Ciprofloxacin DPI in non-cystic fibrosis bronchiectasis: a phase II randomised study

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Abstract

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This phase II, randomised, double-blind, multicentre study (NCT00930982) investigated the safety and efficacy of ciprofloxacin dry powder for inhalation (DPI) in patients with non-cystic fibrosis bronchiectasis.

Adults who were culture positive for pre-defined potential respiratory pathogens (including *Pseudomonas aeruginosa* and *Haemophilus influenzae*) were randomised to ciprofloxacin DPI 32.5 mg or placebo administered twice daily for 28 days (with 56 days' follow-up). Bacterial density in sputum (primary endpoint), pulmonary function tests, health-related quality of life and safety were monitored throughout the study.

Sixty subjects received ciprofloxacin DPI 32.5 mg and 64 received placebo. Subjects on ciprofloxacin DPI had a significant reduction (p<0.001) in sputum total bacterial load at end of treatment (–3.62 $\log_{10}$ [colony-forming units; CFU]/g [range –9.78 to 5.02]) compared with placebo (–0.27 $\log_{10}$ CFU/g [range –7.96 to 5.25]); the counts increased thereafter. In the ciprofloxacin DPI group, 35% (14/40) of subjects reported pathogen eradication at end of treatment, versus 8% (4/49) in the placebo group (p=0.001). No abnormal safety results were reported and rates of bronchospasm were low.

Ciprofloxacin DPI 32.5 mg twice daily for 28 days was well tolerated and achieved significant reductions in total bacterial load compared with placebo in subjects with non-cystic fibrosis bronchiectasis.

Introduction

Non-cystic fibrosis (CF) bronchiectasis is a chronic and debilitating respiratory disease that severely affects the health-related quality of life (HRQoL) of patients. The disease is characterised by abnormal and irreversible bronchial dilatation and is associated with increased morbidity and mortality attributable to airway obstruction, poor gas transfer and chronic bronchial infection [1–3]. Up to 64% of patients with bronchiectasis are chronically infected with pathogenic bacteria, most commonly *Haemophilus influenzae* and *Pseudomonas aeruginosa* [3]. These infections damage host defences and the respiratory epithelium and can result in a vicious cycle of infection and inflammation with persistent symptoms, frequent acute exacerbations and disease progression [4]. One of the main therapeutic challenges is the clinical management of chronic airways infection because of frequent antibiotic resistance (especially to oral antibacterials), common side-effects of systemically administered antibacterials and intolerance to inhaled antibacterials (bronchospasm). These problems make non-CF bronchiectasis a difficult disease to treat and there is currently no approved antibacterial therapy for long-term treatment [3–6].

Off-label treatments for non-CF bronchiectasis include systemic and nebulised antibacterials, oral and inhaled mucolytics, hyperosmolar agents, bronchodilators and sputum clearance techniques [7, 8]. However, these treatments do not adequately manage the number of exacerbations that patients may experience and, in some cases, their benefits have not been investigated fully. The lack of adequate evidence supporting their use for managing exacerbations of bronchiectasis is noted in current European guidelines [9]. There is a need to develop new therapies that will effectively treat the underlying chronic infection, thereby reducing bronchial suppuration and the number of exacerbations and preventing disease progression.

Ciprofloxacin, a broad-spectrum antibacterial, has proven bactericidal activity against pathogens relevant to non-CF bronchiectasis, including *P. aeruginosa* [10]. Ciprofloxacin has been formulated into a dry powder for inhalation (DPI) using Novartis' PulmoSphere™ technology (Novartis Pharma AG, Basel, Switzerland) for use with the small, portable, breath-actuated T-326 inhaler [11]. Controlling the particle size and density of active drug using PulmoSphere™ technology allows for optimal drug delivery to the central and lower airways. Results from clinical trials conducted in healthy volunteers and patients with CF and chronic obstructive pulmonary disease showed that ciprofloxacin DPI was well tolerated, with pharmacokinetics reflecting efficient lung targeting and low systemic exposure [12–14].

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In addition to measures of respiratory function, techniques to assess health status are increasingly being evaluated and have been validated in patients with non-CF bronchiectasis. These include the St George's Respiratory Questionnaire (SGRQ), a self-completed questionnaire devised to measure HRQoL in individuals with chronic airflow limitation [15, 16]. In addition, the Fatigue Impact Scale has been used to measure the correlation between fatigue and markers of disease severity [17].

The aim of this study was to assess the safety and efficacy of ciprofloxacin DPI treatment for 28 days, with 56 days of follow-up, in individuals with non-CF bronchiectasis by examining changes in bacterial load and other important clinical outcomes, as well as tolerability.

Materials and methods

Study subjects

Adult subjects aged ≥18 years were eligible for inclusion into the study if they had: a proven and documented diagnosis of idiopathic or post-infective non-CF bronchiectasis (documentation of investigations to exclude other aetiologies reviewed) confirmed by high-resolution computerised tomography scan (radiology report reviewed); a history of exacerbations (≥2 courses of systemic antibacterials or ≥1 hospitalisation for intravenous antibacterial treatment for pulmonary exacerbations in the previous 12 months); stable pulmonary status, defined as stable symptoms not requiring a new therapeutic intervention in the preceding 30 days; stable disease for at least 30 days before study entry; and if they were able to produce a pre-treatment sputum sample of ≥5 ml that was culture positive for a pre-defined potential respiratory pathogen (*P. aeruginosa* [mucoid or non-mucoid], *Staphylococcus aureus*, *Streptococcus pneumoniae*, *H. influenzae*, *Moraxella catarrhalis*, Enterobacteriaceae, *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*). Further details are included in the online supplement.

Study exclusion criteria included: active non-tuberculosis mycobacterial infection, recent significant haemoptysis (a volume requiring clinical intervention, within the previous 4 weeks) and the use of nebulised antibacterials as maintenance treatment, or systemic antibacterials for an exacerbation, within the 4 weeks before randomisation. Subjects on long-term antibacterials could stop for 1 month, and then enter the study. To concede to clinical practice, chronic macrolide use was allowed as a stable anti-inflammatory maintenance therapy for bronchiectasis, but only if therapy had been commenced for at least the last 30 days before randomisation.

Subjects who had an exacerbation or another indication requiring administration of an antibiotic were to be discontinued from the study.

The conduct of this study met all local legal and regulatory requirements and was in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation guideline E6: Good Clinical Practice. Written informed consent was provided by all subjects.

Study design

This was a multicentre, randomised, placebo-controlled, double-blind (subjects and study personnel) study (NCT00930982). Enrolled subjects received either ciprofloxacin DPI 32.5 mg (corresponding to 50 mg dry powder) or matching placebo twice daily (bid), dispensed from a T-326 inhaler. Subjects were screened up to 21 days prior to Day 1 and received treatment for 28 days, with follow-up visits at end of treatment (EOT), Days 42, 56 and 84 (fig. 1). Study treatments were administered after standard maintenance therapy.

Pulmonary function tests were conducted on Day 1 before first treatment administration, 30±10 minutes after first treatment administration, on Days 8, 29, 42, 56 and 84 and on premature discontinuation from the study. Spontaneous sputum samples for cultures and susceptibility testing were collected at each study visit before administration of treatment and on premature discontinuation from the study. In addition, subjects collected 24-hour sputum samples on the day before Days 1, 8, 29, 42, 56 and 84.

A patient-reported HRQoL measure, the SGRQ, was completed by subjects on Days 1, 29, 56 and 84 and on premature discontinuation from the study.

The incidence of abnormal findings in physical examinations and laboratory test results and the occurrence of adverse events (AEs) were monitored at each visit from screening to Day 84 or until premature discontinuation from the study. Significant bronchospasm (defined as ≥15% decrease in absolute forced expiratory volume [FEV1]), local irritation and coughing were AEs of special interest because of the inhalational administration of treatment. Vital sign parameters (blood pressure and pulse rate) were measured on Days 1, 8, 29 and 84 and on premature discontinuation from the study.

Interim analysis

A planned interim analysis was conducted after the primary endpoint was reached in approximately 70 subjects, assessed at EOT. The independent data monitoring committee

advised the unaltered continuation of the study. Further details are included in the online supplement.

Study endpoints

The primary efficacy endpoint was to determine the effect of ciprofloxacin DPI on total bacterial density of pre-defined potential respiratory pathogens in sputum, by measuring the reduction in $\log_{10}$ colony-forming units (CFU) per gram of sputum after the 28-day treatment period and comparing the difference between ciprofloxacin DPI and placebo in the modified intent-to-treat population (mITT; defined in the online supplement).

Secondary endpoints included: time to exacerbation; emergence of new potential respiratory pathogens; emergence of resistance among baseline pathogens; changes in inflammatory biomarkers; and change in 24-hour sputum volume and colour from baseline. Changes from baseline in pulmonary function (FEV1 and forced vital capacity [FVC]) and in health status (SGRQ) at Days 29, 56 and 84 were also evaluated, in addition to AEs and results of physical examinations, vital signs and laboratory analyses. Study-defined 'eradication' was failure of bacterial growth from a valid post-baseline sputum sample in subjects with a positive baseline culture (all subjects). Samples were taken at screening, randomisation, Day 8 (during treatment), EOT, and 14, 28 and 56 days after EOT. Samples were also taken at premature discontinuation of the study.

Statistical analyses

Two populations were considered for efficacy analysis: the mITT and per protocol (defined in the online supplement). The primary analysis was performed on both mITT and per-protocol populations and was a comparison of change in total bacterial load at EOT between ciprofloxacin DPI and placebo, using a two-way analysis of covariance method with baseline bacterial load as covariate and factors including treatment group and study centre.

Changes in sputum colour and volume were analysed by colour charts and 24-hour sputum volume was analysed by frequency tables. The principal investigator provided investigators with photographs of mucoid, yellow, green and brown sputum. Changes in FEV1 and FVC were analysed by a two-way analysis of covariance with baseline values as covariates and with factors including treatment group and study centre. Lung function parameters (FEV1 and FVC) as absolute raw values and percentage of predicted were analysed with descriptive statistics.

The safety analysis set (defined in the online supplement) was used for all safety assessments. AEs that occurred after the start of study treatment and up to 7 days after EOT were classed as treatment emergent or worsening of existing AEs. Laboratory variables, vital signs and other safety data were described by summary statistics (defined in the online supplement).

Sample size estimation is described in the online supplement.

Results

Study population

In total, 277 subjects were screened and 124 subjects were randomised to treatment (103 completed treatment and 74 completed the study) at 35 centres in six countries (Australia, Germany, Spain, Sweden, UK and USA) from 29 June 2009 to 17 September 2010. Of the randomised subjects, 60 received ciprofloxacin DPI 32.5 mg bid and 64 received placebo bid (fig. 1). Most subjects who discontinued before randomisation provided an inadequate sputum sample (i.e. a sample from which the pre-defined pathogens could not be cultured). All subjects randomised were included in the safety and mITT populations, and 82 subjects (37 and 45 in the ciprofloxacin DPI and placebo groups, respectively) were included in the per-protocol population. Despite the high number of subjects excluded from the per-protocol population (mainly because EOT cultures were not available due to subjects not producing sputum), the results of the efficacy analysis in both the mITT and per-protocol populations were similar. The mITT data for all endpoints are presented here, as are the per-protocol results for the primary endpoint. The remainder of the per-protocol results are presented in the online supplement.

Demographic and baseline characteristics were similar in both treatment groups (table 1). There were no significant differences between ciprofloxacin DPI and placebo for any of the baseline characteristics. Age, sex and race characteristics were similar to those of patients who were screened but not randomised.

Efficacy

Treatment compliance and duration

Treatment compliance, measured by counting the number of both used/unused capsules and used/unused devices, was high across both treatment groups; compliance of ≥80% was reached in 97% of subjects in the ciprofloxacin DPI group and 94% of subjects in the placebo group. The mean treatment duration was 26 days in both treatment groups.

Primary endpoint

A significantly greater mean reduction in CFU count during treatment and at EOT was observed in the ciprofloxacin DPI group (-3.62 $\log_{10}$ CFU/g, range -9.78 to 5.02) versus the placebo group (-0.27 $\log_{10}$ CFU/g, range -7.96 to 5.25; $p<0.001$; fig. 2A). A non-significant reduction in CFU count in the ciprofloxacin DPI group compared with placebo was observed on Days 42 and 56 before the plots joined again at Day 84.. In the per-protocol analysis, a similar pattern of mean reduction in CFU count during treatment and at EOT was observed in the ciprofloxacin DPI group compared with the placebo group ($p<0.001$; fig. 2B). Mean colony counts of selected pathogens at baseline and at EOT are presented in fig. 3.

Secondary endpoints

Fewer subjects reported at least one exacerbation throughout the study in the ciprofloxacin DPI group (22/60 subjects [36.7%]) than in the placebo group (25/64 subjects [39.1%]; hazard ratio estimate 0.802; 95% confidence interval [CI] 0.443 to 1.454; $p=0.605$). The number of subjects with new onset exacerbations requiring intervention per time period is presented in fig. 4. Of these, 14 subjects in the ciprofloxacin DPI group required intervention with antibacterial therapy, including two subjects who required hospitalisation, compared with 18 subjects in the placebo group who required antibacterial therapy, including five subjects who required hospitalisation (hazard ratio estimate 0.674; 95% CI 0.324 to 1.402; $p=0.338$ [stratified log-rank test, stratification by centre, small centres pooled]). All subjects with an exacerbation requiring antibacterial therapy should have been discontinued as per the study protocol; however, three of these subjects (2 in the ciprofloxacin DPI group and 1 in the placebo group) completed the study. Further information on these three subjects is included in the online supplement. The number of exacerbations requiring antibacterial therapy in the first 42 days (28 days of treatment and 14 days of follow-up; a time period likely to be most influenced by the antibacterial treatment) was seven in the ciprofloxacin DPI group and 12 in the placebo group. The rate of exacerbations requiring intervention in subjects with and without *P. aeruginosa* at baseline was similar in the two groups (23.5% in the ciprofloxacin DPI group and 27.8% in the placebo group versus 23.1% in the ciprofloxacin DPI group and 25.0% in the placebo group, respectively). An overview of exacerbations is presented in the online supplement.

Eradication (negative bacterial culture; only results from valid cultures were considered) was observed in 48% (20/42) of subjects in the ciprofloxacin DPI group compared with 12% (6/51) of those in the placebo group at Day 8 ($p<0.001$), and in 35% (14/40) of subjects in the ciprofloxacin DPI and 8% (4/49) of those in the placebo group at EOT ($p=0.001$; table 2). The emergence of a new potential respiratory pathogen during treatment was less frequent in

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subjects receiving ciprofloxacin DPI than in those in the placebo group (12 and 24 subjects, respectively). The new pathogens isolated post-baseline were similar in frequency to those isolated at baseline (table 1), except for *S. maltophilia*, which was isolated in five subjects at baseline (2 on ciprofloxacin DPI and 3 on placebo) compared with 17 subjects post-baseline (10 on ciprofloxacin DPI and 7 on placebo).

The total sputum volume recovered at EOT was less than that at baseline for both groups; mean percentage change from baseline was –17.7% and –9.6% for the ciprofloxacin DPI and placebo groups, respectively. More subjects had clear sputum colour at EOT and at the 4-week follow-up in the ciprofloxacin DPI group compared with the placebo group (table 3).

There was no observed effect on FEV1 or FVC in either the ciprofloxacin DPI or placebo groups. The mean change in percentage predicted FEV1 (± standard deviation) from baseline to EOT for the ciprofloxacin DPI group was an improvement of 0.06±8.36% and a deterioration of –0.40±10.06% for the placebo group.

Mean high-sensitivity C-reactive protein values between randomisation and EOT decreased in the ciprofloxacin DPI group but increased in the placebo group (–1.09 mg/L vs 4.02 mg/L, respectively; p=0.173). Evidence for a treatment effect on absolute neutrophil count was indicated by a significant reduction at EOT for ciprofloxacin DPI compared with placebo (–0.36 × 10^6/mL vs 0.60 × 10^6/mL, respectively; p=0.014).

Increases in minimum inhibitory concentration (MIC) to over 4 mg/L (a level defined as clinically relevant for systemic therapy with ciprofloxacin), which were considered to be probably or possibly related to the administration of study drug, were reported up to the end of the study for six subjects in the ciprofloxacin DPI group and no subjects in the placebo group for the following pathogens: *P. aeruginosa* (n=4), *S. maltophilia* (n=1) and *H. influenzae* (n=1). Of these subjects, one prematurely discontinued the study and four showed MIC decreases to susceptible levels by the end of the study. One subject with mucoid *P. aeruginosa* maintained resistance, which peaked at Day 30 (MIC=64 mg/L) and decreased to 4 mg/L (Day 44 and Day 63) and 8 mg/L at Day 92. One subject in the placebo group experienced a transient MIC increase in *S. maltophilia* at EOT from 1 mg/L to 4 mg/L.

At EOT, the mean change from baseline in SGRQ score for subjects in the ciprofloxacin DPI and placebo groups was –2.52 points and +0.38 points, respectively, indicating an improvement in the ciprofloxacin DPI group. The adjusted mean difference in SGRQ scores for ciprofloxacin DPI compared with placebo was –3.56 (95% CI –7.3 to 0.1; p=0.059);

adjustment was made for baseline SGRQ and study centre. A similar trend was found in the responder analysis: 40% of subjects receiving ciprofloxacin DPI and 32% of subjects receiving placebo reported an improvement in score of more than 4 points at EOT.

Safety

A summary of treatment-emergent, drug-related and serious AEs is presented in table 4. No deaths occurred and no serious AEs within this time period were considered to be related to study treatment. Discontinuations from the study are summarised in fig. 1.

Throughout the study (up to Day 84), 22 subjects in the ciprofloxacin DPI group (3 subjects prematurely discontinued treatment) and 26 subjects in the placebo group (6 prematurely discontinued treatment) reported at least one AE of exacerbation of bronchiectasis. Of these, 18 events reported in 17 subjects in the ciprofloxacin DPI group and 14 events in 13 subjects in the placebo group were classified as 'late events', occurring more than 7 days after EOT. A similar number of subjects prematurely discontinued the study because of AEs in each treatment group: 19 subjects (31.7%) and 23 subjects (35.9%) in ciprofloxacin DPI group and placebo groups, respectively.

AEs of special interest in the ciprofloxacin DPI and placebo groups included bronchospasm (3/60 and 3/64 subjects, respectively; two incidences in each group occurred during treatment and were considered to be treatment related). None of the investigator-reported AEs of bronchospasm (6 in total) met the study-specific definition of bronchospasm. Treatment-emergent AEs of cough (0/60 and 5/64 subjects, respectively) and haemoptysis (1/60 and 2/64 subjects, respectively) were reported.

No significant changes in laboratory parameters were recorded in either treatment group. Ciprofloxacin-induced changes in any liver function test or serum creatinine were not detected.

Discussion

Relatively few randomised clinical trials have been conducted exclusively in subjects with non-CF bronchiectasis. Regular, long-term nebulised gentamicin was observed to be of significant benefit in subjects with non-CF bronchiectasis; however, continuous treatment was required to ensure on-going efficacy [18]. At the 3-month follow-up, outcome measures were similar to baseline [18]. New therapies supported by a robust evidence base are needed.

This study was designed to include subjects who were chronically infected with a relevant pathogen and whose bronchiectasis was of sufficient severity to warrant considering treatment with inhaled antibiotics. We included non-CF subjects with post-infective and idiopathic bronchiectasis, who account for between 70% and 80% of all non-CF bronchiectasis cases [19, 20]. We excluded aetiologies in which response to treatment could be affected by complicating factors; for example, poor mucus clearance attributable to primary ciliary dyskinesia, allergic inflammation and immune deficiency. A relatively large number of study centres were required for recruitment but the results were conclusive despite any variability this may have introduced, and the interaction term between treatment and centre for the main analysis was not significant (p=0.214).

The results of the current study show, for the first time in non-CF bronchiectasis, that ciprofloxacin DPI produced a statistically significant reduction in total bacterial load after 28 days of treatment compared with placebo. The more than 3-log-fold reduction in bacterial counts is equivalent to a greater than 99.9% reduction in bacterial load. Moreover, a greater percentage of subjects receiving ciprofloxacin DPI had negative bacterial culture at EOT than did subjects receiving placebo. A reduction in colony count for the two most prevalent pathogens in non-CF bronchiectasis, *P. aeruginosa* and *H. influenzae*, was observed with ciprofloxacin DPI treatment. Although the study was not powered to show a significant difference in the number of subjects reporting exacerbations, a trend was observed favouring ciprofloxacin DPI, suggesting that it might be a useful agent in the management of this patient population. Reduction of bacterial load in the lungs should reduce both airway inflammation and the risk of exacerbations, which is supported by the observation of a reduction in sputum purulence. Prior data support associations between sputum colour and bronchial inflammation [21]. Hence, the results of this study show an emerging pattern of clinically meaningful effects on the pathophysiology of bronchiectasis.

The most common dosing interval used for the aerosolised antibacterials currently available or in development is a cycle of 28 days on treatment followed by 28 days off treatment. A rapid return to near baseline values in bacterial load was observed between EOT and end of the study. However, at Day 56, which would correspond to the return to treatment in this proposed cycled regimen, the decrease in bacterial burden was still apparent. The rapid drop in bacterial load followed by rebound is consistent with the apparent impact of ciprofloxacin DPI on the pattern of exacerbations, i.e. suppression relative to placebo in the first 42 days of the study and incidence rates becoming similar thereafter.

An important rationale for using this regimen (28 days on/28 days off treatment) is to minimise the development of antibacterial resistance. Resistance can develop after exposure of a pathogen to an antibacterial; the 28-day off-treatment period removes the selective pressure of the antibacterial, allowing pathogen susceptibility to return towards its pre-treatment level [22, 23]. Potential resistance development, as indicated by changes in MIC, was observed in this study: isolates from six subjects in the ciprofloxacin DPI group demonstrated MIC increases by EOT; subsequent MIC decreases in isolates from four of these subjects were reported by Day 56.

In addition to improvements in clinical efficacy parameters, trends towards improvements in patient-reported health status for subjects receiving ciprofloxacin DPI were observed with the SGRQ at EOT, despite the brief treatment period. This was close to a clinically relevant improvement (–4.0 points in SGRQ; lower scores represent improved HRQoL) [24]. This trend was also observed at Day 56 but not at the end of the study, indicating that any reported benefit on health status was temporary.

Ciprofloxacin DPI 32.5 mg bid was well tolerated; the AEs observed are common in subjects with respiratory diseases, with the most frequently reported AE being exacerbations [25, 26]. No significant changes in laboratory parameters were observed and there was a low incidence of drug-related AEs, with no significant differences observed between the ciprofloxacin DPI and placebo groups. The incidence of AEs associated with non-CF bronchiectasis, including bronchospasm, cough and haemoptysis, was low throughout the treatment period.

Ciprofloxacin DPI 32.5 mg achieved a significant reduction in bacterial load compared with placebo in subjects with post-infective or idiopathic non-CF bronchiectasis whose disease profile and severity warranted consideration of inhaled antibiotic therapy. Ciprofloxacin DPI was well tolerated when administered bid for 28 days. The improvements observed with ciprofloxacin DPI in secondary clinical and quality of life-related endpoints were not statistically significant. Further studies powered to evaluate the clinical effects of long-term intermittent ciprofloxacin DPI therapy are therefore needed in this patient population.

Acknowledgements

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Tables

Table 1. Demographic and baseline data (modified intent-to-treat/safety population)

Characteristic	Ciprofloxacin DPI N=60	Placebo N=64
Age (years), mean (SD)	64.7 (11.8)	61.4 (11.9)
Sex, n (%)		
Male	21 (35.0)	21 (32.8)
Female	39 (65.0)	43 (67.2)
Ethnicity, n (%)		
Caucasian	60 (100.0)	63 (98.4)
Asian	0	1 (1.6)
Weight (kg), mean (SD)	70.2 (16.4)	69.1 (17.2)
Body mass index (kg/m^2), mean (SD)	25.6 (5.5)	25.1 (5.6)
FEV1 (% predicted), mean (SD)	57.2 (13.7)	54.6 (14.8)
Number of subjects with exacerbations in previous 12 months, n (%)		
1–2 exacerbations	30 (50.0)	35 (54.7)
3–4 exacerbations	25 (41.7)	26 (40.6)
≥5 exacerbations	5 (8.3)	3 (4.7)
Baseline total bacterial load (log$_{10}$ CFU/g), mean (SD)	7.19 (1.94)	6.92 (1.90)
Baseline bacterial isolates in ≥5% subjects, n (%)*		
Pseudomonas aeruginosa	32 (53.3)	35 (54.7)
Haemophilus influenzae	14 (23.3)	16 (25.0)

Staphylococcus aureus	8 (13.3)	17 (26.6)
Streptococcus pneumoniae	7 (11.7)	2 (3.1)
Moraxella catarrhalis	5 (8.3)	3 (4.7)
Klebsiella pneumoniae	5 (8.3)	0
Proteus mirabilis	3 (5.0)	4 (6.3)
Klebsiella oxytoca	3 (5.0)	2 (3.1)

*No significant differences between ciprofloxacin DPI and placebo for isolates were reported apart from for *K. pneumoniae* (p=0.024).

CFU: colony-forming units; DPI: dry powder for inhalation; FEV1: forced expiratory volume in 1 second; SD: standard deviation.

Table 2. Number of subjects with eradication (negative bacterial culture, modified intent-to-treat population)

Time period	Ciprofloxacin DPI n/N (%)	Placebo n/N (%)	p-value*
During treatment visit (Day 8)	20/42 (47.6)	6/51 (11.8)	<0.001
End of treatment (Day 29)	14/40 (35.0)	4/49 (8.2)	0.001
2-week follow-up (Day 42)	6/36 (16.7)	4/37 (10.8)	0.359
4-week follow-up (Day 56)	4/31 (12.9)	1/28 (3.6)	0.617
8-week follow-up (Day 84)	4/27 (14.8)	2/25 (8.0)	0.763

*p-value based on Cochran–Mantel–Haenszel test stratified by centre/cluster of centre.

DPI: dry powder for inhalation.

Table 3. Sputum colour in the modified intent-to-treat/safety population with available sputum samples

	Ciprofloxacin DPI n (%)	Placebo n (%)	p-value
Baseline	N=60	N=63*	0.220[#]
No sputum/clear	5 (8.3)	7 (11.1)	
Yellow	29 (48.3)	23 (36.5)	
Green	25 (41.7)	28 (44.4)	
Rust	1 (1.7)	5 (7.9)	
End of treatment	N=49	N=52	0.026[#], 0.029[¶]
No sputum/clear	12 (24.5)	9 (17.3)	
Yellow	31 (63.3)	26 (50.0)	
Green	5 (10.2)	17 (32.7)	
Rust	1 (2.0)	0	
4-week follow-up	N=40	N=37	0.494[#], 0.609[¶]
No sputum/clear	10 (25.0)	5 (13.5)	
Yellow	16 (40.0)	22 (59.5)	
Green	11 (27.5)	9 (24.3)	
Rust	3 (7.5)	1 (2.7)	

*No sputum information was available for one patient.

[#]p-value based on Cochran–Mantel–Haenszel test with ridit scores test stratified by centre/cluster of centre; [¶]p-value based on Cochran–Mantel–Haenszel test with ridit scores test stratified by centre/cluster of centre and baseline sputum colour.

DPI: dry powder for inhalation.

Table 4. Summary of adverse events (modified intent-to-treat/safety population)

Adverse event	Ciprofloxacin DPI N=60 n (%)	Placebo N=64 n (%)	p-value
Subjects with any AEs	50 (83.3)	54 (84.4)	1.000
Patients with any treatment-emergent AEs	41 (68.3)	42 (65.6)	0.849
Patients with treatment-related AEs	21 (35.0)	17 (26.6)	0.335
Treatment-emergent AEs reported in >5% subjects			
Product taste abnormal	8 (13.3)	7 (10.9)	0.786
Dysgeusia	4 (6.7)	1 (1.6)	0.197
Cough	0	5 (7.8)	0.058
Exacerbation of bronchiectasis	7 (11.7)	14 (21.9)	0.155
Headache	4 (6.7)	5 (7.8)	1.000
Subjects with treatment-emergent serious AEs*	2 (3.3)	3 (4.7)	1.000
Complex pain syndrome	1 (1.7)	0	0.484
Hallucination	1 (1.7)	0	0.484
Exacerbation of bronchiectasis	0	3 (4.7)	0.245
Sepsis	0	1 (1.6)	1.000
Deaths	0	0	

*None considered to be drug related.

AE: adverse event; DPI: dry powder for inhalation; NA: not available.

Figure legends

Figure 1. Study design and subject disposition.

Protocol violations in screening failures included no positive culture (n=23), inadequate sputum (n=50), forced expiratory volume in 1 second outside range (n=6), exacerbations during screening (n=2), on antibacterials (n=6), no further information (n=25) and other (n=10).

bid: twice daily; DPI: dry powder for inhalation.

Figure 2. Mean bacterial load for modified intent-to-treat population (A) and per-protocol population (B).

Only results from valid cultures were considered. Cultures were excluded: if subjects were administered concomitant antibacterials, if there were >25 squamous epithelial cells in absence of *Pseudomonas aeruginosa* or if there were ≤25 leukocytes for *P. aeruginosa*-negative cultures pre-therapy.

*p<0.001.

CFU: colony-forming unit; DPI: dry powder for inhalation.

Figure 3. Mean colony count of selected pathogens at baseline and at end of treatment.

Only results from valid cultures considered. Cultures were excluded: if subjects were administered concomitant antibacterials, if there were >25 squamous epithelial cells in absence of *Pseudomonas aeruginosa* or if there were ≤25 leukocytes for *P. aeruginosa*-negative cultures pre-therapy.

CFU: colony-forming unit; DPI, dry powder for inhalation.

Figure 4. Occurrence of exacerbations requiring antibacterial intervention throughout the study (modified intent-to-treat population).

Twenty-two subjects in the ciprofloxacin DPI group and 25 subjects in the placebo group experienced an exacerbation. Of these, 14 subjects in the ciprofloxacin DPI group and 18 subjects in the placebo group required antibacterial treatment.
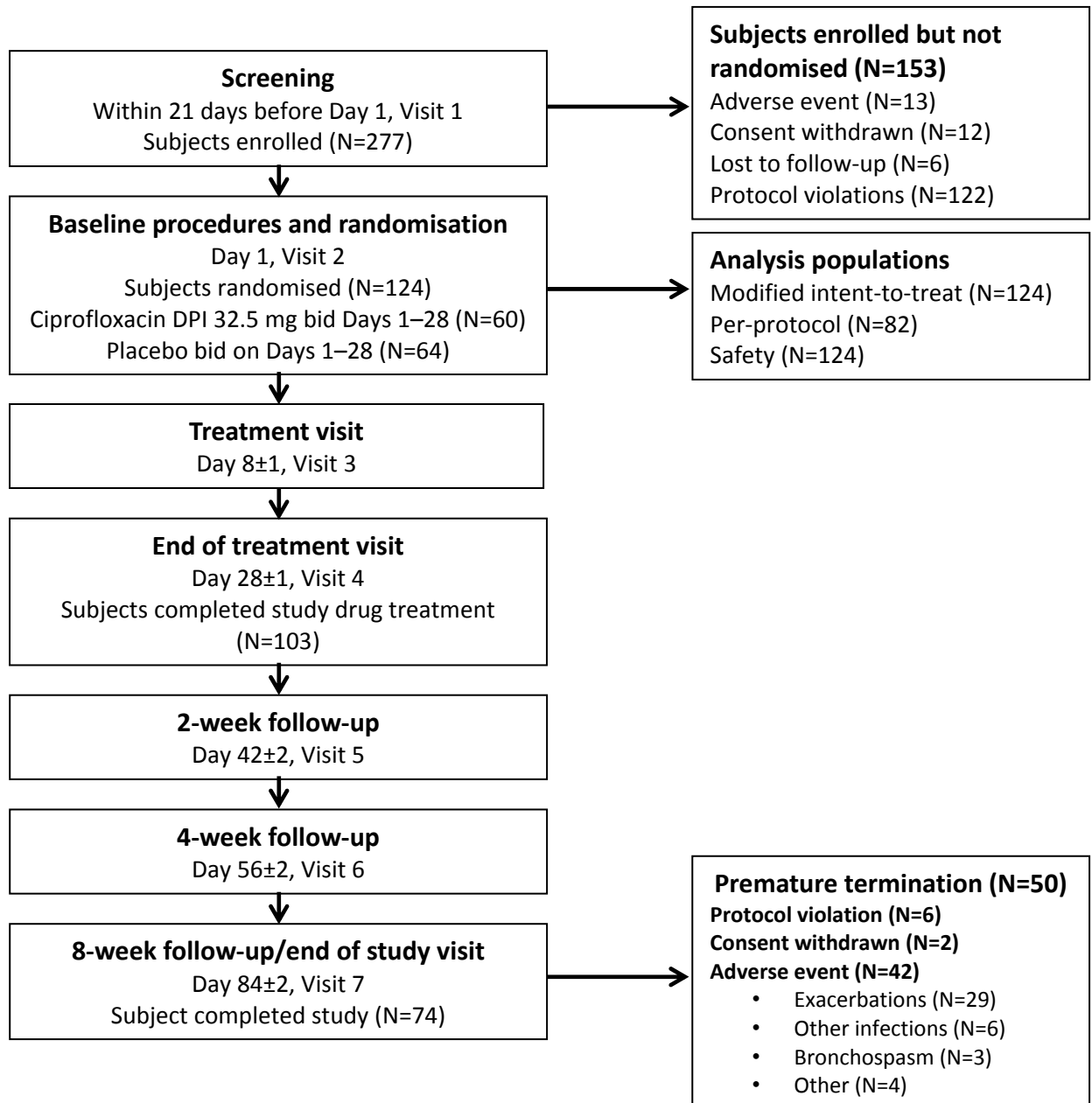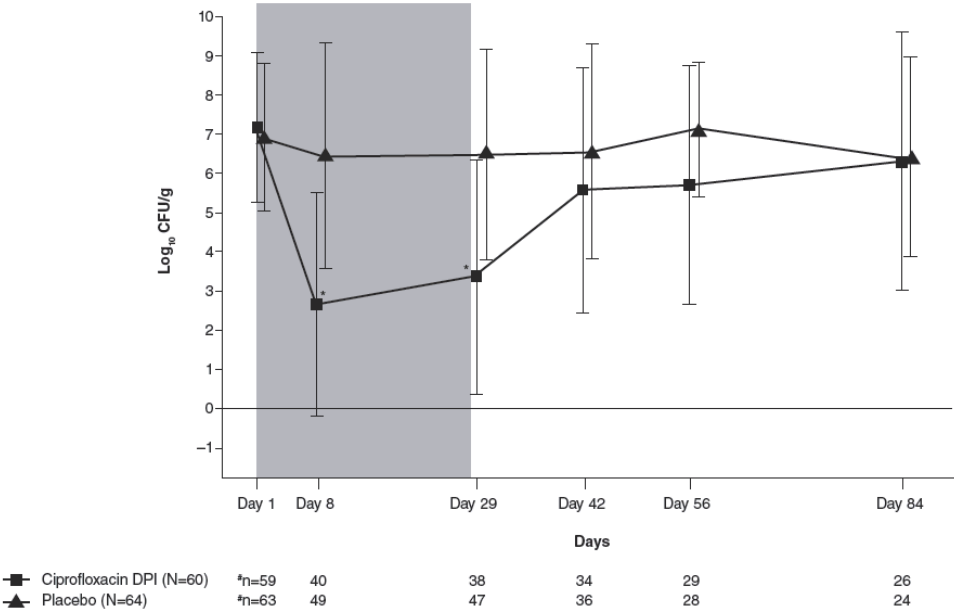
DPI: dry powder for inhalation.

Figures

Figure 1.

Screening Within 21 days before Day 1, Visit 1 Subjects enrolled (N=277)

Subjects enrolled but not randomised (N=153) Adverse event (N=13) Consent withdrawn (N=12) Lost to follow-up (N=6) Protocol violations (N=122)

Baseline procedures and randomisation Day 1, Visit 2 Subjects randomised (N=124) Ciprofloxacin DPI 32.5 mg bid Days 1–28 (N=60) Placebo bid on Days 1–28 (N=64)

Analysis populations Modified intent-to-treat (N=124) Per-protocol (N=82) Safety (N=124)

Treatment visit Day 8±1, Visit 3

End of treatment visit Day 28±1, Visit 4 Subjects completed study drug treatment (N=103)

2-week follow-up Day 42±2, Visit 5

4-week follow-up Day 56±2, Visit 6

8-week follow-up/end of study visit Day 84±2, Visit 7 Subject completed study (N=74)

Premature termination (N=50) Protocol violation (N=6) Consent withdrawn (N=2) Adverse event (N=42) • Exacerbations (N=29) • Other infections (N=6) • Bronchospasm (N=3) • Other (N=4)

Figure 2.

A.

		Day 1	Day 8	Day 29	Day 42	Day 56	Day 84
Ciprofloxacin DPI (N=60)	#n=59	40	38	34	29	26
Placebo (N=64)	#n=63	49	47	36	28	24

B.

		Day 1	Day 8	Day 29	Day 42	Day 56	Day 84
Ciprofloxacin DPI (N=37)	#n=37	28	32	23	20	20
Placebo (N=45)	#n=45	39	41	29	23	24

Figure 3.

Figure 4.