Summary Basis of Approval

I. General Information

Licensed Product Name: Alpha-1-Proteinase Inhibitor (Human)

Proprietary Product Name: Aralast™

Other Name: Alpha-1 Antitrypsin

Name and Address of Sponsor:

Alpha Therapeutic Corporation
5555 Valley Boulevard
Los Angeles, CA 90032

Biologics License Application (BLA) Tracking Number: STN 125039/0

Date of Submission: August 31, 2001

Date of Filing: October 24, 2001

Review Designation: Fast Track

Date of Licensure: December 23, 2002

II. Indications for Use

The Aralast™ brand of Alpha-1-Proteinase Inhibitor (Human) is indicated for augmentation therapy in patients having congenital deficiency of alpha-1-proteinase inhibitor (α_1-PI) with clinically evident emphysema.

III. Dosage Form, Route of Administration, and Recommended Dosage

The Aralast™ brand of Alpha-1-Proteinase Inhibitor (Human) is supplied in 2 dosage sizes:

- 1 g (1,000 mg) of lyophilized Alpha-1-Proteinase Inhibitor (Human) to be reconstituted with 50 mL of Sterile Water for Injection (USP) [SWFI]

- 0.5 g (500 mg) of lyophilized Alpha-1-Proteinase Inhibitor (Human) to be reconstituted with 25 mL SWFI

Aralast™ is supplied as a sterile, non-pyrogenic lyophilized powder in a single use container. The Aralast™ single use container is packaged with: a single use container containing the appropriate volume of SWFI for reconstitution; a sterile, non-pyrogenic, double ended transfer needle for reconstitution; a sterile, a non-pyrogenic, single use 20 micron filter spike; and a product information insert (package insert). The vial of SWFI, transfer needle, and filter spike are provided by other vendors and are approved by the Agency.

The potency of Aralast™ is expressed in milligrams of functional α_1-PI as determined by the inhibition of porcine pancreatic elastase. Each single use container is labeled with the actual potency in milligrams of α_1-PI.

Reconstituted Aralast™ is indicated for intravenous administration. The maximum rate of intravenous infusion should not be more than 0.08 mL per kg body weight per minute. The recommended dose of Aralast™ is 60 mg per kg body weight administered once weekly by intravenous infusion.

IV. Manufacturing, Chemistry, and Controls

Overview of Manufacturing Process

The manufacture of the Aralast™ brand of Alpha-1-Proteinase Inhibitor (Human) begins with Fr.IV$_{1-4}$ precipitate, which is an intermediate by-product generated during the ---------- from pooled Source Plasma by cold ethanol fractionation (i.e., by the Cohn-Oncley process). Fr.IV$_{1-4}$ precipitate undergoes ----------, polyethylene glycol precipitation of impurities, zinc chloride precipitation of α_1-PI, ----------of α_1-PI, solvent-detergent (tri-n-butyl phosphate and polysorbate 80, respectively) treatment for inactivation of enveloped viruses, anion-exchange chromatography to remove solvent and detergent with ----------, -- nanometer nanofiltration for virus removal, and sterile filtration. The sterile bulk solution is aseptically filled into previously sterilized vials, frozen, and lyophilized. The lyophilized vials are stoppered under vacuum then capped and labeled and packaged.

All final container lots meet the requirements of 21 CFR § 610 et seq. for potency, safety, sterility, purity, and identity and the established specifications for Aralast™. --- conformance lots were submitted to the Center for Biologics Evaluation and Research (CBER) in support of the BLA.

Validation of Assays Used for ---------- Final Container Product

The assays/tests used for ---------- final container product include: Quantitative Determination of α_1-PI by ----------; Elastase Inhibitory Activity of α_1-PI; ---------- α_1-PI; Total Protein by ------- method; Quantitative Determination of Albumin by ---- Polyethylene Glycol by ----------; Polysorbate 80 by ---------- method; Tri-n-Butyl Phosphate by ----------; Moisture by ---------- method; Zinc; General Safety; pH; ---------- Test; Sodium by ----------; Solubility of ----------; ---------; and Total Protein by ----. Validation protocols and validation reports were provided for these assays. Where appropriate, assay data demonstrating linearity, precision, accuracy, limit of detection, limit of quantitation, interference, and ruggedness were provided; in addition, data concerning robustness were provided for some of the assays.

Validation of Assays Used to Analyze Patient Samples from Phase III Clinical Trial

The laboratory methods used by the Alpha$_1$ Antitrypsin Genetics Laboratory at the University of Florida College of Medicine (Central Laboratory) include: α_1-PI Phenotype by ----------; Serum α_1-PI Level by ----------; Functional α_1-PI Level (Anti-Neutrophil Elastase Capacity) in Serum; Antigenic α_1-PI Level in Endothelial Lining Fluid (ELF); Antigenic Neutrophil Elastase in ELF by -----; Functional α_1-PI in ELF; α_1-PI-Neutrophil Elastase Complex Concentration in ELF by -----; IL-8 in ELF; Urea Measurement for ELF Estimation; Urine Desmosine; Urine Desmosine, Isodesmosine, and Hydroxylysylpyridinoline; and α_1-PI Antibody Determination. A protocol for the Bronchoaveolar Lavage Procedure was also included. SOP's and validation procedures and data were provided for these assays. Reference standards utilized were characterized in terms of potency, storage, and stability.

Validation of Manufacturing

Clinical trials were carried out with Alpha-1-Proteinase Inhibitor (Human) product manufactured at pilot scale. The validation of manufacturing consisted of demonstrating that the product produced at full scale is bioequivalent to that produced at clinical scale, showing that the manufacturing process is consistent and results in product of requisite purity, potency, efficacy, and safety, and validating normal operating ranges for the process control parameters.

The sponsor's designation of a manufacturing variable as a process control parameter or as an attribute of in-process intermediate did not always correlate with the independent or dependent nature of the variable, that is, as an input or outcome of the process, respectively. Based on experience from development and the manufacture of clinical scale lots, the sponsor set ranges and limits for various process control parameters with some designated as critical. For full scale manufacture, acceptance criteria for attributes

of in-process intermediates and specifications for the final container product were also established on the basis of development work and experience with clinical scale manufacture. However, these acceptance criteria and specifications were sometimes broader than those for the clinical scale lots, e.g., for ----------. Nevertheless, the test results for the attributes of intermediates produced during full scale production usually fell within the same range of values obtained for the clinical scale lots for the more highly purified intermediates, and a number of acceptance criteria and specifications were later tightened. Some acceptance criteria are to be implemented later, e.g., ----------, after data for additional lots are acquired. During the production of the conformance lots, the operating ranges of the control parameters were not covered equally well. To demonstrate bioequivalence and consistency of manufacture, values of the attributes were compared for numerous clinical scale and numerous full scale lots, and these attributes included ----------. However, protocols did not require the measurement of values of each attribute for each intermediate. Impurity profiles of clinical scale and full scale lots were compared and involved antigenic determination of ---------- ---------- all by ---- and found to be quite variable but, in general, similar.

After the production of -- conformance lots in 2001, the sponsor encountered difficulty in that a number of subsequent lots failed to meet release specifications. As a result, CBER requested, during 2002, that the sponsor manufacture -- additional conformance lots. From ---------- of 2002, only -- of a number of lots failed to meet release specifications due to operator error thereby demonstrating that the manufacturing process was then under control. As a post-licensure commitment, the sponsor was requested to include in the post-marketing report information reflecting the rate of final container lots failing to meet release specifications.

Validation of Viral Safety

Fr.IV$_{1-4}$ precipitate, which is the starting material for the manufacture of Aralast™, is prepared from large pools of human plasma by using the Cohn-Oncley cold ethanol fractionation process. The purification of Aralast™ from Fr.IV$_{1-4}$ precipitate includes polyethylene glycol and zinc chloride precipitations and ion exchange chromatography. To reduce the risk of viral transmission, the manufacturing process includes treatment with a solvent-detergent (SD) mixture (tri-n-butyl phosphate and polysorbate 80, respectively) to inactivate enveloped viral agents such as HIV and Hepatitis B and C. In addition, a nanofiltration step (using a --- nanometer filter) is incorporated prior to final sterile filtration to reduce the risk of viral transmission (primarily of non-enveloped viral agents). Based on *in vitro* studies, the process used to produce Aralast™ has been shown to inactivate and/or partition various viruses as shown in the table below.

Summary of Viral Validation Data: Elimination of Deliberately Added Virus

Processing Step	Log_{10} Virus Inactivated or Removed				
	HIV–1*	BVD†	PRV†	HAV‡	PPV‡
Alcohol Fractionation	≥ 4.8				
Solvent Detergent Treatment	≥ 7.2	≥ 4.8	≥ 5.1		
Nanofiltration		≥ 6.0	≥ 5.5	8.6	≥ 5.8
TOTAL Reduction	≥ 12.0	≥ 10.8	≥ 10.6	8.6	≥ 5.8

* HIV-1: Alcohol Fractionation units = log_{10} SFU and SD Treatment units = log_{10} $TCID_{50}$/mL
† BVD (Bovine Viral Diarrhea) and PRV (Pseudorabies Virus): SD Treatment units = log_{10} PFU/mL and Nanofiltration units = log_{10} PFU
‡HAV (Hepatitis A) and PPV (Porcine Parvovirus): Nanofiltration units = log_{10} PFU

Batch Records

Blank batch records and those for the first -- conformance lots were provided. The batch record format was modified at the request of CBER so as to show ranges or limits for all process control parameters and acceptance criteria for all attributes of in-process intermediates as well as the specific values used for the control parameters and the resulting measured values of the assays/tests for in-process attributes.

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Stability Studies of Final Container Product

The sponsor submitted stability data for final container samples of -- lots of Alpha-1-Proteinase Inhibitor (Human) product that had been stored at ----- °C for -- months with testing at ---------- months and others that had been stored at ------ °C for -- months with testing at ---------- months, all according to protocols; the -- lots are clinical scale and represent both fill sizes. Furthermore, stress testing was performed for the -- lots that had been stored at -------°C for -- months by transfer of these to ------ °C storage for -- month (i.e., ---------- °C) with testing at -- months to demonstrate stability with regard to possible temperature deviations that might occur during shipping, i.e., temperatures up to ----------. Tests included ----------
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---------- For each time point, all test results conformed with the corresponding specifications thereby supporting the proposed shelf life and storage conditions.

The sponsor has committed to place the first 3 lots of Aralast™ manufactured post-licensure on stability study with 2 of the 3 lots being the 1.0 or 0.5 g fill size and the other lot being the other fill size and, thereafter, annually to place a lot of Aralast™ manufactured during the given year on stability study with the fill size of the lot alternating yearly. The sponsor has also committed to incorporate a ---------- method into the stability protocol and to establish an appropriate specification as soon as feasible. The sponsor is to carry out full stability testing per the approved protocols under worst case scenario labeling conditions for studies involving storage at different temperatures. Reduced testing is to be implemented only by means of a prior approval supplement. The sponsor is to include these stability data in the post-marketing report in addition to those for the 3 final container lots in support of the dating period and storage conditions of $Fr.IV_{1-4}$ precipitate (see above).

Shelf Life and Storage Conditions of Final Container Product

On the basis of stability data provided for the final container product, a shelf life of 2 years from the date of manufacture was granted with storage at 2-8 °C with permitted removal from 2-8 °C storage and subsequent storage at temperatures not to exceed 25 °C provided that the product is used within 1 month after removal from 2-8 °C storage and prior to the expiration date. The date of manufacture is defined as the date of the first sterile filtration. The expiration date for each lot is placed on the final container vial label when the lot is labeled and packaged.

Stability of Reconstituted Final Container Product

Samples of -- different lots, representing both fill sizes, were reconstituted according to labeling instructions and maintained at 25 °C. ---------- was determined at --

-------- h. Results of this study show that the reconstituted product is stable up to -- h after reconstitution with storage at room temperature.

Labeling

The labeling for Aralast™ is comprised of a product information insert (package insert), vial labels for the 0.5 or 1.0 g fill sizes, and carton labels for the 0.5 and 1.0 g fill sizes. The labeling has been reviewed and approved as part of the BLA.

Pre-Licensing Inspection of Alpha Therapeutic Corporation

A pre-licensing inspection of the Alpha Therapeutic Corporation site at 5555 Valley Boulevard in Los Angeles, CA was carried out by the Agency in February 2002, and at the end of the inspection, a Form 483 was issued to the responsible head. The Form 483 contained observations involving the validation of equipment and validation of cleaning procedures for the facilities and equipment. These observations were subsequently resolved by the sponsor to the satisfaction of the Agency. Thus, the manufacture of Aralast™ is now considered to comply with current Good Manufacturing Practices.

Bioresearch Monitoring Inspections

The Agency conducted Good Clinical Practice inspections of 2 selected clinical investigation sites in January 2002. No Form 483 was issued at the University of Texas Health Center site. However, a Form 483 was issued at the Cleveland Clinic site, and the investigator submitted his responses in February 2002, which were deemed to be acceptable. In addition, the Agency inspected the Central Laboratory site (at the University of Florida), the facility responsible for the analyses of patient samples from the phase III clinical trial, and issued a Form 483 in February 2002. The Central Laboratory investigator submitted his responses in April 2002. Subsequently, at the request of CBER, the sponsor conducted a 100% audit of antigenic α_1-PI serum level assay results, determined by the Central Laboratory, in order to identify all patient samples for which determinations had been repeated. At the request of CBER, supplementary statistical analyses of resulting modified primary endpoint data resulting from the data audit were conducted by the sponsor and submitted to and evaluated by the Agency. CBER concluded that the re-analyses do not change any conclusions involving the primary endpoint data. The investigators have resolved all Form 483 observations to the satisfaction of the Agency.

V. Non-Clinical Pharmacology and Toxicology

All non-clinical pharmacology and toxicology studies of the Aralast™ brand of Alpha-1-Proteinase Inhibitor (Human) were conducted in compliance with Good Laboratory Practice regulations.

Single Dose Toxicity Studies in Mice and in Rabbits

The sponsor conducted 2 single-dose acute intravenous toxicity studies of Aralast™ and a buffer control in male and female CD-1 mice and in male and female ---------- rabbits.

> The **n**o **o**bservable **a**dverse **e**ffect **l**evel (NOAEL) for Aralast™ in mice was determined to be at least 1500 mg/kg or 25 times the expected human dose. No visible lesions were seen at necropsy.
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> The NOAEL of Aralast™ in rabbits is at least 480 mg/kg or 8 times the expected human therapeutic dose. No visible lesions were seen at necropsy.

Repeated Dose Intravenous Toxicity Study in Rabbits

The sponsor conducted a once daily dosing repeat dose toxicity study for 5 days in male and female ---------- rabbits to evaluate the potential toxic effect(s) associated with repeated intravenous exposure to Aralast™ compared to a buffer control; there were 6 animals in each study group. Repeated administration of Aralast™ at 120 mg/kg (twice the human clinical dose of 60 mg/kg) or an equal volume of buffer control was carried out for 5 consecutive days. On Day 6, 3 animals from each group were sacrificed and the remainder on Day 33. A gross necropsy was conducted on all animals, and a full histophathologic evaluation was performed on selected tissues from each group. Blood was drawn prior to the first administration of the test and control articles and just prior to sacrifice. No clinical signs of toxicity were seen in any animal at any time in either the treated or control group, and there was no effect on body weight and no significant perturbations in hematologic, clinical, or biochemical parameters among rabbits examined at Day 6 or Day 33 after administration of the final dose. No visible lesions were observed in any treated animal at Day 33.

Single Dose Pharmacokinetic Study (Plasma Half-Life) in Rabbits

The plasma half-life of Aralast™ was assessed for a lot of Aralast™ in 6 male ---------- rabbits. The animals were administered 60 mg/kg of Aralast™ intravenously and were then serially bled over a 7 day (168 h) period. Plasma samples were obtained prior to dosing and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 32, 48, 72, 96, 120, 144, and 168 h post-dosing. No necropsy was performed. Plasma concentrations were quantitated by -------- assay specific for human α_1-PI. The pharmacokinetic results (mean ± SD) are in the table immediately below and demonstrate that the half-life in the rabbit for the product, a human protein, is ca. 40 h whereas the half-life in humans is ca. 6 days (see below).

Summary of Pharmacokinetic Properties of Aralast™ in Male ---------- Rabbits

C_{max} (mg/mL)	T_{max} (h)	AUC_{0-I} (mg·h/mL)	CI_s (mL/h)	V_d (mL)	$T_{1/2,e}$ (h)
1.276 ± 0.1338	0.33 ± 0.13	33.83 ± 0.8336	4.30 ± 0.300	246 ± 36.7	39.6 ± 4.11

VI. Human Pharmacokinetics and Bioavailability

Pharmacokinetic analysis was done after administration of the first dose of the test article (Aralast™) or the control article (Prolastin®) during the phase III, pivotal clinical trial (Study No. ATC 97-01). For purposes of the pharmacokinetic analysis, the test group consisted of 14 subjects and the control group of 13 subjects. Pharmacokinetic parameters were similar for Aralast™ and Prolastin® with the exceptions of terminal half-life ($T_{½}$) and time to maximum concentration (T_{max}). The $T_{½}$ for Aralast™ was 5.9 ± 1.2 days (95% CI = 5.2-6.5 days) vs. 5.1 ± 0.5 days (95% CI = 4.8-5.4 days) for Prolastin® (*p* = 0.035, 2-sided t-test). The ratio of $T_{½}$ Aralast™/$T_{½}$ Prolastin® = 1.15 (90% CI = 1.03-1.29) was not contained within the bioequivalency limits. The T_{max} for Aralast™ was 1.1 ± 0.3 h (95% CI = 0.9-1.3 h) vs. 1.5 ± 1.4 h (95% CI = 0.6-2.3 h) for Prolastin®. Although the Tmax for Aralast™ did not meet the lower bioequivalency limit [of T_{max} Aralast™/T_{max} Prolastin® = 0.73 (90% CI = 0.40-1.23)], the 2 values were not statistically different (*p* = 0.336, 2-sided t-test). The AUC for Aralast™ was 127 ± 17 mmol·day/L (95% CI = 117-136 mmol·day/L) vs. 136 ± 22 mmol·day/L (95% CI = 123-150 mmol·day/L) for Prolastin® (p = 0.219, 2-sided t-test). The ratio of AUC Aralast™/ AUC Prolastin® = 0.93 (90% CI = 0.84-1.03). The C_{max} for Aralast™ was 37.1 ± 4.8 µmol/L (95% CI = 34.4-39.9 µmol/L) vs. 41.0 ± 7.1 µmol/L (95% CI = 36.8-45.4 µmol/L) for Prolastin® (p = 0.103, 2-sided t-test). The ratio of C_{max} Aralast™/C_{max} Prolastin® = 0.90 (90% CI = 0.82-1.00).

Thus, the pharmacokinetic parameters were similar for Aralast™ and Prolastin® with the exceptions of terminal half-life ($T_{½}$) and time to maximum concentration (T_{max}). However, the differences were judged not to be clinically important.

VII. Clinical Microbiology

There is no clinical microbiology evaluation for the Aralast™ brand of Alpha-1-Proteinase Inhibitor (Human) since it is not indicated as an anti-infective product.

VIII. Clinical Summary

The sponsor conducted the single clinical study ATC 97-01 to demonstrate the safety and efficacy of the Aralast™ brand of Alpha$_1$-Proteinase Inhibitor (Human) in chronic augmentation therapy for congenital α_1-PI deficiency. Clinical study No. ATC 97-01 was a multi-center, randomized, double-blind, controlled, phase III study comparing the sponsor (Alpha Therapeutic Corporation) product, Aralast™ (test drug), to commercially available Alpha$_1$-Proteinase Inhibitor (Human) Intravenous (Prolastin®) (control drug) of the Bayer Corporation. Clinical Study No. ATC 97-01 was conducted from February 1997 to December 1999.

All subjects had been diagnosed as having congenital α_1-PI deficiency and emphysema but had not received α_1-PI augmentation therapy (e.g., Prolastin® or any other investigational α_1-PI product) within the 6 months preceding enrollment into the study. Subjects were at least 18 years of age and had been diagnosed with congenital α_1-PI deficiency with a phenotype associated with development of emphysema, had a definite diagnosis of emphysema, and had a serum α_1-PI level less than 11 µmol/L. Subjects also had an initial forced expiratory volume (FEV_1) greater than or equal to 30% but less than or equal to 80% of predicted and an initial forced expiratory volume/forced vital capacity (FEV_1/FVC) ratio less than 70% or a diffusion capacity of carbon monoxide (DL_{CO}) less than 70% of predicted in addition to an abnormal lung computerized axial tomography (CT) scan consistent with emphysema and the absence of other confounding disease. Subjects were non-smokers who had not smoked for at least 6 months prior to enrollment.

24 subjects were to be randomized to receive either test drug or control drug (at a dose of 60 mg/kg intravenously per week). A total of 28 subjects was ultimately enrolled and randomized into the test or control groups.

> The test group was to have received Aralast™ for all infusions.
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> The control group was to have received Prolastin® for their first 10 weekly infusions and then Aralast™ for all subsequent infusions.

The total duration of the study was 96 weeks.

Safety data (adverse events, hepatic function, renal function, hematological function, viral serology, and clinically important variations in vital signs) were assessed periodically. Serologic tests for viral infections were performed at enrollment and periodically throughout the study. Adverse events (AE's) were monitored at each infusion visit.

The major primary and secondary endpoints were assessed during the initial phase of the trial (Weeks 1 through 24). Additional tests (i.e., CT scans, urine analyses for elastin degradation products, and safety/toxicity measurements) were also performed at Weeks 1 through 24.

A pharmacokinetic comparison of the 2 study drugs was conducted from blood samples drawn during the first week of the study.

Subjects were periodically monitored for serum α_1-PI levels, anti-neutrophil elastase (anti-NE) capacity, pulmonary function, viral serology, and clinical and biochemical parameters to provide an assessment of the safety and efficacy of Aralast™ for the duration of the study.

Study No. ATC 97-01 was terminated early due to a shortage of investigational product. Prior to the study's termination, Prolastin® was substituted, when possible, for Aralast™ when the supply of Aralast™ was insufficient to provide the protocol-stipulated dosage of 60 mg/kg.

Safety

Aralast™ was evaluated for up to 96 weeks in 27 subjects with a congenital deficiency of α_1-PI and clinically evident emphysema. The number of subjects with an adverse event, regardless of causality was 22 of 27 (81.5%). The number of subjects with an adverse event deemed possibly, probably, or definitely related to study drug was 7 of 27 (25.9%).

The frequency of infusions associated with an adverse event, regardless of causality, was 108 of 1127 infusions (9.6%) administered per protocol. The most common symptoms were pharyngitis (1.6%), headache (0.7%), and increased cough (0.6%). Symptoms of bronchitis, sinusitis, pain, rash, back pain, viral infection, peripheral edema, bloating, dizziness, somnolence, asthma, and rhinitis were each associated with ≥ 0.2% of infusions. All symptoms were mild to moderate in severity.

The overall frequency of adverse events deemed to be possibly, probably, or definitely related to study drug was 15 of 1127 infusions (1.3%). The most common symptoms included headache (0.3%) and somnolence (0.3%). Symptoms of chills and fever, vasodilation, dizziness, pruritus, rash, abnormal vision, chest pain, increased cough, and dyspnea were each associated with a single infusion (0.1%). 5 of 27 subjects (18.5%) experienced 8 serious adverse reactions during the study. None of these were considered to be causally related to the administration of Aralast™.

26 of 27 subjects (96.3%) experienced a total of 94 upper and lower respiratory-tract infections during the 96 week study (median: 3.0; range: 1-8; mean ± SD: 3.6 ± 2.3 infections). 29.8% of the respiratory infections occurred in 19 subjects (70.4%) during the first 24 weeks of the 96-week study thereby suggesting that the risk of infection did not change with time on Aralast™. In a *post-hoc* analysis, subjects experienced a range of 0 to 8 exacerbations of chronic obstructive pulmonary disease (COPD) over the 96-week study with a median of less than 1 exacerbation per year (median: 0.61; mean ± SD: 0.83 ± 0.87 exacerbation per year).

Treatment-emergent elevations (greater than 2 times the upper limit of normal) in aminotransferases (ALT or AST), up to 3.7 times the upper limit of normal, were noted in 3 of 27 subjects (11.1%). Elevations were transient lasting 3 months or less. No subject developed any evidence of viral hepatitis or hepatitis seroconversion while being treated with Aralast™, including 13 evaluable subjects who were not vaccinated against hepatitis B. Mild elevations in ALT and AST and occasional mild elevations in bilirubin were common in both the test and control groups. With the exception of 1 subject in the test group with Gilbert's syndrome, the other elevations were without obvious cause. Some of these abnormalities may have been due to the underlying condition of α_1-PI deficiency, which may be associated with liver disease in some afflicted individuals.

No clinically relevant alterations in blood pressure, heart rate, respiratory rate, or body temperature occurred during infusion of Aralast™. Mean hematology and laboratory parameters were little changed over the duration of the study, with individual variations not clinically meaningful.

During the initial 10 weeks of the study, subjects were randomized to receive either Aralast™ or a commercially available preparation of α_1-PI (Prolastin®). Both products were well tolerated with the frequency, severity, and symptomatology of adverse reactions similar in both groups. There were no serious adverse events in the group receiving Aralast™ compared to 2 serious adverse events in the control group, 1 of which was considered to be possibly related to the control drug. In addition, 1 subject in the control group became seropositive to Parvovirus B-19. No seroconversions that were attributable to Aralast™ were observed during the entire 96 week study. No subject developed an antibody to α_1-PI.

Mean hematology and laboratory parameters were similar between the test and control groups and were little changed over the duration of the study. Results exceeding 2 standard deviations above the mean expected variation were rare and sporadic.

Efficacy

Co-primary endpoint 1 was successfully demonstrated, i.e., mean serum α_1-PI trough level prior to infusion across Weeks 8 through 11 for Aralast™ was not inferior to that of Prolastin® (p = 0.026, 90% lower confidence limit 81.7%). The mean serum α_1-PI trough levels measured prior to treatments at Weeks 8 through 11 for the Aralast™ and Prolastin® groups were similar, 15.3 ± 2.5 µmol/L vs. 16.9 ± 2.3 µmol/L, respectively, and both were well above the trough level of 11 µmol/L suggested as a target by the medical literature. Note that the arithmetic average of trough levels from Weeks 8 through 11 were chosen for the 2 co-primary endpoints to assure that steady-state trough levels had been achieved.

Co-primary endpoint 2 was successfully demonstrated, i.e., serum α_1-PI trough levels measured prior to treatment at Weeks 12 through 24 were maintained. The mean slope of the line through the serum α_1-PI trough levels measured prior to treatment at Weeks 12 through 24 for the test group was -0.024 µmol/L/week [90% confidence interval (CI): -0.088 to 0.040]. The slope for the control group (crossed over from Prolastin® to Aralast™ at Week 11) was 0.018 µmol/L/week (90% CI: -0.043 to 0.080). The slope for all subjects combined (test and control groups) was -0.003 µmol/L/week (90% CI: -0.04 to 0.04). The lower limits of the confidence intervals around the slopes of both treatment groups and the combined groups met the acceptance criteria (greater than -0.1 µmol/L/week).

Secondary endpoint 1 was successfully demonstrated, i.e., the mean serum anti-NE capacity trough level measured prior to treatment at Weeks 8 through 11 for the Aralast™ group, 15.3 ± 2.4 µmol/L, was not inferior to that of the Prolastin® group, 15.7 ± 2.6 µmol/L.

Secondary endpoint 2 was *not* successfully demonstrated. The mean change in serum α_1-PI concentration from baseline to trough level measured prior to treatment at Week 7 was 9.7 ± 3.4 µmol/L for the Aralast™ group compared to 11.5 ± 2.3 µmol/L for the Prolastin® group. The null hypothesis was not rejected; so it could not be concluded that the mean change for serum α_1-PI from baseline to trough level measured prior to infusion at Week 7 for the Aralast™ group is not inferior to that for the Prolastin® group.

Secondary endpoint 3 was successfully demonstrated, i.e., the mean change in serum anti-NE capacity from baseline to trough level measured prior to treatment at Week 7 for the Aralast™ group, 12.3 ± 3.0 µmol/L, was not inferior to that of the Prolastin® group, 12.3 ± 2.5 µmol/L.

Only 5 subjects in the Aralast™ group and 3 subjects in the Prolastin® group had evaluable bronchoalveolar lavages (BAL's), both at baseline and Week 7, although all subjects successfully completed the baseline and week 7 BAL procedures. The majority of samples did not meet the BAL sample acceptance criteria. The following data are based on these 8 subjects whose paired baseline and follow-up samples did meet acceptance criteria.

Increases in epithelial lining fluid (ELF) α_1-PI levels from pre-treatment baseline to Week 7 were observed in both the Aralast™ and Prolastin® groups. From baseline to Week 7, the mean ELF antigenic assay α_1-PI level in the Aralast™ group increased from 190 ± 108 nmol/L to 1,294 ± 885 nmol/L ($p = 0.053$) (5.14 ± 0.52 to 6.94 ± 0.78, $\log_e$ transformed, $p = 0.009$) while the mean α_1-PI ELF levels in the Prolastin® group increased from 452 ± 92 nmol/L to 1,640 ± 511 nmol/L ($p = 0.041$) (6.10 ± 0.20 to 7.36 ± 0.35, $\log_e$ transformed, $p = 0.008$). The mean changes in ELF α_1-PI from baseline to

Week 7 were similar and not statistically different for the 2 groups, 1,104 ± 905 nmol/L for the Aralast™ group vs. 1,188 ± 432 nmol/L for the Prolastin® group ($p = 0.888$) (1.81 ± 0.86 vs. 1.26 ± 0.19, $\log_e$ transformed, $p = 0.334$).

Similar point estimate increases in ELF anti-NE capacity at Week 7 were observed in both the Aralast™ and Prolastin® groups. From baseline to Week 7, the mean anti-NE level in the Aralast™ group increased from 1,086 ± 320 nmol/L to 1,635 ± 1,168 nmol/L ($p = 0.436$) (6.96 ± 0.29 to 7.55 ± 0.44, $\log_e$ transformed, $p = 0.086$) while the mean anti-NE level in the Prolastin® group increased from 737 ± 280 nmol/L to 1,516 ± 839 nmol/L ($p = 0.144$) (6.55 ± 0.41 vs. 7.18 ± 0.73, $\log_e$ transformed, $p = 0.090$). Thus, the $\log_e$ transformed data analysis suggested a trend for an increase in ELF anti-NE activity from baseline to Week 7 in both the Aralast™ and Prolastin® groups although the increases were not statistically significant (perhaps due to the limited sample size of evaluable sample-pairs). The mean changes in ELF anti-NE capacity from baseline to Week 7 were similar and not statistically different in both groups, 549 ± 1,419 nmol/L for the Aralast™ group vs. 779 ± 575 nmol/L for the Prolastin® group ($p = 0.803$) (0.69 ± 0.55 vs. 0.63 ± 0.35, $\log_e$ transformed, $p = 0.863$).

Roughly similar changes in ELF α_1-PI:NE complexes, NE, Interleukin–8 (IL-8), and neutrophils from baseline to Week 7 were observed for the Aralast™ and Prolastin® groups. The Aralast™ group showed a statistically significant decrease in the mean level of ELF IL-8 from Weeks 1 to 7, decreasing from 14,316 ± 4,996 ng/mL to 4,012 ± 1,547 ng/mL ($p = 0.007$) (9.51 ± 0.41 to 8.24 ± 0.40, $\log_e$ transformed, $p = 0.005$). The Prolastin® group, which started lower at baseline, 4,111 ± 1,107 ng/mL, showed no such decrease with a value of 5,160 ± 3.676 ng/mL at Week 7 ($p = 1.000$) (8.30 ± 0.27 to 8.39 ± 0.67 ng/mL, $p = 0.730$). Comparative analysis of the mean change from baseline to Week 7 indicated that the mean change (reduction) in ELF IL-8 was significantly greater in the Aralast™ group than in the Prolastin® group, -10,304 ± 4,558 ng/mL vs. 1,048 ± 2,619 ng/mL ($p = 0.008$) (-1.27 ± 0.51 vs 0.09 ± 0.41, $\log_e$ transformed, $p = 0.008$). The comparatively larger decrease in the Aralast™ group compared to the Prolastin® group may be due to the fact that the mean for the Aralast™ group was much higher than the mean for the Prolastin® group at baseline. The clinical significance of the large decrease in the test group mean IL-8 level is uncertain but may be a treatment effect.

The rates of antibiotic usage and respiratory infections were little changed from baseline.

Pulmonary function testing, urine analysis for elastin breakdown products (e.g., desmosine, isodesmosine) and radiographic analysis showed little change throughout the evaluation period. It had been hoped that elastin breakdown products, an unvalidated surrogate for pulmonary elastic fiber degradation, would decrease following product administration, but this was not observed.

Human Pharmacokinetics and Bioavailability

A summary of the human pharmacokinetic and bioavailability study is in Section VI.

IX. Detailed Clinical Summary

The Detailed Clinical Summary is the Appendix of this Summary Basis of Approval.

X. Post-Licensure Commitments

The sponsor has committed to undertake the following post-licensure actions as part of the licensure of the Aralast™ brand of Alpha-1-Proteinase Inhibitor (Human).

- Alpha Therapeutic Corporation will conduct a phase IV study, in part, to further verify changes in levels of alpha-1-proteinase inhibitor in epithelial lining fluid. A study protocol will be submitted for review by the FDA no later than April 1, 2003, and the final study report will be submitted to the FDA within one year after approval of the study protocol.

- Alpha Therapeutic Corporation will place the first three lots of Aralast™ manufactured post-licensure on stability study. Two of the three lots will be the same fill size (either 0.5 gram or 1.0 gram) and one (1) of the lots will be the other size.

- Alpha Therapeutic Corporation will submit a post-marketing report every six months that will include: a list of all bulk and final container lot numbers assigned; the disposition of every bulk and final container lot; a copy of deviation report(s) issued for any bulk lot or any final container lot that is not released; and for each training lot, an identification of the step in the process at which the production was halted and an indication of any in-process intermediate not meeting acceptance criteria. In addition, the six month report will include the final container tri-n-butyl phosphate level for each lot that is taken to final container.

- Alpha Therapeutic Corporation will include in its periodic, post-commitment reports the stability data from Lot Nos.----------,---------- and ---------- to support the Fraction IV_1+IV_4 paste dating period (-- months when stored at ----- °C or colder).

- With regard to post-licensure stability studies, Alpha Therapeutic Corporation will implement a ---------- method and submit these data with other stability data. If ---- test results are obtained by using a method not yet validated, a note to this effect will be added to the data sheet. It is expected that this test method will be validated within 6 to 8 weeks of licensure.

- Alpha Therapeutic Corporation will annually place a lot of Aralast™ on stability study. The fill size of the lot (0.5 gram or 1.0 gram) will vary on alternate years.

- Full stability protocol testing will be conducted at all time points for all lots of Aralast™ on test post-licensure until such time that Alpha Therapeutic Corporation submits a pre-approval supplement requesting a deletion of some time points. Stability studies will reflect a worst case scenario for labeled storage conditions.

XI. Orphan Drug Consideration

There are no orphan drug submissions pending nor is there any orphan drug designation for the Aralast™ brand of Alpha-1-Proteinase Inhibitor (Human).

XII. Marketing History

The Aralast™ brand of Alpha-1-Proteinase Inhibitor (Human) has not been commercially marketed.

XIII. FDA Decision

The Food and Drug Administration concluded that the Aralast™ brand of Alpha-1-Proteinase Inhibitor (Human), manufactured by Alpha Therapeutic Corporation, is safe and effective for its intended use based upon the data submitted by the sponsor.

An approval letter was issued to Alpha Therapeutic Corporation on December 23, 2002.