APPENDIX (SBA, STN 125039/0)

Detailed Clinical Summary

I. Summary of Clinical Review

1. Alpha Therapeutics submitted one clinical trial in support of licensure.
2. The co-primary endpoints of the trial have been met.
3. The product has an acceptable safety profile.
4. The correlation between the A1PI antigenic assay and the functional assay (anti-neutrophil elastase capacity is nominally different in test and control at weeks 8 to 11. This is not thought to be of clinical significance.
5. The vast majority of subjects maintained trough levels > 11µmol/L for both the functional assay (anti-neutrophil elastase capacity) and antigenic assay for a1-PI.
6. The data from the bronchoalveolar lavage are not complete. This is addressed in labeling and in a Phase 4 study the sponsor has agreed to perform.
7. Product review issues raised by CBER during review of the initial submission resulted in a complete response letter to be issued during the initial review cycle. The latter also included requests for the sponsor to clarify certain clinical data.

Disease and Regulatory Background

Alpha 1-proteinase inhibitor (A_1-PI) deficiency

Alpha 1-proteinase inhibitor (A_1-PI, alpha one antitrypsin) deficiency is an autosomal co-dominant disorder in which there are below normal levels of alpha 1-proteinase inhibitor in serum and in the epithelial lining fluid (ELF) of the lung. Patients with this disorder have a high risk for the development of emphysema in the third to fifth decades. Some patients also develop liver disease, which is not thought to be ameliorated by augmentation therapy with a1P.

Alpha 1-proteinase inhibitor, which is synthesized in the liver, is a glycoprotein of molecular mass 52kD. It is a serine protease inhibitor (serapin) that has the primary function of inhibiting neutrophil elastase. It is postulated that emphysema results from the imbalance between the neutrophil elastase in the lung that has the capability to destroy elastin of the alveoli and the a1-PI that is responsible for protecting the lung from the elastase.
The Alpha 1-proteinase inhibitor gene has been found to code for over 70 types of a1PI proteins and the various subtypes of a1PI proteins are classified on the basis of their electrophoretic motilities. Subjects with various subtypes will have differing serum levels of a1-PI.

Phenotype	Molecular/cellular defect	Serum level of a1PI (µM/L)	Lung disease may be present	Liver disease
Pi MM	Normal	21-34	No	No
Pi ZZ	Produced in liver but cannot be transported extracellularly	<5	Yes	Yes
Pi null-null	Deletion of allele	0	Yes	No
Pi SS	Increased intracellular protein degeneration in the liver	10-20	No	No
Pi SZ	Combination of S and Z defects	6-14	Yes	No
Pi MZ	Heterozygous normal and Z	10-20	No	No

The measurement of serum levels of a1-PI is complicated by the fact that many of the commercial standards overestimate the a1-PI levels by 35-40%. In the 1980's the a1-PI levels had been expressed in the units of mg/dL. Levels of 80 mg/dL were speculated to be a threshold serum level, above which there is sufficient a1PI to protect the lung and below which there is an increase risk of emphysema. It should be noted that this rather arbitrary choice of 11 microM as a serum level target of augmentation therapy neglects the observation by Brantly and colleagues at the University of Florida that the lungs of a1-PI-deficient individuals have an increased neutrophil burden compared to normals, and thus might require more aggressive augmentation therapy than that implied by the traditional 11 microM serum level target for antigenic a1-PI).

Investigators now use a "true laboratory standard" that more accurately quantifies the amount of a1-PI present. It is important to point out that no controlled clinical trial data exist that substantiate the notion that maintaining a trough serum level of a1-PI of 11 µM/L with augmentation therapy necessarily has a salutary effect on the progression of emphysema/deterioration of pulmonary function.

American Thoracic Society guidelines published in the American Review of Respiratory Diseases in 1989 recommend consideration of a1-PI as augmentation therapy for patients greater than 18 years of age with evidence of ventilatory impairment upon pulmonary function testing. The therapy is based on the ***concept*** that increasing the level of a1-PI in the serum will increase the level of a1-PI in the lungs, inhibit the activity of neutrophil elastase, and prevent the damage to the lung structure.

Data from the NIH a1PI Registry (American J Respiratory Crit. Care Med 158, 49,1998), a non-randomized, epidemiologic prospective study, suggests that augmentation therapy

may be efficacious in halting the progression of disease ***in the subgroup of patients who have an FEV_1 between 35-49% predicted***. However it should be noted that the primary endpoint evaluating the slope of FEV_1 change in the subgroups of the entire study population who were (ever) on augmentation therapy vs. the slope in those who were never on augmentation therapy with a1-PI did ***not*** show a difference. Although one cannot draw definitive causal inferences from any epidemiologic study, it should also be noted that the NIH Registry did suggest a possible mortality benefit associated with augmentation therapy. Researchers in the field have voiced concern that baseline imbalances in socioeconomic and other factors not fully taken into account in the analyses of this study may have led to an overestimate of possible augmentation therapy effects on mortality.

The only heretofore U.S.-licensed a1-PI concentrate, Prolastin®, produced by Bayer Pharmaceuticals, was licensed in 1986. The clinical data from the Phase 3 trial supporting licensure included serum results from 19 a1-PI deficient subjects of the ZZ subtype. The treatment modality of 60mg/kg was shown to maintain plasma a1-PI levels, measured both antigenically and functionally, above 80 mg/dl in all subjects with a trough level of 120 to 130 mg/dl reached after 6 weeks. Fiberoptic bronchoscopy was performed on a total of nine subjects during the phase 2 and 3 trials. The mean antigenic level of a1-PI in ELF was $0.042 \pm 0.025 \mu M$ prior to treatment, $1.78 \pm 0.51 \mu M$ after 2 months or less of weekly infusions, $1.41 \pm 0.89 \mu M$ after 3 to 4 months of treatment. Functional anti-elastase activities were $0.77 \pm 0.036 \mu M$ prior to treatment, $1.80 \pm 0.51 \mu M$ after 2 months or less of weekly infusions, and $1.12 \pm 0.27 \mu M$ after 3 to 4 months of treatment.

Rationale for maintenance of trough level of 11 µM /L as an "accepted" surrogate measure of clinical efficacy:

An FDA Blood Products Advisory Committee (BPAC) Meeting was held in June 1998 to consider appropriate clinical trial design and endpoints for a1-PI studies. BPAC members voted 11 to 3 with 1 abstention to indicate that FDA should continue to accept maintenance of a plasma level of 11 µM /L in conjunction with demonstration of an appropriately defined increment in epithelial lining fluid as sufficient for demonstrating clinical efficacy of intravenously administered a1-PI products in pivotal phase 3 studies. However, a majority of the committee members had reservations concerning the validity and scientific basis for the conventional target trough level. Committee members were concerned that studies to validate this target level would be difficult to conduct because of the sample size required to demonstrate clinical efficacy, either by decrease in FEV_1, CT changes, or death. The committee members did not specifically comment about what the increment in ELF should be and Dr. Brantly of the National Heart, Lung, and Blood Institute commented (page 151 of BPAC minutes) that bronchoalveolar lavage was a technically difficult procedure. He stated that, "As an individual's lung function begins to deteriorate, the ability to do successful and high quality BAL goes down, and there is a higher chance of inaccuracy as far as biochemical data. I think it would be very difficult to get accurate information in individuals, in my experience, that have FEV_1's less than 50% of predicted."

IV. Regulatory history

IND ---- was originally submitted in June 1993.
The first subject began treatment on March 18, 1997 under the clinical protocol dated December 12, 1996.

There were several protocol amendments:

- Amendment 16 April 7, 1997:
  - Co-primary endpoints were changed to:
    - Maintenance of mean serum a1PI trough at weeks 7 through 10 equivalent to 80% of Prolastin® treated subjects.
    - Maintenance of mean serum a1PI trough levels during weeks 11-24 when all subjects are receiving infusions of test material.

- Amendment 20 November 7, 1997:
  - Inclusion of subjects who had previously received treatment with Prolastin® provided that there was a 6 month wash-out period prior to enrollment

- Amendment 27 November 19, 1998
  - Statistical analysis plan clarifying the statistical methods to be used to evaluate the co-primary endpoints

- Amendment 28 December 10, 1998
  - Revision of statistical plan

- Amendment 32 January 28,1999
  - Notice of unblinding
  - Submission of final analysis plan

May 2000
Alpha Therapeutics submitted a BLA that was designated as “refuse to file” by FDA due to product (CMC) review issues.

September 2000
Alpha Therapeutics applied for, and was granted, fast track status.

August 2001
Current BLA submission submitted.

March 2002
Complete Review letter issued to firm by CBER

June 2002
Sponsor submitted response to complete review letter.

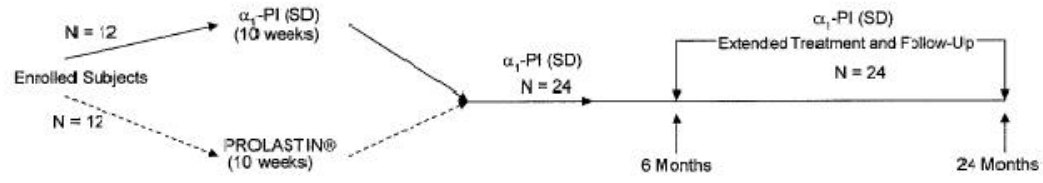
October through December 2002
Sponsor submitted amendments to its response to CBER's complete review letter, the results of a targeted efficacy data audit, and revised draft labeling.

Study design

Clinical trial ATC 97-01 was a multicenter, randomized, double blind, active control Phase 3 non-inferiority study comparing Alpha Therapeutic Corporation's Alpha 1-Proteinase Inhibitor to commercially available Prolastin®.
The overall objective was to demonstrate safety and efficacy in subjects with a1-PI deficiency.

Twenty-four subjects were to be randomized to receive either treatment or control product at the standard dose of 60mg/kg/week for 10 consecutive weeks.
Following the 10 weekly infusions the 12 subjects who were receiving Prolastin® were to be switched to Alpha Theraputic's a1-PI test article and the 12 subjects who were receiving test article were to continue to receive the test article until week 24. During weeks 11-24 mean serum a1-PI trough levels and AE's were to be continued to be determined.

FIGURE 1: SCHEMATIC PARALLEL DESIGN FOR ATC 97-01



The primary objectives would be:

- Demonstrate equivalence between treatment groups in mean serum a1-PI trough levels during weeks 7 through 10
- Determine that serum a1-PI trough levels for all subjects are maintained during weeks 11 to 24.

The secondary objectives would be:

- Demonstrate equivalence between treatment groups in mean serum trough anti-neutrophil elastase (NE) capacity during weeks 7 through 10
- Demonstrate equivalence in mean change from base line to 6 weeks of a1-PI
- Demonstrate equivalence in mean change from base line to 6 weeks of anti-NE capacity
- Demonstrate equivalence in trough serum and ELF a1-PI and anti-NE capacity done at baseline and 7 weeks

Other assessments:

- Pulmonary function tests
- Chest x-rays
- Biochemical determination of degradation products
- Pharmacokinetic data

II. Products used

Test product:
Alpha 1 Proteinase Inhibitor [a1-PI (SD)] is manufactured by Alpha Therapeutic Corporation. The source plasma for a1-PI is tested by ---- of the plasma pools for markers of hepatitis B and C, and HIV1 and 2. The manufacturing process includes solvent/detergent treatment and nanofiltration to achieve viral reduction. The product is supplied as a sterile lyophilized powder in vials containing approximately 500 mg or 1000 mg of a1-PI. Each vial contains the labeled amount of functionally active a1-PI in mg/vial, as determined by capacity to neutralize porcine pancreatic elastase. Each vial is reconstituted with Sterile Water for Injection (SWFI) and prepared according to the lot-specific instructions provided by the manufacturer. The administration of product must begin within 3 hours after the product is reconstituted.

Control product:
The control product was Prolastin®, the licensed product for the indication of augmentation of a1-PI deficiency. The product is supplied as a sterile lyophilized powder in vials containing 500 mg or 1000 mg of a1-PI. Each vial contains the labeled amount of functionally active a1-PI in mg/vial as determined by capacity to neutralize porcine pancreatic elastase. Each vial is reconstituted with Sterile Water for Injection (SWFI) and prepared according to the lot-specific instructions provided by the manufacturer. The administration of product must begin within 3 hours after the product is reconstituted.

Study procedures (refer to Tables 1 and 2 following this section)
Testing Schedule

At enrollment:

1. Genetic screening
2. Medical history and physical exam
3. Blood chemistry –ALT, AST, alkaline phosphatase, total bilirubin, LDH, creatinine albumin, BUN
4. Hematology-CBC including differential WBC, platelets
5. Serum a1-PI level
6. Serum Anti-Neutrophil elastase capacity
7. Antibody determination to a1-PI
8. Viral serology: Antibodies to hepatitis A and C, the presence of circulating HbsAg, antibodies to HIV-1, HIV-2 and Parvovirus B-19
9. Urine Desmosine/Isodesmosine
10. Lung CT scan
11. Chest x-ray
12. Full pulmonary function tests-spirometry, pre-and post-bronchodilator, lung volume measurements, DLCO, carboxyhemoglobin
13. Arterial Blood Gas-resting, room air
14. Bronchoalveolar lavage

Serum a1-PI level and Serum Anti-Neutrophil elastase capacity trough (prior to each infusion) and peak (one hour following each treatment infusion) were to be determined weekly for weeks 1-6.

Serum a1-PI level and Serum Anti-Neutrophil elastase capacity trough were to be determined weekly for each treatment week through week 24 and at day 7 of the last week of Months 9,12,18 and 24 of the extended treatment and follow-up.
Urine desmosine and isodesmosine were to be collected at enrollment and once per week during the first 24 weeks of enrollment and the last week of months 9, 12, 18, and 24 of extended treatment and follow-up.

Blood biochemistry and hematology were to be done every 3 weeks until week 22 and again at week 24.

Chest x-rays were to be performed at enrollment, week 7 and months 12 and 24.
Lung CT scan was to be performed at enrollment and month 12. All x-ray studies were to be read locally at each institution and then to be reviewed independently at one institution.

Pulmonary function tests were to be performed at weeks 7 and 24 and during the last weeks of months 12 and 24.

Biologic Half-life (t ½) of a1-PI was to be obtained at the time of the first infusion for both test and control products by blood sampling at pre-infusion, and post infusion at 1h

±0.25h, 2h±0.25h, and 6h±0.5h, and 12h± 0.5h and then every 24 hr± 6h through day 7 prior to the next infusion

? 1-PI antibody determination was to be done at enrollment, prior to infusion 7 and prior to infusion 24. Assays were to be conducted in the laboratory of Dr. Mark Brantly.

Viral serology performed at enrollment were antibodies to hepatitis A (IgG/IgM and IgM confirmatory), antibodies to hepatitis C, HbsAg, antibodies to HIV-1, HIV-2 and Parvovirus B-19 (IgM and IgG). All subjects who were negative for Parvovirus B-19 at enrollment were to be tested for Parvovirus B-19 by polymerase chain reaction (PCR) prior to Week 2. The same viral serology panel, excluding the Parvovirus B-19, was to be performed prior to treatment at Week 11 and at Week 24. An additional aliquot of serum was to be retained from all viral sampling points for retesting. Analysis of the viral serology for Weeks 24 through 96 will be submitted in a supplemental report.

Bronchoalveolar Lavage (BAL)
All evaluable subjects were to undergo a BAL at baseline preceding infusion 1 and at week 7, six to 7 days after infusion 6.
(BAL) **fluid for each lobe was processed separately (there is a contradiction in the lab methods section 16)** and percentage recovered was to be measured.
BALs were considered to be evaluable if they met the following criteria, which were defined by the testing laboratory prior to treatment of the first subject:

- Return ≥ 20%
- Cells/mL ≥ 5.0×10^4
- $[Urea]_{plasma}/[Urea]_{BAL} \leq 300$
- 90 nmol/L ≤ Initial $[a\ 1\text{-PI}]_{BAL} \leq 600$ nmol/L
- The epithelial lining fluid (ELF) from each BAL was to be analyzed for the presence of a1-PI level and anti-NE activity and the change from baseline in the 2 treatment groups was to be compared.

TABLE 1: SCHEDULE OF TREATMENTS AND TESTING

	M-1	Month1				Month 2				Month 3				Month 4				Month 5		
WEEK/INFUSION #	E-4*	1*	2	3	4	5	6	7*	8	9	10	11[∂]	12	13	14	15	16	17	18	19
Phenotyping	X																			
Medical History and Physical Exam	X[§]	X[§]	X	X	X	X	X	X[§]	X	X	X	X	X	X	X	X	X	X	X	X
Blood Biochemistry and Cell Counts	X	X			X			X			X			X			X			X
Serum α_1-PI Levels	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Anti-NE Capacity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Desmosine/ Isodesmosine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lung CT Scan	X																			
Chest X-Ray	X							X												
Full Pulmonary Function Tests	X							X												
Arterial Blood Gas	X																			
Bronchoalveolar Lavage(BAL)[@]	X							X												
Biologic t½ Determination		X																		
α_1-PI Antibody Determination	X							X												
Viral Serology	X		X[∞]									X								
α_1-PI Infusion and Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Experiences		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

E (Week -4 or M-1) = Randomization and enrollment into the study to obtain baseline values for up to 4 weeks prior to Infusion 1 (Week 1).

@BALs will be performed at enrollment and 6 days (defined as 6 to 7 days) after the sixth consecutive infusion. Epithelial lining fluid (ELF) will be assessed for levels o α_1-PI and anti-NE capacity.

∞Week 2 viral serology will be for Parvovirus B-19 and only for subjects who were Parvovirus B-19 negative at enrollment.

∂All subjects will receive α_1-PI (SD) weekly at a dose of 60 mg/kg body weight beginning at Week 11.

TABLE 2: SCHEDULE OF TREATMENTS AND TESTING

	Month 6				^§EXTENDED TREATMENT/FOLLOW-UP MONTH #			
WEEK/INFUSION #	21	22	23	24*	9	12*	18	24*
Medical History and Physical Exam	X	X	X	X	X	X[§]	X	X[§]
Blood Biochemistry and Cell Counts		X			X	X	X	X
Serum α_1-PI Levels	X	X	X	X	X	X	X	X
Serum Anti-NE Capacity	X	X	X	X	X	X	X	X
Urine Desmosine and Isodesmosine	X	X	X	X	X	X	X	X
Lung CT Scan						X		X
Chest X-Ray						X		X
Full Pulmonary Function Tests				X		X		X
Arterial Blood Gas								X
α_1-PI Antibody Determination				X				
Viral Serology				X		X		X
α_1-PI Infusion and Vital Signs	X	X	X	X	X	X	X	X
Adverse Experiences	X	X	X	X	X	X	X	X

^Throughout the extended treatment and follow-up period (Months 7 to 24), all subjects will receive α_1-PI (SD) weekly at a dose of 60 mg/kg body weight. Vital signs and adverse experiences will be monitored during each extended treatment infusion.

§For weekly infusions during Extended Treatment and Follow-Up Months 7, 8, 10, 11, 13 to 17 and 19 to 23, modified physical exams, vital signs and adverse experiences will be obtained.

Planned inclusion criteria were:

1. Greater than 18 years old
2. Diagnosis of congenital a1-PI deficiency with any of the following combination of alleles: PiZZ, Mheerian, Mprocida, Mmalton, Plowell, Mduarte, Pduarte, Mmineral springs, Wbethesda, Mnichinan, I and all Z null, null- null and null in combination with any of the above alleles.
3. Diagnosis of emphysema
4. Serum a1-PI level less than 11µM
5. Following bronchodilators:
    a. An initial FEV_1 $\geq$30% and $\leq$80% of predicted and an initial $FEV_{1/}$FVC ratio <70%
    b. Or if the initial FEV_1 was >80% of predicted, a DLCO < 70% of predicted, plus an abnormal lung CT consistent with emphysema, and no other confounding disease present.
6. Non-smoker and had not smoked for at least 6 months prior to enrollment
7. Female subject and partner agree to use adequate contraception
8. Agree to the terms for treatment and collection of follow-up data as scheduled in the protocol
9. Able to sign consent form

Planned exclusion criteria:

1. Any a1-PI augmentation therapy, either Prolastin® or other investigational a1-PI product within the preceding 6 months
2. Hospitalization >2x in the past year for lung-related problems or within 4 weeks of enrollment for pneumonia
3. Ongoing recurrent inflammatory process such as:
    a. Diffuse infiltrative parenchymal lung disease as evidenced by lung CT scan and shown to be active by gallium scan or other clincial evidence
    b. Antibiotics within 2 weeks prior to the first infusion or received $\geq$ 6 courses of antibiotic therapy during the preceding year
    c. Demonstrated inability to achieve a constant dose of steroids on a tapering regimen.
4. Seropositivity for HbsAg or HCV IgG Antibody
5. Seropositivity for antibody to HIV-1 and/or HIV-2
6. ALT or AST>3x the upper limit of normal in the preceding 6 months
7. $PaCO_2$ $\geq$46mm Hg or a resting room air PaO_2 $\leq$55mmHg
8. Serum creatinine >1.5 X ULN
9. Selective IgA deficiency (IgA<15mg/dl) or antibody against IgA
10. Antibodies against a1-PI
11. Pregnant or nursing a child
12. Received investigational drug within 2 months of the trial or currently receiving investigational drug.

Randomization
Randomization was to be performed at the site pharmacy from a series of randomization numbers provided by Alpha Therapeutic Corporation. A separate series of randomization numbers was provided at each treatment site to allow for randomization by site.

Blinding
For the first 24 weeks of the study the subjects, investigators, radiologists, testing laboratories, on-site study nurses and home healthcare nurses treating the subjects were to be blinded regarding the subjects first 10 week treatment group and to the identity of the solutions for infusion.
The pharmacist was not to be blinded.
At Alpha Therapeutic Corporation, the clinical manager, director of clinical research, statistician and anyone involved in the analysis or interpretation of the data were to be blinded regarding the subject's treatment group.

Study procedures:
Infusions of test or product were to be performed weekly.
The medication was to be reconstituted by the study site pharmacy and administered by a home health care nurse, who assessed the subject for AE's and completed the CRF.

III. Statistical Analysis

There were 2 co-primary endpoints.

1. Mean serum a1PI trough levels from weeks 8-11 for the test group were not inferior to those of the control group.
    - Prior to breaking the blind, missing data for Weeks 8, 9, 10 and 11 will be imputed by taking the mean across the remaining weeks.
    - A one-sided 5% level Sasabuchi t-test will be performed of the null hypothesis that the mean for test group is less than 80% of the mean for the control group.
2. Maintenance of mean serum a1PI trough levels during Weeks 12 through 24 while receiving weekly test article will be analyzed by computing a regression slope for each subject.
    - The regression slope will be fit to all available data and missing data will not be attributed. The A two-sided 90% confidence interval for the mean slope will be computed to demonstrate that the lower limit of the observed slope did not include -0.1µ mol/L/week.
    - The analysis will be done separately for the subjects who were transferred at Week 11 from control to test drug in order to test for interference due to carryover effect.

Secondary endpoints:
1. Mean serum anti-NE capacity from weeks 8 through 11 for the test group is not inferior to that of the control group, will be performed. The methods used will be the same as for the primary endpoint above.

2. Mean change in serum a 1-PI from baseline to week 7

A test that the mean change for serum a 1-PI from baseline to trough levels at week 7 for the test group is not inferior to that for the control group will be performed using the method of Sasabuchi.

3. Mean change in serum anti-NE from baseline to week 7

A test that the mean change for serum anti-NE from baseline to trough levels at week 7 for the test group is not inferior to that for the control group will be performed using the method of Sasabuchi.

Independent analysis done by CBER medical reviewers included:

1. Confirmed line listings of inclusion criteria including pulmonary function tests (PFTs), reports of CT scans, and chest x-rays.
2. Performed independent review of clinical data to ascertain that the subjects were comparable in the clinical characteristics of pulmonary disease and concomitant medications.
3. Spot-checked data to note consistencies, reviewed areas of missing data
4. Reviewed AE reports and classification of AEs, assessed AEs by lot numbers
5. Reviewed BAL protocol and raw data to assess for deviations of sampling
6. Independent analysis by CBER statistician:
    a. Confirmed analysis using imputation of data
    b. Performed analysis of first primary endpoint without imputation.
    c. Determined correlation between measurements of antigenic and functional a1PI during weeks 1-7 and weeks 8-11 in test and control product.

IV. Clinical trial conduct

The study was initiated on February 19, 1997 and the last infusion #24 was given on August 5, 1998.

The study was opened at 5 sites. Four sites accrued a total of 28 subjects as follows:

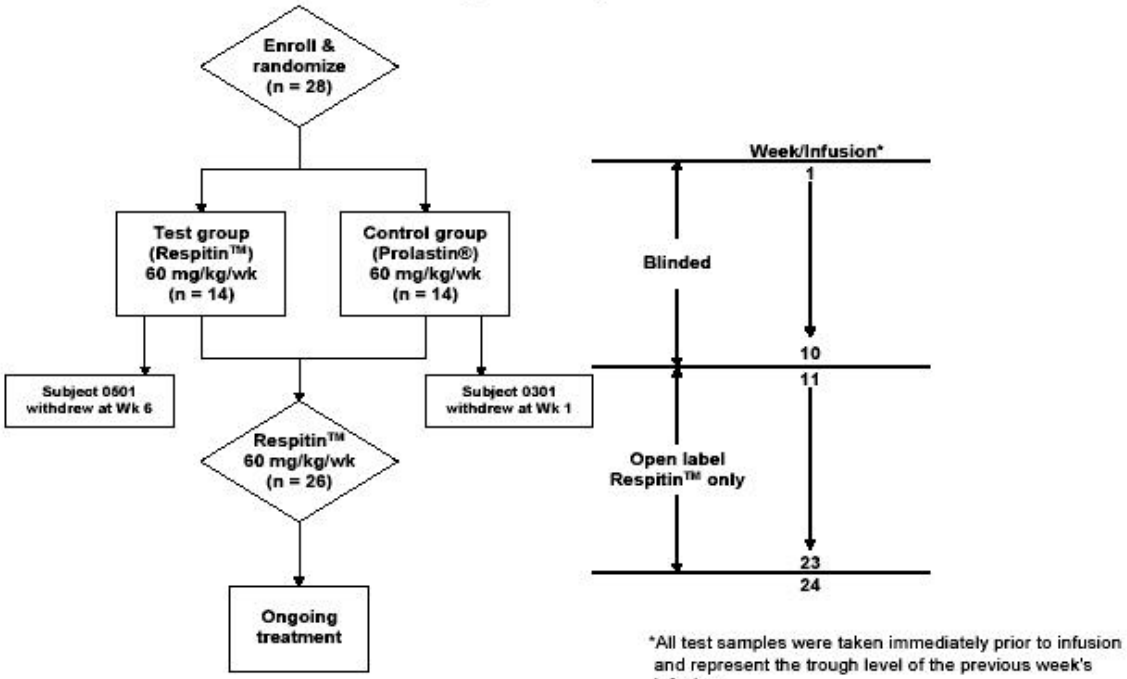
Investigator	Site ID Number	Site	Number of subjects enrolled at site
Jack Clausen, MD	01	UC San Diego	6
James Stoller, MD	03	Cleveland Clinic	10
James Stocks, MD	04	U of Texas, Tyler	8
Edward Campbell, MD	05	U of Utah, Salt Lake City	4

According to the sponsor, the study was unblinded sometime between December 15, 1998 and December 24, 1998 after a discussion with FDA held December 15, 1998. The

study sites were kept blinded until this date. The analysis plan was finalized prior to unblinding of the study.

Disposition of subjects

Figure 1: Design of ATC 97-01



Disposition of subjects
No subjects died during the study.
Two subjects, one each from the test and control groups withdrew from the study.
Subject 301 on Prolastin® discontinued the study at week one after one infusion. The subject experienced bilateral pneumonia after a bronchoscopy to remove a foreign body.
Subject 501 elected to discontinue the study after 6 infusions because she felt that the obligations of the study were too burdensome.
Subject 105 experienced bloating after his weekly infusions and withdrew from the trial after 28 infusions. This is noted in the annual report submitted Sept. 2001 and is not in the BLA report.
According to the 2001 annual report 15 subjects (53.6 %) completed the planned 2-year enrollment (104 weeks). Ten subjects were terminated at weeks 78-95 due to lack of available product.

Study conduct
Study conduct concerning the administration of medication, monitoring of subjects, collection of serum samples and clinical data appears to have been adequate. However the conduct of the study had a flaw concerning adherence to the BAL protocol. In

contrast to the planned BAL protocol in which evaluations were to be performed on all samples, evaluations were done only on paired samples.

Violations and protocol deviations
20 serum specimens were either lost or damaged by overnight courier. (See table in data analysis section)

Violations concerning both groups
Prior to April 1998, both test and control study drug, was administered up to 24 hours following reconstitution despite the protocol instruction that it should be given within 3 hours.

Violations concerning test group
Doses in six instances were 58 mg/kg instead of the 60mg/kg due to transcription errors

Violations concerning control group
Due to a pharmacy error, Subject 402 received 37.8mg/kg instead of 60mg/kg for infusions 16-18 while on test product.

Protocol deviation
Subject 104 in the test group stopped his antibiotics on 12/07/97 and the sponsor approved his participation in the study so that he received his first infusion on 12/11/97.

Inspection of study sites for integrity of data- See Bioresearch Monitoring (BIMO) report.

Good Clinical Practice Inspections were conducted at the central laboratory and clinical investigator sites at the University of Florida, as well as the clinical investigator sites at the Cleveland Clinic and University of Texas, the 2 clinical sites that had the highest enrollment,

Subject demographics
There were 14 subjects enrolled in each treatment group. All subjects were of the ZZ phenotype with the exception of one subject in the Control group who was MmaltonZ. Baseline serum a1 PI levels were comparable in the 2 groups.
The groups were balanced in all aspects below except for history of smoking.

> *Three of the 14 subjects in the test group that had not smoked but all subjects in the control group had a history of smoking.*

Table 5: Baseline Characteristics – All Subjects

Characteristic	Test group (n = 14) n % Mean ± SD (Range)	Control group (n = 14) n % Mean ± SD (Range)	p
Sex			
Male	10 71.4	11 78.6	
Female	4 28.6	3 21.4	1.000[a]
Race			
White	14 100.0	14 100.0	--
Age (years)	45 ± 11 (24 to 64)	49 ± 7 (40 to 62)	0.319[b]
Weight (kg)	84 ± 12 (57 to 106)	91 ± 15 (71 to 116)	0.199[b]
Height (cm)	177 ± 6 (166 to 187)	177 ± 9 (163 to 193)	0.860[b]
Serum α_1-PI (µmol/L)	5.7 ± 1.0 (4.1 to 7.2)	5.7 ± 1.3 (4.1 to 8.2)	0.929[b]
FEV_1 (% predicted)	48 ± 18 (31 to 86)	47 ± 15 (30 to 77)	0.835[b]
Phenotype			
ZZ	14 100.0	13 92.9	1.000[a]
MmaltonZ	0 0.0	1 7.1	
History of smoking			
Yes	11 78.6	14 100.0	0.222[a]
No	3 21.4	0 0.0	
Years since quitting	12 ± 10 (< 1 to 31)	14 ± 9 (1 to 35)	0.605[b]
Vaccinated against			
Hepatitis A			
Yes	1 7.1	0 0.0	1.000[a]
No	13 92.9	14 100.0	
Hepatitis B			
Yes	9 64.3	5 35.7	0.257[a]
No	5 35.7	9 64.3	

SD = standard deviation
[a]Groups compared with Fisher's exact test.
[b]Groups compared with two-sided t-test.

All subjects were Caucasian and over 70% of subjects were males in each group.
All subjects except 305 in the test group met the inclusion criteria for FEV1 between 30 and 80%. This subject had an FEV1 of 86% predicted and a DLCO of 68% predicted. CT scan was read as normal
Subject 105 in the test group was the only subject in the study that had been treated with Prolastin previously. This had been more than 2 years prior to enrollment in this study.

Date of Diagnosis of Illness

	Date of diagnosis	
	I. Emphysema	II. A1PI deficiency
Test	1980-May 1997	1980- September 1997
Control	July 1980-October 1997	July 1980-December 1997

Concomitant medications

All subjects enrolled had the diagnosis of "emphysema" *and the majority of subjects were on inhaled or oral steroids throughout the course of the study*.
Only two subjects in the test group, 104 and 407 were not receiving any therapy for their lung disease.
One subject in the control group, 101, did not receive any pulmonary therapy and 2 subjects, 304 and 503, received only bronchodilators without any steroid therapy.

During the course of the study, 14 subjects required antibiotic treatment for exacerbation of pulmonary infection. Two subjects required 3 courses of Antibiotics and 2 subjects required 2 courses of antibiotics, making for a total of 20 courses of Antibiotics. Of these, 10 courses occurred during the blinded phase of the study, 4 events in the test group and 6 events in the control group.

Efficacy Analysis

Co-primary endpoint 1
A test that the co-primary endpoint, mean serum a 1-PI trough level from Weeks 8 through 11, for the test group is not inferior to that for the control group was performed.

Four subjects (two from each treatment group) were missing data for one or more of the four weeks. No subject missed an infusion, but some samples were lost or damaged. As agreed upon with the FDA, for each of these four subjects, the missing value(s) were assigned the value of the mean of weeks 8-11 for which data were available for that subject.
Group assignments:
Subject 305-test group
Subject 309-control group
Subject 310 Test group
Subject 408-Control group

Table 67: Missing data for Serum α_1-PI Levels, Weeks 8 through 11

	Week number			
Subject	8	9	10	11
0305	**15.0**	15.0	15.3	14.6
0309	**16.9**	***16.9***	19.0	14.8
0310	***16.1***	15.3	16.0	17.0
0408	19.9	***20.0***	21.1	18.9

The null hypothesis tested was that the mean of the test group is less than 80% of the mean for the control group.

Mean serum a 1-PI trough level of each group measured prior to treatment at Weeks 8 through 11

Test group	15.3 ± 2.5 µ mol/L
Control group	16.9 ± 2.34 µ mol/L

$$\frac{\text{Mean test}}{\text{Mean control}} = 90.5\%$$

Lower 95% confidence limit for Mean test / Mean control = 81.7%

($p = 0.026$, one-sided Sasabuchi t-test)

The null hypothesis was rejected.

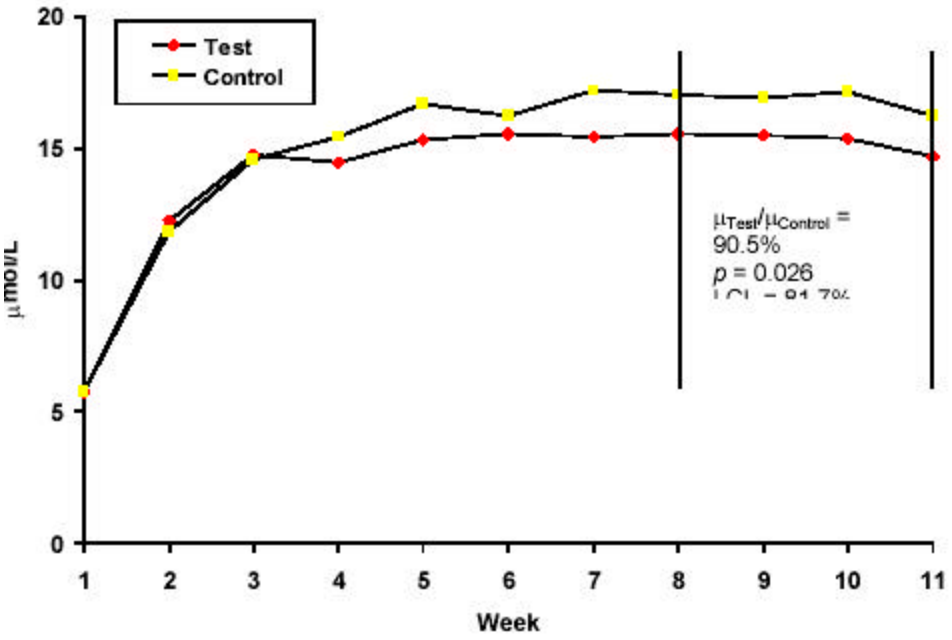
The CBER statistician confirmed this value.

Analysis by CBER statistician conducted without imputation of data for endpoint 1 showed

$$\frac{\text{Mean test}}{\text{Mean control}} = 90.7\%$$

Lower 95% confidence limit for $\frac{\text{Mean test}}{\text{Mean control}} = 84.1\%$

Figure 3: Co-primary endpoint 1: α_1-PI Serum Levels Weeks 8 through 11 (Trough Levels for Infusions 7 through 10)



VII. Co-primary endpoint 2

During weeks 12-24 all subjects received test article. Maintenance of mean serum a 1-PI trough levels during these weeks was analyzed by computing a regression slope for each subject employing a first-order time series autoregressive model. A two-sided 90% confidence interval for the mean slope was computed to demonstrate that the lower limit of the observed slope did not include -0.1 μ mol/L/week.

Twelve subjects (six in the test group and six in the control group) were missing a 1-PI trough level data for one of the 13 infusions; one subject (Subject 0403 in the control group) was missing data for two infusions (infusions 13 and 24). These missing values were not attributed; the regression line was fit through the available data for each subject.

The null hypothesis tested was that the slope of the trough in weeks 12-24 included -0.1 μ mol/L/week for either the test or the control group.

To determine if the study drug received during the blinded portion of the study may have influenced the results obtained for all subjects, the slope of the line was calculated separately for the test and control groups.

Slope test group	= -0.024	90% CI -0.088 to 0.040
Slope control group	= 0.018	90% CI -0.043 to 0.080
Slope combined groups	= -0.003	90% CI -0.04 to 0.04

The null hypothesis was rejected.

The FDA statistician reviewed the data and concurred.

Figure 4: Trough Levels for Serum α_1-PI Mean ± SD

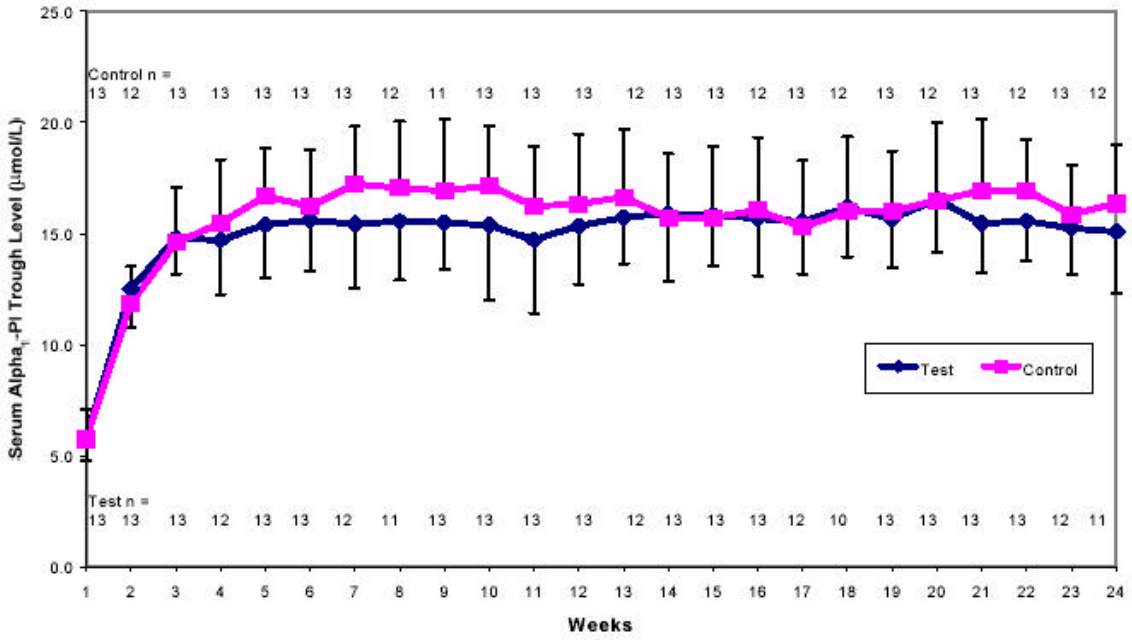


Table 68: Missing data for serum α_1-PI levels, Weeks 12 through 24

	Week number												
Patient no.	12	13	14	15	16	17	18	19	20	21	22	23	24
0104							√						
0105													x
0304									x				
0307												√	
0308		√											
0403		x											√
0404													√
0405											√		
0406							√						
0407						√							
0502					x								
0503							√						
0504							√						

X=accidentally destroyed by Fed EX Checkmark= missing Fed Ex shipment 4/13/98