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DESIGN AND POWERING OF CYSTIC FIBROSIS CLINICAL TRIALS USING PULMONARY EXACERBATION AS AN EFFICACY ENDPOINT

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Abstract

BACKGROUND—Reduction in pulmonary exacerbations is an important efficacy endpoint for CF clinical studies. Powering exacerbation endpoints requires estimation of the future exacerbation incidence in CF study populations, but rates differ across the population.

METHODS—We have estimated exacerbation rates for Epidemiologic Study of CF subpopulations stratified by age, FEV_1 % predicted, sex, weight-for-age percentile, respiratory signs and symptoms, and history of exacerbation and bacterial culture. Sample sizes required to attain 80% power to detect exacerbation reductions of 20% to 80% in 1:1 randomized studies of 3 to 12 month duration were determined. Exacerbation treatments with “any” antibiotic (new oral quinolone, new inhaled antibiotic, or intravenous (IV) antibiotic) and with IV antibiotics were studied.

RESULTS—At all ages, decreased FEV_1, female sex, exacerbation history, and *Pseudomonas aeruginosa* culture history were associated with increased treatment for exacerbation.

CONCLUSIONS—These data should assist investigators in the design of future CF exacerbation studies.

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Keywords

study design; pulmonary exacerbation; sample size

INTRODUCTION

Cystic fibrosis (CF) is a life-shortening genetic disease characterized by chronic pulmonary bacterial infections, local inflammation, and progressive loss of pulmonary function [1]. As their lung disease progresses, persons with CF experience more frequent episodic increases in respiratory signs and symptoms that require aggressive intervention, commonly termed pulmonary exacerbations [2-6]. Pulmonary exacerbations adversely impact health-related quality of life [7-9] and survival [10-13] and lead to significant resource utilization [14, 15]. Despite the lack of a consensus definition of pulmonary exacerbation, they are clinically meaningful [2, 5] and reduction in exacerbations is an important efficacy endpoint for clinical studies of chronic CF therapies [16-21].

In order to adequately power CF clinical trials employing exacerbation as an efficacy endpoint, investigators must be able to predict the relative risk of exacerbation or median time to exacerbation for untreated subjects in their study population. This task is complicated because the risk that an individual will develop signs and symptoms resulting in exacerbation diagnosis and treatment is not uniform across the CF population. For example, diagnoses of pulmonary exacerbation increase with decreasing pulmonary function [2]. We used data from the Epidemiologic Study of CF [22] to model relative risk of exacerbation and median time to exacerbation for different CF subpopulations. We then estimated the effects of duration of measure and magnitude of proposed treatment effects on sample size requirements for randomized clinical trials using relative risk of pulmonary exacerbation as an efficacy endpoint.

METHODS

Data were obtained from ESCF, a prospective, encounter-based, multicenter, observational study designed to evaluate the natural history of CF patients in North America from 1994 to 2005 [22]. Informed consent was obtained based on decisions by local human subjects review boards. Pulmonary function test results were reported as measured values and converted to percent predicted using reference equations from Wang et al. [23] for females through age 15 and males through age 17, and Hankinson et al. [24] at older ages.

To be included in this analysis, patients had to have had a routine (i.e., stable) clinic encounter (index visit) at least twelve months after enrollment in ESCF during which pulmonary function testing was performed within ± 7 days of the visit and no treatment for exacerbation had been administered within ± 14 days. In addition, the patient had to have had at least one routine clinic encounter within the calendar year prior to the index visit (the baseline period) and to have had *at least* 4 encounters spaced roughly quarterly (± 45 days) within a 13.5 month follow up period after the index visit. Patients could be included more than once in the analysis provided that their subsequent index visits did not occur during the

follow up period from previous analyses. Patients missing their date of ESCF enrollment, date of birth, or sex were excluded from the analysis.

Two definitions of treatment associated with pulmonary exacerbations were employed in analyses: intravenous (IV) treatment (treatment with any IV antibiotic) and "any" treatment (defined as treatment with any IV antibiotic, any new inhaled antibiotic, or any new oral fluoroquinolone) within a −7 to +28 day period around an encounter. The first treatment for pulmonary exacerbation after the index visit during the follow up period was characterized for patient subgroups stratified at their index visit by age in years (< 6, 6-12, 13-17, 18-24, or ≥ 25), FEV_1 % predicted (≥ 100, 70 - < 100, 40- < 70, < 40), sex, weight-for-age percentile (WFA) (< 25^{th}, ≥ 25^{th}), presence of signs and symptoms (daily cough, daily sputum production, clubbing, crackles, or wheeze), number of IV treatments for exacerbation during the baseline period (0, 1, 2, ≥ 3), and presence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, or *Haemophilus influenzae* on respiratory tract culture during the baseline period (any positive, no positive). *P. aeruginosa* culture history during the baseline year was further stratified by modified Leeds criteria [25] as either "chronic" infection (2 or more cultures and > 50% of cultures positive for *P. aeruginosa*), "intermittent" infection (2 or more cultures and ≤ 50% positive), or "indeterminate" infection (one positive culture). Patients with no record of IV antibiotic treatment for an exacerbation during the baseline period were considered to have had zero exacerbations, and bacterial culture results obtained at the index visit were used for patients lacking culture results during the baseline period.

Analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC). Median times to treatment for exacerbation during the follow up period were determined for all patient subgroups using Kaplan-Meier estimates generated from the SAS LIFETEST procedure. We also determined proportions of patients treated at least once for exacerbations at 3, 6, 9, and 12 months after the index visit. We used this information to calculate the number of subjects per arm required in 1:1 randomized controlled studies to attain 80% power for a variety of treatment effect sizes, study durations, and patient subgroups based on a log-rank test using the SAS POWER procedure assuming a two-sided alpha of 0.05. Reductions of 20%, 30%, 40%, 50%, 60%, 70% and 80% in the proportion of subjects treated for pulmonary exacerbation were evaluated for studies of 3, 6, 9, and 12 month durations using both exacerbation treatment definitions. Sample sizes were calculated for patient subgroups by age, FEV_1, sex, WFA, signs and symptoms, previous exacerbation history, and bacterial culture status.

RESULTS

A total of 39,326 unique analysis periods were captured among 16,082 eligible ESCF patients, with 10,018 patients contributing at least twice to analyses. Distributions of patients by age, pulmonary function, and other variables are provided in Table 1. Due to inclusion criteria, none of the 9,653 patients under 6 years of age were less than 1 year of age at their index visit; the group had a median age of 3.69 years.

During the follow up period, patients were much more likely to be treated with “any” antibiotic (including oral fluoroquinolones and inhaled antibiotics) than to be treated with IV antibiotics for exacerbation. The median time to receive “any” treatment for all patients was 294 days, with 55.0% having been treated at least once during the follow up period. In contrast, only 34.1% of patients had been treated at least once with IV antibiotics during the same period.

Patient stratification identified subgroups at greater risk for exacerbation treatment during the follow up period. Table 2 shows median times to “any” antibiotic treatment for different subgroups (data not shown for IV treatment), and Table 3 shows the percentages of patients treated with “any” and with IV antibiotics during the follow up period. Likelihood of treatment was strongly influenced by FEV_1 as measured at the index visit. Patients < 6 years of age and patients 6-12 and 13-17 years of age with $FEV_1 \geq 100\%$ predicted had estimated median times to “any” treatment > 365 days: only 35.3%, 36.5%, 46.1%, respectively, were treated at least once during the one-year follow up period (Tables 2 and 3). Median time to IV antibiotic treatment was less than 6 months for patients with $FEV_1 < 40\%$ predicted and about 9 months for patients with FEV_1 between 40 and < 70% predicted; other patients with higher FEV_1 % predicted had median times to IV treatment of more than 12 months. Older patients tended to have lower median times to treatment with “any” antibiotics than younger patients (Table 2), with the exception that patients ≥ 25 years old at their index visit had a slightly longer median time to treatment with any antibiotic (155 days) than patients 18 to 24 years old (143 days).

Females were consistently more likely to receive antibiotic treatment than males irrespective of treatment criteria or subgroup studied (Tables 2 and 3). Overall, patients with lower WFA at their index visit were at a modestly higher risk for treatment, with the greatest differences observed among patients with $FEV_1 < 70\%$ predicted and those < 6 years old. Patients with signs and symptoms of daily cough, daily sputum production, clubbing, crackles, or wheeze at their index visits generally were more often treated with antibiotics than the entire population (“all patients” in Table 3), an exception being patients with wheeze and lower FEV_1.

Strong positive relationships were observed across all lung disease stages between history of exacerbation in the baseline year and antibiotic treatment during the follow up period (Table 3). History of any respiratory culture positive for *P. aeruginosa* in the baseline period increased the probability of treatment for exacerbation during the follow up period among all subgroups. The median time to treatment with “any” antibiotic for patients with a positive *P. aeruginosa* culture was about 6 months, and over two-thirds were treated during the follow up period, compared with less than 40% of patients with no positive *P. aeruginosa* cultures in the prior year (Tables 2 and 3). Similarly, 44.6% of patients with a positive *P. aeruginosa* culture in the prior year were treated with IV antibiotics in the follow up period, compared to 22.5% of patients with no positive cultures during the period. Within the *P. aeruginosa* culture-positive subpopulation, patients identified as having chronic infection in their baseline year generally had shorter median times to treatment with “any” antibiotics than other patients (Table 2), and were uniformly more likely to be treated with IV or “any” antibiotics than were intermittently infected patients (Table 3). Patients with

history of *S. aureus* culture in the baseline period had only modestly lower probability of treatment in the follow up period relative to the entire population (less than a 2% difference). History of *H. influenzae* culture in the baseline period had a more pronounced negative influence, with “any” antibiotic treatment lower than “all patients” by about 10 percentage points and IV antibiotic treatment lower by about 7 percentage points. This effect was most pronounced in children less than 6 years old and older patients with less advanced lung disease (data not shown).

Sample sizes required to attain 80% power to detect a given reduction in treatment for exacerbation in a 1:1 randomized study of all patients varied as a function of antibiotic treatment definition (“any” antibiotics or IV antibiotics) and duration of observation (Figure 1). Because fewer patients had been treated with IV antibiotics than “any” antibiotics at any given time during the follow up, correspondingly more subjects are required in order to adequately power randomized studies using IV treatment than studies using “any” antibiotic treatment as endpoints (Figure 1). Similarly, the increase in the proportion of patients treated for exacerbation as a function of time elapsed from their index visit results in fewer subjects per arm being required to detect a given treatment effect as study observation periods increase from 3 months to 1 year (Figures 1, 2). Studies limited to patient subgroups at greater risk for exacerbation (e.g., with lower FEV_1 % predicted at their index visit, prior history of exacerbation or positive *P. aeruginosa* culture history) require fewer subjects per arm to detect a given treatment effect than studies in patients without these risk factors (Table 4 and Figure 2). Numbers of subjects stratified by subgroups required per study arm to attain 80% power to detect a 40% reduction in the risk of treatment (i.e., hazard ratio = 0.6) with “any” antibiotics and IV antibiotics for exacerbation in a 1:1 randomized 6 month study are provided in Table 4.

DISCUSSION

There is little question that chronic therapies capable of reducing the incidence of CF exacerbations have the potential to reduce health care costs [14, 15], improve patient quality of life [7-9], spare loss of lung function [26], and possibly improve survival [10-13]. However, the use of change in risk of pulmonary exacerbation as an efficacy endpoint for randomized CF trials is challenging. For example, powering of trials employing risk of exacerbation as an endpoint requires knowledge of the underlying risk of exacerbation in the intended study population, but risk of exacerbation is not uniform across the CF population [2].

In practice, many clinical trials have employed physician intervention in their definition of an exacerbation. We have analyzed data collected over 10 years from a large set of CF patients in ESCF to characterize how patient characteristics affect the probability of treatment with antipseudomonal antibiotics for exacerbation and how they affect the corresponding sample size requirements for studies using exacerbation treatment as an efficacy endpoint. We have reported sample sizes required to attain 80% power to detect a 40% reduction in treated exacerbations over a 6 month observation period (Table 4). A treatment benefit of this magnitude (i.e., hazard ratio = 0.6) is consistent with reductions reported in past CF trials of dornase alfa (relative risk = 0.63 for *bid* use, [16]), inhaled

tobramycin (relative risk = 0.64, [17]), chronic azithromycin (relative risk = 0.65, [18]), and inhaled aztreonam (relative risk = 0.55, [21]). The choice of a 6 month observation period was a pragmatic one, in that studies of shorter duration require substantially more subjects to attain adequate statistical power (Figure 1).

Although our data are useful for estimating the likelihood of different subgroups being treated for exacerbation over time, the absolute sample sizes reported in Table 4 are dependent upon several conditions that may not be met in future clinical trials. We have reported results using two indirect measures of pulmonary exacerbation: treatment with "any" antibiotics (defined as new treatment with oral quinolones or inhaled antibiotics or treatment with IV antibiotics) and treatment with IV antibiotics. These measures have been incorporated into exacerbation definitions in the past [16-18, 27], but it should be noted that these treatments tend to be administered in the belief that exacerbation symptoms are caused by *P. aeruginosa.* In this context, our observation that negative, intermittent, or chronic *P. aeruginosa* culture histories in the baseline period are associated with different probabilities of treatment with antipseudomonal antibiotics for exacerbation (Table 3) should not be surprising. The extent to which different culture histories actually affect presentation of signs and symptoms of exacerbation or simply increase the probability of being treated with antipseudomonal antibiotics during exacerbation is not clear. Importantly, the proportion of patients with a history of positive *P. aeruginosa* culture increases with age (Table 1). Clinicians may be less suspicious of *P. aeruginosa* in younger patients in the absence of definitive culture data, in which case using antipseudomonal antibiotic treatment as a measure would likely underestimate exacerbation rates. Use of an exacerbation definition requiring the presence of a constellation of specific clinical signs and symptoms in addition to specific interventions [16] would presumably reduce the overall event rate, thereby increasing sample size estimates. In contrast, a definition consisting solely of presentation of signs and symptoms and for which intervention is not a requirement [28] would likely increase observed exacerbation rates and correspondingly reduce required sample sizes. The use of patient diaries and patient-reported outcome measures [29, 30] are attractive approaches to avoiding the complication of defining exacerbations based on specific clinical interventions. These approaches are likely to increase event rates and thus reduce required sample sizes for clinical trials.

Observed exacerbation rates may be affected not only by the exacerbation definition, but also by the frequency of encounter. Currently, identification of exacerbation occurs at clinic encounters, so an increased encounter frequency may increase the frequency of exacerbations. To be included in the analysis, patients were required to have at least 4 routine clinic encounters during a year of observation, an encounter frequency consistent with current CF practice guidelines [4]. However, controlled clinical trials are often designed with more frequent (e.g., monthly) study visits, and thus observed rates of exacerbation might be higher and required sample sizes correspondingly lower than our predictions based on quarterly encounter data. For example, 52.0% of placebo subjects were treated with IV antibiotics during the 6 month inhaled tobramycin studies, which included at least 8 clinic encounters after treatment initiation [17]. We analyzed 6,098 ESCF patients employing similar inclusion criteria (≥ 6 years old, FEV_1 between 25 and 75% predicted,

and chronic *P. aeruginosa* culture status in the prior year), but our requirement of only 4 quarterly clinic encounters in the follow up period resulted in only 46.1% of these patients treated with IV antibiotics for exacerbation in the 6 months following the index visit. This modest difference in event rates may result in part from differences in encounter frequency.

Even with these caveats, our analyses should be of value to clinical investigators using exacerbation as an efficacy endpoint in CF clinical trials. Despite consistent incremental improvement in the overall health of the CF population [27,31], rates at which patients are treated with antibiotics for pulmonary exacerbations have been remarkably constant over the past two decades [31], suggesting that registry data from the recent past can be useful in predicting future treatment rates. Our data indicate how inclusion/exclusion criteria might be adjusted to select subjects at greater risk for exacerbation (e.g., subjects that are older, have more advanced lung disease, or have a recent history of exacerbation). Conversely, our data suggest that detecting an impact on exacerbation rate in some subpopulations (e.g., subjects with early lung disease) may prove problematic due to sample size requirements.

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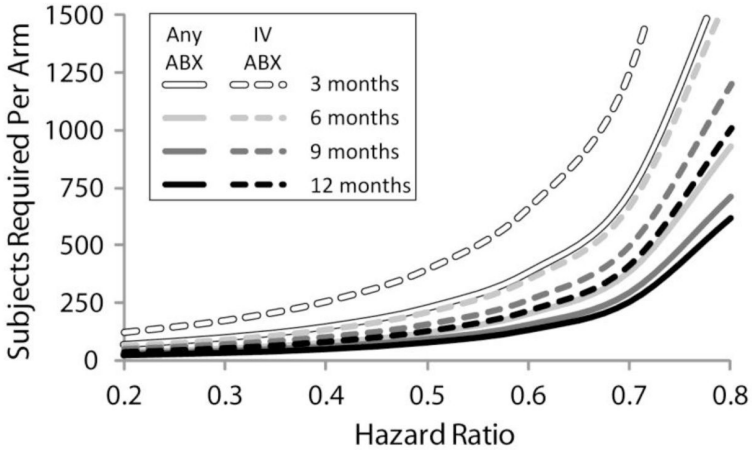

Figure 1. Effects of Treatment Definition and Duration of Observation on Sample Sizes Required to Detect a Given Treatment Effect in a Randomized Controlled Study

Sample sizes per arm required to assure 80% power to detect reductions in exacerbation treatment (as hazard ratios) in 1:1 randomized studies of 3 month (clear lines), 6 month (light gray lines), 9 month (dark gray lines), or 12 month (black lines) durations. Results for exacerbation treatment defined as administration of “any” antibiotics are shown as solid lines and those for treatment defined as administration of IV antibiotics are shown as dashed lines.

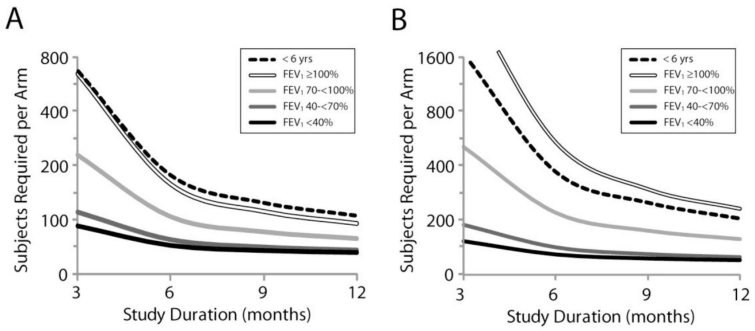

Figure 2. Sample Sizes Required per Study Arm to Retain 80% Power to Detect a 40% Reduction in Risk of Treatment for Exacerbation as a Function of Lung Disease Stage and Study Duration

Panel A: Sample sizes required to detect a reduction in treatment with “any” antibiotics. Panel B: Sample sizes required to detect a reduction in treatment with IV antibiotics. Note that the scale of the vertical axis of panel B is twice the magnitude of that of panel A.

Table 1

Numbers of Patients Contributing to Subgroup Analyses

		FEV_1 Range (% predicted)				
	All	**Age < 6 yrs**	**≥ 100**	**70 to <100**	**40 to <70**	**<40**
All patients	39,326	9,653	5,573	12,752	7,991	3,357
Age Group						
6-12 yrs	13,398	-	4,038	6,926	2,117	317
13-17 yrs	7,698	-	1,293	3,686	2,171	548
18-24 yrs	4,280	-	180	1,364	1,823	913
≥ 25 yrs	4,297	-	62	776	1,880	1,579
Sex, Male	19,930	4,827	2,998	6,497	3,761	1,847
WFA Percentile[a]						
<25th	18,228	3,911	1,791	5,469	4,643	2,414
≥25th	20,988	5,711	3,772	7,255	3,320	930
Signs and Symptoms[a]						
Daily Cough	18,016	2,460	1,683	5,605	5,457	2,811
Daily Sputum	11,087	640	678	3,094	4,156	2,519
Clubbing	20,190	2,139	2,356	6,935	5,880	2,880
Crackles	6,739	392	221	1,338	2,619	2,169
Wheeze	1,778	288	148	483	500	359
Pulmonary Exacerbation History[b]						
None	24,777	7,149	4,566	8,793	3,395	874
One	8,438	1,700	757	2,703	2,335	943
Two	3,384	504	167	816	1,163	734
Three or more	2,727	300	83	440	1,098	806
P. aeruginosa Culture History[c]						
All Negative	15,572	5,761	2,846	4,885	1,647	433
Any Positive	20,269	2,732	2,295	6,749	5,765	2,728
Indeterminate[d]	4,818	685	607	1,797	1,216	513
Intermittent[e]	4,155	1311	626	1,303	684	231
Chronic[f]	11,296	736	1,062	3,649	3,865	1,984

[a] As recorded at the index visit

[b] Number of pulmonary exacerbations treated with IV antibiotics in the 12 months prior to the index visit

[c] Recorded in the 12 months prior to the index visit

[d] Only one culture result reported

[e] ≤50% of cultures positive

$f_{>50\% \text{ of cultures positive}}$

Table 2

Median Time (Days) to Treatment during the Follow Up Period with “Any” Antibiotics for a Pulmonary Exacerbation by Patient Subgroup.

			FEV_1 Range (% predicted)			
	All	**|Age <6 yrs|**	**≥ 100**	**70 to <100**	**40 to <70**	**<40**
All patients	294	(>365)[a]	(>365)	299	147	112
Age Group						
6-12 yrs	364	-	(>365)	365	179	98
13-17 yrs	202	-	(>365)	258	133	96
18-24 yrs	143	-	312	203	127	98
≥ 25 yrs	155	-	302	252	161	125
Sex						
Male	329	(>365)	(>365)	343	168	120
Female	266	(>365)	(>365)	268	133	98
WFA Percentile[b]						
<25th	238	(>365)	(>365)	299	133	106
≥25th	357	(>365)	(>365)	299	168	121
Signs and Symptoms[b]						
Daily Cough	189	(>365)	364	224	133	107
Daily Sputum	154	317	280	210	128	108
Clubbing	203	(>365)	(>365)	266	135	110
Crackles	133	273	(>365)	203	121	103
Wheeze	218	(>365)	(>365)	308	136	126
Pulmonary Exacerbation History[c]						
None	398	(>365)	(>365)	(>365)	231	189
One	193	(>365)	280	193	147	124
Two	119	259	168	121	98	102
Three or more	77	168	134	84	69	65
P. aeruginosa Culture History[d]						
All Negative	(>365)	(>365)	(>365)	(>365)	197	139
Any Positive	187	(>365)	316	216	131	105
Indeterminate[e]	222	(>365)	308	252	175	133
Intermittent[f]	282	(>365)	(>365)	271	159	91
Chronic[g]	147	268	276	189	119	98

[a] When time >365 days, less than half of subjects were treated with “any” antibiotics during the follow up period

[b] As recorded at the index visit

[c] Number of pulmonary exacerbations treated with IV antibiotics in the 12 months prior to the index visit

[d] Recorded in the 12 months prior to the index visit

[e] Only one culture result reported

[f] ≤50% of cultures positive

[g] >50% of cultures positive

Table 3

Percentage of Patients Treated with Either "Any" Antibiotics or IV Antibiotics during the Follow Up Period by Patient Subgroup

					FEV_1 Range (% predicted)							
	All Patients		Age < 6 yrs		≥ 100		70 to <100		40 to <70		<40	
	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV
All Patients	55.0	34.1	35.3	18.8	39.5	16.0	55.0	29.2	76.8	57.0	85.7	72.7
Age Group												
6-12 yrs	49.8	27.6	-	-	36.5	14.5	49.2	25.2	71.8	54.1	84.5	72.5
13-17 yrs	65.5	41.0	-	-	46.1	19.9	60.7	32.0	79.4	59.0	89.0	79.8
18-24 yrs	76.0	56.1	-	-	54.7	21.9	65.6	39.5	80.6	61.7	86.4	76.5
≥ 25 yrs	75.8	54.6	-	-	51.6	12.9	60.5	33.6	75.7	53.1	84.3	68.2
Sex												
Male	52.3	31.2	33.3	17.9	37.9	14.4	51.7	25.2	73.6	53.2	84.1	69.2
Female	57.8	37.1	37.3	19.8	41.4	17.7	58.4	33.3	79.6	60.3	87.6	77.0
WFA Percentile[a]												
<25th	60.5	40.9	39.0	23.3	40.6	17.1	55.2	30.1	78.9	59.9	86.8	74.9
≥25th	50.2	28.2	32.7	15.8	39.0	15.4	54.7	28.4	74.0	53.1	82.6	67.1
Signs and Symptoms[a]												
Daily Cough	67.9	46.7	44.8	26.2	49.5	21.5	62.6	36.3	79.8	60.4	86.8	74.2
Daily Sputum	74.8	54.8	52.9	33.3	57.5	25.7	65.9	40.0	80.3	61.9	87.0	74.6
Clubbing	65.5	43.5	43.8	24.0	42.7	16.7	59.5	32.2	79.3	59.7	86.4	74.0
Crackles	78.1	60.9	58.0	41.6	46.0	25.6	67.0	42.7	82.3	64.8	86.7	74.5
Wheeze	61.5	43.2	40.0	27.3	40.2	18.5	53.6	31.7	75.2	54.3	79.3	66.3
Pulmonary Exacerbation History[b]												
None	42.4	19.4	28.9	12.7	34.4	11.1	46.2	19.3	64.0	37.8	72.1	49.3
One	68.9	47.4	48.6	30.3	58.0	32.6	69.3	43.1	80.2	60.1	85.5	71.0
Two	82.8	67.9	61.1	45.3	73.2	48.7	82.1	61.3	89.4	76.4	90.2	81.9
Three or more	92.0	84.4	68.9	55.5	81.4	69.4	93.0	81.9	95.6	89.0	96.2	91.8

	FEV$_1$ Range (% predicted)											
	All Patients		Age < 6 yrs		≥ 100		70 to <100		40 to <70		<40	
	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV
P. aeruginosa Culture History[c]												
All Negative	38.4	22.5	29.5	16.1	29.2	12.8	41.4	22.3	66.4	50.2	77.9	66.0
Any Positive	69.1	44.6	48.4	25.1	53.0	20.2	65.3	35.0	80.8	60.5	87.8	75.1
Indeterminate[d]	63.9	36.3	45.2	22.9	53.5	20.2	61.7	31.3	74.8	50.0	82.8	64
Intermittent[e]	56.5	32.8	44.6	21.7	44.7	17.9	58.2	38.9	76.3	55.7	86.9	77.3
Chronic[f]	75.9	52.5	58.3	33.3	57.6	21.6	69.6	50.0	83.5	64.6	89.1	77.7

[a] As recorded at the index visit

[b] Number of pulmonary exacerbations treated with IV antibiotics in the 12 months prior to the index visit

[c] Recorded in the 12 months prior to the index visit

[d] Only one culture result reported

[e] ≤50% of cultures positive

[f] >50% of cultures positive

Table 4

Subjects Required per Arm to Detect a 0.6 Hazard Ratio in a 6-Month Controlled Study using Either Treatment with "Any" or IV Antibiotics for Exacerbation as an Endpoint

					FEV_1 Range (% predicted)							
	All Patients		Age < 6 yrs		≥ 100		70 to <100		40 to <70		<40	
	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV
All Patients	202	355	360	745	332	959	212	450	129	195	105	138
Age Group												
6-12 yrs	239	473	-	-	377	1,031	248	556	143	213	103	139
13-17 yrs	161	288	-	-	261	851	188	401	121	183	95	121
18-24 yrs	127	191	-	-	214	630	157	288	119	175	102	127
≥ 25 yrs	134	204	-	-	197	686	193	389	136	216	112	152
Sex												
Male	217	398	374	754	348	1,101	234	535	139	217	111	152
Female	188	320	347	736	315	833	193	386	121	179	99	124
WFA Percentile[a]												
<25th	175	283	315	572	317	868	211	429	123	183	103	131
≥25th	231	455	399	939	339	1010	214	469	138	214	113	159
Signs and Symptoms[a]												
Daily Cough	151	241	260	480	242	666	175	336	121	180	103	134
Daily Sputum	132	198	206	352	207	514	164	298	119	174	103	132
Clubbing	160	263	272	528	305	887	192	392	123	185	103	134
Crackles	123	177	192	279	273	615	163	299	114	168	102	132
Wheeze	165	264	315	557	324	912	197	376	126	190	116	163
Pulmonary Exacerbation History[b]												
None	305	778	471	1258	406	1529	282	807	185	370	152	267
One	155	260	251	436	204	439	155	294	126	200	111	154
Two	109	150	181	268	133	252	113	173	94	124	96	120

	All Patients		Age < 6 yrs		FEV$_1$ Range (% predicted) ≥ 100		70 to <100		40 to <70		<40	
	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV	"Any"	IV
Three or more	86	103	135	188	117	168	88	111	81	96	78	87
P. aeruginosa Culture History[c]												
All negative	327	608	458	901	496	1321	302	620	162	241	127	166
Any positive	150	257	243	535	229	708	170	362	120	179	101	131
Indeterminate[d]	176	358	271	679	240	740	190	482	140	244	120	170
Intermittent[e]	198	374	273	643	290	825	197	418	131	199	99	121
Chronic[f]	130	207	187	355	199	639	154	309	112	162	97	125

[a] As recorded at the index visit

[b] Number of pulmonary exacerbations treated with IV antibiotics in the 12 months prior to the index visit

[c] Recorded in the 12 months prior to the index visit

[d] Only one culture result reported

[e] ≤50% of cultures positive

[f] >50% of cultures positive