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

NCT Number: NCT02870348

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Protocol

A Multi-Center, Open-Label Study to Evaluate the Long-term Safety of Weekly Intravenous Infusions of Alpha$_1$-Proteinase Inhibitor (Human) in Japanese Subjects with Alpha$_1$-Antitrypsin Deficiency

Sponsor: Grifols Japan K.K.

Protocol No.: GTI1401-OLE
Version No.: 2.1 (for Ver2.1J)
Prepared on: January 21, 2019

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

SIGNATURE/APPROVAL PAGE

Sponsor

[redacted], MD

[redacted]

Clinical Development
Grifols Therapeutics LLC.
USA

MD — 22 Jan 2019
Date

PROTOCOL SYNOPSIS

Title of Study		A Multi-Center, Open-Label Study to Evaluate the Long-term Safety of Weekly Intravenous Infusions of Alpha$_1$-Proteinase Inhibitor (Human) in Japanese Subjects with Alpha$_1$-Antitrypsin Deficiency
Protocol Identification No.		GTI1401-OLE
Investigational Drug Code		Alpha-1 MP
Type of Study (Phase of Development)		Clinical safety study (Phase I/II)
Study Objective		To evaluate the long-term safety of 60 mg/kg. Alpha-1 MP administered by weekly IV infusions for approximately one year (52 weeks) or longer (can be renewed annually with the consent of the subjects) in adult subjects with AATD in Japan.
Study Design		This study is a multi-center, open-label study to evaluate the long-term safety of weekly IV infusions of 60 mg/kg Alpha-1 MP in adult subjects with AATD in Japan who have completed the Study GTI1401.
Subject Selection	Study Population	Subjects: Adult subjects with alpha$_1$-antitrypsin deficiency Target sample size: A minimum of 3 subjects
	Inclusion Criteria	1. Subjects who complete participation in the Study GTI1401 (i.e., who have completed the study through the Week 9 Visit) 2. Subjects who will and are able to provide written informed consent.
	Exclusion Criteria	1. Subjects with newly diagnosed severe concomitant disease including, but not limited to, congestive heart failure and liver cirrhosis. 2. Subjects with newly diagnosed malignant tumor (including malignant melanoma; however, other forms of skin cancer are allowed). 3. Female subjects who are pregnant, breastfeeding or, if of child-bearing potential, unwilling to practice a highly effective method of contraception throughout the study or male subjects who have a partner who is of child-bearing potential and is unwilling to practice a highly effective method of contraception throughout the study. 4. Subjects with clinical signs and symptoms of active viral infection of HAV, HBV, HCV, or HIV at the Week 9 Visit of the Study GTI1401 and confirmed by testing.

		5. Subjects with current evidence of smoking or has a positive urine cotinine test at the Week 9 Visit in the Study GTI1401 that is due to smoking. 6. Subjects who currently participate in a study of another investigational product (other than Alpha-1 MP). 7. Subjects who have difficulty in adhering to the protocol or its procedures, in the opinion of the investigator. 8. 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 alpha1-PI)
Endpoints	Safety Variables	The safety variables to be assessed for this study are as follows (No efficacy variables will be assessed for this study): • Adverse events (AEs), serious AEs (SAEs), adverse drug reactions (ADRs), and discontinuations due to AEs or SAEs • Vital signs (heart rate, blood pressure, respiratory rate, and temperature) • Chronic Obstructive Pulmonary Disease (COPD) exacerbations • Pulmonary function tests (PFTs): – Forced Expiratory Volume in 1 second (FEV_1) – Forced Vital Capacity (FVC) • Clinical laboratory parameters: – Hematology – Chemistry – Urinalysis • $Alpha_1$-PI level
	Exploratory Variable	• Computed Tomography (CT) scan (densitometry) CT scan (densitometry) data will be accumulated for future evaluation of lung density
Study Centers and Investigators		Refer to Attachment “Study Centers and Investigators List”
Study Period		March 1, 2016 to March 31, 2022
Remarks		This study will be switched to a post-marketing study after Alpha-1 MP is approved in Japan.

LIST OF ABBREVIATION

Abbreviation	Meaning of Abbreviation (In Japanese)
°C	Degree Celsius （摂氏）
°F	Degree Fahrenheit （華氏）
AATD	Alpha$_1$-Antitrypsin Deficiency （α_1-アンチトリプシン欠乏症）
ADR	Adverse Drug Reaction （薬物有害反応、副作用）
AE	Adverse Events （有害事象）
Alpha-1 MP	Alpha$_1$-Proteinase Inhibitor (human), Modified Process （製法を改良したヒト alpha$_1$-proteinase inhibitor）
alpha$_1$-PI	Alpha$_1$-Proteinase Inhibitor （alpha$_1$-プロテイナーゼインヒビター）
ALT	Alanine Aminotransferase （アラニンアミノ基転移酵素 ）
AST	Aspartate Transaminase （アスパラギン酸アミノ基転移酵素 ）
ATS	American Thoracic Society （米国胸部疾患学会 ）
B19V	Parvovirus B19 （パルボウィルス B19 ）
ChAMP	Pharmacokinetic Comparability of Alpha-1 MP Study （Alpha-1 MP の薬物動態の相互比較性試験 ）
COPD	Chronic Obstructive Pulmonary Disease （慢性閉塞性肺疾患）
CRF	Case Report Form （症例報告書）
CRA	Clinical Research Associate （治験モニター）
CRO	Contract Research Organization （医薬品開発業務受託機関）
CT	Computed Tomography（コンピューター断層撮影）
CV	Coefficient of Variation （変動係数）
DNA	Deoxyribonucleic Acid （デオキシリボ核酸）

dL	Deciliter （デシリットル）
ERS	European Respiratory Society （欧州呼吸器学会）
Ext	Extension （継続）
FEV_1	Forced Expired Volume in 1 second （1 秒量: 1 秒間の努力呼気量）
FVC	Forced Vital Capacity （努力性肺活量）
GCP	Good Clinical Practice （医薬品の臨床試験の実施の基準）
HAV	Hepatitis A Virus （A 型肝炎ウィルス）
HBV	Hepatitis B Virus （B 型肝炎ウィルス）
HCV	Hepatitis C Virus （C 型肝炎ウィルス）
HIV	Human Immunodeficiency Virus （ヒト免疫不全ウィルス）
IB	Investigator's Brochure （治験薬概要書）
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use （日米欧医薬品規制調和国際会議）
ICF	Informed Consent Form （患者同意説明文書）
IgA	Immunoglobulin A （免疫グロブリン A）
IgG	Immunoglobulin G （免疫グロブリン G）

Abbreviation	Meaning of Abbreviation (In Japanese)
IgM	Immunoglobulin M （免疫グロブリン M）
IRB/EC	Institutional Review Board / Ethics Committee （治験審査委員会／倫理委員会）
IUD	Intrauterine Device （子宮内避妊用具）
IUS	Intrauterine Contraceptive System（子宮内避妊システム ）

IV	Intravenous （静脈内）
kg	Kilogram （キログラム）
μM	Micromolar （マイクロモル濃度）
MDI	Metered Dose Inhaler （定量噴霧式吸入器）
MedDRA®	Medical Dictionary for Regulatory Activities （ICH 国際医薬用語集）
mg	Milligram （ミリグラム）
mL	Milliliter （ミリリットル）
NaCl	Sodium Chloride （塩化ナトリウム）
NAT	Nucleic Acid Amplification Technology （核酸増幅法）
NE	Neutrophil Elastase（好中球エラスターゼ）
OLE	Open Label Extension
PFT	Pulmonary Function Test （肺機能検査）
*PI*MM*	Proteinase Inhibitor homozygote for normal M allele 〔Proteinase Inhibitor 対立遺伝子 M（正常）のホモ接合体〕
PI(null)(null)*	Proteinase Inhibitor homozygote for (null) allele 〔Proteinase Inhibitor の対立遺伝子ヌル（零＝欠損）のホモ接合体〕
*PI*SZ*	Proteinase Inhibitor heterozygote for S and Z deficiency alleles 〔Proteinase Inhibitor の対立遺伝子 S（欠乏）及び Z（欠乏）のホモ接合体〕
*PI*Z*	Proteinase Inhibitor Z deficiency allele 〔Proteinase Inhibitor 遺伝子の Z（欠乏）の対立遺伝子〕
*PI*ZZ*	Proteinase Inhibitor homozygote for Z deficiency allele Homozygote for Z (Deficiency) Allele of the Alpha1-Proteinase Inhibitor Gene 〔Proteinase Inhibitor の対立遺伝子 Z（欠乏）のホモ接合体〕
PK	Pharmacokinetic/Pharmacokinetics （薬物動態）
RNA	Ribonucleic Acid （リボ核酸 ）
SAE	Serious Adverse Event （重篤な有害事象）
SAP	Statistical Analysis Plan （統計解析計画書）
SD	Standard Deviation （標準偏差）
SPARK	Alpha-1 MP Safety and Pharmacokinetic Study

	（Alpha-1 MP の安全性及び薬物動態試験 ）
STAMP	Safety and Tolerability of Alpha-1 MP study （Alpha-1 MP の安全性及び忍容性試験）
TEAE	Treatment-Emergent Adverse Event （治療中に発生した有害事象）

Table of Contents

1. INTRODUCTION

In addition to the information provided below, please also refer to the Investigator's Brochure (IB) and any additional data supplied by the sponsor.

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 versus 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 versus 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 versus 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$_{\text{iiyama}}$ 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 in 1987 and in Germany in 1988.

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 and higher purity compared to Prolastin. Alpha-1 MP is approved for 60 mg/kg weekly IV administration in the US, Canada, Colombia, Argentina, Turkey, Chile and Australia for the treatment of patients with severe AATD and clinically evident emphysema under the trade name Prolastin®-C.

Prolastin and Prolastin-C are together licensed in a total of 22 countries, with Prolastin [produced by the original process] authorized in several European countries.

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 Alpha-1 MP or 60 mg/kg 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 pruritus/itching.

Subsequent to the STAMP and ChAMP studies, the SPARK (Alpha-1 MP Safety and PhARmacoKinetic) study was conducted to assess the safety and pharmacokinetics (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

The safety and PK of augmentation therapy with Alpha-1 MP to increase serum $alpha_1$-PI levels, at a dosing regimen of 60 mg/kg in weekly IV infusions over 8 weeks, will be evaluated in patients with AATD (the Study GTI1401, a Phase 1/2 study) in Japan. The current study is an extension of the Study GTI1401 to evaluate the long-term safety of 60 mg/kg Alpha-1 MP.

2. STUDY ADMINISTRATIVE STRUCTURE

Please refer to Appendix 2 for the administrative structure of this study including:

- Sponsor
- Contract research organization
- Study centers
- Laboratory testing services, courier, investigational drug manufacturer

3. STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of this study is to evaluate the long-term safety of 60 mg/kg Alpha-1 MP administered by weekly IV infusions for approximately one year (52 weeks) or longer (can be renewed annually with the consent of the subjects) in adult subjects with AATD in Japan.

3.2 Exploratory Objective

The CT scan (densitometry) will be performed, and CT scan data will be accumulated for future evaluation of lung density.

4. INVESTIGATIONAL PLAN

4.1 Study Design and Plan

4.1.1 Design and Plan of This Clinical Trial

This is a multi-center, open-label study to evaluate the long-term safety of weekly IV infusions of 60 mg/kg Alpha-1 MP in adult subjects with AATD in Japan who have completed the Study GTI1401. The Study GTI1401 is being conducted to evaluate the safety and PK of Alpha-1 MP in subjects with AATD in Japan. In the current study, the GTI1401-OLE, subjects will be administered 60 mg/kg Alpha-1 MP by weekly IV infusion for approximately 1 year or longer to assess the long-term safety of Alpha-1 MP in subjects with AATD.

Unless the sponsor informs of discontinuation of this OLE trial, basically this trial can be renewed annually with the consent of the subjects.

This study will be conducted at three centers in Japan.

At the Week 9 Visit of the Study GTI1401, after giving consent, on the same day, subjects will be assessed for eligibility at the Screening/Extension (Ext) Week 1 Visit for this extension study, the Study GTI1401-OLE (see Section 4.2 for study inclusion and exclusion criteria). If eligible, subjects will be administered weekly IV infusions of 60 mg/kg Alpha-1 MP continuously. The Week 9 Visit of the Study GTI1401 will be the End of Study Visit for the subjects who are enrolled in the Study GTI1401-OLE.

Subjects in the Study GTI1401-OLE will have the option to remain in the Study GTI1401-OLE and continue to receive weekly IV infusions of 60 mg/kg Alpha-1 MP for up to a total of 6 years. The option for continuing the Study GTI1401-OLE for another year will be renewed annually with the consent of the subjects. The annual renewal for participation for another year will occur at the Ext Week 52, for the next 2nd year; at the Ext Week 104, for the next 3rd year; at the Ext Week 156, for the next 4th year, at the Ext Week 208, for the next 5th year; and at the Ext Week 260, for the next 6th year.

If a subject gives consent for remaining in the Study GTI1401-OLE, the subjects will skip the End of Study / Follow-Up Assessment and continue to receive weekly IV infusions of 60 mg/kg Alpha-1 MP for the next year.

A subject may choose to withdraw from the Study GTI1401-OLE at any time. If subjects choose to withdraw from the Study GTI1401-OLE, they will be asked to complete the End of Study /

Follow-Up Assessments, which will be scheduled as close as possible to 30 days (a ±2 days window is allowed) after the last Alpha-1 MP infusion.

Remarks: This study will be switched to a post-marketing study after Alpha-1 MP is approved in Japan.

A Schedule of Study Procedures is provided in Appendix 1.

4.1.2 Type of Study

Clinical safety study

4.1.3 Phase of Development

Phase I/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 in the informed consent form.
The investigator will assess subject eligibility based on the inclusion criteria and the exclusion criteria below.

4.2.1 Inclusion Criteria

A subject must meet all the following inclusion criteria to be eligible for participation in this study:

1. Subjects who complete participation in the Study GTI1401 (i.e., have completed the study through the Week 9 Visit).
2. Subjects who will and are able to provide written informed consent.

<Rationale for establishing the inclusion criteria>

1. The Study GTI1401-OLE is an open-label safety extension study of the Study GTI1401.
2. Subjects' documented consent to participate in the study is required

4.2.2 Exclusion Criteria

A subject who has completed the Study GTI1401 but meets any of the following exclusion criteria is NOT eligible for participation in the study.

1. Subjects with newly diagnosed severe concomitant disease including, but not limited to, congestive heart failure and liver cirrhosis.
2. Subjects with newly diagnosed malignant tumor (including malignant melanoma; however, other forms of skin cancer are allowed).
3. Female subjects who are pregnant, breastfeeding or, if of child-bearing potential, unwilling to practice a highly effective method of contraception (oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device [IUD] or intrauterine system [IUS], condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or abstinence) throughout the study or male subjects who have a partner who is of child-bearing potential and is unwilling to practice a highly effective method of contraception throughout the study.

4. Subjects with clinical signs and symptoms of HAV, HBV, HCV, or HIV viral infection at the Week 9 Visit of the Study GTI1401 and confirmed by testing.
5. Subjects with current evidence of smoking or has a positive urine cotinine test at the Week 9 Visit in the Study GTI1401 that is due to smoking.
6. Subjects who currently participate in a study of another investigational product (other than Alpha-1 MP).
7. Subjects who have difficulty in adhering to the protocol or its procedures, in the opinion of the investigator.
8. 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.

<Rationale for establishing the exclusion criteria>

1. To eliminate predisposition of underlying disease that could impact clinical laboratory assessments and subject safety
2. Same as above [#1]
3. For subject safety: Animal reproduction studies have not been conducted with Alpha-1 MP. It is not known whether Alpha-1 MP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.
4. To eliminate confounding factors that could impact physical assessment and clinical laboratory values, thereby impacting safety assessment
5. To eliminate confounding factors that could cause further decline in lung function and damage to the lungs
6. To exclude any confounding effect on the evaluation of adverse events and safety of this investigational drug
7. To eliminate noncompliance by the subject and other confounders to the safety assessments
8. To eliminate impact that may confound the safety assessment.

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 alpha$_1$-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-OLE

$Alpha_1$-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.
1-2-8, Toranomon, Minato-ku, Tokyo, 105-0001, Japan

Figure 4-1 Sample Labeling for the Investigational Drug (Package)

Protocol: GTI1401-OLE

$Alpha_1$-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.
1-2-8, Toranomon, Minato-ku, Tokyo, 105-0001, Japan

Figure 4-2 Sample Labeling for the Investigational Drug (Vial)

4.3.3 Dose and Dosage Regimen

4.3.3.1 Dose and Dosage Regimen

Subjects will receive an IV infusion 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, Colombia, Argentina, Turkey, Chile and Australia.

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.

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 to the study subject.

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

Additional storage 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. 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 retain the subject number from the Study GTI1401.

If a subject will change to a different study site in the course of the Study GTI1401-OLE due to his/her convenience, a new subject number will be assigned at the new study site based on its site number. In this case, in order to identify the subject as the same person, the matter of transition of the subject should be documented in each case report form of both sites as memorandum.

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

At the Week 9 Visit of the Study GTI1401, subjects will be given the option to participate in the Study GTI1401-OLE. If subjects give the consent for participation, on the same day, subjects will be assessed for eligibility at the Screening / Ext Week 1 Visit for this extension study, the GTI1401-OLE. If eligible, the subjects will receive their first IV infusion of 60 mg/kg Alpha-1 MP for the Study GTI1401-OLE at the Ext Week 1. Subjects will continue to receive weekly IV infusions of 60 mg/kg Alpha-1 MP for approximately one year (52 weeks) or longer.

If a subject gives consent for remaining in the Study GTI1401-OLE at the Ext Week 52 for the next 2nd year, at the Ext Week 104 for the next 3rd year, at the Ext Week 156 for the next 4th year, at the Ext Week 208 for the next 5th year, and at the Ext Week 260 for the next 6th year, the subject will continue to receive weekly IV infusions of 60 mg/kg Alpha-1 MP for the next year.

Each week, designated study site personnel will prepare an infusion bag of Alpha-1 MP for 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 approximately 0.08 mL/kg/min (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 Concomitant Medications during the Study

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

The variables to be assessed for this trial are as follows

Safety Variables	• 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: – Hematology, Chemistry, Urinalysis • Alpha$_1$-PI level
Exploratory Variable	• CT scan (densitometry) CT scan (densitometry) data will be accumulated for future evaluation of lung density.

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:

It 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:

It requires treatment with systemic steroids and/or antibiotics.

Severe:

It 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 (PFT; i.e., spirometry), including FEV_1 (absolute and percent predicted) and FVC, will be performed according to ATS/ERS guidelines (26) at the Ext Week 26 and 52 of the 1st year (at the Ext Week 78 and 104 of the 2nd year, at the Ext Week 130 and 156 of the 3rd year, at the Ext Week 182 and 208 of the 4th year, at the Ext Week 234 and 260 of the 5th year and at the Ext Week 286 and 312 of the 6th year). Pulmonary function tests at the Ext Week 26 and 52 of the 1st year (at the Ext Week 78 and 104 of the 2nd year, at the Ext Week 130 and 156 of the 3rd year, at the Ext Week 182 and 208 of the 4th year, at the Ext Week 234 and 260 of the 5th year and at the Ext Week 286 and 312 of the 6th year) should be conducted prior to Alpha-1 MP infusion. At each visit in which PFTs are scheduled, testing will be performed before 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.

4.6.3 CT Densitometry

The CT densitometry will be performed for measuring lung density; see CT Scan Manual for detailed procedures.

4.7 Evaluation

4.7.1 Evaluation Period

This study consists of a Screening / Ext Week 1 Visit in which the treatment regimen will be initiated as part of a 52-week open-label treatment period. After the treatment period, there will be an End of Study / Follow-Up Assessments scheduled as close as possible to 30 days (a ±2 days window is allowed) after the last Alpha-1 MP infusion. The total duration of study participation for subjects who complete the study will be approximately 56 weeks (a 52-week treatment period + 30 days).

The study can be renewed annually with the consent of the subjects.
If a subject gives consent for remaining in the Study GTI1401-OLE at the Ext Week 52 for the next 2nd year, at the Ext Week 104 for the next 3rd year, at the Ext Week 156 for the next 4th year, at the Ext Week 208 for the next 5th year, and at the Ext Week 260 for the next 6th year, the subject will continue to receive weekly IV infusions of 60 mg/kg Alpha-1 MP for the next year.

If subjects plan to conclude their participation in the study (GTI1401-OLE) at the Ext Week 52 of the 1st year, at the Ext Week 104 of the 2nd year, at the Ext Week 156 of the 3nd year, at the Ext Week 208 of the 4th year, and at the Ext Week 260 of the 5th year or earlier before the Ext Week 52 of the 1st year, the Ext Week 104 of the 2nd year, the Ext Week 156 of the 3rd year, at the Ext Week 208 of the 4th year, at the Ext Week 260 of the 5th year or at the Ext Week 312 of the 6th year, they will be asked to complete the End of Study / Follow-Up Assessments, which will be scheduled as close as possible to 30 days (a ±2 days window is allowed) after the last Alpha-1 MP infusion.

4.7.2 Observation and Measurement

The following is a description of the procedures/assessments to take place at each study visit. See the Schedule of Study Procedures in Appendix 1 for a summary of study visits and the procedures and assessments to be conducted at each visit. Unscheduled visits may be conducted if deemed necessary for the purpose of subject safety.

4.7.2.1 Screening / Ext Week 1 Visit of the 1st year

At the Week 9 Visit of the Study GTI1401, subjects will be given the option for participation in the Study GTI1401-OLE. If subjects opt to participate, on the same day, they will be assessed for eligibility at the Screening / Ext Week 1 Visit of the 1st year for this extension study. Subjects who satisfy the inclusion and exclusion criteria will receive their first IV infusion of Alpha-1 MP at this visit.

Informed consent must be obtained for all prospective subjects prior to the collection of any screening assessments or the conduct of any study procedures. All subjects will start their participation in the study by signing the Informed Consent Form (ICF).

The Screening / Ext Week 1 Visit of the 1st year will occur on the same day as the Week 9 Visit of the prior study (GTI1401). The procedures performed at the Week 9 Visit of the Study GTI1401 will be used for the Screening / Ext Week 1 Visit for the first year of the Study GTI1401-OLE.

Additional procedures and assessments will be performed during the Screening / Ext Week 1 Visit of the 1st year, including:

Visit	Trial Procedures and Evaluations
Screening / Ext Week 1 Visit of the 1st year	Prior to Alpha-1 MP Infusion • Informed consent • Determine eligibility by assessment of inclusion/exclusion criteria • Subject number confirmed • Body weight: Recorded body weight will be used to calculate the Alpha-1 MP dose administration at the OLE-Week 1 Visit (OLE-baseline). This recorded body weight will be used for dose calculation until the next scheduled body weight measurement. • Vital signs immediately before the start of Alpha-1 MP infusion (heart rate, blood pressure, respiratory rate, and temperature) Alpha-1 MP Infusion: • Administer Alpha-1 MP infusion • Vital signs immediately after the completion of Alpha-1 MP infusion (heart rate, blood pressure, respiratory rate, and temperature)

4.7.2.2 The 1st Visit of the 2nd year (at the Ext Week 53), the 3rd year (at the Ext Week 105), the 4th year (at the Ext Week 157), the 5th year (at the Ext Week 209), and the 6th year (at the Ext Week 261)

The following procedures and assessments will be performed in the 1st Visit of the 2nd year (at the Ext Week 53), the 3rd year (at the Ext Week 105), the 4th year (at the Ext Week 157), the 5th year (at the Ext Week 209) and the 6th year (at the Ext Week 261). [Those are the same as Section 4.7.2.3 Weekly On-site Infusion Visits.]

Visit	Trial Procedures and Evaluations
The 1st Visit of the 2nd year or longer (The 2nd year) Ext Week 53 [The 3rd year] Ext Week 105 [The 4th year] Ext Week 157 [The 5th year] Ext Week 209 [The 6th year] Ext Week 261	<u>Prior to Alpha-1 MP Infusion:</u> • AE assessment [see Section 5] • Concomitant medications assessment • COPD exacerbation assessment [see Section 4.6.1] • Vital signs <u>immediately before</u> the start of Alpha-1 MP infusion (heart rate, blood pressure, respiratory rate, and temperature) <u>Alpha-1 MP Infusion:</u> • Administer Alpha-1 MP infusion • Vital signs <u>immediately after</u> the completion of Alpha-1 MP infusion (heart rate, blood pressure, respiratory rate, and temperature)

4.7.2.3 Weekly On-Site Infusion Visits

Subjects will return to the clinical site for weekly IV infusions throughout the study and will undergo the following procedures and assessments.

Visit	Trial Procedures and Evaluations
Weekly On-Site Infusion Visits	Prior to Alpha-1 MP Infusion: • AE assessment [see Section 5] • Concomitant medications assessment • COPD exacerbation assessment [see Section 4.6.1] • Vital signs immediately before the start of Alpha-1 MP infusion (heart rate, blood pressure, respiratory rate, and temperature) Alpha-1 MP Infusion: • Administer Alpha-1 MP infusion • Vital signs immediately after the completion of Alpha-1 MP infusion (heart rate, blood pressure, respiratory rate, and temperature)

4.7.2.4 Quarterly Visits: Ext Weeks 12, 24, 36, and 48 of the 1st year (Ext Weeks 64, 76, 88, and 100 of the 2nd year, Ext Weeks 116, 128, 140, and 152 of the 3rd year, Ext Weeks 116, 128, 140, and 152 of the 3rd year, Ext Weeks 168, 180, 192, and 204 of the 4th year, Ext Weeks 220, 232, 244, and 256 of the 5th year, and Ext Weeks 272, 284, 296, and 308 of the 6th year).

In addition to Alpha-1 MP infusion and the procedures performed during Weekly On-Site Infusion Visits (see Section 4.7.2.3), the following procedures and assessments will be performed during the quarterly on-site visits at Ext Weeks 12, 24, 36, and 48 of the 1st year (at Ext Weeks 64, 76, 88, and 100 of the 2nd year, Ext Weeks 116, 128, 140, and 152 of the 3rd year, Ext Weeks 168, 180, 192, and 204 of the 4th year, Ext Weeks 220, 232, 244, and 256 of the 5th year, and Ext Weeks 272, 284, 296, and 308 of the 6th year).

Visit	Trial Procedures and Evaluations
Quarterly Visits: Ext Weeks 12, 24, 36, and 48 [the 2nd year] Ext Weeks 64, 76, 88, and 100 [the 3rd year] Ext Weeks 116, 128, 140, and 152 [the 4th year] Ext Weeks 168, 180, 192, and 204 [the 5th year] Ext Weeks 220, 232, 244, and 256 [the 6th year] Ext Weeks 272, 284, 296, and 308	<u>Prior to Alpha-1 MP Infusion:</u> • Body weight: Recorded body weight will be used to calculate the Alpha-1 MP dose administration. This recorded body weight will be used for dose calculation until the next scheduled body weight measurement. • $Alpha_1$-PI level

4.7.2.5 Bi-Annual Visits No.1: the Ext Week 26 of the 1st year (the Ext Week 78 of the 2nd year, the Ext Week 130 of the 3rd year, the Ext Week 182 of the 4th year, the Ext Week 234 of the 5th year, and the Ext Week 286 of the 6th year).

In addition to Alpha-1 MP infusion and the procedures performed during Weekly On-Site Infusion Visits (see Section 4.7.2.3), the following procedures and assessments will be performed bi-annually at the Ext Week 26 of the 1st year, at the Ext Week 78 of the 2nd year, at the Ext Week 130 of the 3rd year, at the Ext Week 182 of the 4th year, at the Ext Week 234 of the 5th year and at the Ext Week 286 of the 6th year.

Visit	Trial Procedures and Evaluations
Bi-Annual Visits No.1 Ext Week 26 [the 2nd year] Ext Week 78 [the 3rd year] Ext Week 130 [the 4th year] Ext Week 182 [the 5th year] Ext Week 234 [the 6th year] Ext Week 286	<u>Prior to Alpha-1 MP Infusion:</u> • Laboratory assessments [see Section 4.7.3]: – Urine: ✓ Urine pregnancy test (Potential child-bearing females only; results must be negative for the subject to continue in the study) ✓ Urinalysis ✓ Urine cotinine – Blood: ✓ Hematology ✓ Chemistry • Physical examination (excludes breast and genitourinary) • Pre- and post-bronchodilator PFTs (FEV_1 and FVC) [see Section 4.6.2]

4.7.2.6 Bi-Annual Visits No.2: Ext Week 52 of the 1st year (Ext Week 104 of the 2nd year, Ext Week 156 of the 3rd year, Ext Week 208 of the 4th year, Ext Week 260 of the 5th year and Ext Week 312 of the 6th year).

In addition to Alpha-1 MP infusion and the procedures performed during Weekly On-Site Infusion Visits (see Section 4.7.2.3), the following procedures and assessments will be performed bi-annually at the Ext Week 52 of the 1st year, at the Ext Week 104 of the 2nd year, at the Ext Week 156 of the 3rd year, at the Ext Week 208 of the 4th year, at the Ext Week 260 of the 5th year, and at the Ext Week 312 of the 6th year.

Subjects in the Study GTI1401-OLE will have the option to remain in the Study GTI1401-OLE and continue to receive weekly IV infusions of 60 mg/kg Alpha-1 MP for another year at the Ext Week 52 for the next 2nd year and at the Ext Week 104 for the next 3rd year, at the Ext Week 156 for the next 4th year, at the Ext Week 208 for the next 5th year, and at the Ext Week 260 for the next 6th year. The option for continuing the Study GTI1401-OLE for another year will be renewed annually with the consent of the subjects.

Informed consent must be obtained for all prospective subjects prior to the collection of any screening assessments or the conduct of any study procedures for the second year or longer. All subjects will start their participation in the study for the second year or longer by signing the Informed Consent Form (ICF).

Visit	Trial Procedures and Evaluations
Bi-Annual Visits: No.2 Ext Week 52 [the 2nd year] Ext Week 104 [the 3rd year] Ext Week 156 [the 4th year] Ext Week 208 [the 5th year] Ext Week 260 [the 6th year] Ext Week 312	Prior to Alpha-1 MP Infusion: • Laboratory assessments [see Section 4.7.3]: – Urine: ✓ Urine pregnancy test (Potential child-bearing females only; results must be negative for the subject to continue in the study) ✓ Urinalysis ✓ Urine cotinine – Blood: ✓ Hematology ✓ Chemistry ✓ Viral safety retain samples (Viral nucleic acid technology [NAT] and viral serology). • Physical examination (excludes breast and genitourinary) • Pre- and post-bronchodilator PFTs (FEV_1 and FVC) [see Section 4.6.2] • CT densitometry • Informed consent to remain in GTI1401-OLE for another year (except the Ext Week 312 of the 6th year). If a subject gives consent for remaining in the Study GTI1401-OLE, the subject will skip the End of Study / Follow-Up Assessments scheduled and continue to receive weekly IV infusions of 60 mg/kg Alpha-1 MP for another year.

4.7.2.7 End of Study / Follow-Up Assessments

If a subject decides not to remain in the Study GTI1401-OLE at the Ext Week 52 of the 1st year and at the Ext Week 104 of the 2nd year, at the Ext Week 156 of the 3nd year, at the Ext Week 208 of the 4th year, at the Ext Week 260 of the 5th year, or the Ext Week 312 of the 6th year he or she will complete the End of Study / Follow-Up Assessments scheduled as close as possible to 30 days (a ±2 days window is allowed) after the last Alpha-1 MP infusion. The following procedures and assessments will be performed during this visit:

If a subject decides to conclude the OLE trial earlier before the Ext Week 52 of the 1st year, the Ext Week 104 of the 2nd year, the Ext Week 156 of the 3rd year, the Ext Week 208 of the 4th year, the Ext Week 260 of the 5th year, or the Ext Week 312 of the 6th year, he or she will be asked to complete the End of Study / Follow-Up Assessments, which will be scheduled as close as possible to 30 days (a ±2 days window is allowed) after the last Alpha-1 MP infusion.

Visit	Trial Procedures and Evaluations
End of Study / Follow-Up Assessments	• Laboratory assessments [see Section 4.7.3]: – Urine: ✓ Urine pregnancy test (Potential child-bearing females only) ✓ Urinalysis ✓ Urine cotinine – Blood: ✓ Hematology ✓ Chemistry ✓ Viral safety retain samples (Viral nucleic acid technology [NAT] and viral serology) • CT densitometry: CT scan should only be conducted if it is more than 6 months from previous CT scan. • Physical examination (excludes breast and genitourinary) • Pre- and post-bronchodilator PFTs (FEV_1 and FVC) [see Section 4.6.2] • COPD exacerbation assessment [see Section 4.6.1] • AE assessment [see Section 4.2] • Concomitant medications assessment • Vital signs (heart rate, blood pressure, respiratory rate, and temperature)

4.7.3 Laboratory Tests and Testing Procedures

Detailed descriptions of laboratory test procedures are located in the study Laboratory Manual. Table 4-2 provides a summary of the laboratory tests conducted for this study.

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, glucose, albumin, total protein, total bilirubin aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase	Central laboratory[a]
Urinalysis	pH, protein, glucose, blood, and Microscopic evaluation will be performed only with cause	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 Ext Week 52 visit[b], at the Ext Week 104 visit[b] at the Ext Week 156 visit[b], at the Ext Week 208 visit[b], at the Ext Week 260 visit[b], and at the Ext Week 312 visit[b]: Collection of samples for storage Hepatitis A virus (HAV) RNA, Hepatitis B virus (HBV) DNA, Hepatitis C virus (HCV) RNA, Human immunodeficiency virus (HIV) RNA, Parvovirus B19 (B19V) DNA	Central laboratory[a]

Viral serologic test	Before the intravenous infusion of Alpha-1 MP at the Ext Week 52 visit[b], at the Ext Week 104 visit[b], at the Ext Week 156 visit[b], at the Ext Week 208 visit[b], at the Ext Week 260 visit[b], at the Ext Week 312 visit[b]: Collection of samples for storage Differentiation of HAV antibody (immunoglobulin M [IgM]/immunoglobulin G [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: Central lab: LSI Medience Corporation

b: Section 4.7.3.1. These retain samples will be stored until all analyses in support of studies GTI1401 and GTI1401-OLE are complete.

4.7.3.1 Viral Safety Assessment

Virus safety retain samples (viral NAT and viral serology) collected at the Week 1 (Baseline) Visit of the Study GTI1401 prior to infusion will be used as baseline virus safety retain samples for GTI1401-OLE. In the Study GTI1401-OLE, virus safety retain samples (viral NAT and viral serology; see Table 4-2) will be collected prior to infusion at the Ext Week 52 of the 1st year, at the Ext Week 104 of the 2nd year, and at the Ext Week 156 of the 3rd year, at the Ext Week 208 of the 4th year, at the Ext Week 260 of the 5th year, and at the Ext Week 312 of the 6th year. These samples will be stored until the subject has completed the Study GTI1401-OLE.

Viral NAT and viral serology 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 Drug Concentration Measurements

All subjects will have a blood sample collected quarterly at Ext Weeks 12, 24, 36 and 48 of the 1st year, at Ext Weeks 64, 76, 88 and 100 of the 2nd year, at Ext Weeks 116, 128, 140 and 152 of the 3rd year, at Ext Weeks 168, 180, 192 and 204 of the 4th year, at Ext Weeks 220, 232, 244 and 256 of the 5th year, and at Ext Weeks 272, 284, 296 and 308 of the 6th year for the measurement of trough $alpha_1$-PI levels prior to the IV infusions of 60 mg/kg Alpha-1 MP. 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 trough concentration measurements, the following volumes of blood per subject will be taken during the study planned 56 weeks including End of Study / Follow-Up Assessment if a subject completes the study at the end of the 1st year.

Blood sampling	Volume (mL)	Times	Total volume (mL)
Laboratory tests	6	3	18
Viral tests	34.5	1	34.5
Alpha$_1$-PI concentration	4	4	16
Grand Total over 56 weeks			68.5

4.8 Screening Failures

Screening evaluations (the Week 9 Visit of the Study GTI1401) 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, Colombia, Argentina, Turkey, Chile and Australia. 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 immunoglobulin A (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 subject 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 treatment-emergent adverse events (TEAE).

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 / Follow-Up Assessments 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 the 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 an SAE (Section 5.3.6). If an exacerbation meets criteria for an 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 SAEs that occur after signing the study ICF through the End of Study / Follow-Up Assessments (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** by email.

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 development-related duties for this clinical trial, as instructed below via the SAE report form (see Appendix 3.1 and 3.2)

form 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.

All SAE report forms should be submitted by email to the Eastern Japan Pharmacovigilance Division of CMIC, which is responsible for pharmacovigilance, 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 Pharmacovigilance and Grifols Japan within 24 hours. The following required information should be provided to Grifols Global Pharmacovigilance to perform the preliminary reportable 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 Pharmacovigilance 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 Pharmacovigilance 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 Pharmacovigilance 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 Pharmacovigilance.

5.4.2 Reporting of Pregnancies

Pregnancy itself is not an AE, 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 in a study subject subsequent to informed consent signature through the End of Study / Follow-Up Assessments 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 form (see Appendix 3.3) 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 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 to 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 AE which requires discontinuation of the trial in the opinion 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 opinion 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 opinion 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 a subject from 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, and should also document the date of discontinuation, the reason for discontinuation, the action taken after discontinuation, and the course after discontinuation 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 be asked to return to the study center for the End of Study / Follow-Up Assessments (refer to Section 4.7.2.7 “End of Study / Follow-Up Assessments” and Appendix 1).

- This visit should be made as close as possible to 30 days (a ±2 days window is allowed) 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 should document 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 attempts to communicate with the subject are made, but the investigator is unable to identify the location of the subject, the investigator or subinvestigator should document 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 (IRB) 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 Good Clinical Practice (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 withdrawal of a study center, the investigator should return all trial-related materials (excluding documents to be continuously retained at the study center) to the sponsor. The investigator should retain all the documents to be continuously 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 individual 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 (SD), 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.

8.2 Determination of Target Sample Size

Sample size of this study (GTI1401-OLE) will be contingent on the number of subjects who enter and complete the Study GTI1401 and who consent to enter this extension study. 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 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 data 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 examination that has not been performed, this item should be slash mark (date and initial should be included on blank pages that are slashed through).
(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 official.

(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. The investigator or

subinvestigator will also 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 AEs and SAEs must be recorded. All serious adverse events will be recorded on SAE forms. Original forms of recorded SAEs 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 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 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 should record 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 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 Investigator, and the trial-related health injury is not due to the natural progression of any conditions existing 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

None of the information obtained in this study is allowed to be published 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

March 1, 2016 to March 31, 2022

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: 709-714.

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: 889-898.

13. Janoff A.: Elastases and emphysema. Current assessment of the protease-antiprotease hypothesis.
Am Rev Respir Dis 1985; 132(2): 417-433.

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: 891-897.

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 Invest 1990; 85: 1343-1352.

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): 461-478.

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): 469-475.

19. Stockley RA, Mannino D, Barnes PJ.: Burden and pathogenesis of chronic obstructive pulmonary disease.
Proc Am Thorac Soc 2009; 6: 524-526.

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: 1158-1165.

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. 1450-1467.

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): 1055-1062.

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): 2260-2263.

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): 416-468.

26. Miller MR, Hankinson J, Brusasco V, et al.: Standardisation of spirometry.
Eur Respir J 2005; 26: 319-338.

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: 996-997.

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: 428-433.

29. Karch FE, Lasagna L.: Toward the operational identification of adverse drug reactions.
Clin Pharmacol Ther 1977; 21: 247-254.

30. Naranjo CA, Busto U, Sellers EM, et al.: A method for estimating the probability of adverse drug reactions.
Clin Pharmacol Ther 1981; 30: 239-245.

Appendix 1 Schedule of Study Procedures

Procedures / Assessments Visits	Screening / Ext Week 1 Visit of the 1st year		The 1st Visit of the 2nd year or longer [The 2nd year] Ext Week 53 [The 3rd year] Ext Week 105 [The 4th year] Ext Week 157 [The 5th year] Ext Week 209 [The 6th year] Ext Week 261	Weekly On-Site Infusion Visits Ext Week 2 to Ext Week 52 Ext Week 54 to Ext Week 104 Ext Week 106 to Ext Week 156 Ext Week 158 to Ext Week 208 Ext Week 210 to Ext Week 260 Ext Week 262 to Ext Week 312	Quarterly Visits Ext Weeks 12, 24, 36, 48 Ext Weeks 64, 76, 88, 100 Ext Weeks 116, 128, 140, 152 Ext Weeks 168, 180, 192, 204 Ext Weeks 220, 232, 244, 256 Ext Weeks 272, 284, 296, 308	Bi-Annual Visits		End of Study / Follow-Up Assessments [b]
	Screening	Initiation of Infusion				[No.1] Ext Week 26 Ext Week 78 Ext Week 130 Ext Week 182 Ext Week 234 Ext Week 286	[No.2] Ext Week 52 Ext Week 104 Ext Week 156 Ext Week 208 Ext Week 260 Ext Week 312	
Informed consent	X						X [l]	
Inclusion / Exclusion criteria	X							
Subject number confirmed	X							
Weight [c]	X				X			
CT Scan (densitometry) [d]							X	X
Collection of virus safety retain samples [c]							X	X
Physical exam (excludes breast and genitourinary) [f]						X	X	X

Urine pregnancy test (potential child-bearing females only) [f]						X	X	X
Urine cotinine [f]						X	X	X
Urinalysis [f]						X	X	X
Blood for hematology and chemistry laboratory assessments [f]						X	X	X
Vital signs (heart rate, blood pressure, respiratory rate, and temperature) [g]		X	X	X	X	X	X	X
Pre- and post-bronchodilator PFTs (FEV_1 and FVC) [h]						X	X	X
Blood for $alpha_1$-PI level [i]					X			
Alpha-1 MP IV infusion [j]		X	X	X	X	X	X	
COPD exacerbation assessment [f]			X	X	X	X	X	X
Adverse event assessment [f, k]			X	X	X	X	X	X
Concomitant medications assessment [f]			X	X	X	X	X	X

a: Time period is relative to the Screening / Ext Week 1 Visit. A ±1 day window is allowed for all study visits after the Screening / Ext Week 1 Visit. The Screening / Ext Week 1 Visit and initiation of treatment for the current study (GTI1401-OLE) occurs on the same day as the Week 9 Visit of GTI1401 only for those subjects who give the consent for participation in the Study GTI1401-OLE. The procedures performed at the Week 9 Visit of the Study GTI1401 will be used for the Screening / Ext Week 1 Visit of the Study GTI1401-OLE. Blood samples for virus safety testing (viral NAT and viral serology) collected at the Week 1 (Baseline) Visit of the Study GTI1401 will be used as baseline virus safety retain samples for the Study GTI1401-OLE.

b: Subjects who receive any amount of Alpha-1 MP and discontinue early from the study will be requested to complete the End of Study / Follow-Up Assessments scheduled at the timing as close as possible to 30 days (a ±2 days window is allowed) after their last administration of Alpha-1 MP. If a subject gives consent for remaining in the Study GTI1401-OLE, the subject will skip the End of Study / Follow-Up Assessments and continue to receive weekly IV infusions of 60 mg/kg Alpha-1 MP for another year.

c: Each recorded weight will be used to calculate the Alpha-1 MP infusion dose for the scheduled visit and subsequent weekly Alpha-1 MP infusions until the next scheduled weight is measured.

d: This CT scan will measure lung density. As for the End of Study / Follow-Up Assessments, CT scan should only be conducted if it has passed more than 6 months from previous CT scan.

e: Virus safety retain samples (viral NAT and viral serology) will be collected prior to infusion at the Ext Week 52 of the 1st year, at the Ext Week 104 of the 2nd year, at the Ext Week 156 of the 3rd year, at the Ext Week 208 of the 4th year, at the Ext Week 260 of the 5th year, and at the Ext Week 312 of the 6th year, but will be tested *only* if a subject exhibits clinical signs and symptoms consistent with a viral infection. Additional blood 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.

f: To be conducted prior to Alpha-1 MP infusion (except the End of Study / Follow-Up Assessments).

g: Vital signs will be performed prior to and after each infusion of Alpha-1 MP (except the End of Study / Follow-Up Assessments).

h: Pulmonary function tests at the Ext Week 26 and 52 of the 1st year (at the Ext Week 78 and 104 of the 2nd year, and at the Ex Week 130 and 156 of the 3rd year, at the Ext Week 182 and 208 of the 4th year, at the Ext Week 234 and 260 of the 5th year and at the Ext Week 286 and 312 of the 6th year) should be conducted prior to Alpha-1 MP infusion. The post-bronchodilator PFT should be performed 15 to 30 minutes after bronchodilator administration. For each PFT, four puffs of MDI salbutamol as a short-acting bronchodilator should be administered. The same bronchodilator should be used throughout the study.

i: $Alpha_1$–PI level as measured by nephelometry.

j: Weekly infusions of 60 mg/kg Alpha-1 MP will be performed at the Investigator site.

k: Adverse event assessment includes AEs, SAEs, ADRs, and discontinuation due to AEs or SAEs.

l: Informed consent should be done at the Ext Week 52 and at the Ext Week 104, at the Ext Week 156, at the Ext Week 208, and at the Ext Week 260 for the next year (except the Ext Week 312).

APPENDIX 2

A2.1 Sponsor

1) Sponsor

[redacted]

Grifols Japan K.K.

1-2-8, Toranomon, Minato-ku, Tokyo, 105-0001, Japan

TEL: [redacted] FAX: [redacted]

2) [redacted]

Grifols Japan K.K.

1-2-8, Toranomon, Minato-ku, Tokyo, 105-0001, Japan

TEL: [redacted] FAX: [redacted]

3) [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:

[redacted]

[redacted]

CMIC Co., Ltd.

1-1-1 Shibaura, Minato-ku, Tokyo 105-0023, Japan

TEL: [redacted] (main switchboard)

Monitor (CRA)

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

A2.3 Grifols Therapeutics LLC., USA

[redacted]

[redacted]

Grifols Therapeutics LLC.
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 LLC. or will be carried out by the CMIC Co., Ltd. in conjunction with Grifols Therapeutics LLC. as listed below:

1) Medical Monitor
   Refer to Attachment.

Other duties to be performed by Grifols Therapeutics LLC. in conjunction with the CMIC 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

[redacted]

[redacted]

LSI Medience Corporation

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

TEL: [redacted] FAX: [redacted]

<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

[redacted]

[redacted]

TNT Express Worldwide (Japan) Inc.

TOC Ariake East Tower 6th floor

3-5-7 Ariake, Koto-ku, Tokyo, Japan

3) Investigational drug manufacturer

[redacted],

[redacted]

Grifols Therapeutics LLC.

4201 Research Commons

79 T.W. Alexander Drive

Research Triangle Park NC 27709, USA

TEL: [redacted] FAX: [redacted]

A2.6 Central Evaluation of CT Scan Image

Vida Diagnostics

2500 Crosspark Road

W250 BioVentures Center

Coralville, IA 52241

TEL: [redacted] FAX: [redacted]

Attachment 1

1. List of Investigational Sites and Investigators

Investigational Sites (Address & Tel#)	Department	Principal Investigator
Hokkaido University Hospital Kita 14 Nishi 5, Kita-ku,Sapporo 060-8648 Japan Tel: [redacted]	[redacted]	[redacted]
Juntendo University Hospital 3-1-3 Hongo, Bunkyo-ku, Tokyo 113-8431 Japan Tel: [redacted]	[redacted]	[redacted]
Hirosaki University Hospital 53 Honcho, Hirosaki, Aomori, 036-8563 Japan Tel: [redacted]	[redacted]	[redacted]

2. Medical Monitor

[redacted]**, M.D., Ph.D**

[redacted],
Artage Inc.
5-15-25 Minamiazabu, Minato-ku,
Tokyo 106-0047, JAPAN
TEL/FAX: [redacted]

[redacted]**, M.D., FCCP**

[redacted],
Grifols Therapeutics LLC
4210 Research Commons
79 T.W. Alexander Drive, Research Triangle Park NC 27709, USA
TEL: [redacted] FAX: [redacted]

3. Monitor (CRA)

[redacted]
Orphan Drug Trial Department
Academia Clinical Research Division
CMIC Co., Ltd.

1-1-1 Shibaura, Minato-ku, Tokyo 105-0023, Japan
TEL: [redacted], FAX: [redacted]

APPENDIX 3

A3.1 SAE Report Form

GRIFOLS

Study Number: GTI1401-OLE

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: _____

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

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:_____

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

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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]

A3.2 Supplemental Event Form

GRIFOLS

Study Number: GTI1401-OLE

Subject No.	Serious Adverse Event Report
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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-OLE

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

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

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]

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Emergency contact:

[redacted]

[redacted]

Orphan Drug Trial Department
Academia Clinical Research Division
CMIC Co., Ltd.

1-1-1 Shibaura, Minato-ku, Tokyo 105-0023, Japan
TEL: [redacted] FAX: [redacted]
(Mobile phone No. [redacted])