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 Pharmaceuticals Inc.	
Study Number:	12429	NCT00645788
Study Phase:	IIb	
Official Study Title:	Randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety and efficacy of inhaled ciprofloxacin compared to placebo in subjects with cystic fibrosis	
Therapeutic Area:	Anti-Infectives	
Test Product		
Name of Test Product:	Ciprofloxacin (Cipro Inhale, BAYQ3939)	
Name of Active Ingredient:	Ciprofloxacin	
Dose and Mode of Administration:	Test drug: 32.5 mg Ciprofloxacin dry powder for inhalation (DPI) (total amount of powder 50 mg) 48.75 mg Ciprofloxacin DPI (total amount of powder 75 mg) Dose: • 32.5 mg ciprofloxacin DPI corresponding to 50 mg Ciprofloxacin PulmoSphere® Inhalation Powder BID (twice daily) • 48.75 mg ciprofloxacin DPI corresponding to 75 mg Ciprofloxacin PulmoSphere® Inhalation Powder BID Mode of Administration: Per inhalation using Novartis' (formerly Nektar's) T-326 Powder Inhaler Device (T-326 Inhaler)	
Reference Therapy/Placebo		
Reference Therapy:	Matching placebo 32.5 mg Matching placebo 48.75 mg	
Dose and Mode of Administration:	Dose: Not applicable Mode of Administration : Per inhalation using Novartis' (formerly Nektar's) T-326 Powder Inhaler Device (T-326 Inhaler)	
Duration of Treatment:	Twenty-eight days each of test and reference therapies.	
Studied period:	Date of first subjects' first visit:	05 MAY 2008
	Date of last subjects' last visit:	25 JAN 2011
Premature Study Suspension / Termination:	No	
Substantial Study Protocol Amendments:	The original protocol was dated 23 JAN 2008. There were 7 protocol amendments.	

	Amendment no. 1 (dated 04 SEP 2008) was globally implemented with the following modifications: • Inclusion of subjects 12 to 17 years of age was added based upon the availability of safety and pharmacokinetic (PK) data in this age group. The informed consent procedures for adolescents were added. Exclusion criteria were added pertaining to subjects who were <18 years of age. An examination of the musculoskeletal system was added at all visits except Visit 6 for subjects <18 years of age. A recommendation that subjects <18 years of age who developed arthropathy should consult a specialist for evaluation was added. Text regarding the Cystic Fibrosis (CF) Quality of Life Questionnaire Revised (CFQ-R) was updated to include the use of the child version of the questionnaire (for subjects aged 12 to 13 years). • The inclusion criterion was updated to allow subjects a ±10% variability in forced expiratory volume in 1 second (FEV_1) for inclusion into the study since subjects with stable CF could have had this much variability between visits 1 and 3. • The inclusion criterion specifying that subjects were required to be off antibiotics (except macrolide) and ciprofloxacin was modified. • The exclusion of subjects with *Burkholderia cepacia* colonization of their respiratory tract within the past 12 months was replaced with *Burkholderia cepacia* complex colonization. • Previous experience in humans was updated with new information. • Updated results from clinical studies were added. • The original protocol said that study drug would be dispensed to subjects at Visits 3 and 5. This was changed to Visit 3 only. • Originally, subjects were to remain at the clinic site for 4 hours after the first dose to monitor for bronchospasms. A provision was added to allow discharge earlier than 4 hours after the first dose if the subject was clinically stable based on the investigator's clinical judgment. • Pulse oximetry monitoring was added to every site visit. • Conditions were added under which the first screening visit could be skipped. • Text was added to clarify that the predose values from the pulmonary function tests at the baseline and each treatment visit were used to calculate the primary and secondary efficacy parameters. Amendment no. 2 (dated 16 DEC 2008) was globally implemented with the following modifications: • A third arm of 48.75 mg Ciprofloxacin DPI BID was introduced due to a recommendation from the FDA to incorporate a higher dose group into the ongoing study. • The study was extended to Australia and selected European countries to improve the subject recruitment rate. • Text was added to specify that the blinding of this study was with respect to active and placebo treatment, not between different doses of active treatment. • Descriptions of the plasma and sputum sampling procedures for the ciprofloxacin PK analysis were added. • Text was added reflecting the changes of the statistical analysis

due to the introduction of the 48.75 mg treatment arm and the PK analysis.
- Text was added that in the event that Visit 1 was skipped, the assessments at Visit 1 that were not already scheduled for Visit 2 should be performed at Visit 2.
- The upper limit of stable pulmonary status at Visit 1 was changed from FEV_1 ≤75% to ≤80%.
- The inclusion criterion requiring subjects to be off antibiotics (except macrolide) and Ciprofloxacin (oral) for at least 30 days prior to study drug was revised to allow the administration of non-antipseudomonal antibiotics for other indications.
- Exclusion criteria concerning severe allergic reactions were specified, adding that subjects with invasive disease, acute bronchopulmonary aspergillosis (ABPA) with IgE >500 mg/dL would be excluded.

Amendment no. 3 (dated 17 FEB 2009) was a local protocol only applicable to centers in Germany and consisted of one change. At Visit 1, a chest X-ray within 3 months of dosing was required. To comply with the standard of care in Germany, chest X-rays within 12 months of dosing were accepted for subjects in Germany.

Amendment no. 4 (dated 24 MAR 2009) was a local protocol only applicable to centers in Denmark and Norway, excluding children (12 to 17 years of age) from participating in this study. In the opinion of participating physicians, it was not feasible to include children and adolescents in this study. While only adult subjects aged 18 years of age or older were permitted to be randomized into the study in Norway and Denmark, no subjects were enrolled in Norway and later sites in Norway were cancelled.

Amendment no. 5 (dated 25 JUN 2009) was a local protocol only applicable to centers in Germany, excluding children (12 to 17 years of age) from participating in this study. In the opinion of the German ethics committee, it was not feasible to include children and adolescents in this study. Only adult subjects aged 18 years of age or older were randomized into the study in Germany.

Amendment no. 6 (dated 18 AUG 2009) was globally implemented with the following modifications:
- The sample size was increased from 210 to 245 subjects as recommended by the FDA.
- The inclusion criteria defining stable pulmonary status was changed from an FEV_1 range of ≥35% to ≤80% to ≥35% to ≤75% as recommended by the FDA.
- Used capsules were no longer to be discarded, but were to be returned to the sites for accountability.
- Clarification was added to ensure that the times of the 2 doses before the PK samples were taken were documented.
- Clarification was made to the list of assessments required at Visit 2 in the event that Visit 1 was skipped.
- Clarification was made to statistical text.

Amendment no. 7 (dated 01 JUL 2010) was globally implemented to increase the sample size from 245 to 276 subjects, based on a recommendation of the FDA.

Study Centre(s):	A total of 73 planned centers in 8 countries were Australia (6 centers), Canada (3 centers), Denmark (1 center), Germany (4 centers), Israel (4 centers), Sweden (3 centers), United Kingdom (1 center) and United States (51 centers).
Methodology:	Subjects were screened; those who signed the informed consent entered the washout period (Visits 1-3; up to 4 weeks) then randomized to study treatment, and at Visit 3 underwent assessment for bronchospasm and pulmonary function testing. The subjects who had signed consent for participation in the PK portion of the study, yielded samples of plasma and sputum. Treatment visits included Visit 4 (Day 7 - 9), Visit 5 (Day 14 – 16), and Visit 7 (End of treatment/therapy [EOT], Day 28 – 30). Actions for Visit 6 (Day 21 – 23) involved a phone call, instead of an actual visit to the study center. Study drug was administered at the study site in the presence of the study staff at Visits 4, 5, and 7. There were 2 follow-up visits; Visit 8 (Day +13-+15), and Visit 9 (Day +28-+30). The assessments at baseline and at various visits included a physical examination, pulmonary function testing (performed prior to and 30 minutes following completion of inhalation treatment), pulse oximetry, vital signs, hematology and chemistry, serum and urine pregnancy tests for females of child-bearing potential, CFQ-R, sputum culture and susceptibility testing, PK plasma and sputum sampling in subjects selected to participate in the PK investigation, recording of adverse events (AEs) and concomitant medications, as well as supervised administration of the study drug and dispensing of the study drug. **Pulmonary Exacerbation**: Assessment of pulmonary exacerbation was conducted by the treating physician as part of the physical examination. Pulmonary exacerbation was defined by chest examination findings along with symptoms that included decreased exercise tolerance, increased cough, increased sputum/cough congestion, school or work absenteeism, increased adventitial sounds on the lung examination, and decreased appetite. The pulmonary exacerbation defined as a drop in FEV_1 of ≥10% when detected was documented as part of the pulmonary function test. **Pulmonary Function Testing**: Applicable definitions are as follows: **FEV_1**: The maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration, expressed in liters at body temperature and ambient pressure saturated with water vapor (BTPS). **FVC (Forced vital capacity)**: The maximal volume of air exhaled with maximally forced effort from a maximal inspiration, i.e., vital capacity performed with a maximally forced expiratory effort expressed in liters at BTPS.

	$FEF_{25-75\%}$ (also known as the maximum midexpiratory flow [MMEF]): The mean forced expiration flow over the middle half of the FVC. It should be taken from the blow with the largest sum of FEV_1 and FVC. Pulmonary function testing (spirometry) was conducted in accordance with American Thoracic Society (ATS) standards. The pre- and post dose pulmonary function testing at each During Treatment visit and at EOT was conducted to determine the incidence of drug-induced bronchospasm. Changes in FEV_1 after administration of the study drug were expressed as percentages of the values obtained before administration of the study drug. Drug-induced bronchospasm was defined as a fall in FEV_1 of ≥15% following drug administration and was to be recorded as an AE. **CF Quality of Life Questionnaire Revised (CFQ-R)**: The CFQ-R is a validated disease-specific instrument that measures health-related quality of life (HRQOL) for adolescents and adults with CF and was administered to all subjects consistent with the protocol. An appropriate version was used for adults and adolescents (subjects 14 years of age and older). CFQ-R has shown good reliability (Cronbach α= 0.67 to 0.94) and acceptable test-retest stability (rs = 0.45 to 0.90). It is self-administered and consists of 44 items, divided into 12 generic and disease-specific scales. The scales include: physical functioning, role, vitality, emotional functioning, social functioning, body image, eating disturbances, treatment burden, health perceptions, weight, respiratory symptoms, and digestive symptoms. The CFQ-R Child Version is a self-report, 35 item-instrument for 12 to 13-year-olds. It assesses multiple domains including physical symptoms, emotional and social functioning, body image, eating disturbances, treatment burden, respiratory, and digestive symptoms. The changes from baseline in the Ciprofloxacin DPI-treated subjects compared to the matching placebo-treated subjects at each During Treatment visit, EOT, and Follow-up were performed. **Sputum microbiology**: Sputum or throat swabs for culture and susceptibility testing were collected at all study visits except for Visit 6 that only involved a phone contact. All microbiological studies were conducted by a central laboratory facility. **Colonization by *Pseudomonas aeruginosa***: Sputum collection was attempted at each study visit except at Visit 6. Throat swabs could be used for confirmation of *P. aeruginosa* colonization at Visits 1 and 2. **Density determination for *Pseudomonas aeruginosa***: *P. aeruginosa* density was estimated by determining the number of colony forming units (CFUs) per gram of sputum. The data were

	expressed as log10[CFU] per gram of sputum, displayed versus time. ***P. aeruginosa* ciprofloxacin resistance**: The potential development of ciprofloxacin resistance during the course of the 28-day period of therapy was assessed by determining the change in the distribution of isolate ciprofloxacin MIC values at baseline and each subsequent study visit. **Drug concentration measurement**: For investigating drug exposure and potential relationships to drug effects, plasma and sputum concentrations of ciprofloxacin were determined at baseline, and at any two of the 3 Visits: 4, 5, and 7 [at the time-points described in the next paragraph], including a sparse sampling approach also in all subjects who participated in the PK analysis portion of the study. **Sampling windows for plasma at each visit**: Pre dose (= trough), <15 minutes, 2.0 – 2.5 hours, 4 - 7 hours after end of inhalation. **Sampling of sputum at each visit**: The subjects were asked to donate at least one sputum sample whenever they could produce sputum without being induced. Samples were collected in separate containers with the actual sampling time documented. PK plasma and sputum samples were analyzed for ciprofloxacin using validated HPLC methods. Ciprofloxacin concentrations in plasma and sputum were measured by a validated HPLC-MS/MS method. The bioanalyst was blinded for analysis of all study samples.
Indication/ Main Inclusion Criteria:	Indication: Cystic fibrosis Main Inclusion Criteria: Population characteristics: Subjects were eligible for enrollment into the study if they met the inclusion criteria; viz., subjects with documented diagnosis of CF, chronic colonization with *P. aeruginosa*, stable condition and stable regimen of CF. Documented diagnosis of CF: • documented sweat chloride ≥60 mEq/L by quantitative pilocarpine iontophoresis test (QPIT) or nasal potential difference • or either homozygous for ΔF508 genetic mutation or a compound heterozygous for 2 known CF mutations • clinical findings consistent with CF The following inclusion criteria had to be met at Visit 1 and confirmed again at Visit 3 for subjects to be included in the study: • Subjects, or their legal representative(s), who had given their written informed consent to participate in the study after receiving adequate previous information and prior to any study specific procedures • Children (12 to 17 years) or adults ≥18 years (inclusion of children in all countries except in Norway, Denmark, and

	Germany) • Chronic colonization with *P. aeruginosa* defined as a positive respiratory tract culture (sputum or throat swab) within 12 months prior to screening and at screening (Note: subjects with negative culture at screening could have been rescreened at a later date at the discretion of the investigator) • Ability to perform reproducible pulmonary function tests • Ability to produce sputum (noninduced) • Stable pulmonary status, FEV_1 ≥35% to ≤75% (intraindividual variability ±10% of absolute value). Note: The subject was not eligible for enrollment if the variability resulted in (or led to) an FEV_1 <35% • Room air oximetry ≥88% saturation • Off antibiotics (except macrolide) and ciprofloxacin (oral) for at least 30 days prior to the administration of study drug for pulmonary exacerbation. Non-antipseudomonal antibiotics administered for other indications were allowed • Stable regimen of standard CF treatment including chest physiotherapies and exercise regimens were unchanged during the 30 days prior to the administration of study drug and during the study (including macrolide administration unchanged in the previous 30 days) • Subjects who were able to understand and follow instructions and who were able to participate in the study for the entire period • Women who were willing to use an adequate method of contraception for 3 months after receiving the study drug. Adequate methods of contraception included vasectomy or condom use by their partners, diaphragm with spermicidal gel, coil (intrauterine device), surgical sterilization, or oral contraceptive.
Study Objectives:	<u>Primary:</u> The primary objective was to compare the change in forced expired volume in 1 second (FEV_1) from baseline to Days 28 to 30 between Ciprofloxacin DPI-treated and matching placebo-treated CF subjects after a 4 week treatment period. <u>Secondary:</u> The secondary objectives were: • To compare the change in FEV_1 from baseline to Visits 4, 5, and Follow-up Visits 8 and 9 between the different treatment groups (32.5 mg Ciprofloxacin DPI BID, 48.75 mg Ciprofloxacin DPI BID and matching placebo) • Assess the change in *Pseudomonas aeruginosa* density in the sputum from baseline between the different treatment groups (32.5 mg Ciprofloxacin DPI BID, 48.75 mg Ciprofloxacin DPI BID, and matching placebo) at Visits 4, 5, 7, 8, and 9 • Determine the time to first pulmonary exacerbation requiring any antipseudomonal intervention or hospitalization occurring in subjects given different doses of Ciprofloxacin DPI compared to subjects given matching placebo • Assess the change from baseline FVC and forced expiratory flow ($FEF_{25-75\%}$) rate among the different treatment groups (32.5 mg Ciprofloxacin DPI BID, 48.75 mg Ciprofloxacin DPI BID, and matching placebo) at Visits 4, 5, 7, 8, and 9

	• Determine the incidence of ciprofloxacin-resistant *Pseudomonas aeruginosa* isolates in the Ciprofloxacin DPI-treated groups after 28 days of therapy compared to the placebo-treated group • Determine differences between the different treatment groups (32.5 mg Ciprofloxacin DPI BID, 48.75 mg Ciprofloxacin DPI BID, and matching placebo) concerning quality of life (QOL) as measured by the CF Quality of Life Questionnaire- Revised (CFQ-R) the respiratory symptom score as secondary endpoint at Visits 7 and 9 • Assess the safety profile of subjects given different doses of Ciprofloxacin DPI compared to placebo • Assess the occurrence of drug-induced bronchospasm in subjects given different doses of Ciprofloxacin DPI compared to placebo • Determine plasma and sputum concentrations of ciprofloxacin at predefined time windows on at least 2 occasions during treatment from selected subjects in selected centers
Evaluation Criteria:	Efficacy (Primary): The primary efficacy parameter was the change in Forced expired volume in 1 second; maximal volume of air exhaled in the first second of a forced expiration (FEV_1) from baseline to Day 28 - 30 in subjects on placebo compared to subjects on either 32.5 mg Ciprofloxacin DPI or 48.75 mg Ciprofloxacin DPI therapy administered BID at EOT. Efficacy (Secondary): The secondary efficacy parameters included: • The change in FEV_1 from baseline in subjects on placebo compared to subjects on either 32.5 mg ciprofloxacin DPI BID or 48.75 mg ciprofloxacin DPI BID therapy at Visits 4, 5, 7, 8, and 9 • Change from baseline in subjects on either 32.5 mg ciprofloxacin DPI BID or 48.75 mg ciprofloxacin DPI BID compared to placebo in *P aeruginosa* density in sputum cultures at Visits 4, 5, 7, 8, and 9 • Time to first pulmonary exacerbation that required any (intravenous [IV], oral [PO], or inhaled) anti-pseudomonal intervention or hospitalization in subjects given either 32.5 mg Ciprofloxacin DPI BID or 48.75 mg Ciprofloxacin DPI BID compared to subjects given matching placebo • Change from baseline in subjects on either 32.5 mg Ciprofloxacin DPI BID or 48.75 mg Ciprofloxacin DPI BID compared to placebo in FVC and $FEF_{25-75\%}$ at Visits 4, 5, 7, 8, and 9 • Incidence of ciprofloxacin-resistant *P aeruginosa* isolates in the 32.5 mg Ciprofloxacin DPI BID or 48.75 mg Ciprofloxacin DPI BID-treated group, after 28 days of therapy, compared to the placebo treated group • Change from baseline in subjects on 32.5 mg Ciprofoxacin DPI or 48.75 mg Ciprofloxacin DPI compared to placebo in total cystic fibrosis questionnaire-revised (CFQ-R) including the respiratory symptom score as secondary endpoint score at Visits 7 and 9 • Determination of plasma and sputum concentrations of ciprofloxacin at predefined time windows on at least 2

	occasions during treatment from selected subjects in selected centers Safety: Assessment of the safety profile of subjects given different doses of Ciprofloxacin DPI compared to matching placebo. Also, to assess the occurrence of drug-induced bronchospasm in subjects given different doses of Ciprofloxacin DPI compared to matching placebo. 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.
Statistical Methods:	Efficacy (Primary): The primary efficacy analysis was a comparison between the different treatment groups (32.5 mg Ciprofloxacin DPI BID, 48.75 mg Ciprofloxacin DPI BID, and matching placebo) on change in FEV_1 in liters after the 28-day treatment period in the intent-to-treat (ITT) population. In subjects who prematurely terminated treatment, the last observation was carried forward (LOCF). The parameters of the lung function tests (FEV_1, FVC, and $FEF_{25-75\%}$) were described by the following summary statistics: arithmetic mean, standard deviation, minimum, 25% and 75% percentile, median and maximum. Changes in FEV_1 after administration of the study drug were expressed as percentages of the values obtained before administration of the study drug. These summary statistics were presented by treatment for the data as well as for the change from baseline. The pre dose values were used for the change from baseline efficacy analyses. The post dose evaluations were to monitor for the occurrence of drug induced bronchospasms in subjects given either 32.5 mg Ciprofloxacin DPI BID or 48.75 mg Ciprofloxacin DPI BID compared to matching placebo. Graphical displays of mean values with confidence intervals were included. Change in FEV_1 was analyzed by a three way analysis of covariance with factors treatment group (32.5 mg Ciprofloxacin DPI BID, 48.75 mg Ciprofloxacin DPI BID, and matching placebo), macrolide use (no/yes) and center. The dependent variable was FEV_1 at the last visit of the 28 day treatment period; baseline FEV_1 served as a covariate. To check appropriateness of the main factor model, a model including interactions was calculated. Any evidence of interaction found was explored. Efficacy (Secondary): The secondary efficacy variables were analyzed as follows: • Changes in *P. aeruginosa* density in sputum were analyzed with a log linear model: the depended variable being (the logarithm of log 10(cfu+1)) *P. aeruginosa* density in sputum at EOT. Factors were treatment group, center and macrolide use (no/yes); (the logarithm of) pre-treatment *P. aeruginosa* density in sputum served as a covariate.

	• Time to intervention with an inhaled/IV or oral antipseudomonal treatment was analyzed using a stratified (strata: center, use of macrolides) log rank test. • Changes in FVC, and FEF $_{25-75\%}$ were analyzed analogously to FEV_1, with baseline FVC or FEF $_{25-75\%}$, respectively, serving as a covariate. All other efficacy variables, as well as the above mentioned, were displayed using descriptive statistics. All of these descriptive statistics were also displayed by age group. <u>Safety:</u> Adverse events were documented up to 7 days after EOT. All AEs reported as "ongoing" or "new event" up to 7 days post-therapy were followed up to the 30 day post-treatment time-point. Serious AEs were recorded and documented up to 30 days after EOT. The AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA) coding dictionary, version 13.1.
Number of Subjects:	Total planned enrollment: 210 were originally planned; later increased to 245 per Amendment 6 and to 276 per Amendment 7 Total analyzed: 286 • 32.5 mg Ciprofloxacin DPI: 93 subjects • 48.75 mg Ciprofloxacin DPI: 93 subjects • Matching placebo 32.5 mg: 65 subjects • Matching placebo 48.75 mg: 35 subjects

Study Results

Results Summary — Subject Disposition and Baseline

Of all enrolled 476 subjects, 188 were screening failures and 288 were randomized. Two of those randomized did not take the study drug; therefore, not included in the full analysis, ITT or safety analyses sets. Of these, 286 were included in the ITT/safety population and 217 in the per protocol (PP) population. The full analysis set included 286 subjects [100%]. Of these, 235 subjects [81.6%] completed the study treatments, 209 subjects [72.6%] completed the study.

A total of 286 subjects were valid for ITT/safety analyses; 186 subjects received ciprofloxacin (93 in each of the dosage groups, 32.5 mg or 48.75 mg) and 100 subjects received matching placebo. The demographic characteristics by sex, race, age, weight, height, BMI status on lactation, and stratum information whether macrolide was used (yes or no) were similar for subjects in the ciprofloxacin and matching placebo treatment groups in this population. Almost all subjects were Caucasian (white) (97% in ciprofloxacin and 100% in placebo treatment groups), consistent with the disease etiology that CF is mainly found in subjects of European descent. Only 4 subjects identified as Black or African American were enrolled and randomized to receive ciprofloxacin (3 subjects had 32.5 mg dose and one had 48.75 mg dose). There were approximately 51% male and 49% female subjects in ciprofloxacin group and 58% male vs 42% female subjects in the placebo group. A majority of subjects (65% - 70%) in each treatment group were on macrolide therapy.

Seventy-nine subjects [27.4% of those randomized] had discontinued prematurely from the study; the primary reasons for discontinuation were adverse events (21 subjects [26.6%]), protocol violation (3 subjects [3.8%]), withdrawal of consent (4 cases [5.1%]), lost-to-follow-up (1 subject [1.3%]). A majority of all those who discontinued (50 subjects [63.3%]) cited a reason "other" than those described above. There were three cases of haemoptysis, considered as suspected unexpected serious adverse reaction (SUSAR) leading to unblinding

of the study treatment by decisions of Bayer Global Pharmacovigilance [GPV] due to safety concerns. These subjects (140390006, 140500004 and 400040005) were not included in the PP population for further analyses.

Genotypic testing was performed at baseline and the results for the ITT/safety population showed a vast majority of subjects (88.2% in the ciprofloxacin DPI group and 87.0% in the matching placebo group) consented for genetic testing. While the genetic data were not available for approximately 11% of the subjects, over 70% of subjects in the ITT/safety population were positive for allele 1 and close to 40% of subjects for allele 2 of the F508del mutation marker.

Approximately 45% of subjects in the ciprofloxacin group (51.6% who received 32.5 mg ciprofloxacin DPI mg and 41.9% 48, 75 mg ciprofloxacin DPI) and 38.0% of subjects in the matching placebo group of the ITT/safety population had been hospitalized for their last exacerbation of CF disease.

A vast majority of subjects (close to 80%) in the ITT/safety population had used short acting bronchodilators; while 21.5% and 17.2% of subjects in 32.5 mg ciprofloxacin DPI and 48.75 mg ciprofloxacin DPI, respectively, and 14% of those in combined placebo group had used long-acting bronchodilators. Subjects were on bronchodilators at enrollment as part of standard of care; a stable regimen of standard CF treatment (e.g., bronchodilators) was maintained during the 30 days prior to the administration of study drug and during the study.

Medical history findings showed that in the 32.5 mg ciprofloxacin DPI, 48.75 mg ciprofloxacin DPI and combined placebo groups for all subjects of the ITT/safety population, 17 (18.3%), 22 (23.7%) and 19 (19.0%) subjects, respectively, had bronchiectasis. However, at that time colonization by *Pseudomonas* species was detected in 2 (2.2%) of the subjects in the 32.5 mg ciprofloxacin DPI group, 3 (3.3%) in the 48.75 mg ciprofloxacin DPI group, and 8 (8.0%) in the combined placebo group of the ITT/safety population. This lack of detection could have been a transient feature for the condition of subjects or the assessment at that time.

There were chest X-ray and chemistry and hematological analysis performed at Visit 1 (screening/washout period) for all subjects in the ITT/safety and PP populations, and the data were reported by treatment groups for potentially clinically significant findings. Clinically significant, abnormal chest X-ray findings were reported in 10 (10.8%), 6 (6.5%), and 6 (6.0%) subjects in the 32.5 mg ciprofloxacin DPI, 48.75 mg ciprofloxacin DPI, and combined placebo groups, respectively.

Similar demographic and baseline characteristics were observed for the ITT/safety and PP populations in this study, overall and by treatment groups. There were no major differences between the treatment groups (ciprofloxacin vs matching placebo, and between the two dosage groups of ciprofloxacin) in the ITT/safety population.

Results Summary — Efficacy

Consistent with the descriptions of statistical methods as well as the statistical analysis plan for this study, a hierarchical testing procedure starting with a combined hypothesis was used as described below:

H0: Treatment effect - Ciprofloxacin 32.5 mg = Placebo 32.5 mg
- Ciprofloxacin 48.75 mg = Placebo 48.75 mg

Followed by simultaneous testing of the 2 single hypotheses:

H0: Treatment effect - Ciprofloxacin 32.5 mg = Placebo 32.50 mg
H0: Treatment effect - Ciprofloxacin 48.75 mg = Placebo 48.75 mg

Finally, the two verum arms should be compared:
H0: Treatment effect - Ciprofloxacin DPI 32.5 mg = Ciprofloxacin DPI 48.75 mg

The data in the Table 1 below show that none of the four hypotheses could be rejected. Therefore, the study did not provide primary evidence for efficacy of Ciprofloxacin DPI. However, there seemed to be some evidence for efficacy of Ciprofloxacin DPI for improving lung function as measured by FEV_1, as pooled verum versus pooled placebo has a p value <0.05; and both contrasts, Ciprofloxacin DPI 32.5 mg versus Ciprofloxacin DPI 48.75 mg and matching placebo 32.5 mg vs placebo 48.75 mg were non-significant.

Table 1: Main efficacy criterion: FEV_1 [L] at EOT in pre inhalation period of the ITT/safety population - Overall fit statistics

No interaction model (Phase not in model)	R-square	0.8803		
No interaction model incl. phase	R-square	0.8676		
One way interaction model	R-square	0.8936		
Two way interaction model	R-square	0.9011		
Overall ANCOVA				
		MS, DF, p-value		
No interaction model	Model	13.041,	7,	<0.001
	Error	0.045,	278,	
	Corrected Total	,	285,	
Analysis of effects(type III)				
		MS, DF, p-value		
No interaction model	Covariate	87.614,	1,	<0.001
	Treatment	0.079,	3,	0.154
	Region	0.010,	2,	0.805
	Stratum (Macrolide use)	0.105,	1,	0.126
Contrasts				
		MS, DF, p-value		
No interaction model	**Pooled verum vs. pooled placebo**	**0.232,**	**1,**	**0.023**
Testing hierarchy	Verum vs. pooled placebo	0.117,	2,	0.075
1	Verum vs. matching placebo	0.116,	2,	0.076
	CFX 32.5 mg vs. pooled placebo	0.157,	1,	0.062
2	CFX 32.5 mg vs. matching placebo	0.100,	1,	0.136
	CFX 48.75 mg vs. pooled placebo	0.191,	1,	0.040
3	CFX 48.75 mg vs. matching placebo	0.131,	1,	0.087
4	CFX 32.5 mg vs. CFX 48.75 mg	0.002,	1,	0.851
	Placebo 32.5 mg vs. Placebo 48.75 mg	0.005,	1,	0.735

Abbreviations: FEV_1 = Forced expired volume in 1 second, L = Liter, EOT = end of treatment/therapy, ITT = intent-to-treat, ANOVA = analysis of variance, MS = mean square, DF = degrees of freedom, CFX = ciprofloxacin DPI, DPI = dry powder for inhalation, R-square = Coefficient of determination = Regression sums of squares divided by total sums of squares.
NOTE: Imputation method used was last observation (value) carried forward (LOCF).

The results from the PP population supported the observations from the ITT population.

It appeared that from randomization to EOT, FEV_1 values declined faster in the placebo groups. The differences between verum groups were minimal, as were differences between placebo groups. These data may include FEV_1 values of those subjects for whom the FEV_1 values declined but a diagnosis of pulmonary exacerbation had not been performed.

Analyses of other lung function parameters included:

- Comparison of the change in FEV_1 from baseline to Visits 4, 5, and Follow-up Visits 8 and 9 between the different treatment groups (32.5 mg Ciprofloxacin DPI BID, 48.75 mg Ciprofloxacin DPI BID, and matching placebo)
- Assessment of changes from baseline FVC and forced expiratory flow ($FEF_{25-75\%}$) rate of the different treatment groups (32.5 mg Ciprofloxacin DPI BID, 48.75 mg

Ciprofloxacin DPI BID, and placebo) at Visits 4, 5, 7, 8 and 9

Accordingly, slight improvement in $FEF_{25-75\%}$ was seen from baseline up to and including the EOT Visit. The percentage values of predicted, difference from baseline was 0.29% for the pooled Ciprofloxacin DPI arms (32.5 mg and 48.75 mg, any dose), 0.24% for ciprofloxacin 32.5 mg, 0.35% for Ciprofloxacin DPI 48.75 mg, while the matching placebo arms showed a decrease of 2.0% (combined placebo groups), 2.1% (matching placebo 32.5 mg), and 1.8% (matching placebo 48.75 mg).

Secondary efficacy variables
Microbiological analyses: In both ciprofloxacin DPI treatment groups, the bacterial load was decreasing for the first nine days during treatment. In the 32.5 mg ciprofloxacin DPI arm, bacterial load continued to decrease for up to Day 15. In contrast, total bacterial load in the higher dose 48.75 mg ciprofloxacin DPI arm, initially decreased in bacterial burden, but then increased after Day 5. Also, in comparison with their matching placebo arms, both ciprofloxacin DPI arms transiently showed nominally significant results of reduced total bacterial load for up to Day 15. At EOT, this change in *P. aeruginosa* density in the sputum from baseline was statically not significant. No sustained long-term decrease in the mean total bacterial load was evident due to any of the study treatments.

Exacerbations: Exacerbations with intervention occurred in 16.1%, 17.2%, 20.0%, and 28.6% of subjects in 32.5 mg ciprofloxacin DPI and 48.75 mg ciprofloxacin DPI, matching placebo 32.5 mg, and matching placebo 48.75 mg treatment groups, respectively. None of the tests performed showed statistically significant differences. Thus, no definitive conclusions in favor of ciprofloxacin DPI treatments could be supported based upon statistical analyses of the exacerbation data, while it should be noted that the study was not sufficiently powered to detect a clear effect.

Time to first exacerbations: Analyses of time to first exacerbations included determination of time to first pulmonary exacerbation requiring any anti-Pseudomonal intervention or hospitalization occurring in subjects given different doses of Ciprofloxacin DPI compared to subjects given matching placebo. Three types of exacerbations were defined and assessed that included investigator defined exacerbation, and those requiring antibiotic intervention and others requiring hospitalization. The main focus was on exacerbations requiring intervention.

A descriptive advantage in exacerbations with intervention of ciprofloxacin DPI over the matching placebo was observed. Exacerbations with intervention occurred in 16% of subjects in 32.5 mg ciprofloxacin DPI, in 17.2% of subjects in the treatment group 48.75 mg ciprofloxacin DPI, in 20.0% of subjects in matching placebo 32.5 mg, and in 28.6% of subjects in matching placebo 48.75 mg treatment group. None of the tests performed showed statistically significant differences. Thus, no definitive conclusions in favor of ciprofloxacin treatments could be supported based upon statistical analyses of the exacerbation data. It should be noted that the study was not powered to detect an effect of treatment on time to first exacerbation.

Quality of Life (CFQ-R)

Analyses of subject's assessment of quality of life using CFQ-R instrument, as one of the secondary objectives revealed that both ciprofloxacin DPI treatment groups (32.5 mg and 48.75 mg) showed statistically significant, but transient effect at EOT that did not sustain at the one month Follow-Up period. Accordingly, 32.5 mg ciprofloxacin DPI group vs matching placebo at EOT was statistically significant ($p = 0.007$), but not at one month Follow-up ($p = 0.935$). Similar effect was observed when 32.5 mg ciprofloxacin DPI group or 48.75 mg ciprofloxacin DPI group was compared to pooled matching placebo groups.

Drug dose or drug concentration, and relationships to response

Plasma and sputum concentrations of ciprofloxacin were determined at predefined time windows on at least 2 occasions during treatment from selected subjects in selected centers. As already shown in previous Clinical Pharmacology studies in CF patients, the data confirmed the low systemic exposure after inhalation compared to standard tablet (systemic) treatment.

Summary of efficacy

The primary analysis was a comparison of the change in FEV_1 from baseline to Days 28 to 30 between 32.5 mg ciprofloxacin DPI or 48.75 mg ciprofloxacin DPI-treated, and matching placebo treated CF subjects after a 4 week treatment period. The null hypotheses of no difference between the treatment groups could not be rejected. The analyses were based on a hierarchical model, consistent with the planned analysis. There seemed to be some evidence for efficacy of Ciprofloxacin DPI for improving lung function as measured by FEV_1, as pooled verum vs pooled placebo had a p-value <0.05. However, no statistically significant difference to support the primary objective in favor of 32.5 mg ciprofloxacin DPI or 48.75 mg ciprofloxacin DPI vs matching placebo treatment for CF subjects to achieve intended change in FEV_1 could be found in the planned analyses. Thus, the results in this study failed to show efficacy in the primary efficacy analysis, and did not provide pivotal evidence of efficacy.

Results Summary — Safety

An important secondary objective in this study was to assess the safety profile of subjects given different doses of ciprofloxacin (for inhalation) compared to matching placebo. Another secondary objective was to assess the occurrence of drug-induced bronchospasm in subjects given different doses of ciprofloxacin DPI compared to matching placebo.

The overall safety profile of 32.5 mg ciprlofloxacin DPI was better than that for the higher dose of 48.75 mg ciprofloxacin DPI, since the latter was associated with more cases of drug-related AEs as well as premature discontinuation of the study drug treatment due to AEs.

There were 3 cases of haemoptysis reported during the study that were considered related to the study drug by the investigator. All the 3 cases were considered SUSARs, leading to unblinding of the study treatment by decisions of Bayer Global Pharmacovigilance due to safety concerns. Apart from these 3 cases of haemoptysis, no new unexpected safety events were reported in this study.

Of the 286 subjects included in the safety/ITT analysis, 76 of 93 subjects (81.7%) in the 32.5 mg ciprofloxacin DPI group, 88 of 93 subjects (94.6%) in the 48.75 mg ciprofloxacin DPI group, 57 of 65 subjects (87.7%) in the matching placebo 32.5 mg group, and 31 of 35 subjects (88.6%) in the matching placebo 48.75 mg group had treatment-emergent signs and symptoms.

Overall, no deaths occurred in this study. The highest frequency of SAEs and AEs were reported in 18.3% and 94.6% subjects in the ITT/safety population, respectively, as observed in the 48.75 mg ciprofloxacin DPI group. Similar frequencies in other treatment groups (32.5 mg ciprofloxacin DPI, and matching placebo 32.5 mg or 48.75 mg) were comparable and not different in the ITT/safety population due to lack of statistically significant results.

All treatment-emergent adverse events (TEAEs) of bronchospasm in the ITT/safety population were 4 (4.3%) in the 32.5 mg ciprofloxacin DPI group, 7 (7.5%) in the 48.75 mg ciprofloxacin group, 3 (4.6%) in matching placebo 32.5 mg group, and none in the matching placebo 48.75 mg group. However, the incidence of treatment-emergent bronchospasm defined as ≥15% decline in FEV_1 in the ITT/safety population occurred in 3 (3.2%) subjects in the 32.5 mg ciprofloxacin DPI group, 3 (3.2%) subjects in the 48.75 mg ciprofloxacin DPI group, 3 (4.6%) subjects in the matching placebo 32.5 mg group, and none of the subjects in the matching placebo 48.75 mg group. Thus, there was no statistically significant difference

(p = 0.741) by treatment groups and the incidence of bronchospasm remained at a fairly low frequency. No subject who had drug related TEAE bronchospasm required discontinuation of the study drug and the respective study drug dose was not changed. All cases of bronchospasm resolved by the end of study, as determined by the investigators.

The differences by treatment groups did not show statistical significance (p = 0.115) when the incidence of TEAEs between 32.5 mg ciprofloxacin DPI group and matching placebo were analysed, although the 32.5 mg ciprofloxacin DPI group had slightly lower TEAE incidence rate.

Most of the drug-related TEAEs were in system organ class (SOC) of general disorders and administration site condition, and nervous system disorders. There was no discernable pattern in the frequency of general disorders and administration site condition specifically due to ciprofloxacin DPI since placebo treatment also caused increased frequency. This could have been likely associated with the treatment procedure more than the nature of the study drug treatment. Almost all cases of drug-related TEAEs of the nervous system disorder were reported as dysgeusia; 13 of 93 subjects (14.0%) in the 32.5 mg ciprofloxacin DPI group, 9 of 93 subjects (9.7%) in the 48.75 mg ciprofloxacin DPI group, 4 of 65 subjects (6.2%) in the matching placebo 32.5 mg group, and 1 of 35 subjects (2.9%) in the matching placebo 48.75 mg group reported dysgeusia. Most subjects who experienced any drug-related TEAE, the study drug action involved no change of study drug dose, and the outcomes were 33 of 35 as resolved and 2 as not resolved in the 32.5 mg ciprofloxacin DPI group, 43 of 46 cases as resolved and 3 as not resolved in the 48.75 mg ciprofloxacin DPI group, all 22 cases as resolved in the matching placebo 32.5 mg group, and 9 of 10 cases as resolved and one as unknown in the matching placebo 48.75 mg group.

Twenty-eight of 46 subjects in the 48.75 mg ciprofloxacin DPI group had no change in dose of study drug; drug withdrawn from 9, and 6 subjects had other actions taken. Fifteen of 22 subjects in the matching placebo 32.5 mg group had no change of study drug dose, drug withdrawn from 5, and one subject had other actions taken. Seven of 10 subjects in the matching placebo 48.75 mg group had no change of study drug dose and the study drug withdrawn from 3.

The most common, maximum intensity of the study drug related TEAEs in ITT/safety analysis set (number of subject with at least one TEAE) was mild; 25 of 93 subjects (26.9%) in the 32.5 mg ciprofloxacin DPI group, 34 of 93 subjects (36.6%) in the 48.75 mg ciprofloxacin group, 16 of 65 subjects (24.6%) in the matching placebo 32.5 mg group, and 9 of 35 subjects (25.7%) in the matching placebo 48.75 mg group.

There were 4 of 93 subjects (4.3%) in the 32.5 mg ciprofloxacin DPI group, 4 of 65 subjects (6.2%) in the matching placebo 32.5 mg group, 11 of 93 subjects (11.8%) in the 48.75 mg ciprofloxacin DPI group, and 2 of 35 subjects (5.7%) in the matching placebo 48.75 mg group who had serious adverse events (SAEs) during the study period. Most of the SAEs were in system organ class (SOC) "Infections and infestations", and a majority of the cases with preferred term (PT) "infective pulmonary exacerbation of cystic fibrosis", which coincide with underlying disease condition of the subjects. Overall, the serious TEAE cases did not include any new, unexpected events other than 3 cases of haemoptysis reported as SUSAR cases and remained at a low frequency of occurrence.

Most of the SAEs had moderate intensity, and a few were of mild and severe intensity. Subjects with serious TEAEs by primary SOC, PT and outcome in the ITT/safety population showed that all serious TEAEs, drug-related or not, and required minimal actions for treatment course and resolved by the end of the study, as determined by the investigators.

The frequency of TEAEs in subjects who received 32.5 mg ciprofloxacin DPI was similar to that observed in the matching placebo 32.5 mg group. Several exceptions of TEAE incidence showed higher frequency in subjects who received matching placebo versus 32.5 mg

ciprofloxacin DPI; these included total number of subjects (81.5% vs 73.1%), headache (10.8% vs 1.1%), cough (29.2% vs 20.4%) and sputum increased (13.8% vs 8.6%), respectively. Similarly, the frequency of cough and increased sputum remained slightly higher in the matching placebo 48.75 group compared to the 48.75 mg ciprofloxacin DPI group. This may suggest potential relief of certain signs and symptoms that may be associated with underlying disease condition and possibly reduced due to the active study drug, and possibly supporting a favorable safety profile. The frequency of dysgeusia was 14.0% and 9.6% in the 32.5 mg ciprofloxacin DPI and 48.75 mg ciprofloxacin DPI groups, respectively, and 6.2% and 2.9% in matching placebo 32.5 mg and 48.75 mg groups, respectively.

There were no remarkable differences in the laboratory analysis values for chemistry, hematology, and urinalysis and the vital signs of subjects by any study treatment group during this study.

Other potential laboratory abnormalities:

Treatment emergent high laboratory values (abnormalities) by laboratory system and treatment in the ITT/safety population showed there was a statistical decline in platelet count; however, the changes in values of platelets were not clinically significant. Eight events of elevated liver enzymes were reported as adverse events; 2 of these related to the study drug (both events were reported for the same case number 140020010) and the laboratory findings for that case were as following:

- At Visit 7 the level of serum glutamic oxaloacetic transaminase/aspartate aminotransferase (SGOT/AST) was 175 (while at baseline was 21, at visit 4 it was 23 and at visit 9 it was 20), serum glutamic pyruvic transaminase/alanine aminotransferase (SGPT/ALT) was 105 (at baseline it was 20, visit 4 it was 19, and at visit 9 it was 17), and total bilirubin at visit 7 was 0.2 (while at baseline it was 0.4, and at Visit 4 it was 0.2, while at visit 9 it was also 0.2).

Thus, the elevated values were only observed at Visit 7 and were normalized at Visit 9, and posed no safety concerns.

Summary of safety: Overall, the safety parameters when assessed by type of TEAEs, intensity, relationship to the study drug, seriousness, outcome, remained comparable and showed no distinct differences between the treatment groups. No deaths occurred during the study. There were no safety concerns identified in this study except for the 3 cases of haemoptysis reported as SUSAR, attributable to the study treatments. The safety profile of 32.5 mg ciprofloxacin DPI was slightly better and more tolerable than that for a higher dose, 48.75 mg ciprofloxacin DPI. The subjects tolerated 32.5 mg ciprofloxacin DPI treatment well, and had fewer cases of discontinuation due to AE.

Conclusion(s)
The results in this study failed to show efficacy in the primary efficacy analysis, and did not provide pivotal evidence of efficacy. Although the primary objective was not met, there were indications of a potential positive drug effect on lung function (FEV_1), bacterial load, and quality of life. These may be further explored via other investigations. All other analyses for the secondary objectives did not show any remarkable or statistically significant difference between any dose of ciprofloxacin DPI and matching placebo. The data from FVC assessments showed no remarkable treatment effect on FVC values. The overall safety profile of 32.5 mg ciprofloxacin DPI was better than that for the higher dose of 48.75 mg ciprofloxacin DPI, since the latter was associated with more cases of drug-related AEs as well as premature discontinuation of study drug treatment due to AEs. No deaths occurred during this study. In conclusion, 4 week treatment with 32.5 mg ciprofloxacin DPI BID was safe and well tolerated and had a more favorable overall profile compared to tolerability of similar formulation with higher dose of 48.75 mg ciprofloxacin DPI in subjects with CF.

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