Table 7: Summary of Co-primary Endpoints

Co-primary endpoint	Test Group (n = 13) Mean ± SD (µmol/L)	Control Group (n = 13) Mean ± SD (µmol/L)	Ratio test/control $\mu_{TEST}/\mu_{CONTROL}$ (%)	Lower limit 95% CI	p^a
Serum α_1-PI trough levels, Weeks 8 through 11[b]	15.3 ± 2.5	16.9 ± 2.3	90.5	81.7	0.026
H_0: Mean test group < 80% control group					
H_1: Mean test group ≥ 80% control group					
Decision: Reject H_0					

	Test group (n = 13) Slope (µmol/L/week) (90% CI)	Control group (n = 13) Slope (µmol/L/week) (90% CI)	Combined groups (n = 26) Slope (µmol/L/week) (90% CI)
Serum α_1-PI trough levels, Weeks 12 through 24[c]	-0.024 (-0.088 to 0.040)	0.018 (-0.043 to 0.080)	-0.003 (-0.04 to 0.04)
H_0: Slope over time includes –0.1			
H_1: Slope over time does not include –0.1			
Decision: Reject H_0			

CI = confidence interval; SD = standard deviation.

[a]One-sided Sasabuchi t-test of H_0.

[b]Samples drawn prior to infusions at Weeks 8 through 11, reflecting trough levels for Infusions 7 through 10.

[c]Samples drawn prior to infusions at Weeks 12 through 24, reflecting trough levels for Infusions 11 through 23. Both groups were receiving test drug during this time period.

Secondary endpoints

1. Non-inferiority of trough of anti-neutrophil elastase (anti-NE) capacity at weeks 8-11

H_o: $\frac{\text{Mean test}}{\text{Mean control}} < 80\%$

Mean serum anti-NE trough level of each group measured prior to treatment at Weeks 8 through 11:

Test group 15.3 ± 2.4 µ mol/L
Control group 15.7 ± 2.6 µ mol/L

$\frac{\text{Mean test}}{\text{Mean control}} = 97.5\%$

Lower 95% confidence limit for the ratio of test/control of 87.5%
(p = 0.003, one-sided Sasabuchi t-test)

The null hypothesis is rejected.
Analysis confirmed by CBER statistician.

2. Non-inferiority of a 1-PI trough levels change from baseline to week 7

H_o: $\frac{\text{Mean test}}{} < 80\%$

Mean control

Mean a 1-PI trough levels change from baseline to week 7:
Test group 9.7 ± 3.4 µ mol/L
Control group 11.5 ± 2.3 µ mol/L

Mean test = 84.2%
Mean control

Lower 95% confidence limit for the ratio of test/control of 70.2%
(*p* = 0.301, one-sided Sasabuchi t-test)

The null hypothesis is not rejected.
Analysis confirmed by CBER statistician.

3. Non-inferiority of anti-NE capacity trough levels change from baseline to week 7

H_o: Mean test < 80%
Mean control

Mean Anti-NE capacity trough levels change from baseline to week 7:
Test group 12.3 ± 3.0 µ mol/L
Control group 12.3 ± 2.5 µ mol/L

Mean test = 99.6%
Mean control

Lower 95% confidence limit for the ratio of test/control of 86.0%
(*p* = 0.010, one-sided Sasabuchi t-test)

The null hypothesis is rejected.
Analysis confirmed by CBER statistician.

Table 8: Summary of Secondary Endpoints

Secondary endpoint	Test group (n = 13) Mean ± SD (µmol/L)	Control group (n = 13) Mean ± SD (µmol/L)	Ratio test/control $\mu_{TEST}/\mu_{CONTROL}$ (%)	Lower limit 95% CI	p^a
Serum anti-NE trough levels, Weeks 8 through 11[b] H_0: Mean test group < 80% control group H_1: Mean test group ≥ 80% control group Decision: Reject H_0	15.3 ± 2.4	15.7 ± 2.6	97.5	87.5	0.003
Serum α_1-PI trough levels, change from baseline (Week 1) to Week 7[c] H_0: Mean test group < 80% control group H_1: Mean test group ≥ 80% control group Decision: Do not reject H_0	9.7 ± 3.4	11.5 ± 2.3	84.2	70.2	0.301
Serum anti-NE trough levels, change from baseline (Week 1) to Week 7[c] H_0: Mean test group < 80% control group H_1: Mean test group ≥ 80% control group Decision: Reject H_0	12.3 ± 3.0	12.3 ± 2.5	99.6	86.0	0.010

CI = confidence interval; SD = standard deviation.
[a]One-sided Sasabuchi t-test of H_0.
[b]Samples drawn prior to infusions at Weeks 8 through 11, reflecting trough levels for Infusions 7 through 10.
[c]Samples drawn prior to infusion at Week 7, reflecting change from baseline through Infusion 6.

Individual data concerning a 1-PI trough less than 11 µ mol/L

Subject 0104 was the only subject in the test group who had a 1-PI trough level <11µM after week 3.

Subject 104 a 1-PI Trough levels <11µM

Week	4	5	8	10	11	13	14
a 1-PI trough (µ mol/L)	10.7	10.3	10.0	9.9	9.6	10.6	10.6

While the first 6 infusions of this subject were with the same lot, and each infusion was 7 days apart, the variability in trough levels during this period, which included values < 11 microM, was greater than during the remainder of the 24 week observation period. Therefore the variability cannot be explained by lot-to-lot variability and is consistent with assay variability plus biological intra-subject variability.

VIII. Subject 104 had Gilbert's syndrome, received amoxicillin and was on Prilosec for the duration of the study. The only other subject in the study who took Prilosec was subject 404 in the control group and this subject's levels were not abnormal.
Omeprazole (Prilosec) may interact with other drugs metabolized by the cytochrome P-450 system and can cause mild and, rarely marked elevations of liver function tests.

IX. Serum trough levels fell below the target levels in 2 subjects in the control group while on Prolastin® and in subject 306 while on test drug.

Individual data concerning anti-NE capacity trough less than 11 µ mol/L

Subject 104 anti-NE capacity trough levels <11µM

Week	4	5	7	11	14
anti-NE capacity trough (µ mol/L)	8.9	10.6	10.7	10.8	10.6

A few Control Subjects had sporadic anti-NE capacity trough level <11µM after week 3 .

In addition to the above, subject 401 had anti-NE capacity trough levels < 11µM. Due to a pharmacy error, this subject received only 37.8mg/kg/wk of product instead of 60 mg/kg/wk of product during weeks 16,17, and 18.

The trough levels of a 1-PI measured both antigenically and functionally were above the level of 11µM in the vast majority of measurements.

Additional CBER analysis of correlation of the assays for total a 1-PI and anti NE capacity
The CBER statistician performed an analysis of the correlation of the functional assay (anti-neutrophil elastase capacity) and the antigenic assay for a 1-PI. Comparisons were made of the control and test articles only for weeks 1-11 because all subjects received test article after week 11. In weeks 1-7 this correlation is 0.9 in the subjects receiving Prolastin and 0.87 for the subjects receiving test article. For weeks 8-11 the correlation is 0.71 for the subjects receiving Prolastin and 0.47 for the subjects receiving test article. The lower correlation for test product in weeks 8-11 and the differences in the correlations between the test and control article were the subject of further analysis by the sponsor at the request of FDA. When other time frames were examined, it could not be concluded that any nominal between-product differences in correlation coefficients for antigenic vs. functional a1-PI were of significance.

The sponsor was asked to "analyze, compare, and discuss the relationship between antigenic and functional levels of A1-PI in the final container test product and Prolastin®

and in serum samples from patients receiving the test product and the control Prolastin®. The sponsor was asked to compare the results obtained for the final container test product to results obtained for subject serum samples for each lot of product administered. For subjects enrolled in the control arm of the study and administered test product for the open label phase of the study, the sponsor was asked to analyze and compare the relationship between antigenic and functional levels of A1-PI for both treatment periods."

The sponsor clarified that the A1PI levels for the Prolastin control lots were not assayed by the sponsor.

The sponsor stated that the final container potency values, in g active A1PI per vial, met all final container specs. In the trial, the infusion volume was calculated based on the labeled potency of the specific A1PI lot and the subject's body weight. Because of the adjustment of infusion volume for potency, there is no apparent correlation between potency of functional A1PI in mg/vial to mean functional A1PI trough level in subjects receiving product from a particular vial.

The sponsor compared the subgroup mean (a) antigenic and (b) A1PI levels between weeks 3-11 (reflecting trough levels from infusions 3 to 10) and weeks 13-24 (reflecting trough levels from infusions 13 – 23) for those subjects randomized to receive Prolastin control during the initial 10 weeks and ATC A1PI during weeks 11-24. The sponsor calculated the ratio of antigenic OR functional levels (weeks 4-11)/(weeks 14-24). This ratio was 1.0257 (95% CI 0.9874-1.0652) for antigenic A1PI and was 0.9816 (95% CI 0.945-1.1094) for functional A1PI (anti-neutrophil elastase capacity [ANEC]). Similar ratios and confidence intervals were obtained using log transformed serum values. I calculate a ratio of mean functional to mean antigenic A1PI levels for the Prolastin steady-state period (weeks 4-10) of 15.48/16.61 = 0.93 and for the ATC A1PI period in this Prolastin randomization subgroup 15.78/16.19 = 0.975. Thus, the ratio of functional to antigenic is slightly less for Prolastin than for ATC A1PI by this analysis. It should be noted that the comparison requested by CBER of the ratio of antigenic to functional A1PI in the final container versus subject's plasma should take into account the contribution of the subject's endogenous A1PI. In the case of severely-deficient A1PI patients, this ratio is not expected to be 1.

Analysis of Results of Bronchoalveolar Lavage

Bronchoalveolar lavage (BALs) was performed twice on 26 subjects.

The fluid from each lobe was processed separately according to the BAL worksheet and in contradiction to laboratory methods 16.5.4, which states that the fluid from the lobes was to be combined.

BAL fluid was evaluated for adequacy according to the following criteria:

- Return $\geq$ 20%
- Cells/mL $\geq 5.0 \times 10^4$
- $[Urea]_{plasma}/[Urea]_{BAL} \leq 300$
- 90 nmol/L $\leq$ Initial $[a\ 1\text{-}PI]_{BAL} \leq$ 600 nmol/L

Cells were separated from the ELF fluid, a cell count was determined, and the fluid was frozen for further analysis. A sample was considered "unpaired" and was not analyzed if the subject's other BAL sample was deemed inadequate.

Only 5 of 13 subjects in the test group (38.5%) and 3 of 13 subjects in the control group (23.1%) had BALs both at baseline and at week 7 that met the criteria for evaluation established in the protocol.

For those subjects with unpaired BALs, the unpaired sample was not analyzed. This occurred in 13 pairs.
Two samples from the Tyler site were not analyzed because no second sample was sent due to inadequacy of the BAL return. Nine of the 10 subjects at the Cleveland Clinic site had unevaluable BAL because of low cell counts.
The degree of emphysema may have affected the quality of a BAL. Seven of 14 (50.0%) subjects with FEV1 > 40% had evaluable BALs *while only one of 12 (8.3%) subjects with FEV1< 40% had an evaluable BAL.*

The data are difficult to interpret because of the small sample size and the wide variability of the values. Subject 105 in the test group had levels of anti-NE capacity that decreased from 1,532 nmol/L at baseline to undetectable levels at week 7. The sponsor attributed this unexpected drop to the fact that this subject was taking antibiotics for bronchitis at week 1 and also had an infection at week 7.

The sponsor conducted an analysis on both the untransformed data and on $\log_e$ (natural logarithm) transformed data. In spite of these manipulations of the data, no firm conclusions were drawn from the BAL data from the original submission. The sponsor submitted in June 2002 further analysis using the confidence interval approach on the differences in the six parameters listed below.

1. ELF a 1-PI change from baseline to week 7

   Mean a 1-PI in ELF at baseline:
   Test group 190 ± 108 nmol/L
   Control group 452 ± 92 nmol/L

   Mean a 1-PI in ELF at week 7
   Test group 1,294 ± 885 nmol/L
   Control group 1,640 ± 511 nmol/L

Mean change in a 1-PI in ELF at week 7
Test group 1,104 ± 905 nmol/L
Control group 1,188 ± 432 nmol/L

There is a small sample size and a very large standard deviation. The difference in the changes between the 2 groups is not statistically significant. ($p = 0.888$)

2. ELF Anti-NE levels

Mean Anti-NE in ELF at baseline:
Test group 1,086 ± 320 nmol/L
Control group 737 ± 280 nmol/L

Mean Anti-NE in ELF at week 7
Test group 1,635 ± 1,168 nmol/L
Control group 1,516 ± 839 nmol/L

Mean change in Anti-NE in ELF at week 7
Test group 549 ± 1,419 nmol/L
Control group 779 ± 575 nmol/L

The large standard deviation in the test group makes the data uninterpretable.

3. ELF a 1-PI:NE complex levels

Mean a 1-PI:NE in ELF at baseline:
Test group 16 ± 16 nmol/L
Control group 79 ± 33 nmol/L

Mean a 1-PI:NE in ELF at week 7
Test group 129 ± 219 nmol/L
Control group 215 ± 160 nmol/L

Mean change in a 1-PI :NE in ELF at week 7
Test group 114 ± 206 nmol/L
Control group 136 ± 177 nmol/L

The sponsor states that, "These increases in a 1-PI: NE complexes suggest that the a 1-PI provided by the augmentation therapy was functional and that is it was able to inactivate elastase in the lung tissue."
However, the differences are not significant, probably because of the large standard deviation, and, as seen below, no significant changes in NE were demonstrated as a result of treatment..

4. ELF NE levels

Mean NE in ELF at baseline:
Test group 405 ± 640 nmol/L
Control group 149 ± 69 nmol/L

Mean NE in ELF at week 7
Test group 427 ± 849 nmol/L
Control group 109 ± 94 nmol/L

Mean change in NE in ELF at week 7
Test group 21 ± 215 nmol/L
Control group -40 ± 60 nmol/L

Mean ELF NE levels did not change significantly in either the test or control groups.

5. ELF IL-8 levels

Mean IL-8 in ELF at baseline:
Test group 14,316 ± 4,996 ng/mL
Control group 4,111 ± 1,107 ng/mL

Mean IL-8 in ELF at week 7
Test group 4,012 ± 1,547 ng/mL
Control group 5,160 ± 3.676 ng/mL

Mean change in IL-8 in ELF at week 7
Test group -10,304 ± 4,558
Control group 1,048 ± 2,619 ng/mL

The clinical significance, if any, of the large decrease in the test group mean IL-8 level is uncertain. It was noted that the magnitude of the SD was quite variable.

6. ELF neutrophil counts

Mean neutrophil counts in ELF at baseline:
Test group 12.9 ± 17.4 x 10^7/mL
Control group 6.6 ± 4.0 x 10^7/mL

Mean neutrophil counts in ELF at week 7
Test group 6.7 ± 8.2 x 10^7/mL
Control group 5.3 ± 3.7 x 10^7/mL

Mean change in neutrophil counts in ELF at week 7

Test group -6.2 ± 10.9 x 10^7/mL

Control group -1.4 ± 3.5 x 10^7/mL

The change from baseline was not statistically significant in either group nor was the comparison of change between groups.

Table 11: Summary ELF Data

		Test group (n = 5)			Control group (n = 3)			Comparisons between groups	Change Week 1 to Week 7		
		Week 1[a]	Week 7[b]		Week 1[a]	Week 7[b]			Test group	Control group	
Test	Units	Mean ± SD (Range)	Mean ± SD (Range)	p^c	Mean ± SD (Range)	Mean ± SD (Range)	p^b	Week 1 p^d	Mean ± SD (Range)	Mean ± SD (Range)	p^e
α_1-PI	nmol/L	190 ± 108 (94 to 368)	1,294 ± 885 (361 to 2,495)	0.053	452 ± 92 (366 to 550)	1,640 ± 511 (1,056 to 2,006)	0.041	0.013	1,104 ± 905 (267 to 2,350)	1,188 ± 432 (690 to 1,456)	0.888
Anti-NE	nmol/L	1,086 ± 320 (774 to 1,532)	1,635 ± 1,168 (BDL[f] to 3,101)	0.436	737 ± 280 (450 to 1,010)	1,516 ± 839 (566 to 2,156)	0.144	0.172	549 ± 1,419 (-1,532 to 2,238)	779 ± 575 (116 to 1,146)	0.803
α_1-PI:NE	nmol/L	16 ± 15 (1 to 41)	129 ± 219 (5 to 519)	0.312[g]	79 ± 33 (48 to 114)	215 ± 160 (72 to 388)	0.315	0.009	114 ± 206 (-13 to 478)	136 ± 177 (-42 to 313)	0.880
NE	nmol/L	405 ± 640 (69 to 1,548)	427 ± 849 (4 to 1,942)	0.836	149 ± 69 (81 to 219)	109 ± 94 (37 to 215)	0.250[g]	0.424	21 ± 215 (-139 to 393)	-40 ± 61 (-111 to –4)	0.656
IL-8	ng/mL	14,316 ± 4,996 (6,963 to 20,448)	4,012 ± 1,547 (2,212 to 6,268)	0.007	4,111 ± 1,107 (3,125 to 5,309)	5,160 ± 3,676 (2,663 to 9,381)	1.000[g]	0.015	-10,304 ± 4,558 (-14,180 to –2,503)	1,048 ± 2,619 (-465 to 4,072)	0.008
Neutrophils	x 10^7/mL	12.9 ± 17.4 (2.7 to 43.6)	6.7 ± 8.2 (0.1 to 20.0)	0.275	6.6 ± 4.0 (2.8 to 10.8)	5.3 ± 3.7 (1.3 to 8.5)	0.571	0.574	-6.2 ± 10.9 (-23.6 to 6.0)	-1.4 ± 3.5 (-4.8 to 2.2)	0.499

BDL = below detectable limits; SD = standard deviation.

[a] Sample drawn prior to first infusion. Week 1 is considered baseline.

[b] Sample drawn prior to infusion at Week 7, reflecting trough level from Infusion 6.

[c] Week 1 (preinfusion) compared to Week 7 (preinfusion), two-sided t-test.

[d] Week 1 (preinfusion), test group compared to control group, two-sided t-test.

[e] Change from Week 1 (preinfusion) to Week 7 (preinfusion), test group compared to control group, two-sided t-test.

[f] Treated as zero for calculations.

[g] Data were not normally distributed, so signed rank test was performed.

Since no adjustments have been made for multiple comparisons, the tests of significance should be considered suggestive only.

Urinary levels of elastase breakdown products

a. Desmosine
b. Isodesmosine
c. Collagen degradation products

The desmosine:lysylpyridinoline ratios for both groups were nearly constant and similar for both groups.

Other categories evaluated

1. Pulmonary function

PFT's were performed at screening, week 7 and week 24. There was a great deal of variability in the PFT's and one would not expect a significant change in the PFT's over the 23-week period studied.

Table 20: Pulmonary Function Tests

	Screening		Week 7		Week 24			
	Test (n = 13)[a]	Control (n = 13)[a]	Test (n = 13)	Control (n = 13)	Test (n = 13)	Control (n = 13)	Analysis of variance	
Test	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)	Factor	p^b
FEV1 (% predicted)	49.2 ± 17.9 (31 to 86)	45.0 ± 14.0 (30 to 77)	47.2 ± 18.6 (29 to 91)	45.1 ± 14.0 (24 to 77)	48.2 ± 19.9 (28 to 97)	45.5 ± 12.4 (26 to 73)	Group Week	0.64 0.59
FVC (% predicted)	93.5 ± 24.3 (65 to 144)	89.3 ± 12.1 (68 to 109)	91.5 ± 23.9 (59 to 141)	89.8 ± 13.9 73 to 124	93.5 ± 24.1 (63 to 145)	92.0 ± 14.0 (70 to 120)	Group Week	0.74 0.45
FEV1FVC[c] (% predicted)	53.1 ± 15.1 (25 to 87)	51.2 ± 16.9 (31 to 85)	50.7 ± 17.0 (26 to 90)	51.2 ± 17.2 (33 to 85)	51.9 ± 14.9 (27 to 87)	50.5 ± 16.2 (35 to 92)	Group Week	0.88 0.30
DLCO% predicted)	61.9 ± 15.9 (28 to 80)	63.2 ± 15.0 (43 to 104)	62.2 ± 15.5 (29 to 85)	62.8 ± 19.2 (31 to 107)	63.9 ± 16.7 (28 to 93)	62.1 ± 17.0 (41 to 107)	Group Week	1.00 0.95

SD = standard deviation.

[a]Subjects 0501 (test group) and 0301 (control group), who discontinued treatment after six and one infusion(s), respectively, are not included in this table.

[b]Probabilities are based on analysis of variance (*f* statistic); interaction between groups and weeks was not significant.

[c]Subject 0401 (test group) was missing a value at Week 7; therefore, this subject was excluded from the analysis of variance.

Pharmacokinetics

Summary of FDA pharmacology review

1. $t_{1/2}$ of RespitinTM was longer compared to that of Prolastin (the currently licensed a_1-PI preparation); $t_{1/2}$ of RespitinTM = 5.9 +/- 1.2 days; $t_{1/2}$ of Prolastin = 5.1 +/- 0.5 days.
2. Bioequivalence for RespitinTM and Prolastin was not demonstrated as C.I. for $Tmax_{test}/Tmax_{control}$ was 0.40 to 1.23 (<0.80)
3. Differences in other parameters (Tmax, AUC, Cmax, CL, MRT, Vd) between RespitinTM and Prolastin were not statistically significant.

Antibiotics:

14 subjects, 7 from each group required antibiotic treatment throughout the course of the study.

One subject in the test group was on continuous tetracycline throughout the study because of a skin condition.

2 subjects required 3 courses of antibiotics, 2 subjects required 2 courses of antibiotics for a total of 20 courses of antibiotics.

Other medications for asthma or COPD:

In the test group 2 subjects received no therapy for asthma-104 and 407.

In the control group, 1 subject received no therapy for asthma.

In the test group 3 subjects did not receive steroid therapy, either local or oral for their asthma.

In the control group, 3 subjects did not receive steroid therapy, either local or oral for their asthma.

In the test group 2 subjects did not receive bronchodilators.

In the control group 3 subjects did not receive bronchodilators

Safety analysis (initial 24 week trial period)
All subjects were treated with the same dosage of test and control drugs, 60mg/kg administered intravenously per week. Twenty-six subjects completed all 23 scheduled weekly infusions. Subject 0301 (control group) withdrew after experiencing a serious adverse event (bilateral lower lobe pulmonary infiltrates) following his BAL at Week 1 (after one infusion of control drug). Subject 0501 (test group) withdrew at Week 7 (after receiving six infusions of test drug) due to the extensive follow-up required of study participants.

		Number of Infusions	Maximum infusion rate (mL/kg/min)	Range of infusion rate (mL/kg/min
"Blinded Phase"	Test	133	0.070 ± 0.013	0.038 to 0.085
	Control	131	0.072 ± 0.011	0.042 to 0.088
Combined Phase	Combined	471	0.070 ± 0.013	0.038 to 0.088

There were 605 infusions during the 24-week portion of the study. 474 of the infusions were of test material and 131 were of the licensed product Prolastin®.

Serious adverse events
Two serious events occurred during the course of the 24-week study phase, both in the control group.
1. Subject 103 was hospitalized after developing pneumonia after an off protocol bronchoscopy which was performed to remove a foreign body.
2. Subject 404 was hospitalized after infusion week 1 due to a severe headache deemed to be secondary to DJD and not product infusions.

Weeks 1 through 10 incidences of adverse events, regardless of causality

	Test	Control
Mild	11	19
Moderate	1	7
Severe	0	2

During Weeks 1 through 10,these AEs were reported in the test group

The following symptom was associated with 3 infusions

Headache

The following symptoms were each associated with one infusion:

Chills and fever (temp to 100.2)
Malaise

Back pain
Dizziness
Pruritus
Rash
Abnormal vision (c/w migrainous visual symptom)

In the combined group of all Respitin™ infusions (all infusions in the test group during Weeks 1 through 23 and all infusions in the control group during Weeks 11 through 23), the frequency of infusions associated with an adverse event, regardless of causality, was 20 of 474 infusions.

The most common symptoms were:

Symptom	Number of infusions	
Headache	5	(1% of infusions)
Dizziness (includes lightheadedness)	3	(0.6% of infusions)
Somnolence	3	(0.6% of infusions)
Rash	2	(0.4% of infusions)

The following occurred with one infusion (0.2%) each:
Abdominal pain, back pain, chest pain, chills and fever, malaise, vasodilatation (facial flushing), vomiting, leg cramps, pharyngitis, rhinitis, pruritus, sweating, and abnormal vision.

Thirty lots of test product were used for the 474 infusions. The number of infusions/lot varied from 1 to 57. Only 2 lots were associated with more than 1 AE. No lots were associated with more than 2 AEs.
Lots 7011A had 2 AE's: sleepiness and headache.
Lot 7002A had 2 AEs: stomach pain and headache

Laboratory Abnormalities
Hematology values were similar between the test and control groups. Mild hematological abnormalities were frequent but showed no consistent pattern of either elevation or depression of these values.
Thrombocytopenia was the most frequent hematological abnormality seen and was present in some subjects at the time of screening. The lowest platelet count of 78,000 was seen in subject 304 in the control group. This subject also had low hemoglobin.
Chemistry abnormalities in subjects while receiving test article were mild and all were less than 3.7 x ULN. Subject 104 with the diagnosis of Gilbert's Syndrome had persistently elevated transaminases to 2-3x ULN. Subject 402 had an isolated serum creatinine of 1.7 at week 13 when all other values were within the normal range. Subject 408 had a creatinine value of 1.3 at week 13 and 1.2 at week 22 with all other values being normal.

Viral safety:
All subjects were both HCV and HIV negative at entry into the study and none had converted at week 23. None of the subjects became HBsAg positive during the study although five of 13 evaluable subjects in the test group and eight of 13 subjects in the control group, were not vaccinated against hepatitis B. None of the 21 subjects who were seronegative to HAV (12 in the test group and 9 in the control group) seroconverted during the study.

One subject in the control group converted to Parvovirus positive at week 11 prior to receiving test product.

Following the CBER medical review of the initial 24-week portion of the study, the sponsor was sent a complete review letter on 8 March 2002. Selected clinical issues from that letter, highlights of the sponsor's responses, and a key aspects of the CBER analysis of the sponsor's responses are summarized below:

1. *Subject 104 had persistently low serum levels of alpha-1-proteinase inhibitor (A1-PI) as determined antigenically and functionally (with the anti-neutrophil elastase capacity assay) during the 24 week study period. The levels of both antigenic and functional A1-PI were below 11µM on 12 occasions. There were additional subjects who had serum levels of either antigenic or functional A1-PI below 11µM on more than one occasion. These … may have been due to subject variability and/or test product lot-to-lot variability. The sponsor was asked to comment.*

This subject's A1PI levels hovered around the 11 micromolar cutoff. While the first 6 infusions of this subject were with the same lot, and each infusion was 7 days apart, the variability in trough levels during this period, which included values < 11 microM, was greater than during the remainder of the 24 week observation period. Therefore the variability cannot be explained by lot-to-lot variability and is consistent with assay variability plus biological intra-subject variability.

2. *Protocol ATC 97-01 requires that endothelial lining fluid (ELF) from all BAL samples meeting certain pre-specified criteria be analyzed… FDA requested the sponsor to calculate confidence intervals for the differences between ELF data for week 1 and week 7 for each of the six measured parameters in the paired samples. These calculations were performed on both the original data and the log transformed data. In addition, this should be done for the population with and without the "outlier" subject, subject 105.*

The sponsor presented the requested confidence intervals on original and log-transformed ELF data in Table 3.1 of the submission (attached to original review of complete review of complete response to complete review letter).

3. *The sponsor was asked to submit all data collected between week 24 and two years as described in Protocol Table 2.*

The sponsor has submitted a supplemental clinical report of study ATC 97-01 covering the extension phase from weeks 24-96 dated 10 Feb 2002.

Summary: of Safety Update:

Dates: The first subject entered 19 Feb 1997 and the last terminated 10 Dec 1999. Note that the study was terminated early due to a shortage of Respitin due ----------, and Bayer's Prolastin was then substituted for the ATC test article.

Therapy: Subjects received ATC AIPI IV (Respitin) 60 mg/kg weekly through week 96. Smoking in the 6 months prior to entry was prohibited. Lots used during the extended treatment phase numbered 49. Note: because the supply of Respitin was not adequate, there were times when subjects received Prolastin in the same dose schedule in lieu of ATC Respitin. Sixteen lots of Prolastin were used for this purpose.

Safety assessments: AEs, hepatic, renal, hematologic function at weeks 36, 48, 72, and 96, viral serology, and vital signs.

Surrogate efficacy assessments during weeks 24-96: Serum AAT levels, anti-NE capacity, PFTs, urine elastin degradation products

Sponsor's conclusions from extension phase of study ATC 97-01:

- Serum levels of A1PI and anti-NE capacity (ANEC) were essentially unchanged from the initial 24 week period of the study.
- Rates of antibiotic usage and respiratory infections were little changed from baseline.
- Pulmonary Function Tests (PFTs), urine elastin breakdown products, and radiographic analyses were insensitive measures of efficacy, showing little change over time.
- Of 2226 Respitin ITT infusions over the whole trial period, 188 (8.4%) were associated with AEs, of which 19 (0.9%) signs or symptoms were considered at least possibly related to the product.
- Serious Adverse Events (SAEs) were reported, including one case of pericarditis, none considered by the investigator to be product-related.
- Mild elevations in ALT and AST were common and occasional mild bilirubin elevations were seen. The sponsor found no cause for these, other than one case of Gilbert's syndrome. The sponsor speculated that AAT-deficiency liver disease may have been involved in some affected subjects.
- Vital sign changes were not considered product-related.

- One control subject seroconverted for parvovirus B19 (IaG and IgM at week 11. Subjects were screened for parvovirus B19 at baseline and at week 11. A total of 20 subjects were positive for parvovirus B19 at baseline (77%). No other seroconversions to hepatitis A, B, or C or to HIV were detected. A total of 13 subjects were enrolled without vaccination against HBV.
- No subject developed antibodies to A1PI.
- The safety profile of ATC Respitin is similar to that of Prolastin. AEs are of low incidence and generally only mild or moderate in intensity.

Twenty-six subjects completed the 26 week initial study period and are included in the extension study report. Ten subjects (5 from each original randomization group) withdrew during the extension phase, leaving 16 subjects who completed 96 weeks of treatment. Nine of the 10 were withdrawn by the sponsor due to lack of availability of Clinical Trial Material (CTM). These withdrawals occurred after 19.9 to 23.5 months into the study. Subject 0105 withdrew voluntarily 7.8 months after the initial infusion. Prior to withdrawing from the study, 3 study drug infusions were withheld due to bloating. The investigator later determined that the bloating was due to end-stage pulmonary disease "and an erratic pattern of use of prescribed medications." The subject then withdrew for "personal reasons" after this assessment. Five subjects were treated (with Respitin and/or Prolastin) longer than 96 weeks, as provided by the protocol (subjects 0302, 0303, 0401, 0402, 0403, and 0404).

Protocol violations: 17 infusions were missed. "No subject missed more than three consecutive infusions. A total of 26 infusions in 5 subjects were slightly under or overdosed due to using the wrong body weight, or because of the unavailability of sufficient CTM. Subject 0104 received 50% of the protocol dose for 4 weekly infusions due to product shortage. This under dosage was approved by the IRB.

Some subjects received product that had been reconstituted in a local pharmacy rather than the subject's home and thus exceeded the 3 hour time limit. PFTs were delayed if a respiratory infection were present.

Respitin and Prolastin infusions post week 24 were given at very similar infusion rates and durations (Table 19, attached to Medical review). The rate of infusion was a mean of 54 +/- SD 15 min for ATC A1PI (Respitin).

Comments on efficacy measures during extension phase:

Serum AAT levels and ANEC were measured at months 9, 12, 18, and 24. See table 8 (attached to review). Levels were maintained with some variation, but drop somewhat from week 72 to week 96 to a level of 14.76 micromol/L for AAT and to 8.64 mi cromol/L for ANEC.

The sponsor asserted that the observed mild drop in ANEC at end of study was likely due to delays in blood sampling/visit date due in part to unavailability of product. A somewhat larger drop was seen at week 96 for AAT levels

Urine desmosine and isodesmosine were anticipated to possibly fall with AAT augmentation treatment. No consistent trend over time was observed for urine desmosine:creatinine ratio (Table 9, attached to review) at the U. of Texas lab. An unplanned analysis was also conducted at BU which suggested a slight rise over time in urine desmosine and desmosine:creatinine ratio.
Antibiotic Courses by subject are presented for weeks 2-24 and weeks 25-96 in table 17 (attached to Medical review). No information is provided as to the proportion of these that were prescribed for lower respiratory infections.

Comments on safety measures during study extension phase:

CXR was repeated at weeks 7, 48, and 96. CT was repeated at weeks 48 and 96. Baseline abnormalities in addition to emphysema were comparatively frequent and included bronchiectasis, fibrosis, and nodules. Two subjects had infiltrates (0306 and 0309).

PFT values and changes over time are given in Tables 13 and 15. Mean DLCO (pre-bronchodilator) actually rose from 61.9 at week 0 to 64.6 at week 96 over the course of the trial, but the variation was considerable (SDs of 15.1 and 17.9, respectively).

Mean FEV_1 fell from 42.54 +/- SD 14.84 to 40.40 +/- 17.55 % of predicted at week 96. A similar change over time was seen in the post-bronchodilator values.

Vital Capacity dropped from 93.1 to 88.54 % of predicted, but with large SDs.

ABGs showed a mean drop in PaO_2 from 68.85 +/- SD 10.11 at week 0 to 63.44 +/- 14.18 at week 29 (n = 23), suggesting some deterioration over time in gas exchange despite therapy with ATC Respitin and Prolastin.

$PaCO_2$ rose from a mean of 38.04 (max 81) to 40.61 (max 80).

The sponsor re-coded all COSTART terms that appeared compatible with URIs as pharyngitis.

The overall summary of AE totals *throughout* the study is given in Table 23 (attached). Twenty-six subjects reported AEs, of which 8 reported AE(s) at least possibly related to study drug. Of the 189 AEs reported, 141 (75%) were rated

mild, 27 (14%) moderate, and 5 (2.65%) were rated severe. Sixteen were rated "unknown" in intensity.

Nineteen AEs were regarded at least possibly related to study drug, including 16 mild and 3 moderate. Those rated mild were:

Headache (3 AEs in 2 subjects)
Chest pain (1)
Chills & fever (1)
Vasodilatation (1)
Paresthesias (2 AEs in 2 subjects)
Somnolence (3 episodes in 1 subject)
Dizziness (1)
Increased cough (2 AEs in 1 subject)
Dyspnea (2 AEs in 1 subject)
Rash (1)
Pruritis (1)
Abnormal vision (1)

Those were regarded at least possibly related to study drug and rated moderate in intensity were:

Increased cough
Dyspnea
Chest pain.

The moderate intensity AEs were all reported in the same subject (#0106).

No unusual or worrisome pattern was evident among the non-serious AEs reported.

Five subjects reported 8 AEs during the extension phase, of which none was regarded as related to the study drug. These are listed in Table 27 (attached to Medical review). Two subjects had reported SAEs during the original 26 week portion of the trial. Subject 0302 was hospitalized for 2 days for chest pains attributed to COPD. Subject 0306 was hospitalized 3 times at weeks 59, 85, and 93 for respiratory infections. Subject 0401 was hospitalized at week 68 for pericarditis that developed 5 days after his most recent infusion. His signs and symptoms lasted 49 hours and were considered due to his previously existing medical condition. He had also had pericarditis in 1990.

AEs by Intent-to-treat (ITT) are displayed by body system in Table 24 of the CR to FDA's CR letter. The sponsor also undertook an ad hoc "per protocol" (misnomer) analysis of AEs by censoring AEs reported after the subject first received during the extension phase the first infusion of Prolastin (due to shortage of ATC A1PI). The number or infusions in the "per protocol" AE analysis divided by the number in the

ITT AE analysis is 1127/1799. From this one can gain an impression of the extent of Prolastin use during the extension phase.

Respiratory infections numbered 28 among 19 subjects during weeks 2-24 and 66 among 24 subjects during weeks 25-96.

The use of specific categories of concomitant medications tended to decrease slightly over the trial course.

Laboratory Data:

Mean hematology values were stable over time. Mean AST rose from 36.8 to 40.4 with wide AD. Mean AST rose from 30.9 at week 26 "baseline" to 32.1 at week 96. Mean alk phos rose from 171.6 to 182.2 at week 96. Serum mean creatinine was stable over time, as was BUN. Mean total bilirubin was stable over time. One subject had elevated eosinophil counts at various time points. No terribly remarkable treatment-emergent hematology abnormalities were noted among those with abnormalities flagged by the sponsor.

Subject 0101 had ALT AND AST elevations at baseline (1034 and 66, respectively) and on study at all timepoints for unknown reasons. Subject 0102 had a single rise in alk phos to 277 U at week 72. Subject 0104 had ALT elevations of 105, 70, 64, and 48 at weeks 36, 48, 72, and 96. AST was elevated at 82, 56, 52, and 41 units at the same respective time points, but also had elevations at screening (ALT 61 and AST 89). Other subjects had milder AST and/or ALT elevations that were not noted at baseline, and were not of clinical significance, but the vast majority of subjects with abnormal aminotransferases had abnormalities also at baseline. As stated by the sponsor, some of these AST and ALT elevations could be due to previously unrecognized AAT-deficiency-related liver disease.

Vital Signs

Some vital changes during infusion were noted in Table 40 but were not judged to be of particular clinical significance.

4. *At FDA's request, the sponsor submitted chest x-ray reports and CT scan reports for all subjects in the study.*

No mention of emphysema was present in 5 of the CT reports, 4 of which were from a single study site. However, the protocol only required the CT exam be *compatible with* emphysema should the subject not meet the inclusion criteria for pulmonary function.

REVIEW OF SPONSOR'S 18 Oct 2002 amendment to the BLA submitted in response to CBER's information request relayed to the sponsor during the teleconference of 20 Sept 2002:

> During the September telecon, CBER requested the sponsor undertake a 100% audit of the primary endpoint data relating to antigenic A1PI trough blood levels between weeks 8 and 11 to account for and provide 2 supplementary analyses for subjects who had repeated lab analysis of A1PI levels at the University of Florida's central contract lab. The requested analyses were: to (1) recalculate the primary endpoint using only the first value obtained in any samples analyzed multiple times and (2) recalculate the endpoint using the average of all test values obtained for each sample. ATC undertook a 3rd analysis, which used the results of the repeat value with the last test date.
>
> A total of 130 reported antigenic A1PI values were audited (1 test/week x 5 weeks x 26 subjects). Of these, multiple test results were available for 40 samples (31%). All of those had duplicate values, save for 3 that had 3 test results available per sample. Of the multiple test result values, 23/40 reported the first value and 17/40 reported the 2nd value. Two transcription errors lead to 2 of the latter reports. Reasons recollected by the University of Florida central laboratory staff for the repeat testing were provided by the sponsor.
>
> The results of the re-analyses are shown in Table One (attached to Medical review of CR to CR letter). The supplementary analyses, like the original primary endpoint analysis, reject the null hypothesis and support the biochemical surrogate efficacy of the product.
>
> The sponsor also revised its response to question #2 from the original CR letter, providing correlation coefficients between antigenic and functional A1PI for blood samples from weeks 4-11 separately for both treatment groups. As can be seen in Table 4 (attached to Medical reviiew), no meaningful or statistically significant difference was seen between the correlation coefficients for the ATC product vs. Prolastin. The Pearson correlation coefficients were 0.66 and 0.56 for Prolastin and ATC product, respectively, during weeks 4-11, with overlapping confidence intervals. All subjects' data from weeeks 14 –24) (ATC product only) yielded a CC of 0.66 (95% CI 0.59 to 0.97).

The data in the sponsor's response to the CBER complete review letter were deemed to support the sponsor's conclusions regarding the efficacy and safety of the product and support the conclusion reached in the CBER review of the original study report from the original filed BLA submission regarding the product having a satisfactory benefit:risk profile. Although somewhat supportive, the sponsor's bronchpulmonary lavage data were not considered conclusive. The sponsor has committed to perform a phase IV study to further verify ELF-related endpoints.