/ xxxx		xxxxxxxx
	Week 2	Y					

>Sort order;
Subject Number, Visit

GTI 1401
9 Treatments and Medications
9.3 Treatment Compliance
9.3.1 Summary Table of Treatment Compliance

Safety population

	N (%)
Treatment compliance [%]	xx
N	xx (xx x)
Mean(S.D.)	xx.x
Median	xx , xx
Min , Max	
The number of subjects with treatment compliance >=	xx (xx x)
Infusion compliance [%]	
N	xx
Mean(S.D.)	xx (xx x)
Median	xx.x
Min , Max	xx , xx

* Denominator of tabulation is the number of Safety Population

GTI 1401
9 Treatments and Medications
9.3 Treatment Compliance
9.3.2 Listing of Treatment Compliance

Safety population

Subject Number	Treatment Compliance	>=80%	Infusion Compliance [%]
xx	xx x	Y	xx x
xx	xx x		
xx	xx x	…	

* Treatment compliance = total volume infused / total volume prepared * 100 [%]

>Sort order;
Subject Number

GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.1 Summary Table of Alpha1-PI Concentrations

PK population

Alpha1-PI concentrations [mg/dL]	
Time Points	
Statistics	
Immediately before the intravenous infusion	
N	xx
Mean(S.D.)	xx.x (xx x)
%CV	xx.x
Median	xx.x
Min , Max	xx , xx
Geometric mean	xx.x
Immediately after the intravenous infusion (after flushing the infusion line with physiological saline) (at 0 hours)	
N	xx
Mean(S.D.)	xx.x (xx x)
%CV	xx.x
Median	xx.x
Min , Max	xx , xx
Geometric mean	xx.x
15 minutes after completion of the intravenous infusion	
N	xx
Mean(S.D.)	xx.x (xx x)
%CV	xx.x
Median	
Min , Max	xx , xx
Geometric mean	xx.x

• • •

GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.1 Summary Table of Alpha1-PI Concentrations

PK population

Alpha1-PI concentrations [mg/dL]	
Time Points	
Statistics	
168 hours ± 1 day (7 days after completion of the intravenous infusion) (Week 9)	
N	xx
Mean(S.D.)	xx.x (xx x)
%CV	xx.x
Median	xx.x
Min , Max	xx , xx
Geometric mean	xx.x

>Time points;

- Immediately before the intravenous infusion
- Immediately after the intravenous infusion (after flushing the infusion line with physiological saline) (at 0 hours)
- 15 minutes after completion of the intravenous infusion
- 2 hours after completion of the intravenous infusion
- 4 hours after completion of the intravenous infusion
- 8 hours after completion of the intravenous infusion
- 24 ± 4 hours (1 day after completion of the intravenous infusion)
- 48 ± 4 hours (2 days after completion of the intravenous infusion)
- 120 hours ± 1 day (5 days after completion of the intravenous infusion)

GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.2 Summary Table of Trough (pre-infusion) Levels (Cmin) and mean Cmin

PK population

Cmin [mg/dL]	
Visit	
Statistics	
Week 1	
N	xx
Mean(S.D.)	xx x (xx x)
%CV	xx x
Median	xx x
Min , Max	xx , xx
Geometric mean	xx.x
Week 7	
N	xx
Mean(S.D.)	xx x (xx x)
%CV	xx x
Median	xx x
Min , Max	xx , xx
Geometric mean	xx.x
Week 8	
N	xx
Mean(S.D.)	xx x (xx x)
%CV	xx x
Median	
Min , Max	xx , xx
Geometric mean	xx.x
Week 9	
N	xx
Mean(S.D.)	xx x (xx x)
%CV	xx x
Median	xx x
Min , Max	xx , xx
Geometric mean	xx.x

GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.2 Summary Table of Trough (pre-infusion) Levels (Cmin) and mean Cmin

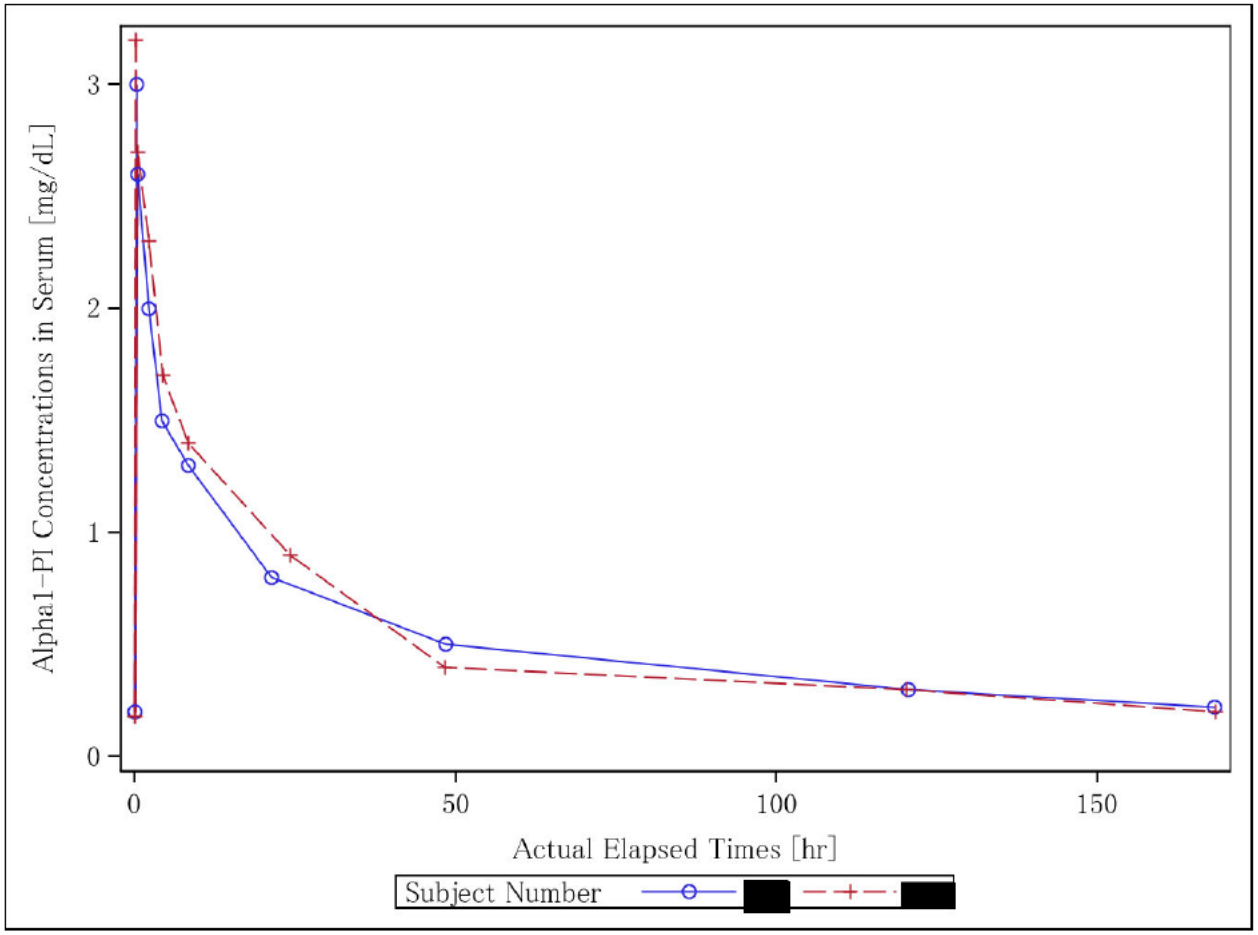
PK population

Cmin [mg/dL] Visit Statistics	
Mean Cmin *	
N	xx
Mean(S.D.)	xx x (xx x)
%CV	xx x
Median	xx x
Min , Max	xx , xx
Geometric mean	xx.x
Subject with mean Cmin of Alpha1-PI Concentration >= 48.672 mg/dL (=11 μM)	xx

* mean Cmin = Average of Cmin of each patient measured at Week 7, Week 8 and Week 9 (Exclude Week 1)

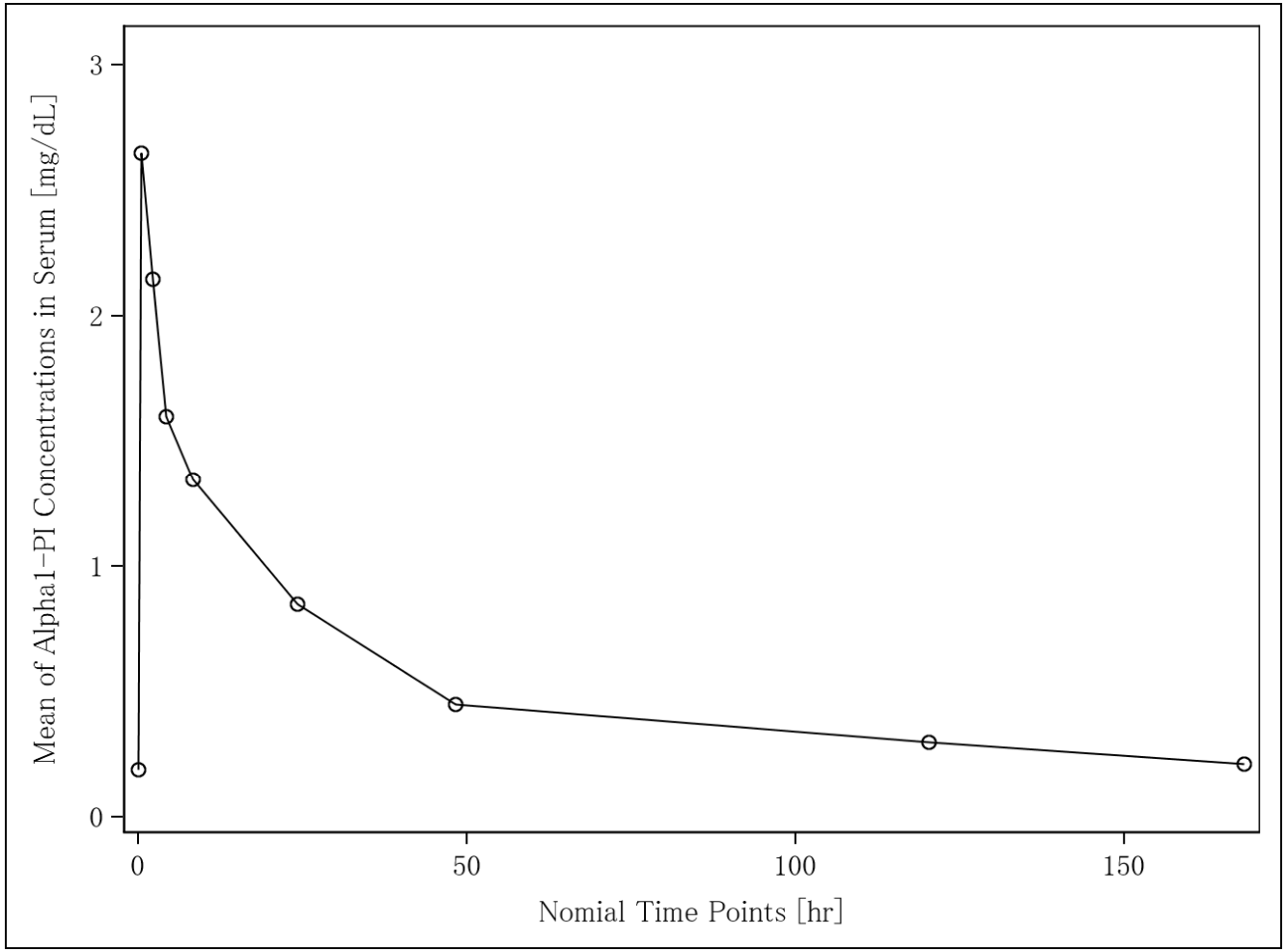
GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.3 Figures of Concentration Versus Time Curves of Individual Subjects

PK population



GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.4 Figures of Concentration Versus Time Curves of All Subjects

PK population



GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.5 Summary of PK Parameters

PK population

Parameter	Statistics	
AUC0-7days [mg・hr/dL]	N	xx
	Mean(S.D.)	xx x (xx x)
	%CV	xx x
	Median	xx x
	Min , Max	xx , xx
	Geometric mean	xx x
Cmax [mg/dL]	N	xx
	Mean(S.D.)	xx x (xx x)
	%CV	xx x
	Median	xx x
	Min , Max	xx , xx
	Geometric mean	
tmax [hours]	N	xx
	Mean(S.D.)	xx x (xx x)
	%CV	xx x
	Median	xx x
	Min , Max	xx , xx
t1/2 [hours]		xx
	Mean(S.D.)	xx x (xx x)
	%CV	xx x
	Median	xx x
	Min , Max	xx , xx
	Geometric mean	xx x

GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.6 Listing of Alpha1-PI Concentrations (Week 8 and 9)

PK population

Subject Number	Actual dose infusion [mL]	Start/ End Date and Time	Scheduled Plasma Collection Time	Exclude from PK Analysis	Nominal Time Point [hr]	Actual Plasma Collection Date / Time	Elapsed Times from the Start of the Study Drug Infusion [hr]	Value of Alpha-PI Concentrations [mg/dL]
xxxx	xx	yyyy-mm-ddThh mm/ yyyy-mm-ddThh mm	IMMEDIATELY BEFORE THE INTRAVENOUS INFUSION		0	yyyy-mm-ddThh mm	xx	xxx xx
			IMMEDIATELY AFTER THE INTRAVENOUS INFUSION		0.25	yyyy-mm-ddThh mm	xx	xxx xx
			15 MINUTES AFTER COMPLETION OF THE INTRAVENOUS INFUSION	Y	0.5	yyyy-mm-ddThh mm	xx	xxx xx
			2 HOURS AFTER COMPLETION OF THE INTRAVENOUS INFUSION		2.25	yyyy-mm-ddThh mm	xx	xxx xx
			4 HOURS AFTER COMPLETION OF THE INTRAVENOUS INFUSION		4.25	yyyy-mm-ddThh mm	xx	BLQ
			……..			……..		xxx xx
xxxx	xx	yyyy-mm-ddThh mm/ yyyy-mm-ddThh mm	IMMEDIATELY BEFORE THE INTRAVENOUS INFUSION		0	yyyy-mm-ddThh mm	xx	xxx xx
			IMMEDIATELY AFTER THE INTRAVENOUS INFUSION		0.25	yyyy-mm-ddThh mm	xx	xxx xx
			15 MINUTES AFTER COMPLETION OF THE INTRAVENOUS INFUSION		0.5	yyyy-mm-ddThh mm	xx	xxx xx
			2 HOURS AFTER COMPLETION OF THE INTRAVENOUS INFUSION		2.25	yyyy-mm-ddThh mm	xx	xxx xx

* BLQ: Below limit of quantification

GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.6 Listing of Alpha1-PI Concentrations (Week 8 and 9)

PK population

Subject Number	Actual dose infusion [mL]	Start/ End Date and Time	Scheduled Plasma Collection Time	Exclude from PK Analysis	Nominal Time Point [hr]	Actual Plasma Collection Date / Time	Elapsed Times from the Start of the Study Drug Infusion [hr]	Value of Alpha-PI Concentrations [mg/dL]

>Sort order;
Subject Number, Nominal Time Point [hr]

GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.7 Listing of Alpha1-PI Concentrations

PK population

Subject Number	Scheduled Plasma Collection Visit	Exclude from PK Analysis	Actual Plasma Collection Date / Time	Value of Alpha-PI Concentrations [mg/dL]
xxxx	SCREENING	Y	yyyy-mm-ddThh:mm	xxx.xx
	Week 1		yyyy-mm-ddThh:mm	xxx.xx
	Week 7		yyyy-mm-ddThh:mm	xxx.xx
……..	……..	……..	……..	
xxxx	SCREENING	Y	yyyy-mm-ddThh:mm	xxx.xx
	Week 1		yyyy-mm-ddThh:mm	xxx.xx
	Week 7		yyyy-mm-ddThh:mm	xxx.xx

* BLQ: Below limit of quantification

>Sort order;
Subject Number, Scheduled Plasma Collection Visit,
Actual Plasma Collection Date / Time

GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.8 Listing of Trough (pre-infusion) levels (Cmin) and mean Cmin

PK population

Subject Number	Visit	Trough Level Cmin [mg/dL]
xxxx	Week 1	xxx
	Week 7	xxx
	Week 8	xxx
	Week 9	xxx
	Mean Cmin *	xxx
xxxx	Week 1	xxx
	Week 7	xxx
	Week 8	xxx
	Week 9	xxx
	Mean Cmin *	xxx

* mean Cmin = Average of Cmin of each patient measured at Week 7, Week 8 and Week 9 (Exclude Week 1)

>Sort order;
Subject Number, Visit (Mean Cmean appear at last record within subject)

GTI 1401
10 Exploratory Analysis
10.1 PK Analysis (GTI1401 only)
10.1.9 Listing of PK Parameters

PK population

Subject Number	AUC0-7days [mg · hr/dL]	Cmax [mg/dL]	tmax [hours]	t1/2 [hours]	Cmin [mg/dL]
xxxx	xxxx	xxxx	xxx	xxx	xxx
xxxx	xxxx	xxxx	xxx	xxx	xxx
xxxx	xxxx	xxxx	xxx	xxx	xxx

>Sort order;
Subject Number

GTI 1401
10 Exploratory Analysis
10.2 Lung Density Analysis (GTI1401 only)
10.2.1 Summary Table of Lung Density

Safety population

Parameter [unit]	Location	Statistics	
Hu value 15 percentile [g/L]	LUNG	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, LEFT	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, LEFT LOWER LOBE	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, LEFT UPPER LOBE	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, RIGHT	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, RIGHT LOWER LOBE	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, RIGHT MIDDLE LOBE	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x

GTI 1401
10 Exploratory Analysis
10.2 Lung Density Analysis (GTI1401 only)
10.2.1 Summary Table of Lung Density

Safety population

Parameter [unit]	Location	Statistics	
		Min , Max	xx , xx
	LUNG, RIGHT UPPER LOBE	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, THIRDS LEFT LOWER	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, THIRDS LEFT MIDDLE	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, THIRDS LEFT UPPER	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, THIRDS RIGHT LOWER	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, THIRDS RIGHT MIDDL	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
	LUNG, THIRDS RIGHT UPPER	N	xx
		Mean(S.D.)	xx (xx x)

GTI 1401
10 Exploratory Analysis
10.2 Lung Density Analysis (GTI1401 only)
10.2.1 Summary Table of Lung Density

Safety population

Parameter [unit]	Location	Statistics	
		Median	xx x
		Min , Max	xx , xx
Mean [hounsfield unit]	LUNG	N	xx
		Mean(S.D.)	xx (xx x)
		Median	xx x
		Min , Max	xx , xx
….	….	….	….

All location for following parameters will be displayed after Air Volume in cm3;

Mean [g/L]
Standard deviation [g/L]
Percent below -856 hu [%]
Percent below -910 hu [%]
Percent below -950 hu [%]
Total volume in cm3 [mL]
Air volume in cm3 [mL]
Tissue volume in cm3 [mL]

GTI 1401
10 Exploratory Analysis
10.2 Lung Density Analysis (GTI1401 only)
10.2.2 Listing of Lung Density

Safety population

Subject Number	Location	Hu Value 15 Percentile [g/L]	Mean [g/L]	Standard deviation [g/L]	Percent below -856 hu [%]	Percent below -910 hu [%]	Percent below -950 hu [%]	Total volume in cm3 [mL]	Air volume in cm3 [mL]	Tissue volume in cm3 [mL]
xxxx	LUNG	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, LEFT	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, LEFT LOWER LOBE	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, LEFT UPPER LOBE	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, RIGHT	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, RIGHT LOWER LOBE	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, RIGHT MIDDLE LOBE	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, RIGHT UPPER LOBE	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, THIRDS LEFT LOWER	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, THIRDS LEFT MIDDLE	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, THIRDS LEFT UPPER	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, THIRDS RIGHT LOWER	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, THIRDS RIGHT MIDDLE	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
	LUNG, THIRDS RIGHT UPPER	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x
xxxx	LUNG	xx x	xx x	xx.x	xx x	xx x	xx x	xx x	xx.x	xx x

>Sort order;
Subject Number, Location

GTI 1401
11 Safety Analysis
11.1 Adverse Events
11.1.1 Overview of AEs

Safety population

	N=88 n (%)
The number of subjects with at least one AE	xx (xx x)
The number of AE	xx
The number of subject with at least one ADR	xx (xx x)
The number of events with ADR	xx
The number of subject with at least one AE with fatal outcome	xx (xx x)
The number of AE with fatal outcome	xx
The number of subject with at least one SAE	xx (xx x)
The number of SAE	xx
The number of subject with at least one AE leading to premature discontinuation from the study	xx (xx x)
The number of AE leading to premature discontinuation from the study	xx
The number of subject with at least one event of Special Interest	xx (xx x)
The number of event of Special Interest	xx

* Denominator of tabulation is the number of Safety population

GTI 1401
11 Safety Analysis
11.1 Adverse Events
11.1.2 Summary Table of AEs

Safety population

	N=88 n (%)
The number of AE	xx
The number of subjects with at least one AE	xx (xx x)
SOC1	xx (xx x)
PT1	xx (xx x)
SOC2	xx (xx x)
PT2	xx (xx x)

* Denominator of tabulation is the number of Safety population

>Table for "11.1.3 Summary Table of ADRs " will be also provided in same layout.
>Row 4 column 3 will be changed to "11.1.3 Summary Table of ADRs"
>Row 10 column 3 will be changed to "The number of ADR"
>Row 12 column 3 will be changed to "The number of subjects with at least one ADR".

>Sort order;
SOC name, PT name (Both alphabetical order)

GTI 1401
11 Safety Analysis
11.1 Adverse Events
11.1.4 Summary Table of AEs by Causality

Safety population

	N=88				
	Definite n (%)	Probable n (%)	Possible n (%)	Doubtful/Unlikely	Unrelated n (%)
The number of AE	xx/108	xx/108	xx/108	xx/108 (xx x)	xx/108
The number of subjects with at least one AE	xx (xx.x)	xx (xx.x)	xx (xx x)	xx (xx x)	xx (xx.x)
SOC1	xx (xx.x)	xx (xx.x)	xx (xx x)	xx (xx x)	xx (xx.x)
PT1	xx (xx.x)	xx (xx.x)	xx (xx x)	xx (xx x)	xx (xx.x)
SOC2	xx (xx.x)	xx (xx.x)	xx (xx x)	xx (xx x)	xx (xx.x)
PT2	xx (xx.x)	xx (xx.x)	xx (xx x)	xx (xx x)	xx (xx.x)

* Denominator of tabulation is the number of Safety population
* If a subject experiences the same adverse event with more than one relationship to study drug, the stronger causal relationship to study drug will be counted only once in the total of those experiencing adverse events in that particular

>Sort order;
SOC name, PT name (Both alphabetical order)

GTI 1401
11 Safety Analysis
11.1 Adverse Events
11.1.5 Summary Table of AEs by Severity

Safety population

		N=88	
	Mild n (%)	Moderate n (%)	Severe n (%)
The number of AE	xx/108 (xx.x)	xx/108 (xx.x)	xx/108 (xx.x)
The number of subjects with at least one AE	xx (xx x)	xx (xx x)	xx (xx x)
SOC1	xx (xx x)	xx (xx x)	xx (xx x)
PT1	xx (xx x)	xx (xx x)	xx (xx x)
SOC2			
PT2	...	...	...

* Denominator of tabulation is the number of Safety population
* If a subject experiences the same adverse event at more than one severity, the most severe rating to study drug will be counted only once in the total of those experiencing adverse events in that particular system organ class / preferred term.

>Listing for "11.1.6 Summary Table of ADRs by Severity" will be also provided in same layout.
>Row 4 column 3 will be changed to "11.1.6 Summary Table of ADRs by Severity"
>Row 10 column 3 will be changed to "The number of ADR"
>Row 12 column 3 will be changed to "The number of subjects with at least one ADR".

>Sort order;
SOC name, PT name (Both alphabetical order)

GTI 1401
11 Safety Analysis
11.1 Adverse Events
11.1.7 Listing of AEs

Safety population

Subject Number	Start / End Date and Time of Events	Relative days *	MedDRA System Organ Class/ Preferred Term/ Verbatim Term	Pattern/ Seriousness / Severity / Action Taken with Study Drug	Causality to Study Drug / Outcome	(a)	(b)	Concomitant Medication/ Other Action
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x	xxxx/ yyyy/ zzzz	INTERMITTENT/ N / MILD / DRUG WITHDRAWN	DOUBTFUL/UN LIKELY/ RECOVERING/ RESOLVING	Y	N	N/ N
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x	xxxx/yyyy/zzzz	CONTINUOUS/ N/ MILD / MODERATE	DEFINITE / RECOVERED / RESOLVED WITH SEQUELAE	Y	Y	N/ N
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x	xxxx/ yyyy/ zzzz	CONTINUOUS N/ MILD / MODERATE	DEFINITE / RECOVERED / RESOLVED WITH		N	Y (xxxxx)/ Y (xxxxx)
…	…		…	…	…			

* Study start date =< Onset date of event: Onset date of event - Study start date + 1,
Study start date > Onset date of event: Onset date of event - Study start date
* (a)TEAE / (b)Did the subject withdraw from the study?

>Listing for "11.1.11 Listing of AEs leading to Premature Discontinuation from the Study" will be also provided in same layout.
>Row 4 column 3 will be changed to "11.1.11Listing of AEs leading to Premature Discontinuation from the Study"

>Sort order;

GTI 1401
11 Safety Analysis
11.1 Adverse Events
11.1.8 Listing of Death

Safety population

Subject Number	Start / End Date of Events	Relative days[1]	Date of Death [Relative days][2]	MedDRA System Organ Class/ Preferred Term/ Verbatim Term	Pattern/ Seriousness / Severity / Action Taken with Study Drug	Causality to Study Drug / Outcome	(a)	(b)	Concomitant Medication/ Other Action/ Cause of Death
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x	yyyy-mm-dd [x]	xxxx/ yyyy/ zzzz	INTERMITTENT/ N / MILD / DRUG WITHDRAWN	DOUBTFUL/UNLIKELY/ RECOVERING/ RESOLVING	Y	N	N/ N/ xxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x		xxxx/ yyyy/ zzzz	CONTINUOUS/ N/ MILD / MODERATE	DEFINITE / RECOVERED / RESOLVED WITH SEQUELAE	Y	Y	N/ N/ xxxxxxxxxx
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x		xxxx/ yyyy/ zzzz	CONTINUOUS N/ MILD / MODERATE	DEFINITE / RECOVERED / RESOLVED WITH		N	Y (xxxxx)/ Y (xxxxx)/ xxxxxxxxxxxxxxxxxxxxxxxxx
…	…			…	…	…			

* [1]Study start date =< Onset date of event: Onset date of event - Study start date + 1,
Study start date > Onset date of event: Onset date of event - Study start date

* [2]Date of death - study start date + 1
* (a)TEAE / (b)Did the subject withdraw from the study?

>Sort order;
Subject Number, Start Date of Events , Start Time of Events
Outcome of AEs is death will be listed.

GTI 1401
11 Safety Analysis
11.1 Adverse Events
11.1.9 Listing of SAE

Safety population

Subject Number	Start / End Date and Time of Events	Relative days *	MedDRA System Organ Class/ Preferred Term/ Verbatim Term	Pattern/ Seriousness / Severity Action Taken with Study Drug	Causality to Study Drug / Outcome	(a)	(b)	Concomitant Medication/ Other Action	Reason for Seriousness / Detail
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x	xxxx/ yyyy/ zzzz	INTERMITTENT/ N / SEVERE DRUG WITHDRAWN	DOUBTFUL/UNLIKELY/ RECOVERING/ RESOLVING	Y	N	N/ N	RESULT IN DEATH / xxxxxxxxxxxxxxxxxxxx
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x	xxxx/yyyy/zzzz	CONTINUOUS/ N/ SEVERE MODERATE	DEFINITE / RECOVERED / RESOLVED WITH SEQUELAE	Y	Y	N/ N	LIFE-THREATENING
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x	xxxx/ yyyy/ zzzz	CONTINUOUS N/ SEVERE MODERATE	DEFINITE / RECOVERED / RESOLVED WITH		N	Y (xxxxx)/ Y (xxxxx)	IMPORTANT MEDICAL EVENT (xxxxxxxxxxxxxxxxxxxx xxxx)
…	…		…	…	…				

* Study start date =< Onset date of event: Onset date of event - Study start date + 1,
Study start date > Onset date of event: Onset date of event - Study start date
* (a)TEAE / (b)Did the subject withdraw from the study?

>Sort order;
Subject Number, Start Date of Events , Start Time of Events

GTI 1401
11 Safety Analysis
11.1 Adverse Events
11.1.11 Listing of Non-Serious COPD Exacerbation

Safety population

Subject Number	Start / End Date and Time of Events	Relative days*	Pattern/ Severity	Action Taken with Study Drug	Causality to Study Drug	Outcome	(a)	(b)	(c)	(d)	(e)	(f)
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x	INTERMITTENT/ MILD	DRUG WITHDRAWN	DOUBTFUL/UNLIKEI	RECOVERING/ RESOLVING	Y	N	N	N	N	N
xxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x	CONTINUOUS/ MODERATE	DOSE NOT CHANGED	DEFINITE	RECOVERED / RESOLVED WITH SEQUELAE	Y	Y	Y	Y/Y/ CLEAR	Y	N
xxxx	yyyy-mm-ddThh:mm / yyyy-mm-ddThh:mm	x	CONTINUOUS/ MODERATE	DOSE NOT CHANGED	DEFINITE	RECOVERED / RESOLVED WITH SEQUELAE	Y	N	N	N	N	N
…	…	…	…	…	…							

* Study start date =< Onset date of event: Onset date of event - Study start date + 1, Study start date > Onset date of event: Onset date of event - Study start date

* (a)Did the subject withdraw from the study as a result of this event? / (b)Did the subject experience increased dyspnea? / (c)Did the subject experience increased cough? / (d)Did the subject expectorate sputum?/ more than usual?/ The color / (e)Did the subject increase their usual treatment? / (f)Did the subject take antibiotics or oral steroids?

>Sort order;
Subject Number, Start Date of Events , Start Time of Events

GTI 1401
11 Safety Analysis
11.2 Laboratory tests
11.2.1 Summary Table of Laboratory Test

Safety population
Albumin [g/L]

Visit Statistics	Original Value	Change from Baseline
Baseline		
N	xx x	-
Mean(S.D.)	xx.x (xx x.)	-
Median	xx x	-
Min , Max	xx x , xx.x	-
Week 5		
N	xx x	xx x
Mean(S.D.)	xx.x (xx x.)	xx x (xx.x.)
Median	xx x	xx x
Min , Max	xx x , xx.x	xx x , xx x
Week 9		
N	xx x	xx x
Mean(S.D.)	xx.x (xx x.)	xx x (xx.x.)
Median	xx x	xx x
Min , Max	xx x , xx.x	xx x , xx x

>All chemistry and hematology laboratory parameter will be summarized in same layout.

>Row 7 column 3 will be changed by the laboratory parameter.

GTI 1401
11 Safety Analysis
11.2 Laboratory tests
11.2.2 Summary Shift Table of Laboratory Test (Low, Normal and High)

Safety population
Albumin

	Baseline				
	Low	Normal	High	Missing	Total
Week 5					
Low	xx	xx	xx	xx	xx
Normal	xx	xx	xx	xx	xx
High	xx	xx	xx	xx	xx
Missing	xx	xx	xx	xx	xx
Total	xx	xx	xx	xx	xx
Week 9					
Low	xx	xx	xx	xx	xx
Normal	xx	xx	xx	xx	xx
High	xx	xx	xx	xx	xx
Missing	xx	xx	xx	xx	xx
Total	xx	xx	xx	xx	xx

>All chemistry and hematology laboratory parameter will be summarized in same layout.

>Row 7 column 3 will be changed by the laboratory parameter.

GTI 1401
11 Safety Analysis
11.2 Laboratory tests
11.2.3 Summary Shift Table of Laboratory Test (Normal and Abnormal)

Safety population
pH

	Baseline			
	Normal	Abnormal	Missing	Total
Week 5				
Normal	xx	xx	xx	xx
Abnormal	xx	xx	xx	xx
Missing	xx	xx	xx	xx
Total	xx	xx	xx	xx
Week 9				
Normal	xx	xx	xx	xx
Abnormal	xx	xx	xx	xx
Missing	xx	xx	xx	xx
Total	xx	xx	xx	xx

>All urine parameter will be summarized in same layout.

>Row 7 column 3 will be changed by the laboratory

GTI 1401
11 Safety Analysis
11.2 Laboratory tests
11.2.3 Listing of Laboratory Parameters

Safety population

Subject Number	Parameter	Visit	Baseline	Date of Sample Collection	Standard Value	Change from Baseline	Normal Range
xxxx	Albumin [g/L]	Week 1	Y	yyyy-mm-dd	xx/H		xx< <xx
		Week 5		yyyy-mm-dd	xx	xx	xx< <xx
		Week 9		yyyy-mm-dd	xx/L	xx	xx< <xx
xxxx	Alkaline Phosphatase	Week 1	Y	yyyy-mm-dd	xx		xx< <xx
		Week 5		yyyy-mm-dd	xx	xx	xx< <xx
		Week 9		yyyy-mm-dd	xx	xx	xx< <xx

* 'H' / 'L' indicates value is higher / lower than normal range respectively.

>Sort order;
Subject Number, Parameter (alphabetical order), Date of Sample Collection

GTI 1401
11 Safety Analysis
11.3 Vital Signs
11.3.1 Summary Table of Vital Signs

Safety population
Pulse rate [BEATS/MIN]

Parameter Visit Statistics	Original Value	Change from Baseline
Week 1 IMMEDIATELY PRIOR TO START OF INFUSION (Baseline)		
N	xx x	-
Mean(S.D.)	xx x (xx x.)	-
Median	xx x	-
Min , Max	xx x , xx.x	-
Week 1 IMMEDIATELY AFTER COMPLETION OF INFUSION		
N	xx x	xx x
Mean(S.D.)	xx x (xx x.)	xx x (xx x.)
Median	xx x	xx x
Min , Max	xx x , xx.x	xx x , xx x
Week 2 IMMEDIATELY PRIOR TO START OF INFUSION		
N	xx x	xx x
Mean(S.D.)	xx x (xx x.)	xx x (xx x.)
Median	xx x	xx x
Min , Max	xx x , xx.x	xx x , xx x
Week 2 IMMEDIATELY AFTER COMPLETION OF INFUSION		
N	xx x	xx x
Mean(S.D.)		xx x (xx x.)
Median	xx x	xx x
Min , Max	xx x , xx.x	xx x , xx x
• • •		
Week 9 IMMEDIATELY AFTER COMPLETION OF INFUSION		
N	xx x	xx x
Mean(S.D.)	xx x (xx x.)	xx x (xx x.)
Median	xx x	xx x
Min , Max	xx x , xx.x	xx x , xx x

GTI 1401
11 Safety Analysis
11.3 Vital Signs
11.3.1 Summary Table of Vital Signs

Safety population
Pulse rate [BEATS/MIN]

Parameter Visit Statistics	Original Value	Change from Baseline

>Following vital sign parameter will be summarized in same layout.
"Systolic blood pressure [mmHg]"
"Diastolic blood pressure [mmHg]"
"Body Temperature [C]"
"Respiratory rate [breaths per minute]"

>Row 7 column 3 will be changed by vital sign parameter to following;
"Systolic bloodp pressure [mmHg]"
"Diastolic blood pressure [mmHg]"
"Body temperature [C]"
"Respiratory rate [breaths per minute]"

GTI 1401
11 Safety Analysis
11.3 Vital Signs
11.3.2 Listing of Vital Signs

Safety population

Subject Number	Parameter	Visit	Baseline	Date / time of Sample Collection	Original Value	from baseline
xxxx	Pulse rate[BEATS/MIN]	Week 1 IMMEDIATELY PRIOR TO START OF	Y	yyyy-mm-ddThh mm	100	-
		Week 1 IMMEDIATELY AFTER COMPLETION OF INFUSION		yyyy-mm-ddThh mm	105	121
		Week 2 IMMEDIATELY PRIOR TO START OF				
		Week 2 IMMEDIATELY AFTER COMPLETION OF INFUSION		yyyy-mm-ddThh mm	98	125
		.....		.....	.....	.....
	Systolic blood pressure [mmHg]	Week 1 IMMEDIATELY PRIOR TO START OF	Y			
	Diastolic blood pressure [mmHg]	Week 1 IMMEDIATELY PRIOR TO START OF	Y			
	Body temperature [C]	Week 1 IMMEDIATELY PRIOR TO START OF	Y	yyyy-mm-ddThh mm	xx	-
	Respiratory rate [breaths per minute]	Week 1 IMMEDIATELY PRIOR TO START OF	Y	yyyy-mm-ddThh mm	xx	-
		.....		.....	.....	.....
xxxx	Pulse rate[BEATS/MIN]	Week 1 IMMEDIATELY PRIOR TO START OF	Y	yyyy-mm-ddThh mm	xx	-

>Sort order;
Subject Number, Parameter , Visit

GTI 1401
11 Safety Analysis
11.4 Electrocardiogram
11.4.1 Summary Table of Electrocardiogram

Safety population

		N=88			
		Baseline			
Electrocardiogram		Normal	Abnormal	Missing	Total
Week 9	Normal	xx	xx	xx	xx
	Abnormal	xx	xx	xx	xx
	Missing	xx	xx	xx	xx
	Total	xx	xx	xx	xx

> Analysis visit for 1401-OLE;
Baseline
Ext Week 26
Ext Week 52

GTI 1401
11 Safety Analysis
11.4 Electrocardiogram
11.4.2 Listing of Electrocardiogram

Safety population

Subject Number	Visit	Baseline	Date of Electrocardiogram Performed	Value
xxxx	Week 1	Y	yyyy-mm-dd	NORMAL
	Week 9		yyyy-mm-dd	NORMAL
xxxx	Week 1	Y	yyyy-mm-dd	ABNORMAL
	Week 9		yyyy-mm-dd	ABNORMAL
...	...		...	...

>Sort order;
Subject Number, Visit

GTI 1401
11 Safety Analysis
11.5 Urine Cotinine Tests
11.5.1 Summary Table of Urine Cotinine Test

Safety population

		N=88			
		Baseline			
Urine Cotinine Test		Negative	Positive	Missing	Total
Week 5	Negative	xx	xx	xx	xx
	Positive	xx	xx	xx	xx
	Total	xx	xx	xx	xx
Week 9	Negative	xx	xx	xx	xx
	Positive	xx	xx	xx	xx
	Total	xx	xx	xx	xx

> Analysis visit for 1401-OLE;
Baseline
Ext Week 26
Ext Week 52

GTI 1401
11 Safety Analysis
11.5 Urine Cotinine Test
11.5.2 Listing of Urine Cotinine Test

Safety population

Subject Number	Visit	Baseline	Date of Sample Collection	Value
xxxx	SCREENING	Y	yyyy-mm-dd	NEGATIVE
	Week 5		yyyy-mm-dd	NEGATIVE
	Week 9		yyyy-mm-dd	NEGATIVE
xxxx	SCREENING	Y	yyyy-mm-dd	POSITIVE
	Week 5		yyyy-mm-dd	POSITIVE
	Week 9		yyyy-mm-dd	POSITIVE
…	…	…	…	…

>Sort order;
Subject Number, Visit

GTI 1401
11 Safety Analysis
11.6 Pulmonary Function Tests
11.6.1 Summary Table of Pulmonary Function Tests (FEV1 and FVC)

Safety population
PRE-BRONCHODILATOR

	Best FEV [L]		Best FVC [L]		FEV1 predicted [%]	
Visit	Original Value	Change from Baseline	Original Value	Change from Baseline	Original Value	Change from Baseline
SCREENING						
N	xx x	-	xx x	-	xx x	-
Mean(S.D.)	xx x (xx x)	-	xx x (xx.x)	-	xx.x (xx.x)	-
Median	xx x	-	xx x	-	xx.x	-
Min , Max	xx x , xx x	-	xx.x , xx x	-	xx x , xx x	-
Week 5						
N	xx x	xx.x	xx x	xx x	xx x	xx.x
Mean(S.D.)	xx x (xx x)	xx.x (xx.x)	xx x (xx.x)	xx x (xx x)	xx.x (xx.x)	xx.x (xx x)
Median	xx x	xx.x	xx x	xx x	xx x	xx.x
Min , Max	xx x , xx x	xx x , xx x	xx.x , xx x	xx x , xx x	xx x , xx x	xx x , xx x
Week 9						
N		xx.x	xx x	xx x	xx x	xx.x
Mean(S.D.)	xx x (xx x)	xx.x (xx.x)	xx x (xx.x)	xx x (xx x)	xx.x (xx.x)	xx.x (xx x)
Median	xx x	xx.x	xx x	xx x	xx x	xx.x
Min , Max	xx x , xx x	xx x , xx x	xx.x , xx x	xx x , xx x	xx x , xx x	xx x , xx x

>Value for "POST-BRONCHODILATOR" will be summarized after "PRE-BRONCHODILATOR"

>Row 7 and column 3 will be change to "POST-BRONCHODILATOR"

>Analysis visit for 1401-OLE;
-SCREENING (Baseline), Ext Week 26, Ext Week 52

GTI 1401
11 Safety Analysis
11.6 Pulmonary Function Tests
11.6.2 Summary Table of Pulmonary Function Tests (FEV1 % Predicted)

Safety population
PRE-BRONCHODILATOR

FEV1 % predicted Visit Statistics	N=88 n
SCREENING	
0=< < 30	-
30=< < 70	xx (xx.x)
70=< <100	-
Missing	-
Total	-
Week 5	
0=< < 30	xx (xx.x)
30=< < 70	xx (xx.x)
70=< <100	xx (xx.x)
Missing	xx (xx.x)
Total	xx (xx.x)
Week 9	
0=< < 30	xx (xx.x)
30=< < 70	xx (xx.x)
70=< <100	xx (xx.x)
Missing	xx (xx.x)
Total	xx (xx.x)

>Value for "POST-BRONCHODILATOR" will be summarized after "PRE-BRONCHODILATOR"

>Row 7 and column 3 will be change to "POST-BRONCHODILATOR"

>Analysis visit for 1401-OLE;

GTI 1401
11 Safety Analysis
11.6 Pulmonary Function Tests
11.6.3 Listing of Pulmonary Function Tests

Safety population

Subject Number	Parameter	Visit	Baseline	Date / Time of Sample Collection	Original Value	Change from Baseline
xxxx	Best FEV1 [L]	SCREENING (PRE-BRONCHODILATOR)	Y	yyyy-mm-ddThh:mm	xx	-
		Week 5 (PRE-BRONCHODILATOR)		yyyy-mm-ddThh:mm	xx	xx
		Week 9 (PRE-BRONCHODILATOR)		yyyy-mm-ddThh:mm	xx	xx
	Best FVC [L]	SCREENING (PRE-BRONCHODILATOR)	Y	yyyy-mm-ddThh:mm	xx	-
		Week 5 (PRE-BRONCHODILATOR)		yyyy-mm-ddThh:mm	xx	xx
		Week 9 (PRE-BRONCHODILATOR)		yyyy-mm-ddThh:mm	xx	xx
	FEV1 predicted [%]	SCREENING (PRE-BRONCHODILATOR)	Y	yyyy-mm-ddThh:mm	xx	-
		Week 5 (PRE-BRONCHODILATOR)		yyyy-mm-ddThh:mm	xx	xx
		Week 9 (PRE-BRONCHODILATOR)		yyyy-mm-ddThh:mm	xx	xx
	Best FEV1 [L]	SCREENING (POST-BRONCHODILATOR)	Y	yyyy-mm-ddThh:mm	xx	-
		Week 5 (POST-BRONCHODILATOR)		yyyy-mm-ddThh:mm	xx	xx
		Week 9 (POST-BRONCHODILATOR)		yyyy-mm-ddThh:mm	xx	xx

>Sort order;
Subject Number, Parameter , Visit

GTI 1401
11 Safety Analysis
11.7 Pregnancy Tests
11.7 Listing for Pregnancy Tests

Safety population

Subject Number	Visit	Date of Sample Collection	Test Result
xxxx	SCREENING	yyyy-mm-dd	NEGATIVE
	Week 5	yyyy-mm-dd	NEGATIVE
	Week 9	yyyy-mm-dd	NEGATIVE
xxxx	SCREENING	yyyy-mm-dd	NEGATIVE
	Week 5	yyyy-mm-dd	NEGATIVE
	Week 9	yyyy-mm-dd	NEGATIVE

>Sort order;
Subject Number, Visit

GTI 1401
11 Safety Analysis
11.8 CT Scan
11.8 Listing for CT Scan

Safety population

Subject Number	Visit	Date of Scan Performed	Apparent Pulmonary Emphysema Diagnosed	Was a CT Scan performed	Lung Density [Unit]
xxxx	SCREENING	yyyy-mm-dd	Y	Y	xx.xx
xxxx	SCREENING	yyyy-mm-dd	N	Y	xx.xx
xxxx	SCREENING	yyyy-mm-dd		N	xx.xx

>Sort order;
Subject Number, Visit

>In this listing, if the record "not done" is exist in data, "not done" record will be presented.

GTI 1401
11 Safety Analysis
11.9 Physical Examination
11.9 Listing for Physical Examination

Safety population

Subject Number	Visit	Date of Examination	Category of Physical Examination	Completion Status for Examination	Reason for Abnormal or Not Done
xxxx	SCREENING	yyyy-mm-dd	GENERAL APPEARANCE	Y	
			HEENT	Y	
			CARDIOVASCULAR	N	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			RESPIRATORY	Y	
			ABDOMINAL	Y	
			SKIN	Y	
			EXTREMITIES	Y	
			NEUROLOGIC	Y	
			MUSCULOSKELETAL	Y	
			LYMPHATIC	Y	
			OTHER / xxxxxxxxxxxxxxxxx	Y	
	Week 9	yyyy-mm-dd	GENERAL APPEARANCE	Y	
			HEENT	Y	
			CARDIOVASCULAR	Y	
			RESPIRATORY	Y	
			ABDOMINAL	Y	
			SKIN	Y	
			EXTREMITIES	Y	
			NEUROLOGIC	Y	
			MUSCULOSKELETAL	Y	
			LYMPHATIC	Y	
			OTHER / xxxxxxxxxxxxxxxxx	Y	

GTI 1401
11 Safety Analysis
11.9 Physical Examination
11.9 Listing for Physical Examination

Safety population

Subject Number	Visit	Date of Examination	Category of Physical Examination	Completion Status for Examination	Reason for Abnormal or Not Done

>Sort order;
Subject Number, Visit, Category of Physical Examination

>In this listing, if the record "not done" is exist in data, "not done" record will be presented.