Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	12965	NCT00930982
Study Phase:	IIb	
Official Study Title:	Randomized, placebo-controlled, double-blind, multi-center study to evaluate the safety and efficacy of ciprofloxacin inhale compared to placebo in patients with non-cystic fibrosis bronchiectasis.	
Therapeutic Area:	Anti-Infectives	
Test Product		
Name of Test Product:	Ciprofloxacin (Cipro Inhale, BAYQ3939)	
Name of Active Ingredient:	Ciprofloxacin	
Dose and Mode of Administration:	32.5 mg ciprofloxacin hydrated corresponding to 50 mg Ciprofloxacin PulmoSphere® inhalation powder twice daily (BID), administered per inhalation using Novartis' (formerly Nektar's) T-326 powder inhaler device (T-326 Inhaler)	
Reference Therapy/Placebo		
Reference Therapy:	Placebo	
Dose and Mode of Administration:	Matching placebo (containing 40 mg dried powder) BID, administered per inhalation using Novartis' (formerly Nektar's) T-326 powder inhaler device (T-326 Inhaler)	
Duration of Treatment:	28 days	
Studied period:	Date of first subjects' first visit:	29 JUN 2009
	Date of last subjects' last visit:	17 SEP 2010
Premature Study Suspension /Termination:	No	
Substantial Study Protocol Amendments:	Amendment no. 1 (dated 23 SEP 2009) incorporated the following substantial changes: • The α-level for the second analysis was set to 0.023 (1-sided) to guarantee an overall 1-sided α-level of 0.025. • Short- and long-acting anticholinergics and the allowed dosage of systemic prednisolone ≤10 mg for <14 days or equivalent were added in list of standard medications. • The inclusion criterion allowed subjects with primary ciliary dyskinesia to participate in the study. • Subjects failing screening due to an inadequate sputum sample were allowed to be re-screened at a later time but assignment (randomization) to a second treatment course was not allowed. • Nebulized antibiotics as maintenance treatment and antibiotic treatment for an exacerbation within the preceding 4 weeks (period prior to randomization) were added as exclusion criteria. Macrolides were allowed if used as stable maintenance treatment.	

	• Antibiotic treatment of any infection for at least 30 days prior to randomization and chronic systemic corticosteroid treatment with >10 mg prednisolone for more than 14 days or equivalent were added as exclusion criteria. • Subjects were withdrawn from study if they required systemic antibiotic treatment during study drug treatment. • Pregnancy test had to be performed as part of safety laboratory procedures at premature discontinuation. Amendment no. 2 (dated 11 NOV 2009) extended the time window between the screening (Visit 1) and the baseline visit (Visit 2) from 14 days to 21 days due to logistical reasons. Amendment no. 3 (dated 07 JAN 2010) reduced the minimum volume of sputum sample for inclusion from 10 mL to 5 mL. Amendment no. 4 (dated 27 JUL 2010) incorporated the following substantial changes: • The modified intent-to-treat (mITT) population comprised of all subjects who received study drug. • The criterion "stable pulmonary status" was added to the list of criteria for assignment of subjects to the per-protocol (PP) population.
Study Centre(s):	This study was conducted at 42 investigational sites in 6 countries: Germany (14 centers), Spain (4 centers), Sweden (1 center), the United Kingdom (6 centers), the United States of America (9 centers), and Australia (8 centers).
Methodology:	Clinical, bacteriological, and laboratory examinations including lung function tests were performed prior to randomization, during treatment, at the end-of-treatment (EOT) visit, and at follow-up visits (2 weeks, 4 weeks, and 8 weeks [last visit] after EOT). The Saint George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Questionnaire – Self Administered Standardized (CRQ-SAS) were used to collect health-related quality of life (HRQoL) data. These subject reported outcomes (i.e., patient-reported outcomes [PRO]) were completed during visits 2, 4, 6, and 7 and, if applicable, at the premature discontinuation visit. In addition, selected subjects from selected centers donated blood and sputum (if possible) samples for pharmacokinetic investigations according to a sparse sampling protocol during pre-defined time windows.
Indication/ Main Inclusion Criteria:	Indication: Non-cystic fibrosis (non-CF) bronchiectasis Main Inclusion Criteria: • Pulmonary stable subjects with a proven and documented diagnosis of non-CF idiopathic or post-pneumonic bronchiectasis (defined as bronchiectasis in which symptoms occurred after severe infection such as whooping cough, measles, community-acquired pneumonia, or tuberculosis) by ▪ High-resolution CT scan including 2 or more lobes and dilated airways compatible with bronchiectasis at initial diagnosis (CT scan only if high-resolution CT scan was not

	available) and ▪ >1 course of systemic antibiotics for exacerbations or ≥1 hospitalization for intravenous (IV) antibiotic treatment for pulmonary exacerbation during the past 12 months. • Stable pulmonary status, as indicated by FEV_1 (percent of predicted) of ≥35% and ≤80%. • Pre-treatment sputum sample available (subject had to be able to produce a sputum sample with a volume ≥5 mL) that was positive for at least one of the pre-defined pathogens. • Stable regimen of standard treatment (at least for the past 30 days prior to randomization) that may have included macrolides if used as stable maintenance treatment for bronchiectasis for at least the last 30 days prior to randomization.
Study Objectives:	Primary: • To determine the effect of ciprofloxacin dry powder for inhalation (DPI) on bacterial density, measured by decadic logarithm (log_{10}) of reduction in colony forming units (CFUs) per gram sputum. Secondary: • To evaluate the emergence of new potential respiratory pathogens, and the emergence of resistance among baseline pathogens in those subjects with persistent infection or colonization. • To determine the efficacy and safety of ciprofloxacin DPI. • To determine plasma and sputum concentrations of ciprofloxacin DPI at predefined time windows at 2 specific visits during treatment from selected subjects in selected centers.
Evaluation Criteria:	Efficacy (Primary): • Change from baseline in total bacterial load in sputum Efficacy (Secondary): • Time to exacerbation • Change in 24-hour sputum volume and color from baseline • Change from baseline in FEV_1 and forced vital capacity (FVC) (post-bronchodilator spirometry) • Changes in inflammatory markers (high-sensitivity C-reactive protein [hsCRP] and absolute neutrophil count [ANC], determined from safety blood samples) • Microbiological response rate of ciprofloxacin DPI per pathogen and per subject • Emergence of new potential respiratory pathogens and emergence of resistance among baseline pathogens • Change from baseline in SGRQ and CRQ-SAS scores at EOT, at the 4-week follow-up, and at the 8-week follow-up Safety: Incidence of abnormal findings in measurements for objective tolerability: physical examination, vital parameters (blood pressure and pulse rate), laboratory findings, and the occurrence of adverse events.

	Pharmacokinetics: For investigation of drug exposure and potential relationship to drug effects, selected subjects from selected centers only participated in pharmacokinetic sampling to determine plasma and sputum concentrations of ciprofloxacin.
Statistical Methods:	Efficacy (Primary): The primary efficacy endpoint was the difference in total bacterial load between ciprofloxacin DPI- and placebo-treated subjects at EOT in the mITT population. The analysis planned and performed was an analysis of covariance (ANCOVA) with baseline total bacterial load as covariate, treatment and center as factors without interaction. Efficacy (Secondary): Pathogen eradication was analyzed using a Cochran-Mantel-Haenszel test stratified for centers. Time to exacerbation requiring intervention with an inhaled, IV, or oral antibacterial treatment was analyzed using a stratified (strata: center) log-rank test. Subjects who discontinued the study prematurely were treated as censored. Changes in FEV_1, FVC, and FEV_1/FVC were analyzed by a 2-way ANCOVA with factors treatment group (ciprofloxacin DPI, placebo) and center. The dependent variables were lung function parameters at the various visits; baseline values served as covariates. For the ANCOVA, the raw values (in liters) were used. All other secondary efficacy variables were displayed using descriptive statistics. Safety: Safety variables were displayed using descriptive statistics.
	Pharmacokinetics: Pharmacokinetic variables were displayed using descriptive statistics.
Number of Subjects:	Planned: 61 randomized subjects per treatment group. Analyzed: 60 randomized subjects treated with ciprofloxacin DPI, 64 randomized subjects treated with placebo.

Study Results

Results Summary — Subject Disposition and Baseline

Out of 277 subjects screened, 124 subjects aged 26 to 86 years were randomized (60 to ciprofloxacin DPI and 64 to placebo). One hundred and three subjects completed study drug treatment, and 74 completed the study (Table 1).

Table 1: Study subjects

Population	Ciprofloxacin N	Ciprofloxacin %	Placebo N	Placebo %	Total N	Total %
Based on screened subjects						
Screened					277	100
Randomized	60		64		124	45
Based on randomized subjects						
Valid for intent-to-treat	60	100	64	100	124	100
Valid per protocol	37	62	45	70	82	66
Prematurely terminated treatment	10	17	11	17	21	17
Prematurely terminated study	21	35	29	45	50	40
Completed treatment	50	83	53	83	103	83
Completed study	39	65	35	55	74	60

In general, the demographic and baseline data of the 2 treatment groups were very similar (Table 2).

Table 2: Demographic and baseline data (population: intent-to-treat / safety)

		Ciprofloxacin DPI N=60 (100%)	Placebo N=64 (100%)	*P* value
Age (years)	Mean (SD)	64.7 (11.8)	61.4 (11.9)	0.121
Gender	Male, n/N (%)	21/60 (35.0)	21/64 (32.8)	0.922
Race	White, n/N (%)	60/60 (100.0)	63/64 (98.4)	
Height (cm)	Mean (SD)	165.3 (8.5)	166.1 (9.2)	0.622
Weight (kg)	Mean (SD)	70.2 (16.4)	69.1 (17.2)	0.706
BMI (kg/m^2)	Mean (SD)	25.6 (5.5)	25.1 (5.6)	0.572
Number of exacerbations in previous 12 months	1, n/N (%)	7/60 (11.7)	4/64 (6.3)	
	2, n/N (%)	23/60 (38.3)	31/64 (48.4)	
	3, n/N (%)	18/60 (30.0)	24/64 (37.5)	
	4, n/N (%)	7/60 (11.7)	2/64 (3.1)	
	5, n/N (%)	0	2/64 (3.1)	
	6, n/N (%)	4/60 (6.7)	0	
	>6, n/N (%)	1/60 (1.7)	1/64 (1.6)	

P values derived from Cochran–Mantel–Haenszel test, stratified by center for gender from analysis of variance (ANOVA), with treatment and center as factors (no interaction model) or age, weight, height, BMI. Since the modified intent to treat population was identical to the intent to treat population for this study, the statistical evaluation refers to the intent to treat population.
BMI: body mass index, SD: standard deviation

Results Summary — Efficacy

The primary analysis was a comparison between ciprofloxacin DPI and placebo of change in total bacterial load after the 4-week treatment period (at Visit 4). The main efficacy analysis demonstrated that the primary efficacy objective was achieved (Table 3). Further sensitivity analyses were performed. Different imputation methods were used and the per protocol (PP) population was considered. In all these analyses, the treatment effect of ciprofloxacin DPI at EOT was significant at an α-level of 0.01.

Table 3: Main efficacy criterion: total bacterial load at end-of-treatment population: intent-to-treat; imputation method: LOCF

ANCOVA	Source	DF	MS	*P* value
No interaction model	Baseline total bacterial load	1	97.93	<0.001
	Center	17	11.68	0.069
	Treatment	1	163.67	<0.001
	Error	102	7.15	
Interaction model	Baseline total bacterial load	1	89.04	<0.001
	Center	17	12.41	0.038
	Treatment	1	109.24	<0.001
	Interaction: Treatment, center	17	8.84	0.214
	Error	85	6.81	
Least square means [log_{10}(cfu+1)/g]	**Effect**		**Estimate**	**95% CI**
No interaction model	Treatment: ciprofloxacin DPI		4.05	3.32 to 4.78
	Treatment: placebo		6.42	5.71 to 7.13

[a] 2 subjects were excluded from the analysis. Both had positive pre-treatment cultures, but no colony forming unit (CFU) counts.
Since the modified intent to treat population was identical to the intent to treat population for this study, the statistical evaluation refers to the intent to treat population.
LOCF: last observation carried forward; CI: confidence interval; DF: degrees of freedom; MS: mean square

This result was stable, independently whether the only measured data at end-of-treatment or imputed data for missing observations were used. Further, a high percentage of subjects (83%) completed treatment. The per-protocol analyses support the intent-to-treat analysis.

The ciprofloxacin DPI treatment effect in reducing the bacterial burden appeared by Visit 3 during treatment (Day 8 ± 1). At the primary end point at the EOT (Day 29+1), ciprofloxacin DPI had achieved a mean reduction of 3.62 log_{10} CFU, compared to a reduction of 0.27 log_{10} CFU for placebo using a pair-wise comparison, no imputation for missing values. Until the end-of-study visit (Visit 7, 8-week follow-up), mean total bacterial load remained lower in the ciprofloxacin DPI group as compared to the placebo group. In both study populations, this difference in log_{10} CFUs was statistically significant at both Visit 3 (during treatment, Day 8) and Visit 4 (EOT, Day 28), i.e., the 95% confidence interval did not include '0' (Table 4).

Table 4: Time course of total bacterial load (population: intent-to-treat; imputation method: next available value)

Time, visit	Ciprofloxacin DPI		Placebo		
	Estimate	95% CI	Estimate	95% CI	*P* value
Baseline, Visits 1-2[a]	7.19	(1.94)	6.92	(1.90)	
During treatment, Visit 3	3.38	2.58 to 4.18	6.37	5.59 to 7.15	<0.001
End of treatment, Visit 4	3.74	2.96 to 4.52	6.40	5.65 to 7.15	<0.001
2-week follow-up, Visit 5	5.30	4.54 to 6.05	6.39	5.57 to 7.21	0.041
4-week follow-up, Visit 6	5.44	4.66 to 6.23	6.11	5.25 to 6.97	0.222
8-week follow-up, Visit 7	5.74	4.45 to 7.04	5.89	4.55 to 7.23	0.856

[a] Empirical mean (SD)
Since the modified intent to treat population was identical to the intent to treat population for this study, the statistical evaluation refers to the intent to treat population.

There was no effect of study drug treatment on FEV_1 in any of the 2 subject populations. The same was true for the other lung function parameters determined, i.e., FVC and Tiffeneau ratio (FEV_1/FVC).

Significant reductions were also achieved in the major species of bacteria, and eradication

(negative bacterial culture) was achieved in more ciprofloxacin DPI-treated subjects (35%) compared to placebo-treated subjects (8%) at the EOT. Other positive clinical trends included a reduction in exacerbations (all 3 classifications of exacerbations), and reduction in inflammatory markers. The patient-reported outcome data showed trends towards higher improvement rates in the ciprofloxacin DPI group than in the placebo group.

Ciprofloxacin DPI treatment was associated with a reduction in the appearance of potential respiratory pathogens in the sputum of subjects. During the first 30 days of the study, there were 14 subjects with new pathogens in the ciprofloxacin DPI group compared to 30 subjects with new pathogens in the placebo group. During Days 31 - 88 off treatment, there were 29 subjects in the ciprofloxacin DPI group and 24 subjects in the placebo group that acquired new pathogens (Table 5).

Thus ciprofloxacin DPI 32.5 mg BID for 28 days produced significant reductions in bacterial burden in subject sputum compared to placebo in non-CF bronchiectasis subjects. During treatment, ciprofloxacin DPI reduced the number of subjects with new respiratory pathogens not present at baseline. Secondary evaluations of eradications, markers for inflammation, exacerbations, and patient reported outcomes all showed promising trends consistent with the hypothesis that reduction in bacterial burden is linked to improved subject outcome.

Table 5: First appearance of potential respiratory pathogens (population: intent-to-treat; imputation method: no imputation)

Any new pathogen	Frequency		Cumulative frequency	
First appearance	Ciprofloxacin DPI N=60 (100%) n (%)	Placebo N=64 (100%) n (%)	Ciprofloxacin DPI N=60 (100%) n (%)	Placebo N=64 (100%) n (%)
Day 4	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)
Day 5	0 (0.0)	2 (3.7)	1 (2.3)	2 (3.7)
Day 7	1 (2.3)	0 (0.0)	2 (4.7)	2 (3.7)
Day 8	5 (11.6)	6 (11.1)	7 (16.3)	8 (14.8)
Day 9	0 (0.0)	2 (3.7)	7 (16.3)	10 (18.5)
Day 10	0 (0.0)	1 (1.9)	7 (16.3)	11 (20.4)
Day 14	0 (0.0)	1 (1.9)	7 (16.3)	12 (22.2)
Day 15	0 (0.0)	1 (1.9)	7 (16.3)	13 (24.1)
Day 28	0 (0.0)	1 (1.9)	7 (16.3)	14 (25.9)
Day 29	5 (11.6)	10 (18.5)	12 (27.9)	24 (44.4)
Day 30	2 (4.7)	6 (11.1)	14 (32.6)	30 (55.6)
Day 36	1 (2.3)	0 (0.0)	15 (34.9)	30 (55.6)
Day 39	1 (2.3)	1 (1.9)	16 (37.2)	31 (57.4)
Day 42	2 (4.7)	2 (3.7)	18 (41.9)	33 (61.1)
Day 43	3 (7.0)	5 (9.3)	21 (48.8)	38 (70.4)
Day 44	4 (9.3)	2 (3.7)	25 (58.1)	40 (74.1)
Day 45	1 (2.3)	1 (1.9)	26 (60.5)	41 (75.9)
Day 57	3 (7.0)	4 (7.4)	29 (67.4)	45 (83.3)
Day 58	0 (0.0)	1 (1.9)	29 (67.4)	46 (85.2)
Day 59	1 (2.3)	1 (1.9)	30 (69.8)	47 (87.0)
Day 78	1 (2.3)	0 (0.0)	31 (72.1)	47 (87.0)
Day 83	1 (2.3)	0 (0.0)	32 (74.4)	47 (87.0)
Day 84	1 (2.3)	0 (0.0)	33 (76.7)	47 (87.0)
Day 85	5 (11.6)	6 (11.1)	38 (88.4)	53 (98.1)
Day 86	3 (7.0)	1 (1.9)	41 (95.3)	54 (100.0)
Day 88	2 (4.7)	0 (0.0)	43 (100.0)	54 (100.0)

Any new bacterial strain was considered a new potential respiratory pathogen. Since the modified intent to treat population was identical to the intent to treat population for this study, the statistical evaluation refers to the intent to treat population.

Results Summary — Safety

In this study, adverse events (AEs) were regarded as "treatment emergent" if they occurred after start of study drug treatment up to 7 days after EOT or, if already present before study drug treatment, worsened after start of study drug treatment up to 7 days after EOT.

No deaths or life-threatening adverse events occurred during this study. Five subjects (2 on ciprofloxacin DPI and 3 on placebo) experienced treatment-emergent serious adverse events (SAEs). None of these events was assessed as drug-related. Thus, no suspected unexpected serious adverse reaction (SUSAR) occurred.

Forty-one subjects (68.3%) of the ciprofloxacin DPI and 42 subjects (65.6%) of the placebo groups reported at least 1 treatment-emergent AE. Treatment-emergent adverse events were experienced in both the ciprofloxacin DPI and placebo groups and were classified as mild in 23 subjects (38.3%) and 26 subjects (40.6%), moderate in 14 (23.3%) and 13 (20.3%), and severe in 4 (6.7%) and 3 (4.7%) of the ciprofloxacin DPI and placebo groups, respectively (Table 6 and Table 7).

Two subjects in the ciprofloxacin DPI group experienced moderate treatment-emergent diarrhea (drug-related: n=1), whereas 1 subject in the placebo group experienced mild treatment emergent, drug-related diarrhea. Two subjects in the ciprofloxacin DPI group experienced mild treatment-emergent nausea (drug-related: n=1) and 1 subject moderate nausea, whereas no subject in the placebo group experienced treatment-emergent nausea.

There were more subjects with infections in the placebo (n=23) than in the ciprofloxacin DPI (n=13) groups, driven mainly by the incidence of exacerbations of bronchiectasis (n=14 in placebo versus n=7 in ciprofloxacin DPI).

Table 6: Incidence of subjects with selected treatment-emergent adverse events by primary system organ class and preferred term (population: intent-to-treat / safety)

Primary system organ class Preferred term	Ciprofloxacin DPI N=60 (100%) n (%)	Placebo N=64 (100%) n (%)
Gastrointestinal disorders		
Any	9 (15.0)	1 (1.6)
Abdominal distension	1 (1.7)	0 (0.0)
Abdominal pain	1 (1.7)	0 (0.0)
Diarrhea	2 (3.3)	1 (1.6)
Dysphagia	1 (1.7)	0 (0.0)
Gastroesophageal reflux disease	1 (1.7)	0 (0.0)
Hematochezia	1 (1.7)	0 (0.0)
Nausea	3 (5.0)	0 (0.0)
General disorders and administration site conditions		
Any	10 (16.7)	14 (21.9)
Product taste abnormal	8 (13.3)	7 (10.9)
Infections and infestations		
Any	13 (21.7)	23 (35.9)
Exacerbation of bronchiectasis	7 (11.7)	14 (21.9)
Candidiasis	0 (0.0)	1 (1.6)
Lower respiratory tract infection	1 (1.7)	0 (0.0)
Sepsis	0 (0.0)	1 (1.6)
Sputum purulent	0 (0.0)	1 (1.6)
Nervous system disorders		
Any	8 (13.3)	6 (9.4)
Dysgeusia	4 (6.7)	1 (1.6)
Headache	4 (6.7)	5 (7.8)
Respiratory, thoracic, and mediastinal disorders		
Any	8 (13.3)	10 (15.6)
Asthma	1 (1.7)	0 (0.0)
Bronchospasm	3 (5.0)	2 (3.1)
Cough	0 (0.0)	5 (7.8)
Dysphonia	0 (0.0)	1 (1.6)
Dyspnea exertional	1 (1.7)	0 (0.0)
Hemoptysis	1 (1.7)	2 (3.1)
Increased upper airway secretion	1 (1.7)	0 (0.0)
Sputum retention	1 (1.7)	0 (0.0)
Throat irritation	0 (0.0)	1 (1.6)
Wheezing	2 (3.3)	0 (0.0)

Mild treatment-emergent abnormal product taste was reported by 8 and 7 subjects on ciprofloxacin DPI and placebo, respectively. All events of abnormal product taste were assessed as drug-related by the investigators. Mild treatment-emergent dysgeusia was reported by 4 subjects on ciprofloxacin DPI and 1 subject on placebo. All events of treatment-emergent dysgeusia were assessed as drug-related by the investigators.

In summary, frequency of AEs was similar in both treatment groups apart from gastrointestinal disorders, dysgeusia, which occurred more frequently in the ciprofloxacin DPI group, and infections, which occurred more frequently in the placebo group.

Table 7: Incidence of subjects with selected treatment-emergent, drug-related adverse events by primary system organ class and preferred term (population: intent-to-treat / safety)

Primary system organ class Preferred term	Ciprofloxacin DPI N=60 (100%) n (%)	Placebo N=64 (100%) n (%)
Gastrointestinal disorders		
Any	4 (6.7)	1 (1.6)
Abdominal pain	1 (1.7)	0 (0.0)
Diarrhea	1 (1.7)	1 (1.6)
Gastroesophageal reflux disease	1 (1.7)	0 (0.0)
Nausea	1 (1.7)	0 (0.0)
General disorders and administration site conditions		
Any	8 (13.3)	11 (17.2)
Product taste abnormal	8 (13.3)	7 (10.9)
Infections and infestations		
Any	0 (0.0)	2 (3.1)
Exacerbation of bronchiectasis	0 (0.0)	1 (1.6)
Candidiasis	0 (0.0)	1 (1.6)
Nervous system disorders		
Any	6 (10.0)	2 (3.1)
Dysgeusia	4 (6.7)	1 (1.6)
Respiratory, thoracic, and mediastinal disorders		
Any	4 (6.7)	8 (12.5)
Bronchospasm	2 (3.3)	2 (3.1)
Cough	0 (0.0)	5 (7.8)
Dysphonia	0 (0.0)	1 (1.6)
Hemoptysis	1 (1.7)	0 (0.0)
Increased upper airway secretion	1 (1.7)	0 (0.0)
Throat irritation	0 (0.0)	1 (1.6)

Note: Non-CF idiopathic or post-pneumonic bronchiectasis was the main inclusion criterion for participation in this study. All adverse events of "bronchiectasis" [correct Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term] were actually events of "exacerbation of bronchiectasis". To distinguish clearly between the inclusion criterion "bronchiectasis" and the adverse event "bronchiectasis" (MedDRA Preferred Term), the term "exacerbation of bronchiectasis" is used for the adverse event throughout this report.

Twenty-two subjects on ciprofloxacin DPI and 26 subjects on placebo reported at least 1 AE of exacerbation of bronchiectasis during any time of the study. No AE of exacerbation of bronchiectasis occurred before the first administration of study drug. Seven subjects on ciprofloxacin DPI (worst severity of event: mild, n=3; moderate, n=2; severe, n=2) and 14 subjects on placebo (worst severity of event: mild, n=5; moderate, n=6; severe, n=3) reported at least 1 treatment-emergent AE of exacerbation of bronchiectasis, i.e., after start of study drug treatment up to 7 days after EOT. Only 1 subject on placebo experienced moderate exacerbation of bronchiectasis assessed as drug-related by the investigator. In 3 subjects of the placebo group, severe treatment-emergent exacerbation of bronchiectasis was also considered an SAE (Table 8).

Eighteen late events of exacerbation of bronchiectasis (worst severity of event: mild, n=8; moderate, n=9; severe, n=1), i.e., events occurring >7 days after EOT, occurred in 17 subjects of the ciprofloxacin DPI group. Fourteen late events of exacerbation of bronchiectasis (worst severity of event: mild, n=5; moderate, n=7; severe: n=2) occurred in 13 subjects of the placebo group. In 1 subject of the ciprofloxacin DPI group, severe exacerbation of bronchiectasis occurring >7 days after EOT was also assessed as an SAE. In 3 subjects of the placebo group, moderate (n=1) and severe (n=2) AEs of exacerbation of bronchiectasis occurring >7 days after EOT were also assessed as serious.

Table 8: Frequency of exacerbations of bronchiectasis (population: intent-to-treat / safety

Type of AE	Ciprofloxacin DPI N=60 (100%)		Placebo N=64 (100%)		Total N=124 (100%)	
	Number of subjects with AE	Number of AEs	Number of subjects with AE	Number of AEs	Number of subjects with AE	Number of AEs
Treatment-emergent	7	7	14	15	21	22
Late event	17	18	13	14	30	32
Total	22	25	26	29	48	54

None of the 6 investigator-reported AEs of bronchospasm matched the study-specific definition of bronchospasm, since they were not confirmed by lung function tests. There were 3 subjects with AEs of bronchospasm in each of the 2 treatment groups. In 1 subject per treatment group, the bronchospasm occurred after EOT. The event of bronchospasm in the placebo group was not treatment-emergent (18 days after EOT). All 4 AEs of bronchospasm during study drug treatment were assessed as drug-related.

Two subjects of the ciprofloxacin DPI group and 5 subjects of the placebo group reported at least 1 AE of cough during the study. No AE of cough occurred before the first administration of study drug. No subject on ciprofloxacin DPI and 5 subjects on placebo (mild: n=4; moderate: n=1) reported at least 1 treatment-emergent AE of cough, i.e., after start of study drug treatment up to 7 days after EOT. In all 5 subjects on placebo, cough was assessed as drug related by the investigator. Two late events of mild cough, i.e., events occurring >7 days after EOT, occurred in 2 subjects of the ciprofloxacin DPI group and none in the placebo group.

One subject of the ciprofloxacin DPI group and 3 subjects of the placebo group reported at least 1 AE of hemoptysis during any time of the study. No AE of hemoptysis occurred before the first administration of study drug. One subject on ciprofloxacin DPI and 2 subjects on placebo reported at least 1 treatment-emergent AE of mild hemoptysis, i.e., after start of study drug treatment up to 7 days after EOT. In all subjects, hemoptysis was assessed as drug-related by the investigator. One late event of mild hemoptysis, i.e., events occurring >7 days after EOT, occurred in 1 subject of the placebo group.

In summary, treatment-emergent AEs of exacerbation of bronchiectasis were substantially less frequent in the ciprofloxacin DPI group as compared to the placebo group. In contrast, late events of exacerbation of bronchiectasis (>7 days after EOT) occurred with a similar frequency in both treatment groups. Overall, bronchospasm was uncommon in both treatment groups. None of the 6 investigator-reported AEs of bronchospasm matched the study-specific definition of bronchospasm, since they were not confirmed by lung function tests. All AEs of bronchospasm during study drug treatment (n=2 per group) were assessed as drug-related.

Cough and hemoptysis were uncommon in both treatment groups but tended to be more frequent in the placebo group.

There was no signal detected for any ciprofloxacin DPI-induced change in any liver function test or any ciprofloxacin DPI-induced change in serum creatinine.

Minimum inhibitory concentration (MIC) increases possibly or probably related to study drug treatment were noted in 6 subjects of the ciprofloxacin DPI group. Of these 6 subjects, 1 dropped out early, 4 showed MIC decreases during the off-treatment follow-up to susceptible, and 1 subject maintained a resistant *Pseudomonas aeruginosa* although the MIC value did decrease during the off-treatment period of 56-day follow-up.

Results Summary — Pharmacokinetics
Plasma concentrations in the range of 0.010 to 0.171 mg/L were observed 15 min to 7 hours after inhalation of the dose indicative of a low systemic drug exposure in the subject population as expected from previous studies in cystic fibrosis and chronic obstructive pulmonary disease (COPD) subjects. For sputum, the observed concentrations ranged between 2.7 to 849.1 mg/L from 15 min to 4 hours after inhalation of the dose and exhibited a high inter-individual variability.

Conclusion(s)

Efficacy

- In this study, ciprofloxacin DPI 32.5 mg BID for 28 days produced significant reductions in bacterial burden in subject sputum compared to placebo in non-CF bronchiectasis subjects. Significant reductions were also observed in the major species of bacteria and eradication (negative bacterial culture) was observed in more ciprofloxacin DPI-treated subjects compared to placebo-treated subjects.

Safety

- A 4 week treatment with ciprofloxacin DPI 32.5 mg BID was safe and well tolerated in subjects with non-CF bronchiectasis.

Publication(s):	None		
Date Created or Date Last Updated:	19 APR 2012	Date of Clinical Study Report:	24 AUG 2011

Product Identification Information

Product Type	Drug
US Brand/Trade Name(s)	Cipro® XR
Brand/Trade Name(s) ex-US	Baycip Baycip XR Ciflox Ciprin Cipro Cipro LP Cipro OD Cipro XL Cipro XR Ciproxan Ciproxin Ciproxin OD Ciproxin RM Ciproxin XR Ciproxina Ciproxina XR Ciproxine Ciprobay Ciprobay XR Ciprouro
Generic Name	Ciprofloxacin hydrated, Ciprofloxacin hydrochloride
Main Product Company Code	BAYo9867
Other Company Code(s)	
Chemical Description	Ciprofloxacin: 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid hydrochloride
Other Product Aliases	

Date of last Update/Change: 11 Feb 2014