

Patient Background Enrollment Fax Form

Patient Information

Patient Name (First/Last): _____ Date of Birth (DOB): _____
Address: _____
City: _____ State: _____ ZIP: _____ Home Phone: _____

Insurance Information (Attach Card)

Primary Insurance: _____ Phone: _____
Subscriber: _____ DOB: _____ Subscriber ID #: _____ Policy/Group #: _____
Secondary/Medigap: _____ Phone: _____
Subscriber: _____ DOB: _____ Subscriber ID #: _____ Policy/Group #: _____
Medicare Part D: Yes No Phone: _____
Subscriber: _____ DOB: _____ Subscriber ID #: _____ Policy/Group #: _____
 Benefit Check (patient will not be contacted)

Diagnosis/ Medical Assessment

Primary Diagnosis: *Alpha₁-Antitrypsin Deficiency* ICD.9 Code: *273.4*
Associated Medical Conditions: _____ ICD.9 Code: _____
Serum AAT Level: _____ mg/dL or _____ µM Date: _____
PFT: FEV₁ % Pred. _____ O₂ Therapy: _____ L/min Date: _____
CXR/CT Results: _____ Date: _____
Phenotype: _____
Current or former smoker? Yes No If former smoker, date stopped: _____
Notes: _____

Therapy

Prescribed Therapy: *GLASSIA [Alpha₁-Proteinase Inhibitor (Human)]* Patient Weight: _____ kg (2.2 lb = 1 kg)
Ordered Dose: _____ mg Frequency: Weekly Other _____ Dosing: _____ Refills (Months): _____
Infusion Location: Home Hospital Physician Office Infusion Center
Preferred Specialty Pharmacy: _____ Preferred Hospital: _____
Is the patient aware of diagnosis and treatment? Yes No

Prescriber

Physician Name: _____ License #: _____
Address: _____ NPI #: _____
City: _____ State: _____ ZIP: _____ DEA #: _____
Phone: _____ Fax: _____ Office Contact: _____

I certify that the prescribed therapy is medically necessary for the treatment of alpha₁-antitrypsin deficiency and that the above information is accurate to the best of my knowledge and belief. I further certify that I have obtained the patient's consent to release this information for the patient's enrollment in the Alpha-1 AATmosphere program. By my signature below, I authorize the Alpha-1 AATmosphere program to (1) provide any information on this form to the insurer of the above named patient for enrollment/verification purposes and (2) forward the above prescription information, by fax or other mode of delivery, to the patient's pharmacy. I understand that any information released will be used only for the purposes for which it has been provided.

Signature _____ Date _____

Please see GLASSIA™ Important Risk Information on reverse side.

Glassia

[Alpha₁-Proteinase Inhibitor (Human)]

Alpha₁-Proteinase Inhibitor (Human), GLASSIA is indicated for chronic augmentation and maintenance therapy in individuals with emphysema due to congenital deficiency of alpha₁-proteinase inhibitor (Alpha₁-PI), also known as alpha₁-antitrypsin (AAT) deficiency.

- The effect of augmentation therapy with GLASSIA or any Alpha₁-PI product on pulmonary exacerbations and on the progression of emphysema in Alpha₁-PI deficiency has not been demonstrated in randomized controlled clinical trials.
- Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with GLASSIA are not available.
- GLASSIA is not indicated as therapy for lung disease in patients in whom severe Alpha₁-PI deficiency has not been established.

Important Risk Information for GLASSIA

GLASSIA is contraindicated in IgA deficient patients with antibodies against IgA. GLASSIA is contraindicated in individuals with a history of severe immediate hypersensitivity reactions, including anaphylaxis, to Alpha₁-PI products.

GLASSIA is made from human plasma. It may carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Administer GLASSIA at room temperature at a rate not greater than 0.04 mL/kg body weight per minute. **If anaphylactic or severe anaphylactoid reactions occur, discontinue the infusion immediately.**

Safety and effectiveness in patients over 65 years of age have not been established.

Two serious adverse reactions observed on two separate occasions during clinical studies with GLASSIA were cholangitis and exacerbation of chronic obstructive pulmonary disease (COPD).

The most common product-related adverse reactions in clinical studies were headache and dizziness.

Please see accompanying GLASSIA™ Prescribing Information for full prescribing details.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use GLASSIA safely and effectively. See full prescribing information for GLASSIA.

GLASSIA (Alpha₁-Proteinase Inhibitor (Human))

Injection Solution - For Intravenous Use Only

Initial US Approval: July 2010

INDICATIONS AND USAGE

GLASSIA is an alpha₁-proteinase inhibitor that is indicated for chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of alpha₁-proteinase inhibitor (Alpha₁-PI), also known as alpha₁-antitrypsin deficiency (1).

- The effect of augmentation therapy with any alpha₁-proteinase inhibitor on pulmonary exacerbations and on the progression of emphysema in Alpha₁-PI deficiency has not been demonstrated in randomized, controlled clinical trials (1).
- Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with GLASSIA are not available (1).
- GLASSIA is not indicated as therapy for lung disease in patients in whom severe Alpha₁-PI deficiency has not been established (1).

DOSAGE AND ADMINISTRATION

- For intravenous use only (2).
- Do not mix with other agents or diluting solutions (2).
- Dose = 60 mg/kg body weight once weekly (2.1).
- Dose ranging studies using efficacy endpoints have not been performed (2.1).
- Use filter needle as indicated in the "Preparation" section (2.2).
- The infusion rate should not exceed 0.04 mL/kg body weight per minute (2.3).

- If adverse events occur, reduce the rate or interrupt the infusion until the symptoms subside. You may then resume the infusion at a rate tolerated by the patient (2.3).

DOSAGE FORMS AND STRENGTHS

Single use vial containing 1 gram of functional Alpha₁-PI in 50 mL of ready to use solution (3).

CONTRAINDICATIONS

- IgA deficient patients with antibodies against IgA (4).
- History of severe immediate hypersensitivity reactions, including anaphylaxis, to Alpha₁-PI products (4).

WARNINGS AND PRECAUTIONS

- IgA deficient patients with antibodies against IgA may develop severe hypersensitivity and anaphylactic reactions (5.1).
- May carry a risk of transmitting infectious agents such as viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite manufacturing steps designed to minimize the risk of viral transmission (5.2, 11).

ADVERSE REACTIONS

The most common product-related adverse reactions (>3%) in clinical studies were headache and dizziness (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Kamada Ltd. at 1-866-GLASSIA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).

See Section 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2010

3200000366-02

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* Sections or subsections omitted from the full prescribing information are not listed

1. INDICATIONS AND USAGE

Alpha₁-Proteinase Inhibitor (Human), GLASSIA is indicated for chronic augmentation and maintenance therapy in individuals with emphysema due to congenital deficiency of alpha₁-proteinase inhibitor (Alpha₁-PI), also known as alpha₁-antitrypsin (AAT) deficiency.

- The effect of augmentation therapy with GLASSIA or any Alpha₁-PI product on pulmonary exacerbations and on the progression of emphysema in Alpha₁-PI deficiency has not been demonstrated in randomized, controlled clinical trials.
- Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with GLASSIA are not available.
- GLASSIA is not indicated as therapy for lung disease in patients in whom severe Alpha₁-PI deficiency has not been established.

2. DOSAGE AND ADMINISTRATION

For Intravenous Use Only.

- Use aseptic technique for all preparation and administration steps.
- Administer GLASSIA alone; do not mix with other agents or diluting solutions.
- Administer product brought to room temperature within three hours of entering the vials.

2.1 Treatment of Congenital Alpha₁-Proteinase Inhibitor Deficiency

The recommended dosage of GLASSIA is 60 mg/kg body weight administered once weekly by intravenous infusion. Dose ranging studies using efficacy endpoints have not been performed.

2.2 Preparation

1. Inspect the vial of GLASSIA. The solution should be clear and colorless to yellow-green and may contain a few protein particles. Do not use if the product is cloudy.
2. Infusion can be made directly from the vial or alternatively, vials may be pooled in an empty, sterile intravenous container.
3. When infusing directly from the vial, use a vented spike adapter and a 5 micron in-line filter (neither is supplied).
4. When infusing from a sterile intravenous container, attach an appropriate intravenous administration set to the intravenous container. Use a vent filter (not supplied) to withdraw the material from the vial and then use the supplied 5 micron filter needle to transfer the product into the infusion container. In addition, during infusion, it is recommended to use a 5 micron in-line filter (not supplied).
5. Administer intravenously to the patient as described in section 2.3.

2.3 Administration

1. Inspect parenteral products visually for particulate matter and discoloration prior to administration whenever solution and container permit.
2. Administer GLASSIA within three hours of entering the vials to avoid the potential ill effect of any inadvertent microbial contamination.
3. Administer GLASSIA at room temperature through an appropriate intravenous administration set at a rate not greater than 0.04 mL/kg body weight per minute. The recommended dosage of 60 mg/kg takes approximately 60-80 minutes to infuse.
4. Monitor the infusion rate closely during administration and observe the patient for signs of infusion related reactions. If infusion related adverse reactions occur, reduce the rate or interrupt the infusion until the symptoms subside. You may then resume the infusion at a rate tolerated by the patient.
5. Following administration, discard all open vials, unused solution and administration equipment.

3. DOSAGE FORMS AND STRENGTHS

GLASSIA is available as a single-use vial containing 1 gram of functional Alpha₁-PI in 50 mL of ready to use solution.

4. CONTRAINDICATIONS

GLASSIA is contraindicated in immunoglobulin A (IgA) deficient patients with antibodies against IgA.

GLASSIA is contraindicated in individuals with a history of severe immediate hypersensitivity reactions, including anaphylaxis, to Alpha₁-PI products.

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity to IgA

GLASSIA may contain trace amounts of IgA. Patients with selective or severe IgA deficiency and with known antibodies to IgA, have a greater risk of developing severe hypersensitivity and anaphylactic reactions. Monitor vital signs continuously and observe the patient carefully throughout the infusion. **IF ANAPHYLACTIC OR SEVERE ANAPHYLACTOID REACTIONS OCCUR, DISCONTINUE THE INFUSION IMMEDIATELY.** Have epinephrine and other appropriate supportive therapy available for the treatment of any acute anaphylactic or anaphylactoid reaction.

5.2 Transmissible Infectious Agents

Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of transmitting an infectious agent has been minimized by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections and by inactivating and removing certain viruses during the manufacturing process (see *Description [11]* for viral reduction measures). Despite these measures, such products may still potentially transmit human pathogenic agents. There is also the possibility that unknown infectious agents may be present in such products.

The physician should weigh the risks and benefits of the use of this product and discuss the risks and benefits with the patient.

All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Kamada Ltd. at 1-866-GLASSIA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

No seroconversions for hepatitis B or C (HBV or HCV) or human immunodeficiency virus (HIV) or any other known infectious agent were reported with the use of GLASSIA during the clinical studies.

6. ADVERSE REACTIONS

Two serious adverse reactions observed on two separate occasions during clinical studies with GLASSIA were cholangitis and exacerbation of chronic obstructive pulmonary disease (COPD).

The most common drug-related adverse reactions considered by the investigator to be at least possibly related to GLASSIA administration observed at a rate of >3% in subjects receiving GLASSIA were headache and dizziness.

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

A total of 65 subjects have received treatment with intravenous GLASSIA in two clinical studies, both performed in the US. Three subjects participated in both studies. However, because of the large temporal difference between studies (> 5 years) and major difference in study designs, each study was analyzed separately without excluding these three subjects who participated in both trials from either study analysis. Thus, safety and efficacy of GLASSIA are reported on all 18 subjects in a Phase I study and all 50 subjects who received GLASSIA in a Phase II/III study, for a total of 68 subjects, representing 65 unique subjects.

In an open label, Phase I non-parallel, dose-escalation study, 18 subjects received a single infusion of GLASSIA at dosages of 30, 60 or 120 mg/kg.

In a randomized, Phase II/III double-blind, active-control study, 50 subjects were scheduled to receive weekly infusions of GLASSIA or the comparator Alpha₁-PI product, Prolastin, at a dosage of 60 mg/kg for a total of 12 doses after which all subjects remaining in the study were treated for another 12 weeks with GLASSIA only. Overall, 17 subjects received 12 doses and 21 subjects received 24 doses of GLASSIA during the study. Eleven subjects received either 22 or 23 doses and one subject did not receive any treatment with GLASSIA during the last 12 weeks of the study.

The population treated with GLASSIA in these two studies was 40-74 years old, 54% male, 100% Caucasian and had congenital Alpha₁-PI deficiency with clinical evidence of emphysema.

Table 1 compares the adverse events reported during the initial 12 weeks (double-blind portion) of the Phase II/III study occurring in all subjects treated with GLASSIA with events in the concurrent Prolastin control group.

Table 1: Number of Subjects/Infusions/Adverse Events Occurring during the First 12 Weeks of Treatment

	GLASSIA	Prolastin
No. of subjects treated	33	17
No. of infusions	393	190
No. of subjects with adverse events regardless of causality (%)	27 (82%)	16 (94%)
No. of subjects with related adverse events according to investigator causality assessment (%)	6 (18%)	6 (35%)
No. of subjects with related serious adverse events	0	0
No. of subjects experiencing an adverse event within 24 hours of infusion, regardless of causality (%)	19 (58%)	14 (82%)
No. of adverse events regardless of causality (mean rate of adverse events per infusion)	70 (0.18)	46 (0.24)
No. of adverse events, regardless of causality, occurring within 24 hours of infusion (% of all adverse events)	35 (50%)	30 (65%)
No. of infusions associated with adverse events occurring within 24 hours of infusion, regardless of causality (% of infusions)	32 (8%)	28 (15%)

Table 2: Adverse Events Occurring in > 5% of Subjects during the First 12 Weeks of Treatment (Irrespective of Investigator Causality Assessment)

	GLASSIA No. of subjects: 33	Prolastin No. of subjects: 17
Adverse Event (AE)	No. of subjects with AE (percentage of all subjects)	No. of subjects with AE (percentage of all subjects)
Cough	5 (15%)	4 (24%)
Upper respiratory tract infection	4 (12%)	0 (0%)
Headache	3 (9%)	4 (24%)
COPD Exacerbation	4 (12%)	5 (29%)

Table 3: Adverse Event Frequency as a % of all Infusions (> 0.5%) (Irrespective of Investigator Causality Assessment)

	GLASSIA ^a No. of infusions: 960	Prolastin ^b No. of infusions: 190
Adverse Event (AE)	No. of AEs (percentage of all infusions)	No. of AEs (percentage of all infusions)
Upper respiratory tract infection	14 (1.5%)	0 (0.0%)
Headache	8 (0.8%)	4 (2.1%)
Nasopharyngitis	8 (0.8%)	0 (0.0%)
Cough	7 (0.7%)	4 (2.1%)
Pharyngolaryngeal pain	7 (0.7%)	1 (0.5%)
COPD	6 (0.6%)	2 (1.1%)

^a Throughout entire 24-week double-blind plus open-label trial period

^b Throughout initial 12-week double-blind period

Table 4: Adverse Events Occurring in > 5% of Subjects during or Within 72 Hours of the End of an Infusion, in the First 12 Weeks of Treatment (Irrespective of Investigator Causality Assessment)

Adverse Event (AE)	GLASSIA	Prolastin
	No. of subjects: 33	No. of subjects: 17
	No. of subjects with AE (percentage of all subjects)	No. of subjects with AE (percentage of all subjects)
Cough	3 (9%)	4 (24%)
Upper respiratory tract infection	3 (9%)	0 (0%)
Headache	3 (9%)	3 (18%)
Sinusitis	2 (6%)	1 (6%)
Chest discomfort	2 (6%)	0 (0%)
Dizziness	2 (6%)	0 (0%)
Hepatic enzyme increased	2 (6%)	0 (0%)

During the 12-week double blind portion of the Phase II/III trial, 4 subjects (12%) had a total of 7 exacerbations of chronic obstructive pulmonary disease (COPD) during GLASSIA treatment and 5 subjects (29%) had a total of 6 exacerbations of COPD during Prolastin treatment. Seventeen additional exacerbations in 14 subjects (28%) occurred during the 12-week open-label treatment period with GLASSIA. The overall rate of pulmonary exacerbations during treatment with either product was 1.3 exacerbations per subject per year.

Most adverse events were mild to moderate in severity, although two episodes of headache and one episode of cholangitis were severe. Two subjects experienced treatment emergent serious adverse events (cholangitis and infective exacerbation of COPD), both of which were considered by the investigator to be unrelated to treatment with GLASSIA.

Out of 68 subjects treated with GLASSIA during clinical studies, 14 (21%) experienced one or more adverse events that were assessed by the investigator as possibly or probably related to treatment (Table 5).

A total of 3 subjects (approximately 5%) receiving GLASSIA reported urticaria, irrespective of the investigator's opinion of cause.

Table 5: Adverse Reactions Assessed by Investigator as Possibly or Probably Related to Treatment with GLASSIA (No. of subjects: 68*; Combined Data from Single-Dose PK Study and 24-Week Clinical Study)

Adverse Event (AE)	No. of subjects experiencing a related event according to investigator causality assessment (percentage of all subjects)
Any event	14 (21%)
Headache	4 (6%)
Dizziness	2 (3%)
Dysgeusia, Influenza-like illness, Lethargy, Pyrexia, Decreased platelet count, Joint swelling, Erythema marginatum, Pruritis, Rash, Urticaria, Hypertension.	1 (1.5%)

* Three (3) subjects participated in both the single-dose PK study and the 24-week trial, such that 65 unique subjects were administered GLASSIA.

Testing for viral markers for HBV, HCV, HIV-1 and HIV-2 showed no seroconversions during either study.

6.2 Post-Marketing Experience

No spontaneous adverse event reports have been received.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with GLASSIA. It is also not known whether GLASSIA can cause fetal harm when administered to pregnant women or can affect reproductive capacity. GLASSIA should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Alpha₁-PI is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GLASSIA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of GLASSIA included 11 subjects of 65 years of age or older. This number of subjects was not sufficient to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation. Safety and effectiveness in patients over 65 years of age have not been established.

11. DESCRIPTION

GLASSIA is a sterile, ready to use, liquid preparation of purified human alpha₁-protease inhibitor (Alpha₁-PI), also known as alpha₁-antitrypsin (AAT). The solution contains 2% active Alpha₁-PI in a phosphate-buffered saline solution.

GLASSIA is prepared from human plasma obtained from US-licensed plasma collection centers by a modified version of the cold ethanol fractionation process and the Alpha₁-PI is then purified using chromatographic methods.

Individual plasma units used for production of GLASSIA are tested using FDA-licensed serological assays for hepatitis B surface antigen (HBsAg) and for antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 (HIV-1/2), as well as by FDA-licensed Nucleic Acid Testing (NAT) for HCV and HIV-1. Each plasma unit must be non-reactive (negative) in all tests. Plasma is also tested by in-process NAT procedures for parvovirus B19 and the limit for B19 DNA in the manufacturing pool is set not to exceed 10⁴ IU per mL.

To reduce the risk of viral transmission, the manufacturing process for GLASSIA includes two steps specifically designed to remove or inactivate viruses. The first of these is nanofiltration (NF) through a 15 nm filter which can remove both enveloped and non-enveloped viral agents and the second is solvent/detergent (S/D) treatment with a mixture of tri-(n-butyl) phosphate (TNBP) and Polysorbate 80 (Tween 80) which inactivates enveloped viral agents such as HIV, HBV and HCV.

The effectiveness of the S/D treatment and nanofiltration procedures for reducing virus content has been assessed using a series of viruses with a range of physico-chemical characteristics. The results of the viral challenge studies are summarized in Table 6.

Table 6: Log₁₀ Virus Reduction during Manufacture of GLASSIA

Process Step	Enveloped Viruses					Non-enveloped Viruses	
	HIV-1	PRV	BVDV	WNV	HAV	PPV	
Nanofiltration	> 5.59	> 5.57	> 5.74	ND	> 4.99	4.04	
S/D treatment	> 6.41	> 6.14	> 5.61	> 6.32	N/A	N/A	
Global Reduction Factor	> 12.00	> 11.71	> 11.35	> 6.32	> 4.99	4.04	

N/A - Not Applicable. The S/D treatment is not relevant for non-enveloped viruses.

ND - Not Done

HIV-1	Human immunodeficiency virus Type 1
PRV	Pseudorabies virus
BVDV	Bovine viral diarrhoea virus
WNV	West Nile virus
HAV	Hepatitis A virus
PPV	Porcine parvovirus

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alpha₁-PI deficiency is a chronic, autosomal, co-dominant hereditary disorder characterized by reduced levels of Alpha₁-PI in the blood and lungs (1, 2). Smoking is an important risk factor for the development of emphysema in patients with Alpha₁-PI deficiency (3). Because emphysema affects many, but not all individuals with the more severe genetic variants of Alpha₁-PI deficiency (AAT deficiency), augmentation therapy with Alpha₁-Proteinase Inhibitor (Human) is indicated only in patients with severe Alpha₁-PI deficiency who have clinically evident emphysema.

A large number of phenotypic variants of Alpha₁-PI deficiency exist, not all of which are associated with the clinical disease. Approximately 95% of identified Alpha₁-PI deficient individuals have the PIZZ variant, typically characterized by Alpha₁-PI serum levels < 35% of normal. Individuals with the Pi(null)(null) variant have no Alpha₁-PI protein in their serum (2, 3). Individuals with the lack of, or low, endogenous serum levels of Alpha₁-PI, i.e., below 11 µM, manifest a significantly increased risk for development of emphysema above the general population background risk (4, 5). In addition, PiSZ individuals, whose serum Alpha₁-PI levels range from approximately 9 to 23 µM are considered to have moderately increased risk for developing emphysema, regardless of whether their serum Alpha₁-PI levels are above or below 11 µM (6).

Augmenting the levels of functional protease inhibitor by intravenous infusion is an approach to therapy for patients with Alpha₁-PI deficiency. However, the efficacy of augmentation therapy in affecting the progression of emphysema has not been demonstrated in randomized, controlled clinical trials. The intended theoretical goal is to provide protection to the lower respiratory tract by correcting the imbalance between neutrophil elastase and protease inhibitors. Whether augmentation therapy with GLASSIA or any

Alpha₁-PI product actually protects the lower respiratory tract from progressive emphysematous changes has not been demonstrated in adequately powered, randomized controlled clinical trials. Although the maintenance of blood serum levels of Alpha₁-PI (antigenically measured) above 11 µM has been historically postulated to provide therapeutically relevant anti-neutrophil elastase protection, this has not been proven. Individuals with severe Alpha₁-PI deficiency have been shown to have increased neutrophil and neutrophil elastase concentrations in lung epithelial lining fluid compared to normal PiMM individuals, and some PiSZ individuals with Alpha₁-PI above 11 µM have emphysema attributed to Alpha₁-PI deficiency. These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of Alpha₁-PI during augmentation therapy.

12.2 Pharmacodynamics

Administration of GLASSIA to patients with Alpha₁-PI deficiency augments the level of the deficient protein. Normal individuals have levels of Alpha₁-PI greater than 22 µM. The clinical benefit of the increased blood levels of Alpha₁-PI at the recommended dose has not been established.

12.3 Pharmacokinetics

A prospective, open-label, uncontrolled multicenter pharmacokinetic study was conducted in 7 females and 11 males with Alpha₁-PI deficiency, ranging in age from 40 to 69 years. Subjects with congenital Alpha₁-PI deficiency received a single dose of GLASSIA either 30 mg/kg, 60 mg/kg or 120 mg/kg. Blood samples for pharmacokinetic study were taken prior to and within 5 minutes of completion of the infusion, and then at 1 hour, 6 hours, 12 hours, 24 hours, 3 days and 7 days.

The mean results for pharmacokinetic parameters in the 60 mg/kg dosage group are shown in Table 7. The pharmacokinetics of GLASSIA were linear over the dose range of 30-120 mg/kg.

Table 7: Pharmacokinetic Parameters for Functional Alpha₁-PI (Dosage 60 mg/kg; n=6)

Pharmacokinetic Parameter	60 mg/kg Dose Group
Terminal Half-Life (h) ^a	111 ± 33
Area under the curve _(0-168 h) (mg·h/mL)	89 ± 10
Clearance (mL/h/kg)	0.68 ± 0.1
Volume of Distribution (L)	3.2 ± 0.3

^a Any assessment of the clinical relevance of half-life in this study should be viewed with caution, due to the short duration of blood sampling.

13. NONCLINICAL TOXICOLOGY

No toxicological effects due to the solvent detergent reagents, TNBP and Tween 80, used in the virus inactivation procedure are expected since the residual levels are less than 5 and 20 ppm, respectively.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenesis, mutagenesis or impairment of fertility have not been conducted.

13.2 Animal Toxicology and Pharmacology

GLASSIA was evaluated in two single dose general toxicology studies in Sprague-Dawley rats and New Zealand White rabbits and one repeated dose study in New Zealand White rabbits.

In single dose studies, one intravenous dose of 0, 60 and 600 mg/kg (rabbits) or 640 mg/kg (rats) was administered and the animals were observed for 14 days. There were no changes in body weight, clinical chemistry, hematology and gross pathology that could be attributed to GLASSIA administration.

In the repeated dose study, New Zealand White rabbits received 300 mg/kg GLASSIA once daily for 5 consecutive days. Animals were monitored for changes in clinical signs, body weight, clinical chemistry, hematology, necropsy and histopathology on day 1 or 14 after the last administration. A minor increase in group mean neutrophils was measured on day 1 after the last GLASSIA administration. Recovery was observed after 14 days.

14. CLINICAL STUDIES

A Phase III randomized, double-blind study with a partial cross-over was conducted to compare GLASSIA to a commercially available preparation of Alpha₁-PI (Prolastin) in 50 Alpha₁-PI-deficient subjects. The study objectives were to demonstrate that the pharmacokinetics of antigenic and/or functional Alpha₁-PI in GLASSIA were not inferior to those of the control product, to determine whether GLASSIA maintained antigenic and/or functional plasma levels of at least 11 µM (57 mg/dL) and to compare Alpha₁-PI trough levels (antigenic and functional) over 6 infusions.

For inclusion in the study, subjects were required to have lung disease related to Alpha₁-PI deficiency and 'at-risk' alleles associated with Alpha₁-PI plasma levels < 11 µM. Subjects already receiving Alpha₁-PI therapy were required to undergo a 5-week wash-out period of exogenous Alpha₁-PI prior to dosing.

Fifty subjects received either GLASSIA (33 subjects) or the comparator product (17 subjects) at a dose of 60 mg/kg intravenously per week for 12 consecutive weeks. From Week 13 to Week 24 all subjects received open-label weekly infusions of GLASSIA at a dose of 60 mg/kg.

Trough levels of functional and antigenic Alpha₁-PI were measured prior to treatment, at baseline and throughout the study until Week 24. The median trough Alpha₁-PI values for Weeks 7-12 for subjects receiving GLASSIA were 14.5 µM (range: 11.6 to 18.5 µM) for antigenic and 11.8 µM (range: 8.2 to 16.9 µM) for functional Alpha₁-PI. Eleven of 33 subjects (33.3%) receiving GLASSIA had mean steady-state functional Alpha₁-PI levels below 11 µM. GLASSIA was shown to be non-inferior to the comparator product.

Serum Alpha₁-PI trough levels rose substantially in all subjects by Week 2 and were comparatively stable during Weeks 7 to 12. All subjects receiving GLASSIA had mean serum trough antigenic Alpha₁-PI levels greater than 11 µM during Weeks 7-12.

A subset of subjects in both treatment groups (n=7 for subjects receiving GLASSIA) underwent broncho-alveolar lavage (BAL) and were shown to have increased levels of antigenic Alpha₁-PI and Alpha₁-PI - neutrophil elastase complexes in the epithelial lining fluid at Week 10-12 over levels found at baseline, demonstrating the ability of the product to reach the lung. An additional study is planned to evaluate changes in functional Alpha₁-PI levels in epithelial lining fluid following administration of GLASSIA and a control Alpha₁-PI product.

The clinical efficacy of GLASSIA in influencing the course of pulmonary emphysema or the frequency, duration, or severity of pulmonary exacerbations has not been demonstrated in randomized, controlled clinical trials.

15. REFERENCES

- WHO. "α₁-Antitrypsin deficiency." Memorandum from a WHO meeting. 1997;75: 397-415.
- Stoller JK, et al. Augmentation therapy with α₁-antitrypsin: patterns of use and adverse events. Chest 2003;123:1425-34.
- Cox DW. α₁-Antitrypsin Deficiency. In: Scriver C, Sly W, eds. The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw Hill, 2002:5559-78.
- Crystal RG, et al. The alpha₁-antitrypsin gene and its mutations. Clinical consequences and strategies for therapy. Chest 1989;95:196-208.
- Crystal RG. α₁-Antitrypsin deficiency: pathogenesis and treatment. Hosp Pract (Off Ed) 1991;26:81-4, 8-9, 93-4.
- Turino GM, et al. Clinical features of individuals with Pi^{SZ} phenotype of α₁-antitrypsin deficiency. Am J Respir Crit Care Med 1996;154:1718-25.

16. HOW SUPPLIED/STORAGE AND HANDLING

Each carton of GLASSIA contains a single use vial containing 1 gram of functional Alpha₁-PI in 50 mL of solution and a sterile filter needle (NDC 0944-2884-01).

- Store GLASSIA at 2-8 °C (36-46 °F). Do not freeze.
- Stability data support short and moderate temperature excursions similar to those that may be encountered when using this product.
- Keep vial in carton until required for use.
- Do not use after the expiration date printed on the label.
- GLASSIA contains no preservatives and no latex.

17. PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reactions, including hives, generalized urticaria, chest tightness, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Advise patients to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.
- Inform patients that GLASSIA is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses and, theoretically, the CJD agent). Explain that the risk of GLASSIA transmitting an infectious agent has been reduced by screening the plasma donors, by testing the donated plasma for certain virus infections, and by a process demonstrated to inactivate and/or remove certain viruses during manufacturing (see *Warnings and Precautions* [5.2]). Symptoms of a possible virus infection include headache, fever, nausea, vomiting, weakness, malaise, diarrhea, or, in the case of hepatitis, jaundice.
- Inform patients that administration of GLASSIA has been demonstrated to raise the plasma level of Alpha₁-PI, but that the effect of this augmentation on the frequency of pulmonary exacerbations and on the rate of progression of emphysema has not been established by clinical trials.

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