Official Title: Phase I/II Multicenter, Open-label Trial to Evaluate the Safety and Pharmacokinetics of Alpha-1 MP in Patients with Alpha1-Antitrypsin Deficiency

NCT Number: NCT02870309

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Protocol

Phase I/II Multicenter, Open-label Trial to Evaluate the Safety and Pharmacokinetics of Alpha-1 MP in Patients with Alpha$_1$-Antitrypsin Deficiency

Sponsor: Grifols Japan K.K.

Protocol No.: GTI1401
Version No.: 1.3 (for Ver1.5J)
Prepared on: 05 July 2016

Phase I/II Multicenter, Open-label Trial to Evaluate the Safety and Pharmacokinetics of Alpha-1 MP in Patients with Alpha1-Antitrypsin Deficiency

SIGNATURE/APPROVAL PAGE

Sponsor

[redacted], MD Date

Grifols Therapeutics Inc.
USA

PROTOCOL SYNOPSIS

Title of Study		Phase I/II Multicenter, Open-label Trial to Evaluate the Safety and Pharmacokinetics of Alpha-1 MP in Patients with Alpha$_1$-Antitrypsin Deficiency
Protocol Identification No.		GTI1401
Investigational Drug Code		Alpha-1 MP
Type of Study (Phase of Development)		Clinical pharmacology study/Exploratory study (Phase I/II)
Study Objective		To evaluate the safety and pharmacokinetics of weekly intravenous infusions of 60 mg/kg of Alpha-1 MP for 8 weeks in subjects with alpha$_1$-antitrypsin deficiency
Study Design		This study is a multicenter, open-label trial to evaluate the safety and pharmacokinetics of weekly intravenous infusions of 60 mg/kg of Alpha-1 MP for 8 weeks.
Subject Selection	Study population	Subjects: Adult patients with alpha$_1$-antitrypsin deficiency Target sample size: A minimum of 3 subjects
	Inclusion criteria	1. Subjects aged ≥20 years at the time of providing informed consent 2. Subjects with clinically apparent pulmonary emphysema diagnosed by CT scan 3. Subjects with documented serum alpha$_1$-PI levels of <50 mg/dL as measured by nephelometry. In subjects with no previously documented serum alpha$_1$-PI levels, their serum alpha$_1$-PI levels measured by nephelometry during the screening period must be <50 mg/dL. 4. Subjects whose percentage of forced expired volume in 1 second/Forced vital capacity (FEV_1/FVC) after inhalation of a bronchodilator is <70% during the screening period 5. Subjects who are willing and able to provide signed written informed consent
	Exclusion criteria	1. Subjects with moderately or severely deteriorated lung function in the 4 weeks before the Week 1 (baseline) visit 2. Subjects whose percentage of forced expired volume in 1 second (%FEV_1) after inhalation of a bronchodilator is <30% during the screening period 3. Subjects who have undergone lung transplantation or liver transplantation 4. Subjects who have undergone any lung surgery (excluding lung biopsy) in the past 2 years 5. Subjects with increased liver enzymes (AST, ALT, and ALP) ≥2.5 times the upper limit of normal

		6. Subjects with severe complications, including but not limited to, congestive heart failure and liver cirrhosis 7. Subjects who have developed any malignant tumor (including malignant melanoma; however, other forms of skin cancer are excluded) in the past 5 years 8. Pregnant women, breastfeeding women, or women of childbearing potential who do not intend to use effective contraceptive methods throughout the trial period or male subjects who have a partner who is of childbearing potential and is unwilling to use effective contraceptive methods throughout the trial period. 9. Subjects with a past history of HAV, HBV, HCV, or HIV infection, or subjects currently presenting with clinical signs or symptoms suggestive of such infection 10. Subjects with a smoking history in the past 6 months, or subjects tested positive for urinary cotinine levels at the screening visit 11. Subjects participating in another clinical trial within 4 weeks before the Week 1 (baseline) visit 12. Subjects with a history of anaphylactic or severe systemic reactions to any plasma derived alpha$_1$-PI product or other blood products 13. Subjects who have continuously received any systemic steroid therapy at a prednisone-equivalent dose >5 mg/day within 4 weeks before the Week 1 (baseline) visit (Note: inhaled steroids are not regarded as systemic steroids) 14. Subjects who have used any systemic or aerosolized antibiotic drug for the treatment of COPD exacerbation within 4 weeks before the Week 1 (baseline) visit 15. Subjects with a previous or current diagnosis of selective, severe IgA deficiency 16. Subjects who are mentally challenged and cannot independently give consent 17. Subjects who have difficulty in adhering to the protocol or its procedures in the opinion of the investigator 18. Subjects who have medical conditions that may confound the results of this clinical trial or may endanger these subjects during their participation in this clinical trial in the opinion of the investigator
Investigational Drug		Alpha-1 MP: Sterile, lyophilized preparation (each vial contains approximately 1000 mg of functionally active alpha$_1$-PI)
Endpoints	Safety evaluation	To evaluate adverse events (nature, severity, frequency) occurring after the start of investigational drug administration until the end of the follow-up period (i.e., 1 week after the last dose for subjects entering the extension trial [Study No. GTI1401-OLE] after this clinical trial; 4 weeks after the last dose for subjects not entering the extension trial), all clinically unfavorable signs

		(including abnormal changes in clinical laboratory values [blood chemistry, hematology, urinalysis] and vital signs [blood pressure, pulse rate, respiratory rate, body temperature]) and symptoms will be investigated. In addition, COPD exacerbations and pulmonary function tests (FEV_1 and FVC) will be evaluated.
	Pharmaco kinetic evaluation	To evaluate alpha$_1$-PI trough concentrations, samples will be collected prior to infusion at Weeks 1 (baseline), 7, and 8 and at Week 9 visits. For PK parameters ($AUC_{0\text{-}7\ days}$, C_{max}, t_{max}, and $t_{½}$), blood samples for PK evaluation will be collected at 10 time points until the 7th day after the last dose in Week 8 (i.e., immediately before dosing, and at immediately post-infusion [0], 0.25, 2, 4, 8, 24, 48, 120, and 168 hours after dosing [Week 9]).
Study Centers and Investigators		Refer to Attachment “Study Centers and Investigators List”
Study Period		January 2016 to March 2017.

List of Abbreviation

Abbreviation	Full expression without abbreviation
°C	degree Celsius
°F	degree Fahrenheit
AATD	$Alpha_1$-Antitrypsin Deficiency
ADR	Adverse Drug Reaction
AE	Adverse Events
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
B19V	Parvovirus B19
ChAMP	Pharmacokinetic Comparability of Alpha-1 MP Study
C_{max}	Maximum concentration
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRA	Clinical Research Associate
CRO	Contract Research Organization
CT	Computed Tomography
CV	Coefficient of variation
dL	Deciliter
DNA	Deoxyribonucleic Acid
ERS	European Respiratory Society
FEV_1	Forced Expired 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
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed Consent Form
IgA	Immunoglobulin A

IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRB/EC	Institutional Review Board / Ethics Committee
IUD	Intrauterine Device
IUS	Intrauterine Contraceptive System
IV	Intravenous
kg	Kilogram
µM	Micromolar
MDI	Metered dose inhaler
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
NaCl	Sodium chloride
NAT	Nucleic Acid Amplification Technology
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 Homozygote for Z (Deficiency) Allele of the Alpha1-Proteinase Inhibitor Gene
pH	Potential of hydrogen; acidity / alkalinity measure
PK	Pharmacokinetics
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SPARK	Alpha-1 MP Safety and Pharmacokinetic Study
STAMP	Safety and Tolerability of Alpha-1 MP study
$t_{½}$	Terminal half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time to reach C_{max}

Table of Contents

1. INTRODUCTION

1.1 Alpha$_1$-Antitrypsin Deficiency

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 (1-3).

The most frequent mutation causing severe AATD is called PI*Z and was first described in a Swedish patient with emphysema (4). 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 (5). The estimated world-wide prevalence of PI*ZZ and PI*SZ (heterozygous abnormal) individuals is approximately 163,700 and 903,000, respectively (6).

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 (7). 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 (7). 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 (7). 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 [8]).

1.2 Alpha$_1$-PI Replacement Therapy

Within the lung airways, neutrophil recruitment is thought to be an important component of continuing inflammation and progression of COPD (9). When neutrophils phagocytize, an array of enzymes, including proteases such as neutrophil elastase (NE) may destroy tissue. Alpha$_1$-PI is the most abundant circulating tissue inhibitor of NE (10,11) and constitutes an important part of the lung's protective protease inhibitory shield and maintenance of the normal protease:antiprotease balance in the lungs (12). In AATD, there appears to be an inadequate protective protease inhibitory shield (12-14), a disruption of the normal protease:antiprotease balance (12,15,16) and an unopposed action of NE leading to destruction of lung matrix and the development of emphysema (12-14,17-19).

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 (16,20-22). The restored antiprotease shield then protects the lung from elastolytic damage and slows or prevents the development of pulmonary emphysema (23,24).

The serum level of alpha$_1$-PI in normal individuals ranges from approximately 20 to 53 μM (5), and the historical serum alpha$_1$-PI therapeutic target trough level of 11 μM was proposed as a "protective threshold" to prevent the development of progressive lung disease (20,21). This was based on a comparison of the apparent risk of emphysema among AATD individuals (PI*null/null, PI*ZZ, and PI*SZ) which Gadek and colleagues at the National Heart, Lung, and Blood Institute had conducted, and they inferred "that the hypothetical 'threshold' level of serum alpha$_1$-antitrypsin necessary to protect against lung proteolysis resides in the range of ~ 35% of normal" (20). Subsequently, it was demonstrated that augmentation with 60 mg/kg alpha$_1$-PI administered by weekly IV infusions consistently achieved trough serum alpha$_1$-PI concentrations above 11 μM (22). As previously noted, Japanese patients homozygous for the S$_{iiyama}$ AATD variant have serum alpha$_1$-PI levels in the range of 2.1 to 7.7 μM (Section 1.1), which is below the suggested 11 μM "protective threshold" serum alpha$_1$-PI level.

1.3 Alpha-1 MP: Human Alpha$_1$-Proteinase Inhibitor from a Modified Manufacturing Process

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. Prolastin is currently authorized in 14 European Union countries as well as in Switzerland and Brazil. 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, Columbia, Argentina, and Tarky for the treatment of patients with severe AATD and clinically evident emphysema under the trade name Prolastin®-C.

Two studies have examined Alpha-1 MP at the 60 mg/kg dose given weekly by IV infusion to AATD subjects. The STAMP (Safety and Tolerability of Alpha-1 MP) study was a multi-center, open-label study to evaluate the safety and tolerability of Alpha-1 MP. In the

STAMP study, 38 subjects with AATD were treated with Alpha-1 MP at 60 mg/kg for 20 weeks. Suspected adverse drug reactions (ADRs; i.e., drug-related adverse events [AEs]) were chills, malaise, headache, rash, and hot flush. The ChAMP (pharmacokinetic Comparability of Alpha-1 MP) study was a multi-center, randomized, double-blind, crossover study to evaluate the pharmacokinetic (PK) comparability of Alpha-1 MP and Prolastin in 24 subjects with AATD. The study consisted of two 8-week double-blind treatment periods during which study subjects received either 60 mg/kg of Alpha-1 MP or 60 mg/kg of Prolastin, weekly by IV infusion, followed by 60 mg/kg weekly of Alpha-1 MP in an 8-week open-label treatment phase. Alpha-1 MP was determined to be pharmacokinetically equivalent to Prolastin, and the elimination half-life of Alpha-1 MP was 146 hours (*i.e.*, 6 days) as measured by functional activity assay. The only suspected ADR for Alpha-1 MP in the ChAMP study was mild pruritis/itching.

Subsequent to the STAMP and ChAMP studies, the SPARK (Alpha-1 MP Safety and PhARmacoKinetic) study was conducted to assess the safety and PK of weekly IV infusions of Alpha-1 MP at 120 mg/kg compared to the US-approved 60 mg/kg dose in 30 subjects with AATD. The study was a crossover design; thus, subjects received Alpha-1 MP at either 60 or 120 mg/kg for 8 weeks and then were switched to the alternate dose for an additional 8 weeks. Subjects completed a 2-week washout period prior to switching to the alternate dose. Results from the study showed that steady-state serum concentrations of Alpha-1 MP were dose-proportional between the 60 mg/kg and 120 mg/kg doses. The weekly dose of 120 mg/kg Alpha-1 MP provided an average mean trough level of alpha1-PI of 27.7 μM, which was within the reported range of alpha1-PI serum levels (20 to 53 μM) in normal, non-AATD individuals. Both the 60 mg/kg and 120 mg/kg weekly doses of Alpha-1 MP were safe and well tolerated.

1.4 Rationale for this Clinical Trial

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 (see Section 1.1). 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 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.

2. STUDY ADMINISTRATIVE STRUCTURE

Please refer to Appendix 2 for the study administrative studructure of this study such as;

- SPONSOR
- CONTRACT RESEARCH ORGANIZATION
- STUDY CENTERS
- LABORATORY TESTING SERVICES, TRANSPORTER, INVESTIGATIONAL DRUG MANUFACTURER

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the safety of 60 mg/kg Alpha-1 MP administered by weekly IV infusions over 8 weeks in Japanese subjects with AATD.

3.2 Secondary Objective

The secondary objective of this 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.

3.3 Exploratory Objective

The following PK parameters for Alpha$_1$-PI are to be measured 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

4. INVESTIGATIONAL PLAN

4.1 Study Design and Plan

4.1.1 Design and Plan of this Clinical Trial

This study is a multicenter, open-label trial to evaluate the safety and pharmacokinetics of weekly intravenous infusions of 60 mg/kg of the investigational drug in subjects with AATD. The trial will be conducted at approximately 5 medical institutions in Japan, aiming to enroll a minimum of 3 adult subjects or more. The trial will consist of a screening period scheduled within 3 weeks before trial entry, an open-label treatment period for 8 weeks, and a PK evaluation period for 1 week. 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. Subjects will participate in this trial for approximately 14 weeks from the start of the screening period through the completion of the trial.

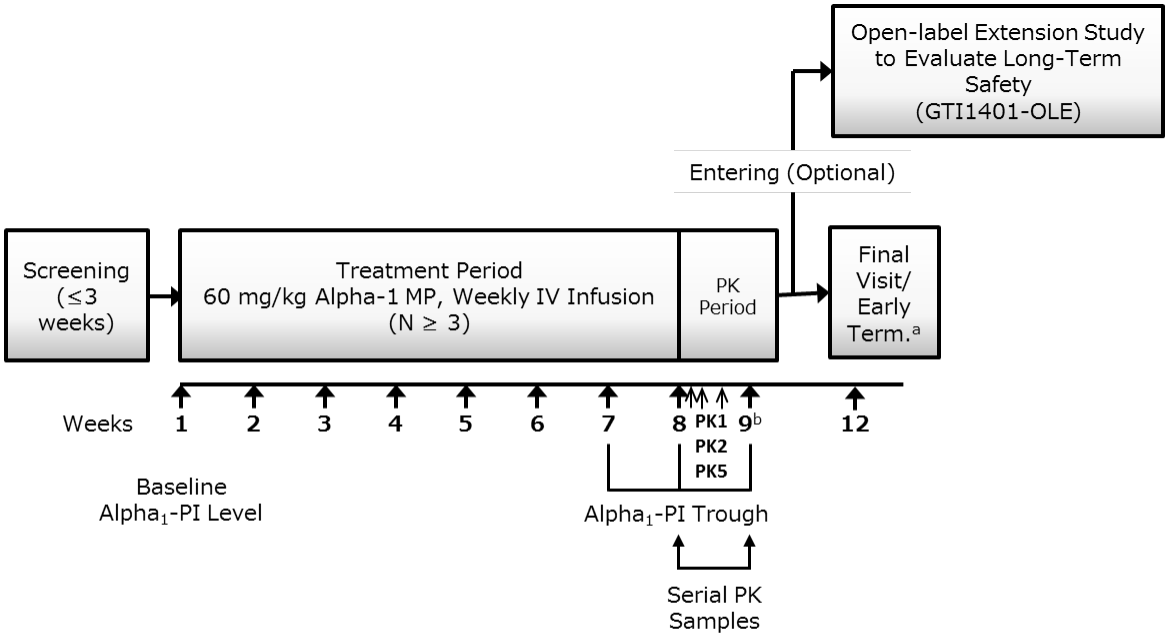
At the screening visit (scheduled within 3 weeks before trial entry), after providing informed consent (agreement based on adequate explanation and understanding of the treatment plan), subjects will be evaluated for eligibility for participation during the screening period (refer to Section 4.2.1 “Inclusion Criteria” and Section 4.2.2 “Exclusion Criteria”). Subjects considered eligible will enter the 8-week treatment period to receive a total of 8 weekly intravenous infusions of 60 mg/kg of Alpha-1 MP. The initial intravenous infusion will be given at the Week 1 (baseline) visit. During the treatment period, subjects will receive weekly intravenous infusions of Alpha-1 MP at the Weeks 1 (baseline), 2, 3, 4, 5, 6, 7, and 8 visits. After the last intravenous infusion of Alpha-1 MP at the Week 8 visit, subjects will enter the 1-week PK evaluation period. During this PK evaluation period, subjects will visit the study center to undergo blood sampling for PK evaluation at the PK1 visit (the next day of the Week 8 visit), the PK2 visit (2 days after the Week 8 visit), the PK5 visit (5 days after the Week 8 visit), and at the Week 9 visit. At 30 days after the last dose (Week 8), subjects will visit the study center for follow-up/study completion (Week 12). All subjects will undergo blood sampling for the measurement of $alpha_1$-PI trough concentrations at the Weeks 1 (baseline), 7, and 8 visits (blood samples will be collected before dosing) as well as at the Week 9 visit.

Blood samples for the evaluation of PK parameters will be collected from Week 8 to Week 9. The blood sample collected before the infusion of Alpha-1 MP at the Week 8 visit and the blood sample for PK evaluation collected at the Week 9 visit (7 days after the infusion at the Week 8 visit) will be also used for the measurement of $alpha_1$-PI trough concentrations for Weeks 8 and

9. For details of the total of 10 sequential PK blood sampling time points, refer to Section 4.7.2.2 and Appendix 1.

At the Week 9 visit, subjects will be asked whether they would like to participate in the extension trial (GTI1401-OLE). Subjects intending to participate in the extension trial will be able to continue the treatment with intravenous infusions of 60 mg/kg of Alpha-1 MP for at least another year (subjects will be further asked whether they would like to continue the treatment at yearly intervals) for the purpose of evaluation of the safety of long-term Alpha-1 MP treatment. Subjects not intending to enter the extension trial will visit the study center for follow-up/study completion at 30 days (4 weeks) after the last dose of Alpha-1 MP (Week 12).

The entire design of this clinical trial is shown in Figure 4-1, and its schedule is provided in Appendix 1.



[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 4-1 Overall study schema

4.1.2 Type of Study

Safety and clinical pharmacology study

4.1.3 Phase of Development

Phase II

4.2. Selection of Subject Population

Eligible subjects must provide written consent to participate in this clinical trial of their own free will after being fully informed of the contents of the trial based on the written information and informed consent form.

After obtaining written informed consent from each subject, the investigator or subinvestigator will screen the subject within 21 days before the first investigational drug infusion. The investigator will assess subject eligibility based on the inclusion criteria and the exclusion criteria below.

4.2.1 Inclusion Criteria

1. Subjects aged ≥20 years at the time of providing informed consent
2. Subjects with clinically apparent pulmonary emphysema diagnosed by CT scan
3. AATD subjects with documented serum alpha$_1$-PI levels of <50 mg/dL (i.e., 11 μM) as measured by nephelometry. In subjects with no previously documented serum alpha$_1$-PI levels, their serum alpha$_1$-PI levels measured by nephelometry during the screening period must be <50 mg/dL.
4. Subjects whose percentage of forced expired volume in 1 second/forced vital capacity (FEV_1/FVC) after inhalation of a bronchodilator is <70% during the screening period [equivalent to the criterion for the diagnosis of COPD]
5. Subjects who are willing to and able to provide signed written informed consent

<Rationale for establishing the inclusion criteria>

1. This criterion has been established as the target age group of subjects for this clinical trial.
2. This criterion has been established to include subjects with clinically evident emphysema based on the diagnostic criteria for designated intractable diseases with clinically evident pulmonary emphysema in this clinical trial. This CT scan will measure lung density.
3. This criterion has been established to enroll only subjects with alpha$_1$-PI deficiency in this clinical trial.

4. This criterion has been established to specify the acceptable levels of percentage of FEV_1/FVC for this clinical trial [equivalent to the criterion for the diagnosis of COPD].
5. This criterion has been established because written consent to participate in this clinical trial from each patient is required.

4.2.2 Exclusion Criteria

1. Subjects with moderately or severely deteriorated lung function in the 4 weeks before the Week 1 (baseline) visit
2. Subjects whose percentage of forced expired volume in 1 second (%FEV_1) after inhalation of a bronchodilator is <30% during the screening period
3. Subjects who have undergone lung transplantation or liver transplantation
4. Subjects who have undergone any lung surgery (excluding lung biopsy) in the past 2 years
5. Subjects with increased liver enzymes (AST, ALT, and ALP) ≥2.5 times the upper limit of normal
6. Subjects with severe complications including but not limited to congestive heart failure and liver cirrhosis
7. Subjects who have developed any malignant tumor (including malignant melanoma; however, other forms of skin cancer are excluded) in the past 5 years
8. Pregnant women, breastfeeding women, or women of childbearing potential who do not intend to use effective contraceptive methods (use of oral, injection, or implant hormonal contraceptives; placement of an intrauterine device (IUD) or intrauterine contraceptive system; concomitant use of spermatocidal foam, gel, film, cream, suppository and condoms or cervical caps; male sterilization; or abstinence) throughout the trial period or male subjects who have a partner who is of childbearing potential and is unwilling to use effective contraceptive methods throughout the trial period.
9. Subjects with a past history of HAV, HBV, HCV, or HIV infection, or subjects currently presenting with clinical signs or symptoms suggestive of such infection
10. Subjects with a smoking history in the past 6 months, or subjects tested positive for urinary cotinine levels at the screening visit
11. Subjects participating in another clinical trial within 4 weeks before the Week 1 (baseline) visit
12. Subjects with a history of anaphylactic or severe systemic reactions to any plasma derived $alpha_1$-PI product or other blood products
13. Subjects who have continuously received any systemic steroid therapy at a prednisone-equivalent dose >5 mg/day within 4 weeks before the Week 1 (baseline) visit (Note: inhaled steroids are not regarded as systemic steroids)
14. Subjects who have used any systemic or aerosolized antibiotic drug for the treatment of COPD exacerbation within 4 weeks before the Week 1 (baseline) visit

15. Subjects with a previous or current diagnosis of selective, severe IgA deficiency
16. Subjects who are mentally challenged and cannot independently give consent
17. Subjects who have difficulty in adhering to the protocol or its procedures in the opinion of the investigator
18. Subjects who have medical conditions that may confound the results of this clinical trial or may endanger other subjects during the participation in this clinical trial in the opinion of the investigator

<Rationale for establishing the exclusion criteria>

1. This criterion has been established to exclude subjects with this medical condition because the condition will affect pulmonary function tests (PFTs) and clinical laboratory tests, thereby precluding appropriate safety evaluation.
2. This criterion has been established to determine the range of percentage of forced expired volume in 1 second ($\%FEV_1$) to be excluded.
3. Same as 1 above.
4. Same as 1 above.
5. This criterion has been established to exclude subjects with any underlying disease that may affect clinical laboratory values and safety evaluation.
6. Same as 5 above.
7. Same as 5 above.
8. This criterion has been established because animal reproduction studies have not been conducted with $Alpha_1$-PI, the safety of $Alpha_1$-PI in pregnant women and their fetuses as well as its effects on fertility have not been established yet, and no results on the excretion of $Alpha_1$-PI into breast milk are available.
9. Same as 1 above.
10. This criterion has been established to exclude smokers who may be at risk for further deterioration of lung function and lung damage.
11. This criterion has been established to exclude any effect on the evaluation of adverse events and safety of this investigational drug.
12. Same as 11 above.
13. This criterion has been established to reduce clinical changes associated with the use of concomitant drugs and exclude factors that may affect symptomatic improvement.
14. Same as 1 above.
15. Same as 11 above.
16. This criterion has been established to exclude subjects in whom it is difficult to confirm whether they intend to consent or not.
17. This criterion has been established to exclude subjects who cannot adhere to the protocol.
18. Same as 11 above.

4.3. Investigational Drug

4.3.1 Investigational Drug

4.3.1.1 Investigational drug code

Alpha-1 MP

4.3.1.2 Investigational drug name

Alpha-1 MP

4.3.1.3 Content and dosage form

Alpha-1 MP is a stable, sterile, lyophilized preparation of human alpha$_1$-PI, also known as α_1-antitrypsin. Alpha-1 MP is supplied as a white to beige, lyophilized powder contained in a glass vial. Each vial of Alpha-1 MP contains the labeled amount of functionally active alpha$_1$-PI in milligrams per vial (each vial contains approximately 1,000 mg of functionally active alpha$_1$-PI). Alpha-1 MP contains no preservatives. Alpha-1 MP is reconstituted using a dissolving solution (20 mL of water for injection) as instructed in the Pharmacy Manual. Alpha-1 MP must be administered by an intravenous route.

Further information on the investigational drug is provided in the investigator's brochure.

4.3.1.4 Composition of the Preparation

The composition of the preparation per vial is shown in Table 4-1.

Table 4-1 Composition of Alpha-1 MP Preparation

Component	Content (per vial)	Quality standards
Alpha$_1$-Proteinase Inhibitor (Human)	Nominal 1,000 mg	WHO Standard
NaH_2PO_4	0.4 mmol	United States Pharmacopeia
NaCl	2.0 mmol	United States Pharmacopeia

4.3.2 Investigational Drug Labeling

4.3.2.1 Packaging

An individual package contains 10 labeled, transparent vials.

4.3.2.2 Labeling

The labels for the investigational drug on an individual package and a vial include the following information: the statements "For Investigational Use", investigational drug name, protocol No.,

instructions for use, expiration date, serial number, storage conditions, quantity, and sponsor's name and address. Sample labels on an individual package and a vial are shown below.

GRIFOLS
Protocol: GTI1401

Alpha1-Proteinase Inhibitor (Human), Modified Process
(Alpha-1 MP)

Contents:
- 10 Alpha-1 MP Vials
- 12 Filter Needles
- 12 Transfer Needles

SHIP AND STORE AT TEMPERATURES NOT TO EXCEED 25°C.
DO NOT FREEZE.
Reconstitute with 20 mL Sterile Water for Injection for a vial.
For intravenous administration only.
Dosage per Protocol.
For Clinical Trial Use Only.
Site No.: _____
Investigator's Name: _____

LOT
EXP.
mg α1-PI / vial

Grifols Japan K.K.
Level 19 Hilton Plaza West Office Tower
2-2-2 Umeda, Kita-ku, Osaka 530-0001, Japan

Figure 4-2 Sample Labeling for the Investigational Drug

Protocol: GTI1401

Alpha1-Proteinase Inhibitor (Human), Modified Process
(Alpha-1 MP)

Store at temperatures not to exceed 25°C. Do not freeze.
Reconstitute with 20 mL Sterile Water for Injection
For intravenous administration only. Dosage per Protocol.
For Clinical Trial Use Only.

Site No.: _____
Investigator's Name: _____
Patient ID: _____

LOT
EXP.
mg α1-PI / vial

Grifols Japan K.K.
Level 19 Hilton Plaza West Office Tower
2-2-2 Umeda, Kita-ku, Osaka 530-0001, Japan

Figure 4-3 Sample Labeling for the Investigational Drug

4.3.3 Dose and Dosage Regimen

4.3.3.1 Dose and dosage regimen

Subjects will receive a total of 8 IV infusions of 60 mg/kg Alpha-1 MP administered weekly.

The prescribed infusion rate for Alpha-1 MP is not to exceed 0.08 mL/kg/min as determined by the response and comfort of the subject. The recommended dose for this trial takes approximately 15 minutes per IV bag to infuse (based on ~70 kg subject).

4.3.3.2 Rationale for the dose

The recommended dose of Alpha-1 MP (commercially available as Prolastin-C) is 60 mg/kg body weight administered once weekly. Alpha-1 MP is currently approved for 60 mg/kg weekly IV administration in the US, Canada, Columbia, Argentina, and Turkey. As such, Alpha-1MP at a dose of 60 mg/kg body weight will be used in this study.

4.3.3.3 Rationale for the dosage regimen

Given that Alpha-1 MP has a serum half-life of approximately one week in Caucasians (see Section 1.3), weekly infusion is the preferable treatment regimen. Furthermore, the recommended dose of Alpha-1 MP is 60 mg/kg body weight administered once weekly. In

this study, subjects will receive IV-administered Alpha-1 MP once weekly for 8 weeks for a total of 8 infusions.

4.3.4 Storage of the Investigational Drug

Alpha-1 MP should be stored at a temperature not to exceed 25°C. Do not freeze. Alpha-1 MP must be stored in a secure area accessible only to designated study site personnel until dispensed for the study subject.

Alpha-1 MP should be kept at room temperature after reconstitution and should be administered within 3 hours after reconstitution.

Additional details are provided in the Pharmacy Manual.

4.3.5 Accountability of the Investigational Drug

Alpha-1 MP is to be used only for the study in accordance with the directions given in this protocol. The Primary Pharmacist responsible for management of the Investigational Product at the site, is responsible for the distribution of Alpha-1 MP in accordance with directions given in the protocol and Pharmacy Manual.

The Primary Pharmacist is responsible for maintaining accurate records of Alpha-1 MP for his/her site. Alpha-1 MP inventory/dispensing documentation verifying the receipt, dispensing, destruction, or return must be maintained and kept current by the Investigator, or designee. The inventory must be made available for inspection by the study monitor. Alpha-1 MP supplies must be accounted for by the study monitor and inventory/dispensing logs must be verified by the monitor prior to Alpha-1 MP return or destruction. Written documentation of all used and unused inventory is required. At the end of the study, a copy of the inventory/dispensing log(s) will be retrieved by the monitor and returned to Grifols Japan K.K.

4.4 Assignment Method

4.4.1 Subject Number

Within each study site, subjects in the study will receive a consecutive subject number. Subject numbers are generated beginning with the study center number (2 digits, assigned by the sponsor) followed consecutively with a unique number for each subject (2 digits, starting with 10). For example, if the Investigator’s center number is 10, subject numbers will be 1001, 1002, 1003, etc., in consecutive order. Subject numbers, once assigned, will not be reused at any center.

4.4.2 Blinding

This study is an open-label trial; thus, blinding procedures are not applicable.

4.4.3 Schedule for Investigational Drug Administration to Each Subject

Subjects will receive a total of 8 IV infusions of 60 mg/kg Alpha-1 MP administered weekly. Weekly infusions of Alpha-1 MP will be performed at the Investigator's study site under the care and supervision of the treating Investigator, or designee, during scheduled study visits at Weeks 1 (Baseline), 2, 3, 4, 5, 6, 7, and 8. Subjects will receive their first infusion of Alpha-1 MP at the Week 1 (Baseline) Visit and their last infusion at the Week 8 Visit.

Each week, designated study site personnel will prepare an infusion bag of Alpha-1 MP at the calculated volume based on the subject's body weight, and the subject will receive the contents of the infusion bag via IV administration.

The prescribed infusion rate for Alpha-1 MP is not to exceed 0.08 mL/kg/min as determined by the response and comfort of the subject. The recommended dose for this trial takes approximately 15 minutes per IV bag to infuse (based on ~70 kg subject). After completion of the infusion bag, each subject will receive a minimum of 25 mL of 0.9% Sodium Chloride for Injection to flush the IV line.

For each infusion, the total infusion volume prepared, total infusion time, total volume infused, and, if necessary, any infusion interruption with explanation will be documented.

Complete details are provided in the Pharmacy Manual.

4.4.4 Treatment Compliance

The volume of the Alpha-1 MP administered will be documented in the subject's source documentation and case report form (CRF). Reasons for any deviation from the administration of less than 100% of the prepared Alpha-1 MP dose (i.e., volume) must be recorded in the CRF and in the subject's source documentation.

4.5 Concomitant Medications and Other Restrictions

Concomitant medications must be recorded in the subject's source documentation and CRF, including the trade or generic names of the medication, dose, route of administration, duration, and frequency.

4.5.1 Prohibited Medications (Before Trial Entry)

Use of the following medications, as specified below, would exclude a subject from participating in this study:

- Systemic steroids above a stable dose equivalent to 5 mg/day prednisone (e.g., 10 mg every 2 days) within 4 weeks prior to the Week 1 (Baseline) Visit (Note: inhaled steroids are not considered systemic steroids)
- Systemic or aerosolized antibiotics for a COPD exacerbation within the 4 weeks prior to the Week 1 (Baseline) Visit

4.5.2 Prohibited Concomitant Medications

Use of the following medications is prohibited during study participation:

- Any other alpha$_1$-PI treatment
- Investigational products not part of this study

4.6. Endpoints

No efficacy variables will be assessed for this the study. The variables to be assessed for this study 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:
  - $AUC_{0\text{-}7\ days}$
  - C_{max}
  - t_{max}
  - $t_{½}$

4.6.1 Exacerbation of Chronic Obstructive Pulmonary Disease (COPD)

All COPD exacerbations occurring during the study will be recorded. The subject will be assessed for signs and symptoms of exacerbations at each study visit. 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 an SAE. If an exacerbation meets criteria for an 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.

This study will use the definition of exacerbation published in the "Outcomes for COPD pharmacological trials: from lung function to biomarkers," a report from an American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force (25). The definition of an exacerbation of COPD is an increase in respiratory symptoms (dyspnea, increased cough, and/or production of sputum) over baseline that usually requires medical intervention. Exacerbation severity is defined as:

- **Mild**: which involves an increase in one or more respiratory symptoms (dyspnea, cough, and/or sputum) that is controlled by the subject with an increase in the usual medication.
- **Moderate**: which requires treatment with systemic steroids and/or antibiotics.
- **Severe**: which describes exacerbations that require hospitalization (an emergency department stay > 24 hours is considered a hospitalization).

4.6.2 Pulmonary Function Test (PFT)

Pulmonary function tests (i.e., spirometry), including FEV_1 (absolute and present predicted) and FVC, will be performed according to ATS/ERS guidelines (26) at Screening Visit and Weeks 5, 9 and 12 (Appendix 1). Pulmonary function tests at Week 5 should be conducted prior to Alpha-1 MP infusion. At each visit in which PFTs are scheduled, testing will be performed pre-infusion both pre- and post-bronchodilator administration. The post-bronchodilator PFT should be performed 15 to 30 minutes after bronchodilator administration. For each PFT, 4 puffs of metered dose inhaler (MDI) salbutamol as a short-acting bronchodilator should be administered. The same bronchodilator should be used throughout the study.

4.7. Evaluation

4.7.1 Evaluation Period

This clinical trial will consist of the screening period scheduled within 3 weeks before trial entry; the open-label treatment period for 8 weeks; the PK evaluation period for 1 week; the Week 9 visit (at this visit, subjects will be asked whether or not they would like to enter an extension trial [GTI1401-OLE]); and the follow-up/study completion visit for subjects not intending to enter the extension trial (30 days [4 weeks] after the last dose of Alpha-1 MP). Subjects will participate in this trial for approximately 14 weeks from the start of the screening period through the completion of the trial (refer to Appendix 1 "Trial Schedule").

4.7.2 Observation and Measurement

The trial procedures and evaluations at each visit are described below. For a summary of the scheduled visits and the trial procedures and evaluations at each visit, refer to Appendix 1 "Trial Schedule." Unscheduled visits may be requested for subjects to ensure their safety if necessary.

4.7.2.1 Screening period

Prior to collection of screening evaluation data or the start of the trial, written consent must be obtained from all candidate subjects. Trial entry will start after the subjects sign their informed consent forms. Subject eligibility will be evaluated during the screening period.
The screening visit will occur within 3 weeks before the Week 1 (baseline) visit.

Visit	Trial Procedures and Evaluations
Screening (within 3 weeks)	• Informed consent • Eligibility evaluation based on the inclusion/exclusion criteria • PFT (FEV_1 and FVC) before and after administration of a bronchodilator (refer to Section 4.6.2) • Assignment of subject numbers • Medical history • Age, sex, • CT scan (This CT scan [densitometry] will be performed for documentation of emphysema at each study site, and CT scan data will be evaluated centrally for lung density at Vida Diagnostics, Inc.; see CT Scan Manual for detailed procedures) • Body height

	• Body weight • Physical examination (excluding breast and urogenital examination) • Laboratory tests (refer to Section 4.7.3) Urine samples: Urinalysis Urine pregnancy test: To be performed only in women of childbearing potential. Only women tested negative for pregnancy can continue the trial. Urinary cotinine level: Subjects tested positive for urinary cotinine are considered ineligible. Blood samples: Blood chemistry, hematology • $Alpha_1$-PI measurement: To be performed in subjects with no previously documented $alpha_1$-PI levels as measured by nephelometry (if it is unknown whether the subject's $alpha_1$-PI level is <50 mg/dL or not) • COPD exacerbation (refer to Section 4.6.1) • Adverse events (AEs) • Concomitant medications • 12-lead ECG

4.7.2.2 Treatment period

During the 8-week treatment period, subjects will receive a total of 8 weekly intravenous infusions of 60 mg/kg of Alpha-1 MP. Weekly infusions of Alpha-1 MP will be given at the scheduled Week 1 (baseline), 2, 3, 4, 5, 6, 7, and 8 visits at each study center. Visit dates after the Week 1 (baseline) visit will be arranged at 1-week intervals as specified in the protocol according to the actual date of the Week 1 (baseline) visit (±1 day).

Subjects meeting all of the inclusion criteria and not meeting any of the exclusion criteria will make the Week 1 (baseline) visit within 21 days after the screening visit. Subjects considered eligible will receive the initial intravenous infusion (intravenous drip) of Alpha-1 MP at the Week 1 (baseline) visit.

The 1-week PK evaluation period will start at the Week 8 visit and end at the Week 9 visit. At the Week 8 visit, subjects will undergo blood sampling for PK evaluation immediately before the intravenous infusion of Alpha-1 MP; immediately after the intravenous infusion; and at 15 minutes, 2, 4, and 8 hours after completion of the intravenous infusion. Subjects will visit the study center 1 day (PK1), 2 days (PK2), and 5 days (PK5) after the Week 8 visit to provide PK evaluation blood samples at 24 ± 4 hours (1 day), 48 ± 4 hours (2 days), and 120 hours ± 1 day (5 days), respectively, after the intravenous infusion of Alpha-1 MP at the Week 8 visit. The date of Week 9 visit will be scheduled in the week specified in the protocol according to the actual date of the Week 1 (baseline) visit (±1 day).

Visit	Trial Procedures and Evaluations
Week 1 (Baseline)	[Before intravenous infusion of Alpha-1 MP] • Reevaluation of the inclusion/exclusion criteria • Body weight: Recorded body weight will be used to calculate the Alpha-1 MP dose administered at the Week 1 (baseline) visit. This recorded body weight will be used for dose calculation until the next scheduled body weight measurement. • Laboratory tests (refer to Section 4.7.3) Urine samples: Urinalysis Blood samples: Viral safety assessment: Blood samples for viral nucleic acid amplification (NAT) and viral serologic test will be collected 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. All collected blood samples will be stored until completion of the tests in this clinical trial (GTI1401) and the extension trial (GTI1401-OLE). Blood chemistry, hematology, $alpha_1$-PI concentrations • COPD exacerbation (refer to Section 4.6.1) • Adverse events • Concomitant medications • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) immediately before the start of intravenous infusion of Alpha-1 MP [At the time of intravenous infusion (intravenous drip) of Alpha-1 MP] • Intravenous infusion of Alpha-1 MP • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) immediately after the completion of intravenous infusion of Alpha-1 MP • 12-lead ECG immediately after the end of intravenous infusion of Alpha-1 MP • Observation of the subject for at least 30 minutes after the intravenous infusion
Weeks 2,3,4,6	[Before intravenous infusion of Alpha-1 MP] • COPD exacerbation (refer to Section 4.6.1) • Adverse events • Concomitant medications • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) immediately before the start of intravenous infusion of Alpha-1 MP [At the time of intravenous infusion of Alpha-1 MP] • Intravenous infusion of Alpha-1 MP • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) immediately after the completion of intravenous infusion of Alpha-1 MP • Observation of the subject for at least 30 minutes after the intravenous infusion

Week 5	[Before intravenous infusion of Alpha-1 MP] • Body weight: Recorded body weight will be used to calculate the Alpha-1 MP dose administered at the Week 5 visit. This recorded body weight will be used for the weekly dose calculations thereafter. • Laboratory tests (refer to Section 4.7.3) Urine samples: Urinalysis Urine pregnancy test: To be performed only in women of childbearing potential. Only women tested negative for pregnancy can continue the trial. Urinary cotinine level: Subjects tested positive for urinary cotinine due to smoking must be withdrawn from the trial. Blood samples: Blood chemistry, hematology • PFT (FEV1 and FVC) before and after administration of a bronchodilator (refer to Section 4.6.2) • COPD exacerbation (refer to Section 4.6.1) • Adverse events • Concomitant medications • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) immediately before the start of intravenous infusion of Alpha-1 MP [At the time of intravenous infusion of Alpha-1 MP] • Intravenous infusion of Alpha-1 MP • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) immediately after the completion of intravenous infusion of Alpha-1 MP • Observation of the subject for at least 30 minutes after the intravenous infusion
Week 7	[Before intravenous infusion of Alpha-1 MP] • COPD exacerbation (refer to Section 4.6.1) • Adverse events • Concomitant medications • Laboratory tests (refer to Section 4.7.3) Blood samples: $Alpha_1$-PI trough concentrations

	• Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) immediately before the start of intravenous infusion of Alpha-1 MP [At the time of intravenous infusion of Alpha-1 MP] • Intravenous infusion of Alpha-1 MP • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) immediately after the completion of intravenous infusion of Alpha-1 MP • Observation of the subject for at least 30 minutes after the intravenous infusion
Week 8 (At the start of the PK evaluation period)	[Before intravenous infusion of Alpha-1 MP] • COPD exacerbation (refer to Section 4.6.1) • Adverse events • Concomitant medications • Laboratory tests (refer to Section 4.7.3) Blood samples: $Alpha_1$-PI trough concentrations (To be used as a PK sample immediately before the start of intravenous infusion [refer to the description below]) • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) immediately before the start of intravenous infusion of Alpha-1 MP [At the time of intravenous infusion of Alpha-1 MP] • Intravenous infusion of Alpha-1 MP • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) immediately after the completion of intravenous infusion of Alpha-1 MP • Observation of the subject for at least 30 minutes after the intravenous infusion [PK sampling time points] • Immediately before the intravenous infusion • Immediately after the intravenous infusion (after flushing the infusion line with physiological saline) (at 0 hours) • At 15 minutes after completion of the intravenous infusion • At 2 hours after completion of the intravenous infusion

	• At 4 hours after completion of the intravenous infusion • At 8 hours after completion of the intravenous infusion • At 24 ± 4 hours (1 day after completion of the intravenous infusion) • At 48 ± 4 hours (2 days after completion of the intravenous infusion) • At 120 hours ± 1 day (5 days after completion of the intravenous infusion) • At 168 hours ± 1 day (7 days after completion of the intravenous infusion) (Week 9)
PK1, PK2, and PK5	• COPD exacerbation (refer to Section 4.6.1) • Adverse events • Concomitant medications [PK sampling time points] After the intravenous infusion of Alpha-1 MP at the Week 8 visit: • At 24 ± 4 hours (1 day after completion of the intravenous infusion) [PK1] • At 48 ± 4 hours (2 days after completion of the intravenous infusion) [PK2] • At 120 hours ± 1 day (5 days after completion of the intravenous infusion) [PK5]
Week 9 (At the completion of the PK evaluation period/clinical trial)	At the Week 9 visit, subjects will be given an explanation about the extension trial (GTI1401-OLE) and asked whether or not they would like to enter the trial. For subjects intending to enter the extension trial and considered eligible for participation in the trial, the Week 9 visit will be the visit for study completion for GTI1401 as well as the screening/Week 1 visit for the extension trial. Subjects entering the extension trial will continue the treatment with intravenous infusions of 60 mg/kg of Alpha-1 MP weekly for at least another year for the purpose of evaluation of the safety of long-term Alpha-1 MP treatment (subjects will be further asked whether or not they would like to continue the treatment at yearly intervals). • Physical examination (excluding breast and urogenital examination)

	• Laboratory tests (refer to Section 4.7.3) Urine samples: Urinalysis Urine pregnancy test: To be performed only in women of childbearing potential Urinary cotinine level Blood samples: $Alpha_1$-PI trough concentrations (To be used as a PK sample at 168 hours after completion of the intravenous infusion [7 days after completion of the intravenous infusion at the Week 8 visit]) Blood chemistry, hematology • PFT (FEV_1 and FVC) before and after administration of a bronchodilator (refer to Section 4.6.2) • COPD exacerbation (refer to Section 4.6.1) • Adverse events • Concomitant medications • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature) • 12-lead ECG (Note: For subjects to be enrolled in the GTI1401-OLE, this 12-lead ECG will be performed prior to the Alpha-1 MP infusion for GTI1401-OLE).

4.7.2.3 Visit for follow-up/study completion (Week 12) (for subjects not entering the extension trial [GTI1401-OLE])

Subjects not entering the extension trial (GTI1401-OLE) will visit the study center at 30 days (4 weeks) after completion of the last intravenous infusion of the investigational drug (Week 8) and at 3 weeks after the Week 9 visit to complete the follow-up/study completion examinations (Week 12). The date of Week 12 visit will be scheduled in the week specified in the protocol according to the actual date of the Week 1 (baseline) visit (±1 day).

Visit	Trial Procedures and Evaluations
Visit for follow-up/study completion (Week 12) (for subjects not entering the extension trial [GTI1401-OLE])	• Physical examination (excluding breast and urogenital examination) • Laboratory tests (refer to Section 4.7.3) Urine samples: Urinalysis Urine pregnancy test: To be performed only in women of childbearing potential. Urinary cotinine level Blood samples: Blood chemistry, hematology • PFT (FEV_1 and FVC) before and after administration of a bronchodilator (refer to Section 4.6.2) • COPD exacerbation (refer to Section 4.6.1) • Adverse events • Concomitant medications • Vital signs (pulse rate, blood pressure, respiratory rate, and body temperature)

4.7.3 Laboratory Tests and Testing Procedures

Detailed procedures for laboratory tests are provided in the Laboratory Manual for this clinical trial. Table 3-1 summarizes the laboratory tests to be performed in the clinical trial.

Table 4-2 Laboratory Tests, Procedure Name, Description, and Laboratory

Test	Parameter	Laboratory
Hematology	Hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count and differential counts	Central laboratory[a]
Blood chemistry	Sodium, potassium, creatinine, calcium, blood urea nitrogen, bicarbonate, albumin, AST, ALT, alkaline phosphatase, glucose, total protein, total bilirubin	Central laboratory[a]
Urinalysis	pH, protein, glucose, blood and microscopic evaluation of blood cells Microscopy will be performed when indicated.	Central laboratory[a]
Urinary cotinine	Cotinine level	Local laboratory

Urine pregnancy test	To be performed only in women of childbearing potential. Only women tested negative for pregnancy can continue the trial.	Local laboratory
Viral NAT	Before the intravenous infusion of Alpha-1 MP at the Week 1 (baseline) visit[b]: Collection of samples for storage HAV RNA, HBV DNA, HCV RNA, HIV RNA, parvovirus B19 (B19V) DNA	Central laboratory[a]
Viral serologic test	Before the intravenous infusion of Alpha-1 MP at the Week 1 (baseline) visit[b]: Collection of samples for storage Differentiation of HAV antibody (IgM/IgG), differentiation of HBV core antibody (IgM/IgG), HCV antibody, HIV-1/-2 +Group O antibody, differentiation of B19V antibody (IgM/IgG)	Central laboratory[a]
$Alpha_1$-PI concentration	Blood sample collected for the measurement of serum $alpha_1$-PI concentration	Central laboratory[a]

a: The central laboratory will be at LSI Medience Corporation.
b: Refer to Section 4.7.3.1 These blood samples will be stored until completion of the tests in this clinical trial (GTI1401) and the extension trial (GTI1401-OLE).

4.7.3.1 Viral safety assessment

Virus safety retain samples (viral NAT and viral serology; see Table 4-2) will be collected at the Week 1 (Baseline) Visit prior to infusion and will be stored until all analyses in support of the this study (GTI1401) and the open-label extension study (GTI1401-OLE) are complete. These virus safety retain samples will be tested *only* if a subject exhibits clinical signs and symptoms consistent with a viral infection while participating in the study. Additional samples for viral NAT and viral serology *may be* collected and tested if the subject exhibits clinical signs and symptoms consistent with a viral infection while participating in the study.

4.7.4 Measurement of Serum $Alpha_1$-PI Concentrations

All subjects will have a blood sample collected for the measurement of trough $alpha_1$-PI levels at Weeks 1, 7 and 8 (prior to the infusions of Alpha-1 MP) and through Week 9 for PK evaluation. All samples for measurement of $alpha_1$-PI concentration will be analyzed using an antigenic content assay that is validated according to current regulatory and industry expectations.

4.7.5 Volume of Blood Sampling

For laboratory tests (hematology and Blood chemistry), viral tests (Viral NAT and Viral serologic test) and alpha$_1$-PI concentration (alpha$_1$-PI trough concentration and samples for PK measurement), the following volume of blood per a subject will be taken throughout the study.

Blood sampling	Volume (mL)	Times	Total volume (mL)
Laboratory tests – Screening	9	1	9
Laboratory tests – Week 1 to Study Completion	6	4	24
Viral tests	34.5	1	34.5
alpha$_1$-PI concentration	4	12	48
Grand Total over 8 weeks			115.5

4.8 Screening Failures

Screening evaluations will be used to determine the eligibility of each subject for enrollment. Subjects who fail to meet eligibility criteria during screening evaluations will be considered screen failures and will not participate in the study.

5 ADVERSE EVENTS (AEs)

5.1 Warnings/Precautions

Alpha-1 MP is human alpha$_1$-PI produced by a modification of the Prolastin process and is approved as Prolastin-C for 60 mg/kg weekly IV administration in the US, Canada, Columbia, Argentina, and Turkey. For complete Alpha-1 MP safety information, refer to the current Alpha-1 MP IB.

Immunoglobulin E-mediated anaphylactic reactions to plasma-derived, alpha$_1$-PI preparations may occur in recipients (27) with or without documented prior histories of severe allergic reactions to blood products. Very rarely, an anaphylactoid reaction may occur in subjects with no prior history of severe allergic reactions to plasma-derived alpha$_1$-PI administration (28).

Individuals with selective IgA deficiency should not receive alpha$_1$-PI since these subjects may experience severe reactions, including anaphylaxis, to IgA which may be present in the preparation.

It is not known whether alpha$_1$-PI is excreted in human breast milk, can cause fetal harm when administered to pregnant women, or can affect reproductive capacity. Subjects who are pregnant must not enter the study, and subjects who become pregnant during the study must be withdrawn.

Overdose with plasma-derived alpha$_1$-PI has not been reported. In an overdose situation, supportive care should be given and the subject managed accordingly.

The manufacturing process for all Grifols plasma-derived products begins with the screening of plasma donors and the testing of individual plasma donations and plasma manufacturing pools for specific markers of viral infection. To provide additional assurance of the pathogen safety margin of the final product, in vitro laboratory spiking studies were performed to validate the capacity of key steps of the Alpha-1 MP manufacturing process to inactivate and/or remove pathogenic agents.

5.2 Monitoring of Adverse Events

Subjects must be carefully monitored for AEs. This monitoring includes clinical and laboratory tests and physical signs. Adverse events should be assessed in terms of their seriousness, severity, and causal relationship to the investigational product.

5.3 Definitions and Handling of Adverse Events

5.3.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product or study treatment and which does not necessarily have a causal relationship with this administration. An AE can therefore be any unfavorable and unintended sign (including any abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

5.3.2 Definition of Suspected Adverse Drug Reactions (ADRs)

All noxious and unintended responses to a medicinal product or study treatment related to any dose should be considered suspected ADRs. 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.

5.3.3 Causal Relationship of Adverse Events

The Investigator is required to provide a causality assessment for each AE reported to the Sponsor. The Sponsor will consider the Investigator's causality assessment. Assessment of the causal relationship to the study drug will be made according to the following classifications based on Karch FE, et al. (29):

Definite: An event that follows a reasonable temporal sequence from administration of the treatment or in which the treatment level has been established in body fluids or tissues, that follows a known response pattern to the suspected treatment, and that is confirmed by improvement on stopping the treatment (dechallenge), and reappearance of the event on repeated exposure (rechallenge).

Probable: An event that follows a reasonable temporal sequence from administration of the treatment that follows a known response pattern to the suspected treatment, that is confirmed by dechallenge, and that could not be reasonably explained by the known characteristics of the patient's clinical state.

Possible: An event that follows a reasonable temporal sequence from administration of the treatment, that follows a known response pattern to the suspected treatment, but that could have been produced by the patient's clinical state or other modes of therapy administered to the patient.

Doubtful/Unlikely: An event that follows a reasonable temporal sequence from administration of the treatment; that does not follow a known response pattern to the suspected treatment; but that could not be reasonably explained by the known characteristics of the patient's clinical state.

Unrelated: Any event that does not meet the criteria above.

The operational tool to decide the AE causal relationship is based on algorithms by Karch FE *et al.* and Naranjo CA et al. (29,30).

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.

In addition, when a causal relationship between the study treatment and the AE cannot be ruled out by the Investigator and/or Sponsor, it means that the AE cannot be labeled "unrelated".

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.

5.3.4 Severity of Adverse Events/ Suspected Adverse Drug Reactions

AEs and suspected ADRs will be classified depending on their severity according to the following definitions:

Mild:	an AE which is well tolerated by the subject, causing minimum degree of malaise and without affecting normal activities.
Moderate:	an AE that interferes with the subject's normal activities.
Severe:	an AE that prevents the subject from performing their normal activities.

AE and suspected ADR severity gradation must be distinguished from AE and suspected ADR seriousness gradation, which is defined according to event consequence. For example, headache can be mild, moderate, or severe but unusually is serious in all these cases.

The Investigator will be responsible for assessing the AE and suspected ADR severity during the clinical trial, taking into account current criteria included in this section.

5.3.5 Expectedness of Adverse Events/ Suspected Adverse Drug Reactions

An AE or suspected ADR is considered "unexpected" if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information. The expectedness of an event shall be determined by the Sponsor according to the reference document (i.e., IB).

Events not listed in the IB are considered "unexpected" and those listed are considered "expected." When new serious ADRs (potentially related SAEs) are received, it is the Sponsor's responsibility to determine whether the events are "unexpected" for expedited safety reporting purposes.

5.3.6 Seriousness of Adverse Events/Adverse Drug Reactions; Serious Adverse Events (SAEs)

An AE or suspected ADR is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

1. Death
2. Life-threatening AE (life-threatening in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3. In-patient hospitalization or prolongation of existing hospitalization
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/ birth defect
6. An important medical event (important medical event in the definition of "serious" refers to those events which may not be immediately life-threatening, or result in death, or hospitalization, but from medical and scientific judgment may jeopardize the subject or/and may require medical or surgical intervention to prevent one of the other outcomes listed above)

This definition permits either the Sponsor or the Investigator to decide whether an event is "serious". If either the Sponsor or the Investigator believes that the event is serious, the event must be considered "serious" and evaluated by the Sponsor for expedited reporting.

A distinction should be drawn between serious and severe AEs. The term "severe" is used to describe the intensity (severity) of a specific event; the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious", which is defined on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) is a medical term while severity is a subjective term.

According to the medical criteria, an AE or a suspected ADR can be classified as serious, although it does not fulfill the conditions fixed in this section, if it is considered important from a medical point of view.

5.3.7 Recording of Adverse Events

All AEs and SAEs occurring after the subject has signed the ICF through the End of Study must be fully recorded in the subject's CRF and SAE form if applicable. If no AE has occurred during the study period, this should also be indicated in the CRF.

It is responsibility of the Investigator to ensure that AEs are appropriately recorded.

At each visit, AEs will be elicited by asking the individual a non-leading question such as "Do you feel different in any way since the last visit?". Moreover, AEs will also be collected through directly observed events or spontaneously volunteered by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome wherever possible.

The following variables must be recorded on the AE CRF entry:

1. The verbatim term (a diagnosis is preferred)
2. Date/time of onset
3. Date/time of resolution
4. Severity (mild, moderate, severe)
5. Causality (unrelated, doubtful/unlikely, possible, probable, definite)*
6. Seriousness (yes, no)
7. Action taken (with regard to investigational product)
8. Other action (to treat the event)
9. Outcome and sequel (follow-up on AE)

**Causality assessment will be only made when the AE occurs after the subject has initiated at least one infusion of the investigational product. Any AE occurring before subject's exposure to investigational product will be always labeled as "unrelated".*

In addition to the Investigator's own description of the AEs, each AE will be encoded by the Sponsor (or Contract Research Organization [CRO]) according to the Medical Dictionary for Regulatory Activities (MedDRA®).

For example, a laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the Investigator, should be reported as an AE. Each

event must be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome. Each event must be adequately supported by documentation as it appears in the subject's medical or case file.

5.3.8 Method and Duration of Follow-up of Subjects Experiencing Adverse Events

In so far as is possible, all individuals will be followed up until the AE or suspected ADR has been resolved. If an AE/suspected ADR/SAE is present when the subject has completed the study, the course of the event must be followed until the final outcome is known, or the event has been stabilized and no further change is expected and the Investigator decides that no further follow-up is necessary.

5.3.9 Events of Special Interest

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 (Section 4.6.1). 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 (Section 5.3.6). If an exacerbation meets criteria for a SAE, it will be reported as such (Section 5.4.1), and the standard of care should be followed. Results from standard of care should be obtained and reported.

5.4 Reporting of Serious Adverse Events (SAEs)/Pregnancies

5.4.1 Reporting of Serious Adverse Events (SAEs)

The investigator must report all serious adverse events (SAEs) that occur up to the end of this clinical trial after each subject has signed the informed consent form for participation in this clinical trial (refer to Section 5.3.6). SAEs should be reported by using designated report forms. If the investigator becomes aware of an SAE, the investigator must send a signed and dated SAE report form that completely describes the SAE to the sponsor **within 24 hours**.

Each SAE should be followed up until it resolves or becomes stable. After initial reporting of an SAE, all related information on the follow-up and outcome of the SAE should be provided for the CMIC Co., Ltd. (CMIC) to which the sponsor entrusts the pharmacovigilance duties for this clinical trial. as instructed below via the SAE report form (see Appendix 3.1 and 3.2) in a timely manner (within 24 hours of both of identification for already obtained information and

awareness for new related information). In addition, additional information/report may be requested by the sponsor or CMIC HOLDINGS Co., Ltd. (CHD) to which the sponsor entrusts the development-related duties for this clinical trial.

All SAE report forms should be submitted by email to the Eastern Japan Pharmacovigilance Division of the CMIC Co., Ltd. (CMIC), which is the devision of the affiliate company of CHD in responsible for pharmacovogilance, as shown below.

Eastern Japan Pharmacovigilance Division, CMIC Co., Ltd Email: [redacted] FAX: [redacted] (back-up only)

After receiving the SAE information, CMIC will send a provisional assessment in English to both Grifols Global Pharmacoviligence and Grifols Japan within 24 hours. The following required information should be provided to Grifols Global Pharmacoviligence to perform the preliminary reportability assessment:

- Day 0 of SAE notification (Actual date when CMIC receives the SAE notification from the investigator)
- Patient (ID or subject no., gender, and date of birth)
- SAE verbatim term
- SAE seriousness criteria
- Relationship of the SAE to the study drug
- SAE onset date
- Outcome of the SAE
- Brief summary of the SAE/additional details (if applicable)

CMIC will translate the source documents to English and send them to Grifols Global Pharmacoviligence and Grifols Japan by day 2 post-SAE notification for unexpected fatal or life-threatening cases/day 7 post-SAE notification for all other cases. Grifols Global Pharmacoviligence will process the case in the Grifols safety database and create a narrative and Company assessment. The CIOMS report will be provided by Grifols Global Pharmacoviligence to CMIC and Grifols Japan by day 4 post-SAE notification for unexpected fatal or life-threatening cases)/day 10 post-SAE notification for all other cases. CMIC will translate the CIOMS report to Japanese and create the appropriate files for submission to the PMDA. After approval by Grifols Japan, CMIC will transfer the final files to Grifols Japan for Grifols Japan to submit the case to the authorities. Grifols Japan will send the acknowledgment of the submission to CMIC and Grifols Global Pharmacoviligence.

5.4.2 Reporting of Pregnancies

Pregnancy itself is not an "adverse event," but if a female subject becomes pregnant during the trial period, the subject should be withdrawn from the trial (administration of the investigational drug should be discontinued immediately) and the subject should be followed up to collect information on the exposure to the investigational drug in regard to the gestation and pregnancy status. The investigator should report all pregnancies that occur up to the end of this clinical trial after each subject has signed the informed consent form for participation in this clinical trial to the sponsor.

Any pregnancy that is not confirmed at the entry to this clinical trial and occurs during the trial period will not be regarded as an adverse event unless it is suspected of being related to the investigational drug. However, if a female subject or the partner of a male subject becomes pregnant, the investigator should complete a pregnancy report (see Appendix 3.3) form and send it to the sponsor as soon as possible. A copy of the report form should be retained at the study center for the purpose of follow-up until completion of the pregnancy (delivery, miscarriage, abortion).

For any pregnancy resulting in a live birth (delivery of a neonate), the neonate should be followed up until 1 month after birth. Any deformity, complication, abnormal outcome, or birth defect observed in the neonate must be reported as an SAE within 24 hours of awareness by the investigator or those involved in the trial.

6. TRIAL DISCONTINUATION CRITERIA AND PROCEDURES FOR INDIVIDUAL SUBJECTS

6.1 Discontinuation Criteria

The investigator or subinvestigator will discontinue a subject who meets any of the criteria for discontinuation/dropout shown below and cannot continue the trial, and take appropriate action for the benefit of the subject. If a subject is withdrawn from the trial, the investigator will ask the subject to visit the study center for study termination and follow up any adverse event that has not been resolved.
The investigator or subinvestigator will enter the date of discontinuation, the reason for discontinuation, and comments in a case report form. The date of discontinuation should be the day of determination or confirmation of discontinuation by the investigator or subinvestigator for subjects .

(1) When a subject or the subject's legally acceptable representative requests withdrawal of consent or discontinuation of the trial
(2) When a subject develops any complication, or when a subject has any medical condition that may pose unnecessary risks or harm in the subject because of its severity, duration, or the need for changes in therapy in the opinion of the investigator
(3) When a subject develops an adverse event, which requires discontinuation of the trial in the opinon of the investigator or subinvestigator
(4) When a subject develops HAV, HBV, HCV, B19V, or HIV infection during the trial period. When a subject shows clinical signs or symptoms suggestive of viral infection and is confirmed by viral safety assessment to have developed any of the infections described above
(5) When a subject has a positive test for urinary cotinine due to smoking
(6) When a subject has exacerbated symptoms of an underlying disease, which requires discontinuation of the trial in the opinon of the investigator or subinvestigator
(7) When a female subject has become pregnant (refer to Section 5.4.2)
(8) When a subject fails to visit the study center for required tests, and it is difficult to continue the trial in the opinion of the investigator or subinvestigator
(9) When a subject is found in significant violation of a protocol
(10) Other cases which require discontinuation of the trial in the opinon of the investigator or subinvestigator
(11) When the sponsor informs of discontinuation of the entire trial or discontinuation of the trial in a study center

6.2 Discontinuation Procedures

When discontinuing this clinical trial according to the discontinuation criteria during the period between the start of investigational drug administration and the completion of the follow-up period, the investigator or subinvestigator should follow the procedures below:

(1) The investigator or subinvestigator should provide appropriate medical care or take appropriate measures to ensure the safety of the subject.
(2) The investigator or subinvestigator should investigate the contents of the investigation, observation, and examination performed at the time of trial discontinuation, the date of discontinuation, the reason for discontinuation, the action taken after discontinuation, and the course after discontinuation, and enter the information in a case report form.

(3) When administration of the investigational drug is discontinued due to the development of an adverse event, the investigator or subinvestigator should follow the procedures described in Section 5.3 “Definitions and Handling of Adverse Events (AEs).”

(4) If a subject who has received Alpha-1 MP at any dose discontinues this clinical trial early, this subject will not be replaced by a new subject.

(5) If a subject who has received Alpha-1 MP at any dose discontinues this clinical trial early, this subject will be asked to return to the study center for the follow-up/study completion procedures scheduled at the Week 12 visit (refer to Section 4.7.2.3 “Visit for follow-up/study completion” and Appendix 1). 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. If no follow-up investigation can be made for reasons such as “failed to return,” the investigator or subinvestigator should contact the subject whenever possible and enter the method for communication, the date of communication, the condition of the subject, and the reason for not having returned in a case report form. If attempting to comminucate with the subject but unable to identify the location of the subject, the investigator or subinvestigator should also enter the fact, the method for communication, and the date of communication in a case report form.

7. TRIAL COMPLETION, DISCONTINUATION, OR INTERRUPTION

7.1 Completion of the Clinical Trial

(1) When this clinical trial is completed, the investigator should report the completion of the trial in writing to the head of each study center.

(2) When receiving the report of the completion of the trial, the head of each study center should inform the institutional review board and the sponsor of the fact in writing.

7.2 Discontinuation or Interruption of the Clinical Trial

The sponsor, the institutional review board, and/or the regulatory authority may discontinue or interrupt the entire clinical trial or the trial in a specific study center.

7.2.1 Discontinuation or Interruption of the Clinical Trial by the Sponsor

The sponsor should discontinue or interrupt the entire clinical trial in the following cases:

(1) If the development of the investigational drug is discontinued

(2) If there is any ethically or medically unavoidable reason, such as to ensure the safety of subjects

7.2.2 Discontinuation or Interruption of the Clinical Trial at a Study Center

(1) If the sponsor becomes aware of any serious noncompliance[*1] or persistent noncompliance[*2] related to the GCP Ordinance, the protocol, or the clinical trial contract by an investigator or subinvestigator or a study center through monitoring and/or auditing, and considers that such noncompliance has interfered with the proper conduct of the trial (except for the cases stipulated in Article 46 of the GCP Ordinance), the sponsor should cancel the clinical trial contract with the study center and discontinue the trial at the study center.

*1 Serious noncompliance refers to any violation that may compromise the human rights, safety, and welfare of subjects and the reliability of this clinical trial.

*2 Persistent noncompliance refers to any repeated noncompliance to which no appropriate action has been taken in spite of the request for improvement by the sponsor irrespective of its seriousness.

(2) The sponsor should discuss whether or not to continue this clinical trial in all or some of the study centers in the following cases:

1) If a study center(s) cannot respond to any necessary modification in the protocol
2) If the sponsor cannot accept an approval condition(s) proposed by the head of a study center based on the opinion of the institutional review board of the study center
3) If the institutional review board of a study center considers that the clinical trial should not be continued and the head of the study center requests discontinuation of the trial

(3) If deciding to discontinue or interrupt this clinical trial, the sponsor should immediately report the fact and the reason for discontinuation or interruption to the head of a study center. The head of the study center should immediately report the fact to the investigator and the institutional review board in writing.

(4) If judging that it is absolutely necessary to discontinue or interrupt the clinical trial at a study center for any ethically or medically unavoidable reason, such as to ensure the safety of subjects, the investigator may discontinue or interrupt the trial at the study center. At this time, the investigator should immediately report to the head of the study center in writing, and the head of the study center should immediately report to the sponsor and the institutional review board in writing.

(5) In the case of discontinuation of the clinical trial or withdrawel of a study center, the investigator should return all trial-related materials (excluding documents to be continously retained at the study center) to the sponsor. The investigator should retain all the documents to be continously retained at the study center until a notification of destruction is received from the sponsor.

(6) For the procedures for discontinuation of the clinical trial in invidual subjects, refer to the procedures stipulated in Section 6. “Trial Discontinuation Criteria and Procedures for Individual Subjects.”

8 STATISTICAL METHODS AND DETERMINATION OF TARGET SAMPLE SIZE

8.1 Statistical Analysis Plan

Data handling and evaluation procedures will be described in the Statistical Analysis Plan (SAP).

8.1.1 Analysis Sets

The Safety Population will include all subjects who receive any amount of Alpha-1 MP.

8.1.2 Descriptive Statistics

Demographic and baseline characteristics, safety variables, and alpha$_1$-PI levels will be summarized using the safety population. For continuous variables, mean, standard deviation, median, minimum, and maximum will be provided. For categorical/qualitative data, absolute and relative frequency counts will be provided.

All subject data will be presented in data listings.

8.1.3 Statistical Analysis of PK Parameters

Descriptive statistics, including n, mean, standard deviation (SD), % coefficient of variation (CV), median, minimum, and maximum, will be calculated for each PK parameter determined from alpha$_1$-PI concentration data by the antigenic content assay. All PK parameters will be calculated using non-compartmental methods with WinNONLIN software (Pharsight Corporation, Cary, NC), which will be further described in the SAP.

8.2 Determination of Target Sample Size

The targeted sample size is a minimum of 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.

9. CASE REPORT FORMS

9.1 Completion and Reporting of Case Report Forms

(1) After completion of the treatment perod or the follow-up period in each subject, the investigator or subinvestigator should immediately complete a case report form according to the "Procedure for Completion, Modification, or Revision of Case Report Forms" provided by the sponsor, and submit the form with a signature or name and seal to the sponsor. When this clinical trial is discontinued, the investigator or subinvestigator should immediately complete a case report form for each subject. The investigator should retain copies of the completed forms.

(2) A clinical trial collaborator(s) appointed from the "List of Subinvestigators and Clinical Trial Collaborators" by the head of a study center is allowed to translate any date from source documents to case report forms. The investigator should check all entries on each case report form, confirm that none of the case report forms include any problems, and sign or affix the investigator's name and seal on them with the date of confirmation.

9.2 Guidance for Completion of Case Report Forms

(1) Subject identification codes should be used to identify individual subjects.

(2) Case report forms should be completed using a pen or ballpoint pen (black or blue ink).

(3) Any test report or photograph should be affixed on a case report form with a tally impression.

(4) For any observation, investigation, or examiantion that has not been performed, this item should beslash mark

(5) Every entry on a case report form should be consistent with its source document.

9.3 Identification of Data to be Recorded Directly on Case Report Forms and to be Considered to be Source Data

Data to be recorded directly on case report forms and to be considered to be source data include the following:

[Assessment results and comments]

- Results of the assessments specified in the protocol and comments
- Comments about subject demographics

- Results of the assessments of severity, seriousness, and causal relationship of adverse events, and comments or reasons
- Other comments to complement data

10. PROTOCOL ADHERENCE, DEVIATIONS OR MODIFICATIONS, AND AMENDMENTS

10.1 Protocol Adherence

This clinical trial will be conducted in compliance with the protocol based on the agreement between the investigator and the sponsor.

(1) After examining the ethical and scientific validity of the contents of the protocol, the investigator will prove that he/she has agreed on the contents of the protocol and agreed to adhere to the protocol by affixing his/her signature, or his/her name and seal, with a date on a written separate agreement along with the sponsor's signing oficial.

(2) The investigator and the sponsor will submit the approved protocol to the head of the study center to obtain the approval of the protocol from the institutional review board.

(3) The sponsor will obtain documents related to the instructions and decisions of the head of the study center (including a copy of a dated approval letter of the institutional review board). Approval of the conduct of the clinical trial by the head of the study center and the institutional review board will be regarded as approval of the protocol at the study center.

(4) The sponsor should not supply the study center with the investigational drug before concluding a trial contract based on the documents related to the instructions and decisions of the head of the study center.

(5) If the investigator is replaced by a new investigator or if any amendment is made to the protocol, the new investigator will prove that he/she has agreed on the contents of the protocol and agreed to adhere to the protocol again through the above procedures.

10.2 Protocol Deviations or Modifications

(1) The investigator or subinvestigator should not implement any deviation from the protocol or any modification to the protocol without obtaining prior written agreement between the investigator and the sponsor and written approval based on prior review by the institutional review board, except when there are medically unavoidable reasons, such as the need to eliminate immediate hazards to the subjects, or when the modification(s) involves only administrative aspects of the trial.

(2) The investigator or subinvestigator will record all deviations from the protocol.

(3) The investigator or subinvestigator will prepare a document explaining the reason for any noncompliance with the protocol for medically unavoidable reasons, such as the need to eliminate immediate hazards to the subjects, submit the document to the sponsor, and retain a copy of the document.

(4) When considering it appropriate to make an amendment(s) to the protocol based on the contents of a deviation(s) or a modification(s) and the reasons for them, the investigator may recommend such amendment to the Sponsor.

10.3 Protocol Amendments

(1) The sponsor will discuss with the medical expert and make a modification(s) or an amendment(s) to the protocol as needed in the following cases:

1) When the sponsor becomes aware of any information on the quality, efficacy, or safety of the investigational drug or other important information that would interfere with the proper conduct of the clinical trial. Independently from the protocol amendments discussed here, the sponsor may make a modification(s) or an amendment(s) to protocol attachments regarding minor matters not related to the core of the protocol (e.g., trial organization name, administrative matters).
2) When a modification(s) is made to the protocol for medically avoidable reasons.
3) When the head of the study center recommends a protocol amendment based on the opinion of the institutional review board of the study center

(2) Approval of protocol amendment

When any amendment is made to the protocol, approval for the protocol amendment will be obtained from the study center according to Section 10.1 “Protocol Adherence.”

11 TRIAL MANAGEMENT

11.1 Investigator, Other Trial Staff, External Committees

The information on the major trial staff members involved in the conduct of this clinical trial (the names and addresses of the investigator, monitors, clinical laboratory(ies), other technical department(s) and/or institutions, as well as members of a clinical trial committee if established, etc.) is provided in Section 2 “Study Administrative Structure.”

The investigator and the trial staff members will receive appropriate training for this clinical trial study group, the kick-off meeting at the study center, or other individual institutions.

11.2 Quality of Data

11.2.1 Sponsor

11.2.1.1 Quality Control

The sponsor will apply quality control based on standard operating procedures to each stage of data handling to ensure that all trial-related data are reliable and have been processed correctly.

11.2.1.2 Quality Assurance

The sponsor will implement monitoring and auditing according to the agreed monitoring procedure and auditing procedure stipulated by the sponsor to conduct this clinical trial in compliance with the protocol, the standard operating procedures, the standards stipulated in Clause 3 of Article 14 (Marketing Approval of Drugs, etc.) and Article 80-2 (Handling of Clinical Trials) of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices (hereinafter referred to as the Drugs and Medical Devices Law), and the GCP Ordinance (including revised ordinances and related notifications). The clinical research associate (CRA) will visit each study center periodically to verify whether the clinical trial is being conducted in compliance with the protocol, GCP, and other legal requirements described above. The means to confirm that the case report forms have been adequately and clearly completed at each study center include cross-checking the case report form entries with source documents and clarification of administrative matters. The verification method using data query is described in the Data Management Plan.

11.2.2 Study Centers

The study centers will apply quality control based on standard operating procedures to conduct this clinical trial and generate, record, and report data in compliance with the GCP Ordinance

and the protocol. In addition, the study centers will undergo investigations by representatives of the Minister of Health, Labour and Welfare or the sponsor (inspection, direct access, etc.) for the purpose of investigation and verification of records, etc. to be retained at the study centers.

11.3 Management of Documents

Trial data will be recorded on the case report forms and updated at all times by the clinical trial collaborator directly responsible for the trial data at the study center. Entries on the case report forms must be able to be verified against source documents. For any data to be recorded directly on case report forms, the case report forms are considered to be source data.

The representative of the sponsor or the person appointed by the sponsor will periodically monitor the data included in the case report forms at each study center, and compare them with source documents to verify the integrity of the data. Examples of source documents include medical records of individual subjects, which are separate documents from the case report forms.

All adverse events and serious adverse events must be recorded. All serious adverse events will be recorded on SAE forms. Original forms of recorded SAE will be retained at each study center, and copies of the original forms will be provided for designated personnel according to the procedures at each study center.

11.4 Retention of Records

11.4.1 Retention of Records at the Study Center

The person responsible for record retention appointed by the head of the study center will retain the following essential documents and records that are required to be retained at the study center by GCP at the place designated by the study center until at least the date of marketing approval granted for the test drug. If the sponsor discontinues the clinical trial, the person responsible for record retention will retain these essential documents and records until the date on which 3 years have elapsed after the day of discontinuation. However, if the sponsor needs retention for a longer period of time than the above periods, the study center should discuss the retention period and the retention method with the sponsor.

[Documents to be retained by the institutional review board]

- Written procedures of the institutional review board
- Member list
- Documents reviewed by the institutional review board (protocol, case report forms,

written information and informed consent forms, investigator's brochure, list of subinvestigators and clinical trial collaborators, documents explaining payments related to the clinical trial, documents explaining compensation for subject health injury, reports on the safety of subjects, etc., other documents considered necessary by the investigator or the institutional review board)

- Notifications sent from the head of the study center or the investigator to the institutional review board (notifications regarding clinical trial discontinuation, interruption, completion)
- Minutes of the institutional review board (written opinions, etc. of the evaluation committee used as reference at reviews will be also retained)

[Documents to be retained by the clinical trial office or the investigator]

- Procedures for conducting the clinical trial
- Source documents
- Protocol
- Written agreements, informed consent/assent forms (consent document for investigation for definitive diagnosis and consent document for participation of the clinical trial), other documents prepared by the medical institution personnel as stipulated by the GCP Ordinance
- Documents obtained from the institutional review board
- Documents obtained as stipulated by the GCP Ordinance
- Records about the management of the investigational drug and other trial-related records

The investigational drug is categorized as a specified biological product; therefore, each study center should retain the following records for the period stipulated by the Drugs and Medical Devices Law (for 20 years) by affixing the sticker accompanied by the investigational drug to a blood product management record that is used to manage other blood products.

[Information to be retained as a specified biological product]

- Manufacturing number
- Dates of administration
- Name and address of each patient

11.4.2 Retention of Records by the Sponsor

The person responsible for record retention appointed by the sponsor will retain the following essential documents and records that are required to be retained by the sponsor by GCP according the sponsor's procedures until the date on which 5 years have elapsed after the day

of marketing approval granted for the test drug. If the sponsor discontinues the clinical trial, the person responsible for record retention will retain these essential documents and records until the date on which 3 years have elapsed after the day of discontinuation.
The investigational drug is categorized as a specified biological product; therefore, the sponsor should retain the following records for the period stipulated by the Drugs and Medical Devices Law (for 30 years).
[Information to be retained as a specified biological product]

- Records about the manufacturing of the investigational drug
- Name and address of the study centers
- Records of distribution of the investigational drug to each study center (including manufacturing number)
- Records of disposal of the investigational drug

11.4.3 Retention of Records at Other Organizations

The central laboratory and other organizations involved in this clinical trial will retain written agreements and documents to be retained stipulated in the written agreements until at least the day of marketing approval for the test drug. If the sponsor discontinues the clinical trial, these organizations will retain the written agreements and the documents to be retained stipulated in the written agreements until the date on which 3 years have elapsed after the day of discontinuation. Records should be retained appropriately at each organization according to the written operating procedures confirmed by the sponsor.

11.5 Access to Information through Monitoring

Trial data will be recorded on the case report forms and updated at all times by the clinical trial collaborator directly responsible for the trial data at the study center, and the integrity of the records will be verified by the clinical research associate (CRA). The representative of the sponsor or the CRA appointed by the sponsor may investigate the records.

As stipulated in GCP, the CRA will verify whether the data recorded on the case report forms are consistent and in compliance with the protocol and whether the data entered are complete and consistent through direct access to source documents of the investigator. “Source documents” include subject files describing the date of visit, laboratory test results, concomitant treatment, vital signs, medical history, physical examination, adverse events, investigational drug distribution records, and other appropriate information, and the files should be retained separately from the case report forms. The investigator will agree to solve any issues detected through the CRA’s monitoring in cooperation with the CRA.

11.6 Access to Information for Auditing or Inspection

The investigator and study centers should permit monitoring and auditing by the sponsor and inspection by the institutional review board and the regulatory authority, and provide direct access to all trial-related records including the source documents shown below.
After discussing the method, timing, and schedule of direct access with the investigator or subinvestigator and the clinical trial office in advance, the CRA and the auditor will verify through direct access that all trial-related records have been sorted and retained appropriately in accordance with the "Good Clinical Practice (GCP Ordinance, Ministry of Health and Welfare Ordinance No.28 dated March 27, 1997)" and that the contents of the records are accurate and complete.

11.6.1 Source Documents

In this clinical trial, the following documents and records will be defined as source documents:

(1) Medical records (including laboratory test slips, etc.)
(2) Records of diagnostic imaging (films, records, etc.)
(3) Records of pulmonary function tests
(4) Laboratory test reports
(5) Prescription records
(6) Medical procedure records
(7) Subject screening list, etc.
(8) Documents regarding investigational drug management
(9) Informed consent documents
(10) Other medical data that allow confirmation of entries on the case report forms

12. ETHICS

12.1 Declaration of Helsinki

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" adopted by the World Medical Association General Assembly in Helsinki in 1964 and amended by the World Medical Association General Assembly in Fortaleza in 2013.

12.2 Adherence to the Drugs and Medical Devices Law and the GCP Ordinance

This clinical trial will be conducted in compliance with the standards stipulated in Clause 3 of Article 14 and Article 80-2 of Drugs and Medical Devices Law and the GCP Ordinance (including revised ordinances and related notifications).

12.3 Institutional Review Board (IRB)

12.3.1 Review of the Conduct of this Clinical Trial

Prior to the conduct of the trial in each study center, the institutional review board will review the protocol, case report forms, and written information and informed consent forms, etc. as well as the appropriateness of the conduct of this clinical trial in terms of its ethical and scientific validity.

12.3.2 Review of the Continuation of this Clinical Trial

The institutional review board will review whether this clinical trial is being conducted appropriately at the study center at least once per year to examine whether or not to continue the trial.

12.4 Informed Consent of Subjects

12.4.1 Timing and Method of Obtaining Informed Consent

The investigator or subinvestigator will fully explain the contents of this clinical trial to each subject by using a written information and informed consent form to obtain written consent of his/her own free will from the subject at the time of screening prior to any trial-related procedure, and provide the subject with a copy of the signed and dated informed consent form and the

written information used for explanation.
If information becomes available that may be relevant to the subject's willingness to continue participation in the trial, the investigator or subinvestigator will inform the subject of the information immediately, confirm whether the subject is willing to continue participation in the trial, and then obtain written consent of his/her own free will from the subject in the same manner. For subjects withdrawing their consent, the investigator or subinvestigator will ask them why they withdrew their consent and whether they agree on the use of their trial data obtained so far, and document the communication of this information.

12.4.1.1 Preparation of written information and informed consent form

With the cooperation of the sponsor, the investigator or subinvestigator will prepare written information and an informed consent form to be used to obtain informed consent for the participation in this clinical trial from subjects. These documents will be revised as needed. These prepared or revised documents will be submitted to the sponsor and approval of the institutional review board of the study center will be obtained in advance.
The written information should include the following: the objectives and methods of the clinical trial; the expected clinical benefits and risks or inconveniences for the subject; the availability of alternative treatments for the subject and their important potential benefits and risks; the statement that the subject may refuse to participate or withdraw from the clinical trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled; and other information.
The language used in the written information should be understandable to the subject and should be as non-technical as possible, and the written information should not contain any language that causes the subject to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the subinvestigator, the clinical trial collaborator, the study center, or the sponsor from liability for negligence.
It is necessary to combine written information with an informed consent form, and these documents should be prepared or revised in accordance with the GCP Ordinance (Ministry of Health and Welfare Ordinance No.28 dated March 27, 1997) and the ethical principles that have their origin in the Declaration of Helsinki.

12.4.1.2 Revision of the written information and informed consent form

If any new important information becomes available that may be relevant to the subject's consent, the investigator should immediately revise the written information and informed consent form, report the revision to the head of the study center, and obtain approval for the revised written information and informed consent form from the institutional review board in advance. In addition, the investigator or subinvestigator should also inform subjects already participating in the trial of the new information immediately to confirm whether they are willing to continue their participation in the trial, and use the revised informed consent form and other

written information to provide explanations again to obtain written consent for continuation of the participation in the trial of their own free will from the subjects.

(1) If any new important information becomes available that may be relevant to the subject's consent, the investigator should immediately revise the written information and informed consent form based on the information with the cooperation of the sponsor. The investigator should obtain approval for the revised written information and informed consent form from the institutional review board in advance.

(2) The investigator or subinvestigator should also inform subjects already participating in the trial of the new information immediately, and use the revised informed consent form and other written information to provide explanations again to obtain written consent for continuation of the participation in the trial of their own free will from the subjects. When consent is obtained from a subject again, the informed consent form with the subject's name and seal, or signature, and date will be retained (such as by affixing the form on the medical record) and the date of consent will be entered on the case report form.

(3) The investigator or subinvestigator will provide a copy of the new informed consent form with the subject's name and seal, or signature, and date and the written information to the subject.

12.4.1.3 Information to be included in the written information

The written information should include at least the following information as required by Clause 1 of Article 51 of the GCP Ordinance:

(1) That the clinical trial involves research
(2) The purpose of the clinical trial
(3) The name, title, and contact information of the investigator or subinvestigator
(4) Trial methods (including the research aspects of the trial, subject selection criteria)
(5) The expected clinical benefits and risks or inconveniences
(6) The availability of alternative treatments for the target disease in this clinical trial and their important potential benefits and risks
(7) The expected duration of the subject's participation in the clinical trial
(8) That the subject's participation in the clinical trial is voluntary and that the subject may refuse to participate or withdraw from the clinical trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled
(9) That the CRA, the auditors, the institutional review board (IRB), and the regulatory authorities will be granted direct access to the subject's medical information, without violating the confidentiality of the subject, and that by signing an informed consent form, the subject is authorizing such access.
(10) That the subject's privacy will remain confidential even if the results of the clinical trial are published

(11) The contact information of the study center for further information regarding the clinical trial and the rights of the subject and for inquiry or contact in the event of trial-related injury
(12) The compensation and/or treatment available to the subject in the event of trial-related injury
(13) The type of the institutional review board that investigates and reviews the appropriateness, etc. of the clinical trial; the matters that are investigated and reviewed in each institutional review board; and other matters regarding the institutional review board in relation to the clinical trial. That the subject can see the procedures, etc. of the institutional review board.
(14) The planned number of subjects involved in the clinical trial
(15) That the subject will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the clinical trial
(16) The foreseeable circumstances and/or reasons under which the subject's participation in the clinical trial may be terminated
(17) The anticipated expenses, if any, to the subject for participating in the clinical trial
(18) The anticipated prorated payment, if any, to the subject for participating in the clinical trial
(19) The subject's responsibilities
(20) Other necessary matters in relation to the protection of the human rights of the subject

12.4.1.4 Method of obtaining informed consent

(1) Prior to the participation of each subject in the clinical trial, the investigator or subinvestigator will fully explain the contents of the trial to the subject by using the written information approved by the institutional review board to obtain written consent of his/her own free will from the subject.
(2) The investigator or subinvestigator should provide the subject ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial before obtaining informed consent from the subject. At this time, the investigator or subinvestigator, or the clinical trial collaborator should answer all questions about the trial to the satisfaction of the subject.
(3) The investigator or subinvestigator who provided explanations and the subject should affix their names and seals to or sign, and date the informed consent form. If a clinical trial collaborator provided supplemental explanations, the clinical trial collaborator should also affix his/her name and seal to or sign, and date the informed consent form.
(4) After obtaining informed consent for the participation in the clinical trial from the subject, unless otherwise stipulated by the study center, before the participation of the subject in the trial, the investigator or subinvestigator should immediately provide a

copy of the informed consent form and the written information to the subject after retaining the informed consent form with their names and seals, or signatures, and date (such as by affixing the form on the medical record) and recording the date of informed consent on the case report form.

(5) The investigator or subinvestigator should ask whether the subject is being treated by any primary physician. If the subject is being treated by his/her primary physician, the investigator or subinvestigator should inform the primary physician of the participation of the subject in the trial before the start of investigational drug administration with the subject's consent. In addition, the name and the medical institution of the primary physician and the date of report should be recorded in the medical record.

12.5 Protection of the Privacy of Subjects

With regard to the conduct of this clinical trial, due consideration will be given to the protection of the privacy of subjects at the time of handling of their case report forms, informed consent forms, source documents, and other data including the personal information of the subjects as well as at the time of publication of the clinical trial results.

The investigator or subinvestigator should use subject identification codes and not use medical record numbers when entering any information that can identify individual subjects on the case report forms, etc. If other documents or materials (laboratory test slips, packages of the investigational drug, etc.) include any information that can identify individual subjects, such as subject name, such information should be masked so that individual subjects cannot be identified before submission of the document or material to the sponsor.

The investigator or subinvestigator will inform subjects that the monitors, the auditors, the institutional review board (IRB), and the regulatory authorities pay due attention to the confidentiality of subjects with respect to their personal information obtained through direct access to source documents, etc. and their personal information provided at the time of drug marketing (importing) approval application.

The investigator will prepare and retain a subject identification code list (including subject names corresponding to subject identification codes) that is used to identify individual subjects.

13. FINANCING

13.1 Compensation for Health Injury and Insurance

(1) If a subject suffers any injury directly resulting from the use of the study drug or a study procedure ("trial-related health injury"), the study center will provide the subject with adequate treatment and other appropriate measures. Among the medical expenses required for the treatment, the sponsor will pay for medical expenses that are not covered by the health insurance, provided the subject has followed the directions given by the lnvestigator, and the trial-related health injury is not due to the natural progression of any condition exsisting before the subject participated in the study. No other compensation will be offered.

(2) If any trial-related health injury occurs and results in legal liability, except when the study center is liable, the sponsor will be legally liable to the trial-related health injury. If it is not clear who will be legally liable to the trial-related health injury, the study center and the sponsor should discuss in good faith to solve the issue.

(3) The sponsor has taken out an insurance policy to cover trial-related health injury.

(4) If any health injury results from the intention or negligence of a subject or a study center, the health injury should be discussed based on the trial contract.

13.2 Payments to Subjects and Planned Trial-related Expenses

Any expense for testing or diagnostic imaging for a subject during the trial period will be paid by the sponsor as an expense for medical treatment designed for evaluation. Expenses such as transportation expenses for a subject should be paid with approval of the institutional review board after discussion by the study center and the sponsor. Methods for payment will be discussed with the study center and determined.

14 PUBLICATION POLICY

14.1 Use of the Data on this Clinical Trial

All of unpublished information that was provided by the sponsor related to the investigational drug, including but not limited to clinical applications, formulation, manufacturing method and other academic data should be treated as confidential. Investigator can use the information only for the purposes of this trial. In addition, all information about the trial, including the study results, is the confidential information of the sponsor. If you want to use for any purpose other than this trial, or disclose to a third party, you must obtain written consent from the sponsor previously.

14.2 Publication of the Trial Results

Any of the information obtained in this study, it is not allowed to publish without prior consultation with the sponsors. For the method of the publication, the sponsor will determine after the end of the trial.

Sponsor is committed to honoring the principles of academic freedom while, at the same time, protecting its confidential information, the subjects, and the integrity of the study, and the study documentation all in compliance with applicable law. Institution and/or Investigator recognize that, with respect to any study that is part of a multi-site study, there is a need for a coordinated approach to any publication or presentation of results from the sites. Accordingly, the Institution/Investigator shall not publish or present any results from this study to any third parties until: (1) Sponsor publishes the results; (2) Institution and/or Investigator receives written notification from Sponsor that publication of the results is no longer planned; or (3) twelve (12) months following the close of Study, whichever occurs first.

Institution and/or Investigator shall submit to Sponsor for its review a copy of any proposed publication at least thirty (30) calendar days prior to the planned date of submission for publication or presentation. Institution and Investigator shall consider in good faith all comments received from Sponsor during the review period and shall delete Sponsor's confidential information (other than study results).

If Sponsor determines that the publication contains patentable subject matter which requires protection, Sponsor may require the delay of submission for publication or presentation for an additional period of time for the purpose of filing patent applications or otherwise take measures to protect such information.

Institution and/or the Investigator shall acknowledge Sponsor's support in all publications and presentations.

15. PLANNED TRIAL PERIOD

January 1, 2016 (IRB submission) to March 31, 2017 (Data lock)

16. LITERATURE REFERENCES

1. Mulgrew AT, Taggart CC, McElvaney NG. Alpha-1-antitrypsin deficiency: current concepts. Lung 2007;185:191-201.

2. Kohnlein T, Welte T. Alpha-1 antitrypsin deficiency: pathogenesis, clinical presentation, diagnosis, and treatment. Am J Med 2008 Jan;121(1):3-9.

3. Fregonese L, Stolk J. Hereditary alpha-1-antitrypsin deficiency and its clinical consequences. Orphanet J of Rare Diseases 2008;3(16):1-9.

4. Eriksson S. Pulmonary emphysema and alpha$_1$-antitrypsin deficiency. Acta Medica Scandinavica 1964;175:197-205.

5. McElvaney NG, Stoller JK, Buist AS, et al. Baseline characteristics of enrollees in the National Heart, Lung and Blood Institute Registry of α_1-antitrypsin deficiency. Chest 1997;111:394-403.

6. de Serres FJ, Blanco I, Fernández-Bustillo E. PI S and PI Z alpha-1 antitrypsin deficiency worldwide. A review of existing genetic epidemiological data. Monaldi Arch Chest Dis 2007;67(4):184-208.

7. Seyama K. State of alpha$_1$-antitrypsin deficiency in Japan. Respirology 2000;5: S35-S38.

8. Test instructions – test: α_1-antitrypsin http://data.medience.co.jp/compendium/module_detail.cgi?field=06&m_class=02&s_class=0013. Last checked: 18 March 2015.

9. Woolhouse IS, Bayley DL, Stockley RA. Sputum chemotactic activity in chronic obstructive pulmonary disease: effect of α_1-antitrypsin deficiency and the role of leukotriene B_4 and interleukin 8. Thorax 2002;57:709-14.

10. Carrell RW, Jeppsson JO, Laurell CB, et al. Structure and variation of human α_1-antitrypsin. Nature 1982;298(5872):329-334.

11. Travis J. Structure, function, and control of neutrophil proteinases. Am J Med 1988; 84(6A):37-42.

12. Gadek JE, Fells GA, Zimmerman RL, et al. Antielastases of the human alveolar structures: implications for the protease-antiprotease theory of emphysema. J Clin Invest 1981;68:889-98.

13. Janoff A. Elastases and emphysema. Current assessment of the protease-antiprotease hypothesis. Am Rev Respir Dis 1985;132(2):417-33.

14. Hubbard RC, Fells G, Gadek J, et al. Neutrophil accumulation in the lung in α_1-antitrypsin deficiency: spontaneous release of leukotriene B_4 by alveolar macrophages. J Clin Invest 1991;88: 891-7.

15. American Thoracic Society/European Respiratory Society Statement: Standards for the diagnosis and management of individuals with Alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med 2003;168:818-900.

16. Crystal RG. α_1-Antitrypsin deficiency, emphysema, and liver disease: Genetic basis and strategies for therapy. J Clin Investigation 1990;85:1343-52.

17. Janoff A, Sloan B, Weinbaum G, et al. Experimental emphysema induced with purified human neutrophil elastase: tissue localization of the instilled protease. Am Rev Respir Dis 1977;115(3):461-78.

18. Senior RM, Tegner H, Kuhn C, et al. The induction of pulmonary emphysema with human leukocyte elastase. Am Rev Respir Dis 1977;116(30):469-75.

19. Stockley RA, Mannino D, Barnes PJ. Burden and pathogenesis of chronic obstructive pulmonary disease. Proc Am Thorac Soc 2009;6:524-6.

20. Gadek JE, Klein HG, Holland PV, et al. Replacement therapy of alpha 1-antitrypsin deficiency: reversal of protease-antiprotease imbalance within the alveolar structures of PiZ subjects. J Clin. Invest 1981;68:1158-65.

21. Gadek JE, Crystal RG. α_1-Antitrypsin Deficiency In: The Metabolic Basis of Inherited Disease. Stanbury, JB, Wyngaarden JB, Fredrickson DS et al. (Eds) 5th Ed. McGraw-Hill, NY 1983. pp. 1450-67.

22. Wewers MD, Casolaro MA, Sellers SE, et al. Replacement therapy for alpha$_1$-antitrypsin deficiency associated with emphysema. N Engl J Med 1987;316(17):1055-62.

23. Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV_1 decline in individuals with severe deficiency of α_1-Antitrypsin. Am J Respir Crit Care Med 1998;158:49-59.

24. Seersholm N, Wencker M, Banik N, et al. Does α_1-antitrypsin augmentation therapy slow the annual decline in FEV_1 in patients with severe hereditary α_1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) α_1-AT study group. Eur Respir J 1997;10(10):2260-63.

25. Cazzola M, MacNee W, Martinez FJ, et al. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008;31(2):416-68.

26. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-38.

27. Meyer FJ, Wencker M, Teschler H, et al. Acute allergic reaction and demonstration of specific IgE antibodies against α-1-protease inhibitor. Eur Respir J 1998;12:996-7.

28. Wencker M, Banik N, Buhl R, et al. Long-term treatment of α_1-antitrypsin deficiency-related pulmonary emphysema with human α_1-antitrypsin. Eur Respir J 1998;11:428-33.

29. Karch FE, Lasagna L. Toward the operational identification of adverse drug reactions. Clin Pharmacol Ther 1977; 21: 247-54.

30. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-45.

APPENDIX 1

Trial Schedule (Examinations, Observations, Tests, and Evaluations and their Timing)

Trial period	**Screening**	**Treatment[a]**												**Follow-up**
Visit[a]	Day −21 to the day before Week 1	Week 1 (baseline)	Week 2	Week 3	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.

m: Subjects will be observed for at least 30 minutes after each intravenous infusion of Alpha-1 MP.

APPENDIX 2

A2.1 Sponsor

1) Sponsor

[redacted]

Grifols Japan K.K.
Level 19, Hilton Plaza West Office Tower
2-2-2 Umeda, Kita-ku, Osaka 530-0001, Japan
TEL: [redacted] FAX: [redacted]

2) [redacted]

[redacted]

Grifols Japan K.K.
Level 19, Hilton Plaza West Office Tower
2-2-2 Umeda, Kita-ku, Osaka 530-0001, Japan
TEL: [redacted] FAX: [redacted]

3) [redacted]

[redacted]

Japan Anti-Tuberculosis Association
1-3-12 Misaki-cho, Chiyoda-ku, Tokyo, Japan
TEL: [redacted] FAX: [redacted]
<Main duties>

To give the sponsor medical advice on the following matters when necessary:

(i) Appropriateness of the investigational plan, the protocol, etc.
(ii) Action to be taken against adverse events and evaluation of them
(iii) Appropriateness of subject data handling and result assessment after completion of the trial
(iv) Appropriateness of the clinical study report
(v) Other medical issues concerning the trial

A2.2 Contract Research Organization

In this clinical trial, trial-related duties will be entrusted to the contract research organization below:

CMIC HOLDINGS Co., Ltd.

[redacted]

1-1-1 Shibaura, Minato-ku, Tokyo 105-0023, Japan
TEL: 03-6779-8000 (main switchboard)

Monitor (CRA) and Medical Monitor
Refer to Attachment.

<Main duties>

(i) Duties related to the selection of study centers and investigators
(ii) Duties related to negotiations and confirmation with investigators and study centers
(iii) Duties related to the request for study centers to conduct the trial and the conclusion of a trial contract with each study center
(iv) Duties related to the completion or discontinuation of the trial at study centers
(v) Duties related to trial monitoring
(vi) Duties related to supplying and retrieving of the investigational drug
(vii) Duties related to the collection of case report forms and data verification against source documents
(viii) Duties related to the confirmation of GCP essential documents at study centers
(ix) Quality control functions as part of the entrusted duties
(x) Duties related to data management
(xi) Duties related to statistical analysis
(xii) Medical writing (protocol, written information and informed consent form, clinical study report, etc.)
(xiii) Duties related to auditing
(xiv) Safety Information handling and reporting
(xv) Duties related to the medical monitoring

A2.3 Grifols Therapeutics Inc., USA

Grifols Therapeutics Inc.
[redacted]
4201 Research Commons
79 T.W. Alexander Drive
Research Triangle Park, NC 27709 USA
TEL: [redacted] FAX: [redacted]

In this clinical trial, several trial-related duties will be provided by Grifols Therapeutics Inc. or will be carried out by CMIC HOLDINGS Co., Ltd. in conjunction with Grifols Therapeutics Inc. as listed below:

1) Medical Monitor
Refer to Attachment.

Other duties to be performed by Grifols Therapeutics Inc. in conjunction with the CMIC HOLDINGS Co., Ltd.

(i) Duties related to statistical analysis
(ii) Duties related to supplying and retrieving of the investigational drug
(iii) Medical writing (protocol, written information and informed consent form, clinical study report, etc.)

A2.4 Study Centers

Study centers

Refer to Attachment.

Investigators

Refer to Attachment.

<Main duties>

(i) Preparation of written information and informed consent forms
(ii) Selection of subjects and informed consent procedure
(iii) Agreement on and adherence to the protocol
(iv) Control of the investigational drug
(v) Administration of the investigational drug to subjects
(vi) Conduct of various tests
(vii) Entering data into case report form and confirmation of the data in the case report forms
(viii) Preparation and retention of study records

A2.5 Laboratory Testing Services, Transporter, Investigational Drug Manufacturer

1) Laboratory testing services

LSI Medience Corporation

[redacted], [redacted]

3-30-1 Shimura, Itabashi-ku, Tokyo 174-8555, Japan

TEL: 03-5943-9270 FAX: 03-5375-9211

<Main duties>

(i) Collection of laboratory test samples
(ii) Measurement of laboratory test parameters
(iii) Reporting of test results to study centers and the sponsor
(iv) Assurance of the testing methods and data quality

(vi) Transportation and interim storage of viral safety assessment samples

2) Transportation and storage of the investigational drug

TNT Express Worldwide (Japan) Inc.

[redacted], [redacted]

TOC Ariake East Tower 6th floor, 3-5-7 Ariake, Koto-ku, Tokyo, Japan

3) Investigational drug manufacturer

Grifols Therapeutic Inc.

[redacted]

4201 Research Commons

79 T.W. Alexander Drive

Research Triangle Park, NC 27709 USA

TEL: [redacted] FAX: [redacted]

A2.6 Central Evaluation of lung density of CT Scan Image

Vida Diagnostics

2500 Crosspark Road

W250 BioVentures Center

Coralville, IA 52241

TEL: +1-855-900-VIDA (8432) FAX: +1-610-602-5941

Attchement 1

1. List of Investigational Sites and Investigators

Investigational Sites (Address & Tel#)	Department	Principal Investigator
[redacted] Japan Tel: [redacted]	[redacted]	[redacted] **Masaru Suzuki**
[redacted] Tel: [redacted]	[redacted]	[redacted] **Kuniaki Seyama**
[redacted] Tel: [redacted]	[redacted]	[redacted]

2. Medical Monitor

[redacted]
To be updated.

[redacted]
[redacted], Grifols Therapeutics Inc.
4210 Research Commons
79 TW Alexander Drive, RTP, NC 27709
TEL: [redacted] FAX: [redacted]

3. Monitor (CRA)

[redacted], [redacted]
1-1-1 Shibaura, Minato-ku, Tokyo 105-0023, Japan
CMIC HOLDINGS Co., Ltd.
TEL: [redacted], FAX: [redacted]

APPENDIX 3

A3.1 SAE Report Form

GRIFOLS

Study Number: GTI1401

Subject No.	Serious Adverse Event Report
☐☐☐ – ☐☐☐☐	Page 1 of 3

Study Treatment : Alpha-1 MP

I. Event Information

1. Report Status
☐ Initial
☐ Follow-up

2. Date of this Report:
__ __/__ __ __/__ __ __ __
DD MMM YYYY

3. Country of Origin

4. BDSS# (Company use)
_____

5. Date of Birth
__ __/__ __ __/__ __ __ __
DD MMM YYYY

6. Gender
☐ Male ☐ Female

7. Weight
☐ lb
☐ kg

8. Race
☐ White or Caucasian
☐ Black or African American
☐ Asian
☐ American Indian or Alaskan Native
☐ Native Hawaiian or Other Pacific Islander
☐ Other, specify: _____

9. Reason for Seriousness (check all that apply):
☐ Resulted in death, if yes please complete section 18.
☐ Life-threatening
☐ Required/prolonged hospitalization on
__ __/__ __ __/__ __ __ __
DD MMM YYYY
☐ Persistent or significant disability/incapacity
☐ Congenital anomaly/birth defect
☐ Important medical event:_____

10. Ethnicity
☐ Hispanic or Latino
☐ Not Hispanic or Latino

11. Event Term/Diagnosis

12. Describe details of event (attach additional sheet, if extra space is needed)

13. Event Onset/Start Date
__ __/__ __ __/__ __ __ __
DD MMM YYYY
Start Time:__ __:__ __ (24 hrs

14. Event Stop Date
☐ Ongoing
__ __/__ __ __/__ __ __ __
DD MMM YYYY
Stop Time:__ __:__ __ (24 hrs)

15. Relationship to Study Treatment
☐ Unrelated/Not related, specify event cause
_____
☐ Doubtful/ Unlikely Related (classified as potentially related)
☐ Possibly Related
☐ Probably Related
☐ Definitely Related

Version 1.0: 01 October 2015

Subject No.	Serious Adverse Event Report
___ ___ ___ – ___ ___ ___ ___	Page 2 of 3

16. Severity	17. Event Outcome	18. Death Details
☐ Mild ☐ Moderate ☐ Severe	☐ Recovered/Resolved ☐ Recovering/Resolving ☐ Recovered/Resolved with Sequelae ☐ Not Recovered/Not Resolved ☐ Fatal (see block #18) ☐ Unknown	Date of death:__ __/__ __ __/__ __ __ __ DD MMM YYYY Autopsy ☐ Yes ☐ No Specify why not : _____ Is death certificate attached? ☐ Yes ☐ No

II. Study Treatment Information

19. Study Treatment started on	20. Study Treatment stopped on	21. Frequency of dosing	22. Route of administration/Mode of Topical application (check all that apply)
__ __/__ __ __/__ __ __ __ DD MMM YYYY __ __:__ __ (24 hrs)	__ __/__ __ __/__ __ __ __ DD MMM YYYY __ __:__ __ (24 hrs)		

23. Lot number	24. Expiration Date	25. Dose	26. Action taken with study treatment due to this SAE (check all that apply)
			☐ No change/None ☐ Dose reduced ☐ Restarted ☐ Interrupted ☐ Discontinued ☐ Other, specify: _____

27. Did event abate after stopping or reducing study treatment?	28. Did event reappear after reintroduction of study treatment?
☐ Yes ☐ No ☐ Not Applicable	☐ Yes ☐ No ☐ Not Applicable

III. Other Medical Information

29. Medical History	30. Relevant Lab/Confirmatory tests: include units and reference ranges/imaging reports (OR attach the report) ☐ Check if reports are attached

31. **Treatment Medications:** Drug(s) used to treat serious adverse event.

Trade and Generic name	Total daily dose	Route of administration	Start Date [dd/mmm/yyyy]	Stop Date [dd/mmm/yyyy]	Indication

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31a. Other non-drug treatments for the SAE (e.g. surgery, etc.)

32. Concomitant drug(s): Only those drugs and other therapies the subject received at onset of the event (including other therapies) or up to 1 month prior to the event; exclude those to treat event.

Trade and Generic name	Total daily dose	Route of administration	Start Date [dd/mmm/yyyy]	Stop Date [dd/mmm/yyyy]	Indication

IV. Reporter/Investigator Information

33. Reporter's name/Title (please print)	**34. Reporter's Phone #**	**35. Reporter's e-mail**
36. Principal Investigator Name (please print)		**37. Principal Investigator's Phone #**
38. Principal Investigator's Signature		**39. Date**
40. Hospital Name and Address		

Please submit Hospital Discharge Summary for hospital admissions
Please submit relevant test results and lab tests to provide support
Submit additional sheets, if extra space is needed.

Please send Serious Adverse Event report by e-mail to:

Eastern Japan Pharmacovigilance Division, CMIC Co., Ltd. within 24 hours of notification.
E-mail: [redacted]
FAX (back-up only): [redacted]

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A3.2 Supplemental Event Form

GRIFOLS

Study Number: GTI1401

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Directions: Enter additional serious adverse events including supplemental event data. Choose the correct answer and enter the corresponding number in the block provided. For "Relationship", if #1 "Not Related" is chosen, ensure to specify the cause.

Event/Diagnosis	**Event Start Date** (dd/mmm/yyyy)	**Event Stop Date** (dd/mmm/yyyy)	**Relationship to Study Drug** 1. Unrelated/Not related-specify 2. Doubtful/Unlikely (classified as related) 3. Possibly Related 4. Probably Related 5. Definitely Related	**Action Taken with Study Drug** 1. No change 2. Dose reduced 3. Interrupted 4. Discontinued 5. Other, Specify	**Severity** 1. Mild 2. Moderate 3. Severe	**Outcome** 1. Recovered/Resolved 2. Recovering/Resolving 3. Recovered/Resolved with Sequelae 4. Not Recovered/Not Resolved 5. Fatal (see block #18 on main SAE form) 6. Unknown	Did event abate after stopping or reducing drug? **(Yes/No)**	Did event reappear after reintroduction of drug? **(Yes/No)**

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A3.3 Pregnancy Report Form

GRIFOLS

Study Number: GTI1401

Subject No.	Pregnancy Report Form
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PART A ☐ Initial ☐ Follow-up

Study Treatment: Alpha-1 MP

I. Patient Identification

1. Date of this Report: DD MMM YYYY	2. Initials PRIVATE	3. Gender ☐ Male ☐ Female	4. BDSS# (Company use) _____
5. Date of Birth DD MMM YYYY	6. Height ☐ in ☐ cm	7. Race ☐ White or Caucasian ☐ Black or African American ☐ American Indian or Alaskan Native ☐ Native Hawaiian/Other Pacific Islander ☐ Asian ☐ Other, specify: _____	
8. Age at Onset (years)	9. Weight ☐ lb ☐ kg		

10. Ethnicity ☐ Hispanic or Latino ☐ Not Hispanic or Latino	11. Fetal Drug Exposure ☐ via Mother ☐ via Father	12. Study Withdrawal: ☐ No ☐ Yes , Date DD MMM YYYY ☐ Unknown

II. Maternal Identification

(**Complete only if Fetal Exposure is via Father**)

13. Initials PRIVATE	14. Date of Birth DD MMM YYYY	15. Ethnicity ☐ Hispanic or Latino ☐ Not Hispanic or Latino	16. Race NOTE: Add Ethnicity here ☐ White or Caucasian ☐ Black or African American ☐ Asian ☐ American Indian or Alaskan Native ☐ Native Hawaiian/Other Pacific Islander ☐ Other, specify: _____
17. Age at Onset (years)	18. Weight ☐ lb ☐ kg	19. Height ☐ in ☐ cm	

III. Further Details of Pregnancy

20. Date of Last Menstrual Period ☐ Unknown DD MMM YYYY	21. Expected Date of Conception DD MMM YYYY	22. Expected Date of Delivery DD MMM YYYY	23. Gestational age at exposure to study treatment: ☐ N/A Wks:_____ Days:_____
24. Date of Positive Pregnancy Test DD MMM YYYY	26. Previous Pregnancies: Total #:_____ FullTerm:___ Premature:___ Spontaneous Abortions:___	27. Maternal Health Status ☐ Diabetes ☐ Hypertension during or prior to pregnancy ☐ Other, specify:_____	
25. Was serum b-HCG performed? ☐ No ☐ Yes, Date:__ __/__ __ __/__ __ __ __ DD MMM YYYY		28. Social Habits During this Pregnancy ☐ Smoking, # of cigarettes per day:_____ ☐ Alcohol consumption. # of drinks per week:_____ ☐ Drug use, details (confidential): _____	

IV. Study Treatment Information

29. Study Treatment Start Date DD MMM YYYY	30. Study Treatment Stop Date DD MMM YYYY	31. Dose (specify units)	32. Route of administration
		33. Lot number:	34. Expiration Date:

V. Other Concomitant Medication Information

35. Trade / Generic Name	Total Daily Dose	Route of administration	Start Date [dd/mmm/yyyy]	Stop Date [dd/mmm/yyyy]	Indication

VI. Reporter/Investigator Information

36.Reporter's name/Title (please print)	37. Reporters Phone #	38. Reporters e-mail
39. Investigator Name (please print)	40. Investigator's Phone #	
41.Investigator's Signature	42.Date	

Please send Pregnancy Report Form by e-mail to Eastern Japan Pharmacovigilance Division, CMIC Co., Ltd.
within 24 hours of notification.
E-mail: [redacted]
FAX (back-up only): [redacted]

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Subject No.	Pregnancy Report Form
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Part B ☐ Initial ☐ Follow-up

I. Maternal Outcome

1. Were there any maternal complications during the pregnancy or delivery? ☐ No ☐ Yes, specify:

☐ No information available, specify reason:

2. Date of abortion: (dd/mmm/yyyy) __ __/__ __ __/__ __ __ __ (DD/ MMM/ YYYY) ☐ N/A

☐ Spontaneous abortion
☐ Elective abortion
☐ Therapeutic abortion, reason for therapeutic abortion:

II. Fetal Outcome

☐ No information available ☐ Live birth ☐ Still birth ☐ Multiple birth

4. Date of Delivery	5. Gestational age at delivery	6. Type of Delivery	7. Gender
__ __/__ __ __/__ __ __ __ (DD MMM YYYY)			☐ Male ☐ Female

8. Birth length	9. Birth Weight	10. Apgar Score – 1 Min	11. Apgar Score – 5 Mins	12. Apgar Score – 10 Min
☐ in ☐ cm	☐ lb ☐ kg			

13. Were there any congenital fetal/infant abnormalities? ☐ No ☐ Yes, describe:

14. Were there any post-natal medical problems with the child? ☐ No ☐ Yes, describe:

If any fetal/infant complications occurred please complete a Clinical Adverse Event Report Form.
Please include results of prenatal testing, history of previous pregnancies and family history of birth defects or congenital anomalies.

IV. Reporter/Investigator Information

15. Reporter's name/Title (please print)	16. Reporter's Phone #	17. Reporter's e-mail

18. Investigator Name (please print)	19. Investigator's Phone #

20. Investigator's Signature	21. Date

22. Hospital Name and Address

Please send Pregnancy Report Form by e-mail to Eastern Japan Pharmacovigilance Division, CMIC Co., Ltd. within 24 hours of notification.
E-mail: [redacted]
FAX (back-up only): [redacted]

Version 1.0: 01 October 2015

Emergency contact:
CMIC HOLDINGS Co., Ltd.
Business Innovation Unit (BIU)
1-1-1 Shibaura, Minato-ku, Tokyo 105-0023, Japan
TEL: [redacted] FAX: [redacted]

[redacted] (Mobile phone No. 080-xxxx-xxxx)