**Title page**

# Ciprofloxacin DPI (BAY q3939)

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**Introductory note for reviewers**

This briefing document provides 3 levels of review with increasing levels of detail:

- The executive overview (Section 1, starting on Page 12) provides a coherent narrative of the disease under study, key development program characteristics of ciprofloxacin DPI, study results, and conclusions. References are made to the respective supporting sections in the core document.
- The core document (from Section 2 to Section 7; starting on Page 25) includes detailed summaries and discussions in support of the executive overview.
- The appendices (located in in Section 9, starting on Page 98) provide additional or more detailed descriptions of *e.g.*, bioanalytical methodology and additional efficacy and safety analyses for the Phase II/III studies. These appendices are additionally referenced in the core document when relevant.

This review structure allows review at varying levels of detail; however, reviewers who read at multiple levels will necessarily encounter repetition of key materials across the levels.

For those reviewing this document in electronic format, references to tables and figures are electronically linked to the corresponding table or figure. For those reviewing this document in paper format, the page number is provided when the table or figure is in a different section. Note that variability among printers may cause page numbers of printed documents to differ slightly from those provided.

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# Abbreviations and definition of terms

## Abbreviations

| | |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ANCOVA | Analysis of covariance |
| AUC | Area under the curve |
| BID | *Bis in die* (2 times a day) |
| BMI | Body mass index |
| CF | Cystic fibrosis |
| CFU | Colony-forming unit |
| CI | Confidence interval |
| $C_{max}$ | Maximum (peak) concentration |
| CMC | Chemistry, Manufacturing, and Controls |
| COPD | Chronic obstructive pulmonary disease |
| CSR | Clinical study report |
| CYP | Cytochrome P450 |
| DNA | Deoxyribonucleic acid |
| DPI | Dry powder for inhalation |
| EOS | End of study |
| EOT | End of treatment |
| EU | European Union |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| $FEV_1$ | Forced expiratory volume (in 1 second) |
| FVC | Forced vital capacity |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| h | Hour |
| HR | Hazard ratio |
| HRQoL | Health-related quality of life |
| IRR | Incidence rate ratio |
| ITT | Intent to treat (population) |
| i.v. | Intravenous |
| LOCF | Last observation carried forward |
| $log_{10}$ | Decadic logarithm |
| LS | Least square |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MIC | Minimum inhibition concentration |
| min | Minute |
| MMRM | Mixed model for repeated measurements |
| NCFB | Non-cystic fibrosis bronchiectasis |
| NDA | New drug application |
| NTM | Non-tuberculous mycobacteria |
| OD | *Omni dei* (once a day) |
| OR | Odds ratio |
| PD | Pharmacodynamics |
| PiF | Peak inspiratory flow |
| PK | Pharmacokinetics |
| p.o. | *Per os* (orally) |
| PRO | Patient-reported outcome |
| QoL | Quality of life |
| QOL-B | Quality of life-Bronchiectasis (questionnaire) |
| RSDS | Respiratory symptoms domain score (of the QOL-B) |
| SAE | Serious adverse event |
| SAF | Safety analysis set |

| | |
|---|---|
| SAP | Statistical analysis plan |
| SCS | Symptoms component score (of the SGRQ) |
| SD | Standard deviation |
| SGRQ | St. George's respiratory questionnaire |
| SMQ | Standardized MedDRA query |
| SOC | System organ class |
| SS | Steady state |
| $t_{1/2}$ | Half life |
| TEAE | Treatment-emergent adverse event |
| TID | *Ter in die* (3 times a day) |
| US | United States (of America) |
| USPI | United States prescribing information |
| WHO | World health organization |
| w/w | weight/ weight (mass fraction) |

# Definition of terms

| | |
|---|---|
| Cipro 28 / ciprofloxacin DPI 28 (group) | Ciprofloxacin DPI 28 days on/off therapy (group), *i.e.*, ciprofloxacin DPI 32.5mg BID administered in cycles of 28 days on-therapy and 28 days off-therapy. |
| Cipro 14 / ciprofloxacin DPI 14 (group) | Ciprofloxacin DPI 14 days on/off therapy (group), *i.e.*, ciprofloxacin DPI 32.5mg BID administered in cycles of 14 days on-therapy and 14 days off-therapy. |
| Placebo 28 (group) | Placebo 28 days on/off therapy (group), *i.e.*, placebo BID administered in cycles of 28 days on-therapy and 28 days off-therapy (matching ciprofloxacin DPI 32.5 mg BID 28 days on/off therapy). |
| Placebo 14 (group) | Placebo 14 days on/off therapy (group), *i.e.*, placebo BID administered in cycles of 14 days on-therapy and 14 days off-therapy (matching ciprofloxacin DPI 32.5 mg BID 14 days on/off therapy). |
| Pooled placebo (group) | Placebo 28 and placebo 14 treatment groups combined; primary comparator group for ciprofloxacin DPI efficacy and safety assessments. |

# 1. Executive overview

## 1.1 Introduction

There is pressing and unmet medical need for effective reduction of exacerbations in patients with non-cystic fibrosis bronchiectasis (NCFB), which is categorized by FDA as an orphan disease. There are no approved drug therapies available in NCFB for reduction of exacerbations.

Bayer seeks approval for the proposed indication for ciprofloxacin dry powder for inhalation (DPI) 32.5 mg twice daily (BID) 14 days on/off:

*Ciprofloxacin DPI is indicated for reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients (18 years of age and older) with respiratory bacterial pathogens.*

The overall efficacy evaluation is based on the totality of evidence across the endpoints in the two Phase III studies, including exacerbation-related endpoints, microbiology, and patient-reported outcomes for two different treatment regimens delivering ciprofloxacin DPI 32.5 mg BID, compared against placebo. Although the two pivotal trials showed heterogeneity with regard to the efficacy endpoints, the observed treatment effects on efficacy were consistently in favor of the ciprofloxacin treatment regimens compared to standard of care alone.

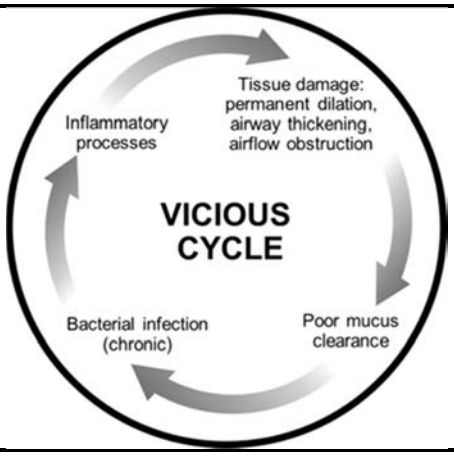
The safety observed with ciprofloxacin DPI 32.5 mg BID *vs.* placebo was consistently favorable throughout the entire clinical development program.

The beneficial treatment effects of ciprofloxacin DPI, and the favorable safety and tolerability of ciprofloxacin DPI observed in the Phase II/III clinical studies, translate into a positive benefit/risk profile for this orphan disease.

## 1.2 Non-cystic fibrosis bronchiectasis

NCFB is a severe, debilitating, chronic respiratory disease, characterized by abnormal and irreversible dilatation of the airways due to repeated airway infection and inflammation. The disease is associated with poor health-related quality of life (HRQoL) and substantial morbidity and mortality. In patients with NCFB, mucus pools in the airways and becomes an ideal environment for the growth of pathogens. Mucus then transforms into purulent sputum. The purulence continues to accumulate in the airways, becoming an environment that fosters repeated infections, inflammation, further airway damage, and, in a cyclic manner, increasingly severe disease with progressive lung damage (Figure 1-1).

**Figure 1-1: Schematic display of vicious cycle in patients with NCFB**




Source: Adapted from [1, 2]

Patients with NCFB carry a heavy disease burden and suffer from daily debilitating symptoms of excessive sputum production and persistent chronic cough, hemoptysis, fatigue, and increased anxiety and depression (Section 2.3). These chronic symptoms negatively impact daily life, physical, and social functioning. Acute exacerbations of the disease, which are mostly associated with bacterial infections, are a major driver of morbidity and mortality and often require Emergency Room visits or hospitalization. During an exacerbation of NCFB, patients experience an increase in daily symptoms that can persist for weeks (Section 2.4). Since the presence of bacteria in the bronchi increases the risk of exacerbations (Section 2.5), reducing bacterial load in the lungs through antibiotic treatment is an important strategy to alleviate the adverse long-term outcomes of the disease. However, there are currently no approved antibiotics to reduce the frequency of exacerbations in NCFB (Section 2.6).

Epidemiological data on NCFB are sparse, but it is evident that the prevalence is increasing with age (Section 2.1). Current US data report an overall prevalence of 139 patients per 100,000 adults, ranging from 7 per 100,000 among subjects aged 18 to 34 years to 812 per 100,000 among the elderly aged ≥75 years. In the US, NCFB is considered an orphan disease. However, NCFB will likely become an increasing issue for patients in ageing populations.

Patients with NCFB are burdened with debilitating symptoms and increased morbidity and mortality, while their attending physicians are frustrated by the lack of approved therapies and the resulting difficulties while trying to help their patients. Pulmonary exacerbations play a major role in disease progression, and the introduction of approved treatment options to reduce the number of exacerbations in NCFB patients is thus urgently required.

The FDA has granted ciprofloxacin DPI a number of regulatory designations, reflecting their recognition of the potential of ciprofloxacin DPI to address the medical need of NCFB patients. These include Breakthrough Therapy and Fast Track Designations, along with Orphan Drug and Qualified Infectious Disease Designations.

## 1.3 The initial development of ciprofloxacin DPI to treat NCFB

Ciprofloxacin was first brought to the US market by Bayer in 1987 and has since been utilized in treatment of many types of infectious diseases (Section 3); it is included in the World Health Organization (WHO) List of Essential Medicines. Ciprofloxacin is a broad-spectrum antibiotic with potent bactericidal activity against an extended spectrum of gram-negative and gram-positive pathogens frequently found in sputum isolates of patients with NCFB, including *Pseudomonas aeruginosa, Haemophilus influenzae, Streptococcus pneumoniae, Moraxella catarrhalis*, and *Staphylococcus aureus*.

Ciprofloxacin shows concentration-dependent bactericidal activity. Therefore, a ciprofloxacin therapy that achieves sufficiently high drug concentrations directly in the lungs of NCFB patients (Section 4) should reduce the burden of pathogenic bacteria, resulting in a reduction of exacerbations, and ultimately disrupting the vicious cycle of this disease.

The evidence indicating that this therapeutic approach could be successful in NCFB is two-fold:

1) **Experience with approved inhaled antibiotics in cystic fibrosis (CF):**
   The inhaled antibiotics tobramycin (Tobi® Podhaler™) and aztreonam (Cayston™) have been approved for the management of, and improvement of respiratory symptoms, in CF patients with *P. aeruginosa*, respectively [3-5]. CF is a disease in which the airways frequently show chronic bacterial infection and bronchiectatic changes. These inhaled antibiotics are considered standard of care in this disease, and their successful use in patients with CF provides a compelling basis for a similar approach for patients with NCFB.

2) **Experience with off-label inhaled antibiotics and systemic antibiotics in NCFB:**
   Physicians trying to reduce the bacterial burden in NCFB patients are forced into unsatisfactory options: a) prescribe CF products off-label, b) choose a generic antibiotic intravenous formulation (not optimized for the topical treatment of the lungs) and work with a compounding pharmacy to prepare it for use with a generic nebulizer, or c) treat repeatedly with high doses of systemic antibiotics. None of these options are approved for reduction of exacerbations in NCFB. There are, however, reports of encouraging results supporting effectiveness of inhaled antibiotics in patients with NCFB [6-9].

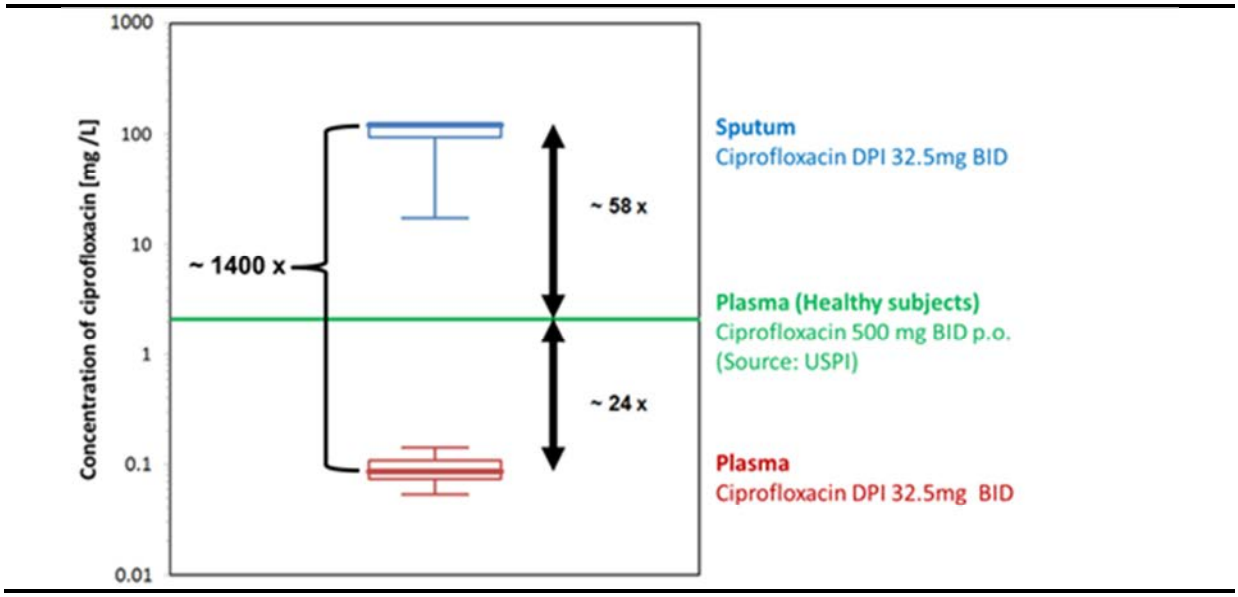
Bayer pursued the clinical development of a dry powder formulation for inhalation, utilizing PulmoSphere™ technology, to deliver high concentrations of ciprofloxacin directly to the lungs, while minimizing systemic exposure. Ciprofloxacin DPI is administered via the T-326 inhaler, which is approved as part of another drug-device combination product, TOBI® Podhaler™ (tobramycin inhalation powder), for management of CF patients with *P. aeruginosa*.

Compared with existing nebulizers [10], dry powder inhalers provide advantages in terms of administration time, maintenance, size, weight, user convenience, and proportion of dose delivered to the lungs. The T-326 dry powder inhaler builds on these advantages with the utilization of the PulmoSphere™ technology for ciprofloxacin dry powder formulation which optimizes the ciprofloxacin DPI inhaler drug-device product.

In a comprehensive Phase I program it was demonstrated that NCFB patients produce a sufficient peak inspiratory flow (Section 4.1.2), and that aerosolized drug particles reach the ventilated areas of the lungs (Section 4.1.2).

As shown in Figure 1-2, inhaled ciprofloxacin administration results in high local unbound ciprofloxacin concentrations, approximately 58-fold higher than usually achieved with systemic administration of therapeutic doses of ciprofloxacin, while unbound systemic peak concentrations are approximately 24-fold lower than usually achieved with systemic administration of therapeutic doses of ciprofloxacin (Section 4.2.2).

**Figure 1-2: Local and systemic peak concentrations after inhalation of ciprofloxacin DPI**




This low systemic exposure is of particular importance, as it reduces the potential risk of adverse events. The dosage of ciprofloxacin DPI 32.5 mg BID was selected to achieve a consistently high antimicrobial activity in the lungs, providing optimal treatment effect, and a low systemic exposure supporting patient safety and compliance (Section 4.2.5). *In vitro* pharmacokinetic/pharmacodynamic (PK/PD) testing models (Section 4.2.8) showed that ciprofloxacin DPI 32.5 mg BID is active against the clinically relevant target pathogens, including those with reduced susceptibility to ciprofloxacin.

These pharmacokinetic (PK) and PK/PD data formed the rationale for further development of ciprofloxacin DPI for bronchiectasis. One Phase II study and two Phase III studies (RESPIRE 1 and RESPIRE 2) were conducted in NCFB patients. A 28-day on/off cyclic regimen was studied in all studies because this regimen had been previously used with other antibiotics in patients with CF, while a new 14-day on/off regimen was included in the RESPIRE studies with the goal to reduce the treatment-free interval, during which pathogens have an opportunity to regrow.

## 1.4 Phase II/III studies

The randomized, placebo-controlled Phase II study in patients with NCFB (Study 12965) included one treatment cycle of 28 days (including a follow-up period of several weeks) and showed a clinically meaningful reduction in bacterial load (Figure 5–1), which is the underlying concept of ciprofloxacin DPI treatment. Moreover, analyses of the exacerbation frequency were indicative of an exacerbation reduction among patients treated with ciprofloxacin DPI (Section 5.2).

The Phase III studies RESPIRE 1 (Study 15625) and RESPIRE 2 (Study 15626) were replicate, randomized controlled studies with 4 treatment arms over 48 weeks of treatment (study design described in Section 5.3.1). Treatment groups were compared to the placebo group, with placebo defined as placebo inhaler and standard of care active treatment. Eligibility criteria were selected to represent NCFB patients expected to be treated with long-term inhaled antibiotic therapy in the real world, including the array of pathogens normally found in these patients.

The primary efficacy measure of time to first exacerbation was agreed with FDA as an appropriate endpoint to demonstrate efficacy. The frequency of exacerbations was chosen as the first secondary endpoint and was also embedded in the formal testing strategy (Appendix Table 9-3).

A qualifying exacerbation in the RESPIRE studies was defined as an exacerbation that required systemic antibiotic treatment and was associated with presence of fever or malaise / fatigue and worsening of at least 3 signs/symptoms (*i.e.*, dyspnea, wheezing, cough, sputum volume [24 hour], and sputum purulence [color]).

In accordance with FDA advice, two active treatment groups delivering ciprofloxacin DPI 32.5 mg BID on two alternate schedules (ciprofloxacin DPI 28 days on/off or ciprofloxacin DPI 14 days on/off [referred to as "**ciprofloxacin DPI 28**" and "**ciprofloxacin DPI 14**", respectively]) were separately compared with the pooled placebo group (placebo 28 days on/off and placebo 14 days on/off averaged [referred to as "pooled placebo"]). Additional analyses included an integrated analysis of ciprofloxacin DPI 14 and 28 across both studies as well as a comparison of pooled ciprofloxacin DPI data *vs.* pooled placebo data within each RESPIRE study. The program was not designed to differentiate the two dosing regimens. The blinded study treatment was evaluated on the background of standard therapy.

The Phase III clinical development program was designed to demonstrate the safety and efficacy of ciprofloxacin DPI for treatment of NCFB patients.

The measures of efficacy included:

- Increase in the time to the first exacerbation (primary endpoint),
- Reduction in the frequency of exacerbations (first secondary endpoint),
- Improvement in health-related, patient-reported outcomes,
- Improvement in the eradication of baseline bacterial pathogens and decrease in acquisition of new pathogens.

## 1.5 Efficacy outcomes observed in the Phase III RESPIRE studies

The overall efficacy evaluation is based on the totality of evidence across the primary and secondary endpoints, including exacerbation-related endpoints, microbiology, and patient-reported outcomes for both treatment regimens. This approach to efficacy evaluation is utilized due to the heterogeneity of statistical evaluations, while treatment effects are consistently positive. There was a range of positive treatment effect between studies and regimens; treatment effect estimates (hazard ratios [HRs]) for the primary endpoint ranged from 0.53 to 0.87 for ciprofloxacin DPI 14 and from 0.71 to 0.73 for ciprofloxacin DPI 28.

**Exacerbation-related efficacy endpoints (time to first exacerbation, frequency of exacerbations)**

In RESPIRE 1, the ciprofloxacin DPI 14 dose regimen increased the time to first exacerbation event (primary efficacy variable), with HR=0.53, 97.5%-confidence interval (CI) of [0.36; 0.80]), and p-value of p=0.0005 (Section 5.3.2.1). Since a large number of patients did not experience an exacerbation and, therefore, it was not possible to calculate a median with the Kaplan-Meier method, *post hoc* extrapolation was performed and estimated a 222-day delay in median time to first exacerbation (Figure 1–4). The ciprofloxacin DPI 28 regimen resulted in a positive trend for efficacy in the primary efficacy variable for increasing the time to first exacerbation event, with a HR of 0.73 (97.5%-CI: [0.50; 1.07]; p=0.0650). Using *post hoc* extrapolation, a 107-day delay in median time to first exacerbation was estimated.

Table 1–1 summarizes the results of the statistical analyses of the primary efficacy endpoint (time to first exacerbation) and the first secondary endpoint (frequency of exacerbations). For the exacerbation frequency, differences between treatment groups were expressed as "incidence rate ratio" (IRR), with estimates <1.0 indicating outcomes in favor of ciprofloxacin DPI *vs.* pooled placebo. Positive point estimates and trends were produced by both ciprofloxacin DPI treatment arms for the endpoints related to exacerbation.

**Table 1–1: Results of the primary and secondary efficacy analyses related to exacerbation (primary tests as per statistical analysis plan) in RESPIRE 1 (FAS)**

| | Cipro 14 N=137 | Cipro 28 N=141 | Pooled placebo N=138 |
|---|---|---|---|
| **Time to first exacerbation** [a] | | | |
| Estimated median time | 432 | 317 | 210 |
| **Patients with exacerbation** | | | |
| n (%) | 53 (38.7) | 67 (47.5) | 79 (57.2) |
| **Time to first exacerbation** | | | |
| Median time [97.5%-CI] [b] | >336 [290; >336] | 336 [206; >336] | 186 [136; 282] |
| Hazard ratio (HR) [c] | 0.53 | 0.73 | --- |
| 97.5%-CI for HR [c] | [0.36; 0.80] | [0.50; 1.07] | --- |
| p-value [d] | 0.0005 | 0.0650 | --- |
| **No. of exacerbations** | | | |
| Mean number ± SD | 0.85 ± 1.24 | 1.01 ± 1.41 | 1.17 ± 1.27 |
| Incidence rate ratio (IRR) [e] | 0.73 | 0.86 | --- |
| 97.5%-CI for IRR [e] | [0.52; 1.03] | [0.63; 1.18] | --- |
| p-value [d] | 0.0382 | 0.2944 | --- |

CI = Confidence interval; Cipro 14 = Ciprofloxacin DPI 14 days on/off; Cipro 28 = Ciprofloxacin DPI 28 days on/off; SD = Standard deviation

Note: Exacerbations are defined as events with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of at least 3 signs/symptoms over 48 weeks. "Time to first exacerbation" was the primary efficacy analysis. For the secondary efficacy endpoint "frequency of exacerbations", a pre-specified extrapolation approach was used to take account of patients with premature study discontinuation.

a: Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution (*post hoc* analysis).

b: Median time to first exacerbation in days based on Kaplan Meier estimate.

c: Hazard ratio (HR) based on Cox Proportional Hazards model; HR for the comparison of active treatment *vs.* pooled placebo (HRs <1 indicate better outcome on active treatment).

d: Wald-type test.

e: Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment *vs.* pooled placebo (IRRs <1 indicate better outcome on active treatment).

In RESPIRE 2, two different α-levels were used for the two treatment regimens (α=0.049 for ciprofloxacin DPI 14 and α=0.001 for ciprofloxacin DPI 28 (Appendix 9.3.3). The statistically significant result in the primary efficacy endpoint for the ciprofloxacin DPI 14 regimen was not replicated (Section 5.3.2.2), with a HR of 0.87 (95.1%-CI: [0.62; 1.21]), a corresponding p-value of p=0.3965, and a 43-day delay in median time to first exacerbation estimated *post hoc* by extrapolation (Table 1–2 and Figure 1–4).

In contrast, ciprofloxacin DPI 28 in RESPIRE 2 showed consistency in the primary efficacy variable with a HR of 0.71 (99.9%-CI: [0.39; 1.27]), a corresponding p-value of p=0.0511, and a 148-day delay in median time to first exacerbation estimated by extrapolation. Both ciprofloxacin DPI treatment regimens in RESPIRE 2 produced positive point estimates for the exacerbation-related endpoints. Comparison of the placebo groups in RESPIRE 1 and RESPIRE 2 demonstrated a lower event rate and increased time to first event in RESPIRE 2.

**Table 1–2: Results of the primary and secondary efficacy analyses related to exacerbation frequency (main tests as per statistical analysis plan) in RESPIRE 2 (FAS)**

| | Cipro 14 N=176 | Cipro 28 N=171 | Pooled placebo N=174 |
|---|---|---|---|
| **Time to first exacerbation** [a] | | | |
| Estimated median time | 431 | 536 | 388 |
| Patients with exacerbation n (%) | 68 (38.6) | 56 (32.7) | 73 (42.0) |
| **Time to first exacerbation** | | | |
| Median time [b] | >336 | >336 | >336 |
| Hazard ratio (HR) [c] | 0.87 | 0.71 | --- |
| 99.9%-CI for HR [c] | --- | [0.39; 1.27] | --- |
| 95.1%-CI for HR [c] | [0.62; 1.21] | --- | --- |
| p-value [d] | 0.3965 | 0.0511 | --- |
| **No. of exacerbations** | | | |
| Mean number ± SD | 0.58 ± 0.84 | 0.40 ± 0.64 | 0.70 ± 1.02 |
| Incidence rate ratio (IRR) [e] | 0.81 | 0.56 | --- |
| 99.9%-CI for IRR [e] | --- | [0.33; 0.95] | --- |
| 95.1%-CI for IRR [e] | [0.61; 1.08] | --- | --- |
| p-value [d] | 0.1471 | 0.0003 | --- |

CI = Confidence interval; Cipro 14 = Ciprofloxacin DPI 14 days on/off; Cipro 28 = Ciprofloxacin DPI 28 days on/off; SD = Standard deviation

Note: Exacerbations are defined as events with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of at least 3 signs/symptoms over 48 weeks. "Time to first exacerbation" was the primary efficacy analysis. For the secondary efficacy endpoint "frequency of exacerbations", no extrapolation approach was used.

a: Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution (*post hoc* analysis).

b: Median time to first exacerbation in days based on Kaplan Meier estimate.

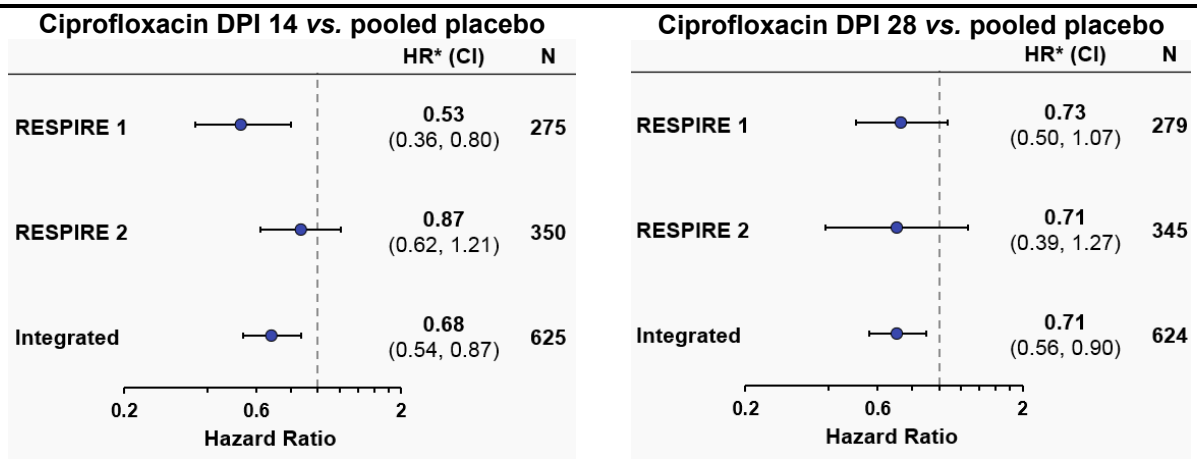
c: Hazard ratio (HR) based on Cox Proportional Hazards model; HR for the comparison of active treatment *vs.* pooled placebo (HRs <1 indicate better outcome on active treatment).

d: Wald-type test.

e: Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment *vs.* pooled placebo (IRRs <1 indicate better outcome on active treatment). Time in study was used as an offset in the Poisson model.

In order to evaluate the totality of study results, a pre-specified integrated analysis across RESPIRE 1 and RESPIRE 2 was conducted to estimate the treatment effect in all patients who received ciprofloxacin DPI 14, and all patients who received ciprofloxacin DPI 28, compared to all patients who received placebo (Section 5.3.2.4.1). For the primary endpoint, HRs for ciprofloxacin DPI 14 and ciprofloxacin DPI 28 were 0.68 and 0.71, respectively (Figure 1–3).

**Figure 1–3: Time to first exacerbation by single study and in the integrated analysis of RESPIRE 1 and RESPIRE 2 (FAS)**

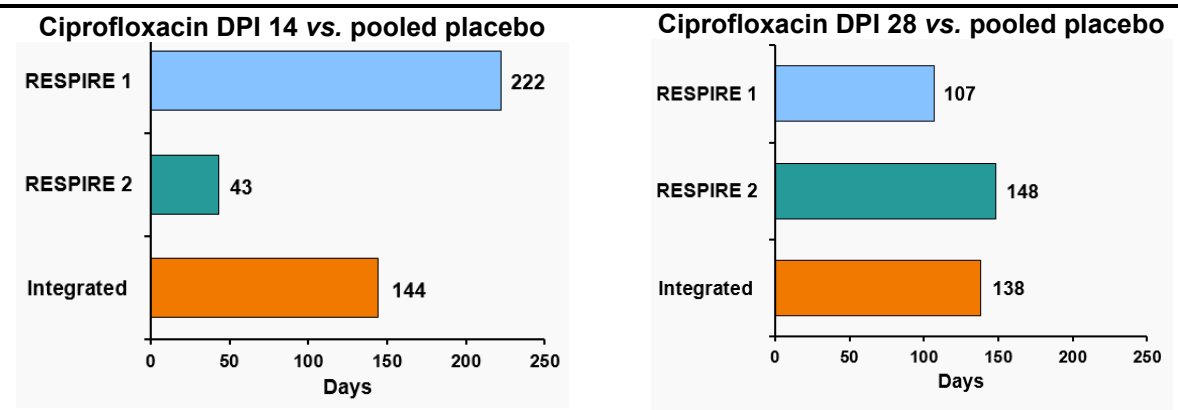



CI=Confidence interval; HR=Hazard ratio

*: HRs are based on Cox Proportional Hazards model for the comparison of active treatment *vs.* pooled placebo (HRs <1 indicate better outcome on active treatment). CIs are 97.5% for RESPIRE 1 and 95.1% (ciprofloxacin DPI 14) / 99.9% (ciprofloxacin DPI 28) for RESPIRE 2. CIs are 95.0% for integrated analysis.

The estimation of the median time to first exacerbation using extrapolation based on integrated data indicated a delay of 144 days and 138 days on treatment with ciprofloxacin DPI 14 and ciprofloxacin DPI 28, respectively (Figure 1–4).

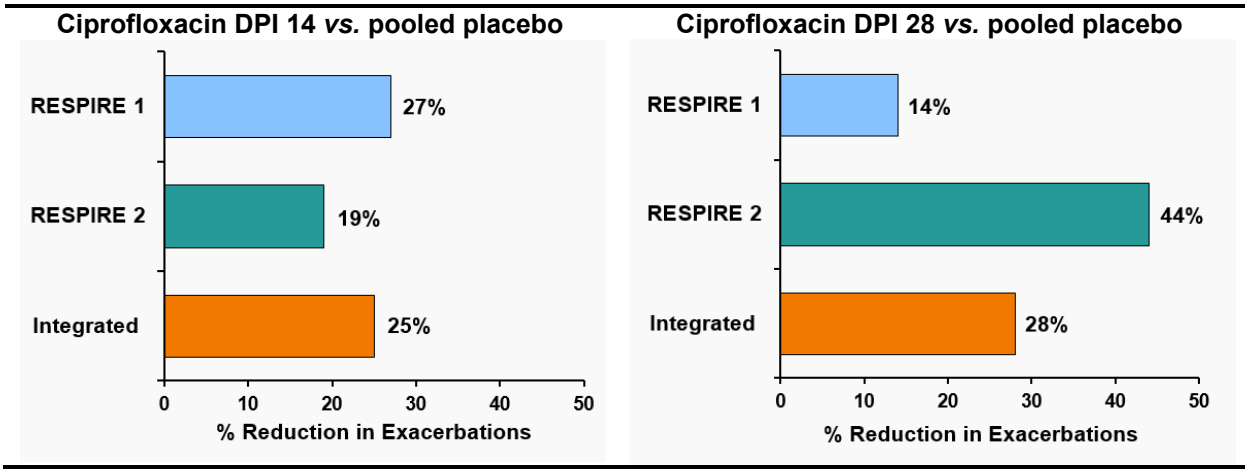
**Figure 1–4: Increase in median time to first exacerbation by single study and in the integrated analysis of RESPIRE 1 and RESPIRE 2 (FAS)**




Note: Estimates of median time to first exacerbation are based on Weibull regression model. Provided is the difference in estimated median time to event between ciprofloxacin DPI and pooled placebo.

In the integrated analysis, the reduction in frequency of exacerbations was calculated as 25% in the ciprofloxacin DPI 14 group and 28% in the ciprofloxacin DPI 28 group (Figure 1–5). The range of treatment effects was also apparent in the two treatment arms, most especially for ciprofloxacin DPI 28 (14% and 44% in RESPIRE 1 and RESPIRE 2, compared to 27% and 19% for ciprofloxacin DPI 14).

**Figure 1–5: Decrease in frequency of exacerbations by single study and in the integrated analysis of RESPIRE 1 and RESPIRE 2 (FAS)**




Note: Decrease in frequency from Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment *vs.* pooled placebo.

The overall treatment effect can also be illustrated by showing the total number of exacerbations recorded for each treatment group in RESPIRE 1 and RESPIRE 2 (Table 1–3). This tabulation shows the overall treatment effects of ciprofloxacin DPI 14 and ciprofloxacin DPI 28 across both trials. Both ciprofloxacin DPI treatment regimens were associated with a marked decrease in total number of exacerbations, and a corresponding decrease in the frequency of exacerbations per patient.

**Table 1–3: Overall number of exacerbations in RESPIRE 1 and RESPIRE 2 (FAS)**

| | | Exacerbations | |
|---|---|---|---|
| **Treatment group** | **Total patients** | **Total** | **Mean/patient** |
| Ciprofloxacin DPI 14 | 313 | 188 | 0.60 |
| Ciprofloxacin DPI 28 | 312 | 184 | 0.59 |
| Pooled placebo | 312 | 248 | 0.79 |

Note: Given is the absolute number of exacerbations and the arithmetic mean (related to patients in FAS).

In order to assess the totality of data, additional analyses were conducted on pooled ciprofloxacin DPI 14 and ciprofloxacin DPI 28 compared to pooled placebo within RESPIRE 1 and within RESPIRE 2 (Section 5.3.2.4.2). Overall, the results of pooled data of both ciprofloxacin DPI 14 and ciprofloxacin DPI 28 were strongly supportive of the overall effect of increasing time to next exacerbation and reducing the frequency of exacerbations for ciprofloxacin DPI treatment *vs.* pooled placebo in the RESPIRE program (Table 5–4). Given that the total dose delivered with either dose regimen was the same, this analysis provides valuable insight into the efficacy of ciprofloxacin DPI in NCFB.

In conclusion, the efficacy analyses of time to first exacerbation and frequency of exacerbations (including pooled and integrated data) showed marked treatment effects of ciprofloxacin DPI in a heterogeneous patient population.

**Patient-reported outcomes (SGRQ, QOL-B)**

The treatment effect of ciprofloxacin DPI was also evaluated based on the patient-reported outcomes (PROs) data. The St. George's Respiratory Symptom Questionnaire (SGRQ) - symptoms component score (SCS), and the Quality of life-Bronchiectasis (QOL-B) questionnaire - respiratory symptoms domain score (RSDS) were formally evaluated as the secondary endpoints (Section 5.3.3.1). Both scores are calculated to range between 0 and 100 score points; lower scores in SGRQ and higher scores in QOL-B correspond to a better health status.

In RESPIRE 1, both ciprofloxacin DPI 14 and ciprofloxacin DPI 28 showed a positive treatment effect *vs.* placebo in the SGRQ SCS. Moreover, there was a positive trend *vs.* placebo for SGRQ SCS observed in RESPIRE 2 (Section 5.3.3.2).

In both RESPIRE 1 and RESPIRE 2, the QOL-B RSDS treatment differences between ciprofloxacin DPI and pooled placebo from baseline to end of treatment (EOT) were small (Section 5.3.3.3). An analysis of treatment response pattern over time (*i.e.,* the treatment difference between ciprofloxacin DPI and placebo in mean changes from baseline) suggested that the overall treatment effect of ciprofloxacin DPI in the QOL-B RSDS was greater at the end of on-cycles than at the end of off-cycles (Figure 5–13).

**Microbiological outcomes**

The proportion of patients with complete eradication of all baseline pathogens at EOT in RESPIRE 1 was nearly twice as high in the ciprofloxacin DPI 14 group compared with the pooled placebo group (28.5% *vs.* 16.7%), and the odds ratio (OR) was 2.35 in favor of ciprofloxacin DPI 14. In RESPIRE 2, ciprofloxacin DPI 14 produced a smaller treatment effect (OR=1.34). The treatment effect for the 28-day regimen was consistent but smaller in both studies (OR=1.16 in both RESPIRE 1 and RESPIRE 2; Section 5.3.4, Figure 5–15).

The proportions of patients with new pathogens at EOT in RESPIRE 1 were numerically smaller in the ciprofloxacin DPI groups (5.1% in the ciprofloxacin DPI 14 group and 3.5% in the ciprofloxacin DPI 28 group) than in the pooled placebo group (8.0%), and associated ORs favored ciprofloxacin DPI (OR=0.56 and OR=0.36, respectively). In RESPIRE 2, the proportions of patients with new pathogens at EOT were numerically smaller in the two ciprofloxacin DPI groups (4.0% and 4.1%, respectively) than in the pooled placebo group (10.0%), and the associated ORs thus both in favor of ciprofloxacin DPI (Section 5.3.4; Table 5–5).

**Efficacy summary**

The overall efficacy evaluation is based on the totality of evidence across the primary and secondary endpoints, including exacerbation-related endpoints, microbiology, and patient-reported outcomes for both treatment regimens (Section 5.3.6).

The range of efficacy with respect to the primary efficacy endpoint was highest for ciprofloxacin DPI 14 in RESPIRE 1 (HR=0.53; 222-day estimated delay in median time to first exacerbation), lowest for ciprofloxacin DPI 14 in RESPIRE 2 (HR=0.87; 43-day estimated delay), while ciprofloxacin DPI 28 produced an intermediate level of efficacy in both RESPIRE 1 (HR=0.73; 107-day estimated delay) and RESPIRE 2 (HR=0.71; 148-day estimated delay).

Overall, the point estimates in the analyses of the exacerbation-related variables were consistently in favor of ciprofloxacin DPI, and positive trends were also seen in the analyses of the HRQoL and microbiological efficacy variables.

Taking the results of the individual Phase III studies together with the pooled and integrated analysis results, there is a clear positive treatment effect of ciprofloxacin DPI.

## 1.6 Safety of ciprofloxacin DPI

The safety observed with ciprofloxacin DPI 32.5 mg *vs.* placebo was consistently favorable throughout the entire clinical development program. A total of 933 patients (62.6% women, mean age: 62.1 years) constituted the integrated Phase III safety population (622 thereof exposed to ciprofloxacin DPI) and are representative of the target population of NCFB patients (Section 6.2.1). There were no clinically meaningful differences between the two active treatment groups, or between the two active treatment groups *vs.* pooled placebo with regards to the incidence of any treatment-emergent adverse events (TEAEs), any serious TEAEs, deaths, and TEAEs requiring permanent discontinuation of study drug treatment (Table 6–2). Most of the reported TEAEs were mild to moderate and transient (Section 6.2.3.2).

Special emphasis was put on local TEAEs (such as bronchospasm, hemoptysis, cough, dyspnea, hypersensitivity reactions) and events pertinent to the fluoroquinolone class (Section 6.2.6). The frequencies were generally small and the numerical group differences were not indicative of an increased risk of local irritation, hypersensitivity, or any fluoroquinolone class-specific adverse events on treatment with ciprofloxacin DPI for either regimen compared with placebo inhalation.

The cumulative rates of patients with bacterial resistance development were numerically higher in the two active treatment groups compared with placebo (Section 6.3). However, the resistance rates at the end of the studies were low, suggesting that the beneficial treatment effects of ciprofloxacin DPI outweigh the potential risks associated with resistance development.

## 1.7 Conclusion, proposed indication, and dosing regimen

There is pressing and unmet medical need for effective reduction of exacerbations in patients with NCFB. There are no approved drug therapies available for patients with NCFB for reduction of exacerbations. The beneficial treatment effects of ciprofloxacin DPI, and the favorable safety and tolerability of ciprofloxacin DPI observed in the Phase II/III clinical studies, translate into a positive benefit/risk profile (Section 7). Ciprofloxacin DPI represents a meaningful advance for reduction of exacerbations in patients with NCFB.

The RESPIRE studies were not designed to evaluate which ciprofloxacin DPI dosing regimen was more effective, and in fact they provide support for either dose regimen. Clinical studies with cyclic on/off inhaled antibiotic therapy in patients with CF, a related disease in which the airways frequently show bronchiectatic changes, reported that patients usually have more symptoms and decrease in lung function during the off-treatment period [11-14]. Moreover, the Phase II NCFB study indicated clinically meaningful reduction of bacterial load as early

as 8 days after the start of the ciprofloxacin DPI treatment (Figure 5–1), and the reduction of the time off-treatment could potentially decrease the risk of pathogen regrowth.

Based on these data, Bayer seeks approval for the proposed indication for ciprofloxacin DPI 14 days on/off:

*Ciprofloxacin DPI is indicated for reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients (18 years of age and older) with respiratory bacterial pathogens.*

*The recommended dose is the oral inhalation of the contents of one 32.5 mg ciprofloxacin DPI capsule, twice daily for 14 days using the DPI inhaler in alternating periods of 14 days. After 14 days of therapy, patients should stop ciprofloxacin DPI inhaler therapy for the next 14 days, and then resume therapy for the next 14 day on and 14 day off cycle.*

# 2. Non-cystic fibrosis bronchiectasis (NCFB) - Unmet medical need and patient burden

## 2.1 Etiology and pathophysiology of NCFB

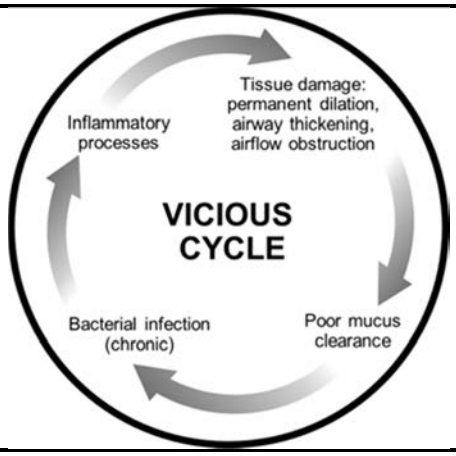
NCFB is a disease in which the structural architecture of the airways is abnormally dilated. The clinical presentation of NCFB is dominated by chronic productive cough, shortness of breath, malaise, hemoptysis, and recurrent infective exacerbations (see Section 2.3). Exacerbations are an indicator of substantial morbidity (see Section 2.4).

NCFB is heterogeneous in its etiology, magnitude of severity, and extent of lung involvement. There are many known causes or associated conditions, including previous pulmonary infections, immunodeficiency, allergic bronchopulmonary aspergillosis (ABPA), rheumatoid arthritis and others. In a significant number of patients (40% to 50%), no cause can be identified even after extensive investigation [15, 16].

Nonetheless, the common feature of NCFB is impaired mucociliary clearance leading to the pathophysiologic model of the vicious cycle depicted in Figure 2-1 [1, 2, 17]. The impaired mucociliary clearance leads to formation of mucus plugs, rendering the airways vulnerable to bacterial infection, which can become persistent. This persistent infection promotes inflammation, and contributes to the pathophysiology of irreversible tissue damage. The vicious cycle theory has been substantiated in several studies since it had been hypothesized in 1986 by Peter Cole [1]. A direct relationship has been established between airway bacterial load and increased airway inflammation (including myeloperoxidase, neutrophil elastase, and serum inflammatory markers) [18]. The same study demonstrated a direct relationship between airway bacterial load and number of subsequent exacerbations [18]. Inflammation expressed by sputum neutrophil elastase activity was also associated with severity of dyspnea, $FEV_1$ status and decline, as well as the radiological extent of bronchiectasis [19], thereby providing additional evidence to support the pathogenesis model of the vicious cycle in NCFB lungs.

Therapeutic strategies are therefore directed at the essential components of this vicious cycle. Yet, there are no approved medicines specifically for NCFB, leaving physicians to rely on drugs that are available and approved for chronic obstructive pulmonary disease (COPD) or CF patients, with comprehensive benefit/risk profiles described only in these patients.

**Figure 2-1: Schematic display of vicious cycle in patients with NCFB**




Source: Adapted from [1, 2]

## 2.2 Prevalence of NCFB in the US population

In the US, NCFB is currently considered an orphan (*i.e.*, rare) disease and ciprofloxacin dry powder for inhalation (DPI) was granted Orphan Drug Designation for NCFB in the US in 2014. The prevalence of bronchiectasis increases with age, and bronchiectasis is more than 10-fold more common in individuals over 75 years of age compared with younger adults (45 to 54 years of age; [20, 21]). In addition, the prevalence is higher in women than in men [20, 21].

There was an estimated NCFB prevalence of 52 per 100,000 adult persons in 2001, based on a retrospective analysis of health-care claims processing systems of more than 30 US health plans [20], and the prevalence was described to be increasing. In a Medicare population, the prevalence of NCFB increased by 8.7% per year between 2000 and 2007 [22]. Using a retrospective cohort design and health-care claims data, the prevalence of NCFB was estimated to be 139 cases per 100,000 adults in 2013, and confirmed to be higher among women *vs.* men (180 *vs.* 95 per 100,000), and increasing with age (7 per 100,000 persons aged 18 to 34, and 812 per 100,000 years for persons ≥75 years) [21]. Despite a predominance of patients older than 65 years, patients who are younger, especially those aged less than 45 years warrant special consideration. Young bronchiectasis patients suffer from significant disease burden and will require long term therapeutic solutions to treat their disease.

## 2.3 Clinical signs and symptoms

All NCFB patients caught in the aforementioned vicious cycle are prone to persistent, debilitating symptoms and frequent exacerbations, during which the daily symptoms are acutely worsened beyond normal day-to-day variation.

NCFB causes significant morbidity, including daily symptoms of cough and sputum production; some patients will have hemoptysis, most will describe fatigue, many will describe increased levels of anxiety and depression, reduced physical performance, and social

distress [23-25]. The most common signs and symptoms, each reported for ≥50% of patients participating in the US Bronchiectasis Research Registry, include daily bouts of coughing (73%), daily productive cough (53%), dyspnea when active (54%), and fatigue (50%) [26]. The chronic symptoms negatively impact daily life and physical functioning, and patients also abstain from social interactions and activities [27]. In addition, fatigue and sleep problems are common.

In addition to the daily symptoms, patients suffer from acute exacerbations that have a major impact not only on the symptom burden, but also on disease prognosis (see Section 2.4). An exacerbation adds acutely to the patients' chronic disease burden often resulting in decreased mobility and bedridden state [28].

## 2.4 Clinical relevance of exacerbations

An exacerbation is generally described as the acute worsening of signs and symptoms over more than just the daily variations. NCFB studies performed previously have used various signs and symptoms including or excluding the need for antibiotic therapy to define an exacerbation. Only recently, a consensus definition for clinical research was proposed, in which a "medical intervention" is a required criterion based on the recognition that the patient and the clinician deemed the change in symptoms significant enough to warrant intervention [29]. This consensus definition comprises a deterioration for at least 48 hours in 3 or more of the key symptoms (cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, hemoptysis) AND a clinician determines that a change in NCFB treatment is required.

Exacerbations are in most cases associated with infections and treated as such [18, 30, 31]. They usually require medical intervention and may result in Emergency Room visit or hospitalization. Even with treatment, symptoms may linger for weeks [30]. In a prospective, observational cohort study, the median overall exacerbation length was 16 days (interquartile range: 10 to 29 days) with lung function statistically abnormal for 2 weeks; 16% of patients continued to have symptoms for more than one month after the initiation of antibacterial exacerbation therapy [30].

Exacerbations are a major driver of morbidity and mortality in NCFB. Exacerbations are linked to increased systemic and airway inflammation and progressive lung damage [18, 31, 32]. It has been demonstrated that patients with a history of frequent exacerbations will continue to have frequent exacerbations, and more exacerbations were associated with worse quality of life [31]. Patients with frequent exacerbations experience more hospitalizations and show higher mortality rates compared to patients with less frequent exacerbations. For example, the hazard ratio (HR) for hospital admission was 1.67 (95%-confidence interval [CI]: [0.78; 3.58]) for patients with 1 to 2 exacerbations in the past year, and 2.25 (95%-CI: [0.89; 5.70]) for patients with ≥3 annual exacerbations compared to those with no exacerbations [31]. Mortality doubled for the patients with ≥3 annual exacerbations [31].

## 2.5 Role of microbiological colonization/infection

Up to 70% of NCFB patients managed in bronchiectasis clinics are persistently infected with respiratory pathogens [31]. Chronic infection with respiratory pathogens, in particular but not only with *P. aeruginosa*, is an important risk factor for frequent exacerbations. Other bacteria

such as *H. influenzae*, *S. aureus* or *S. pneumoniae* are also associated with an increase in exacerbation frequency [31]. A relationship between bacterial load and exaggerated inflammatory response has been observed, as well as a greater risk of exacerbations with increased bacterial load [33]. Chronic infection with pathogens, and especially but not exclusively with *P. aeruginosa*, is associated with decreased health-related quality of life (HRQoL) and lung function, and increased frequency of exacerbation, hospitalization and mortality [18, 31, 34]. In one study, infection with *P. aeruginosa* doubled the risk for hospital admission (HR=2.16 (95%-CI: [1.36; 3.43]), and infection with other pathogens resulted in a HR of 1.66 (95%-CI: [1.12; 2.44]) [31].

## 2.6 Treatment goals

Currently, there are no approved drugs for the management of NCFB. There are no US-based guidelines are available for the treatment of NCFB, though other countries or regions have published treatment guidelines [35-37]. The agreed general treatment objectives in NCFB are to prevent exacerbations, reduce symptoms, improve quality of life, and stop disease progression. To reach these treatment goals, airways clearance techniques, use of inhaled agents to enhance airway clearance (*e.g.*, hypertonic saline), anti-inflammatory drugs (*e.g.*, inhaled corticosteroids), bronchodilators, and long-term antibiotic treatment are therapies used today in NCFB patients [26]. Most of the treatment recommendations in the recently published EU guidelines for NCFB have “low” or “very low” quality of evidence with the exception of pulmonary rehabilitation program patients with impaired exercise capacity (“high”) [37]. The guidelines refrain from generally recommending any treatment for all NCFB patients and stress to tailor treatment to each individual patient according to their baseline symptom and/or co-morbidity profile [37].

According to the recently published European Guidelines for the Management of Bronchiectasis, which are based on the published literature up to December 2016, long-term antibiotic treatment to reduce exacerbations are recommended for patients with ≥3 exacerbations per year, especially for those chronically infected with *P. aeruginosa*. If inhaled antibiotic is contraindicated, not tolerated or not feasible, the European guidelines recommend to use long-term macrolide therapy [37]. The choice of long-term macrolide therapy has to be made carefully, as a potential non-tuberculous mycobacteria (NTM) (co-)infection has to be taken into consideration. Macrolides are a critical component of the combination therapy recommended for treatment of respiratory NTM infections, and it has clearly been demonstrated that macrolide monotherapy can increase the risk of macrolide resistance in NTM [37, 38].

As there is clear evidence that NCFB patients who have more frequent exacerbations have worse quality of life and worse prognosis [31], the reduction of exacerbations must be a central goal of long-term management. Efforts have been made to define groups of NCFB patients with similar clinical and biological characteristics and long-term outcomes that would guide individual management, but no phenotypes have yet been established [39, 40].

The management of NCFB is often complex and burdensome [41]. In addition to physiotherapy and/or airways clearance techniques, patients are likely to be receiving multiple drugs, some of which will be administered by inhalation. The administration time for nebulized drugs may range from a few minutes up to 20 minutes, but time adds up to 20 to 40

minutes with multiple doses per day and the nebulizer set-up and cleaning/sterilization and thereby take an substantial time toll from the patient's life [10]. In addition, the efficiency of drug delivery is poor especially in the older nebulizers, typically around 15% of the dose in the vial will be delivered to the lung [10]. Therefore, treatment decisions must also take the treatment burden into consideration.

Patients are often prescribed therapies (*e.g.*, bronchodilators, inhaled corticosteroids, and inhaled antibiotics) that are approved for other indications such as COPD or CF, with no or limited evidence from small clinical trials on efficacy and safety in NCFB. CF is a disease commonly associated with bronchiectasis, and inhaled antibiotics are now considered standard of care for CF patients chronically infected with *P. aeruginosa* [42]. Translating such therapies to all patients with NCFB has not been proven successful; yet, there are patients with bronchiectasis due to reasons other than CF that are similar to those with CF, especially in terms of frequent exacerbations, and who respond favorably to the use of long-term inhaled antibiotics.

Smaller studies [6, 7] and a recently published single-center experience [8] have demonstrated clinical benefit in reducing exacerbations with inhaled antibiotics in NCFB patients. Data published from the US Bronchiectasis Research Registry indicate that 10% of their NCFB patients have received long-term inhaled antibiotic therapy off-label [26]. Inhaled antibiotics used include tobramycin, aztreonam, gentamicin, amikacin, and colistin. Some of these drugs are available as products developed for inhalation, while others are intravenous (i.v.) solutions that are nebulized through a generic nebulizer with unknown efficiency, efficacy and safety profile.

Despite all the positive indications for clinical efficacy of inhaled antibiotic therapy in NCFB patients, there is still a significant and unmet need for an approved therapy with established favorable safety and efficacy results, which will reduce exacerbations and disease burden for patients with NCFB.

**Summary of Section 2 (Non-cystic fibrosis bronchiectasis - Unmet medical need and patient burden):**

- NCFB is a poorly understood and understudied disease. While there is evidence that supports the role of antibiotics to improve outcomes in this disease, there are no FDA approved therapies.
- Although NCFB is currently considered an orphan (rare) disease, epidemiological data suggests prevalence is increasing. Ciprofloxacin DPI was granted Orphan Drug Designation for NCFB in the US on 17-Apr-2014.
- NCFB has many systemic and local causes and thus is a heterogeneous disease. In a significant number of patients (>40%) no specific etiology can be identified.
- The underlying pathophysiological process for all NCFB etiologies is characterized by a vicious cycle of poor mucus clearance, infection, inflammation and irreversible lung tissue damage. Patients caught in that vicious cycle are prone to consistent, debilitating symptoms and frequent exacerbations.

- Symptoms pose a substantial burden on patients. In addition, exacerbations of NCFB add significantly to the patients' disease burden.
- There is clear evidence that NCFB patients who have more frequent exacerbations have worse quality of life and worse prognosis, including hospitalizations, death, and future exacerbations.
- Bacterial infection is a central part of the disease. NCFB patients with chronic bacterial respiratory infection (*e.g.*, with *P. aeruginosa*) are at an increased risk of experiencing more hospitalizations, lower health-related quality of life, and frequent exacerbations.
- Long-term inhaled antibiotics applied to interfere with the vicious cycle at the bacterial infection site have been successful in the management of CF patients. Today they are standard of care in CF patients chronically infected with *P. aeruginosa*. Some clinicians have used inhaled antibiotics in their NCFB patients with success, as reported in publications, and registry data suggest inhaled antibiotics are already used in a subset of NCFB patients.
- Reducing bacterial load in the lungs is an important treatment strategy to reduce the frequency of exacerbations in patients with NCFB.

# 3. Rationale for product development - Overview of ciprofloxacin DPI clinical development program

Ciprofloxacin is a well-established fluoroquinolone antibiotic developed by Bayer that has received marketing authorization worldwide since 1987 in different formulations (tablets for oral administration [including extended release tablets], solution for i.v. administration, and suspension) for various indications. Given systemically, ciprofloxacin is active against pathogens that can be found in the lungs of patients with NCFB, such as *P. aeruginosa*, *H. influenzae*, *S. pneumoniae*, *S. aureus*, and *M. catarrhalis*.

The considerations outlined in Section 2 clearly indicate that NCFB is a serious lung disease promoted by bacterial infection that requires effective treatment in terms of exacerbation reduction; however, no approved therapies are currently available. In order to address this significant unmet medical need, Bayer launched a comprehensive development program to effectively deliver ciprofloxacin to the site of infection, with the goal of preventing or reducing acute exacerbations in patients with NCFB.

A DPI formulation along with an inhaler device was chosen to afford patients the benefits of both portability and simplicity. The features of the device, which has been approved as part of another drug-device combination product (TOBI® Podhaler™), for use in patients with CF for about 4 years, provides distinct advantages over existing nebulizers in terms of the time required for inhalation, maintenance, size, weight, and convenience (see Section 4.1.1). The Phase I study program confirmed the suitability of the inhalable formulation of ciprofloxacin DPI, as it achieved consistently high drug concentrations at the site of infection, while minimizing systemic exposure (see Section 4.2).

In addition, Bayer has conducted an extensive Human Factors Engineering program, in accordance with FDA guidance, in order to optimize the user interface of this product for patients with NCFB with the goal of ensuring that these patients understand how to use the drug/device combination safely and effectively. This program consisted of an evidence-driven, iterative process based on 7 formative studies conducted over 4 years, feedback from the Agency, and a confirmatory Human Factors Validation study (No. 19139) completed in late 2016. This study showed that the device is safe and effective for the intended use, users, and use environment, based on data and residual risk analysis.

A dose of ciprofloxacin DPI 32.5 mg given twice daily (BID) was identified in the Phase I program as the optimal dosage for further development in NCFB, as this dosage provided high local drug concentrations, low systemic exposure, good safety and tolerability, and patient convenience in order to promote treatment compliance (for details see Section 4). Two Phase II studies were subsequently performed; one study investigated patients with CF (Phase II CF Study 12429), while the other study was performed in patients with NCFB (**Phase II NCFB Study 12965**). Due to the differences between NCFB and CF, data from the CF study 12429 are not further detailed in this document. In the Phase II NCFB study patients were treated with ciprofloxacin DPI 32.5 mg BID for 28 days, followed by an off-phase of 28 days and an additional follow-up period. The rationale to study a cyclic 28-day treatment period followed by 28 days off-treatment (referred to as "28-day regimen") was based on therapy regimens approved for antibiotics for inhalation in CF (*e.g.*, tobramycin or aztreonam for inhalation). The efficacy results of the Phase II NCFB study (12965) and the resulting rationale for using the 14-day regimen in the Phase III studies are outlined in Section 5.2.

Finally, the two randomized and placebo-controlled **Phase III studies RESPIRE 1 (15625)** and **RESPIRE 2 (15626)** were initiated to evaluate the efficacy and safety of ciprofloxacin DPI 32.5 mg BID given 28 days on/off (referred to as "ciprofloxacin DPI 28) or 14 days on/off (referred to as ciprofloxacin DPI 14") ) to prolong the time to first pulmonary exacerbation and to reduce the frequency of pulmonary exacerbations among NCFB patients over a treatment period of 48 weeks (see Section 5.3 for efficacy results and Section 6 for safety results).

The clinical study program was designed in close collaboration with the FDA. The potential for ciprofloxacin DPI to address the important unmet medical need of patients with NCFB is reflected in the following designations that were granted by the FDA:

- Breakthrough Therapy Designation (BTD) on 29-Aug-2016,
- Fast Track Designation (FTD) on 09-Mar-2016,
- Qualified Infectious Disease Product (QIDP) status on 17-Oct-2014, and
- Orphan Drug Designation (ODD) on 17-Apr-2014.

Based on the results of the clinical development program, ciprofloxacin DPI has been submitted to the FDA on 30-Jun-2017 (NDA 209367) for approval for the following indication:

*"Ciprofloxacin DPI is indicated for reduction of exacerbations in non-cystic fibrosis bronchiectasis (NCFB) adult patients (≥18 years of age) with respiratory bacterial pathogens".*

**Summary of Section 3 (Rationale for product development - Overview of ciprofloxacin DPI clinical development program):**

- Ciprofloxacin is a well-established antibiotic that has been marketed worldwide since 1987 in oral, parenteral, and topical formulations for various indications.
- The aim of ciprofloxacin DPI development in NCFB was to reduce the bacterial load through the delivery of high concentrations of antibiotic directly into the lung.
- The potential of ciprofloxacin DPI to address the significant unmet medical need of patients with NCFB was recognized by several designations granted by the FDA: Breakthrough Therapy Designation, Fast Track Designation, Qualified Infectious Disease Product Designation, and Orphan Drug Designation.

# 4. Biopharmaceutics and clinical pharmacology of ciprofloxacin DPI

Ciprofloxacin DPI is a drug-device combination intended for inhalation, aiming to reduce the number and frequency of acute exacerbations in patients with NCFB by delivering high bactericidal activity directly to the area of the respiratory tract where infections may develop.

The clinical Phase I program addressed biopharmaceutical aspects, *i.e.*, suitability of the drug-device combination for use in the patient population, and evaluated the pharmacokinetic/pharmacodynamic (PK/PD) properties of the drug-device combination with the objective to achieve a clinical dosing regimen with a favorable risk *vs.* benefit ratio. The following subsections provide a brief overview of the corresponding results.

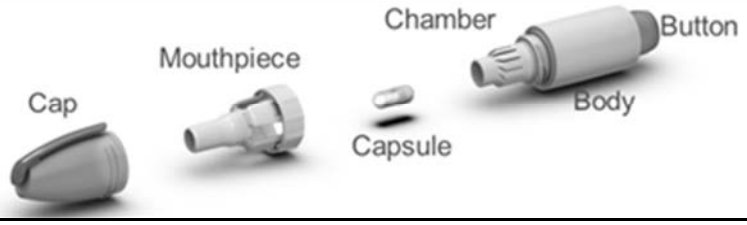
## 4.1 Biopharmaceutical evaluations

### 4.1.1 Dry powder characteristics and device used for inhalation

The ciprofloxacin dry powder is dosed in hypromellose capsules containing the single dose of 32.5 mg ciprofloxacin in 50 mg of powder, manufactured according to the PulmoSphere™ technology (Novartis Pharmaceuticals) [43, 44]. The formulation was optimized for pulmonary deposition to achieve high target concentrations in the lung. The highly porous spherical particles can achieve 90% to 95% w/w of drug load, highly homogenous particle size distribution with a mass median aerodynamic diameter (MMAD) in the range of 1 to 5 µm and largely reduced inter-particle cohesion due to enrichment of surface energy-lowering phospholipids at the particle surface. These factors lead to reduced inter-patient variability in lung deposition from 30% to 50% for micronized drug blends to about 10% to

20% for PulmoSphere™ formulations [44], requiring lower total doses to achieve comparable exposure [43].

**Figure 4–1: Schematic display of the portable breath-actuated Dry Powder Inhaler after unscrewing the mouth piece - Inhalation characteristics**




Source: Data on file

Drug administration is performed by oral inhalation using the breath-actuated, handheld T-326 Dry Powder Inhaler, which is marketed (*e.g.*, in the US and the EU) as part of the drug-device combination product for inhalation of tobramycin dry powder for the management of CF patients with *Pseudomonas aeruginosa* (US: TOBI® Podhaler™, NDA #201-688).

Generally, the objective of local pulmonary delivery for antibiotics is to achieve high therapeutic concentrations with sufficient residence at the target site in the intended patient population while, at the same time, minimizing systemic exposure and thus reducing potential side effects. The advantage of ciprofloxacin DPI over established liquid inhalation systems for antibiotics is the high and reproducible deposition of ciprofloxacin in the lung (see Appendix Figure 9–1), significantly reduced application time (seconds compared to several minutes), reduced handling time for the device compared to nebulizers (requiring cleaning and sterilization), and the easy use of the small T-326 device compared to cumbersome nebulizer systems [45].

### 4.1.2 Biopharmaceutical characterization of the drug/device combination

#### 4.1.2.1 Plan for biopharmaceutical characterization of the drug/device combination

As stipulated in various guidelines [46-50] for the development of dry powder inhalers and as part of the standard development process for inhalation products, patient device interface studies were conducted to examine the flow characteristics and patterns of drug delivery achieved by representative patient populations with varying degrees of disease severity, for whom the final drug product is intended.

Two biopharmaceutical aspects were considered most relevant to demonstrate the suitability of the chosen drug-device combination for clinical use in a patient population known to exhibit a wide spectrum of impaired lung function:

1) The device has to exhibit aerodynamic features allowing the patients to aerosolize and inhale the drug powder formulation reproducibly and completely, independent of the severity of impaired lung function. The key parameter for the assessment of the device suitability in clinical practice was the peak inspiratory flow (PiF), which can be produced by a patient during the inhalation maneuver. For the T-326 inhaler device it should be

above a level of 45 L/min to guarantee homogenous aerosolization of the powder. PiF data were evaluated in NCFB patients in Bayer study No. 17607.

2) The deposition pattern following inhalation of ciprofloxacin DPI doses has to be quantified and evaluated with respect to reproducibility of pulmonary drug deposition in the target population. The deposition data were evaluated in Bayer study No. 11523 using gamma-scintigraphy to determine the whole lung deposition of radiolabeled ciprofloxacin DPI quantitatively and to assess regional lung deposition.

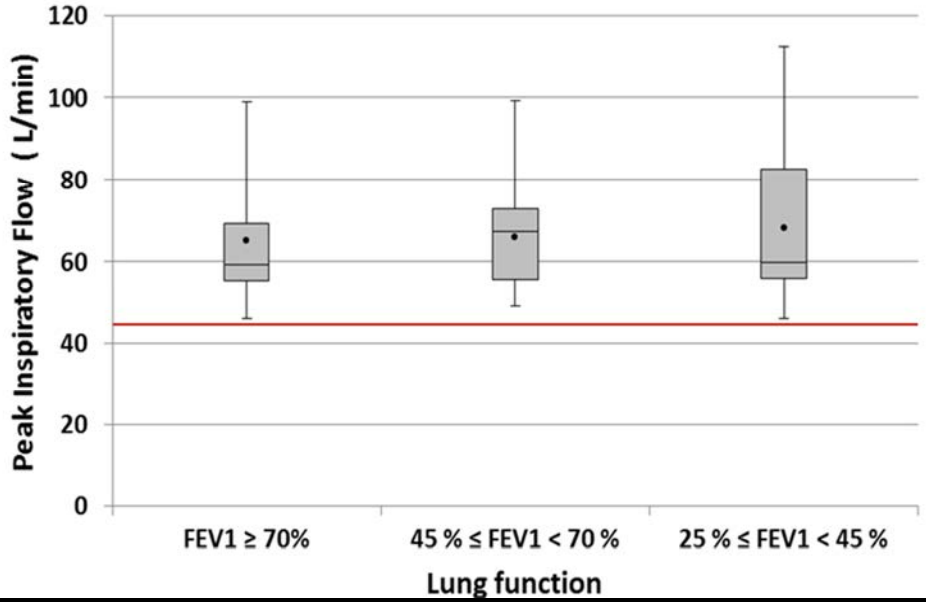
### 4.1.2.2 Main results of biopharmaceutical studies

Appendix Figure 9–1 provides an overview of the device characteristics and the deposition pattern of ciprofloxacin DPI.

Assessment of device performance

Study No. 17607 showed that NCFB patients are able to generate sufficiently high PiFs to operate the inhaler in the aerodynamic range needed to achieve uniform aerosol generation according to the *in vitro* specifications (aerodynamic particle size distribution and delivered dose). Comparable peak inspiratory flows above 46 L/min (*i.e.*, exceeding the specified minimum requirement of PiF ≥45 L/min) were reached in patients even with severely impaired lung function (see Figure 4–2).

**Figure 4–2: Peak Inspiratory Flows generated with the T-326 device by NCFB patients with varying degrees of impaired lung function, based on study No. 17607**



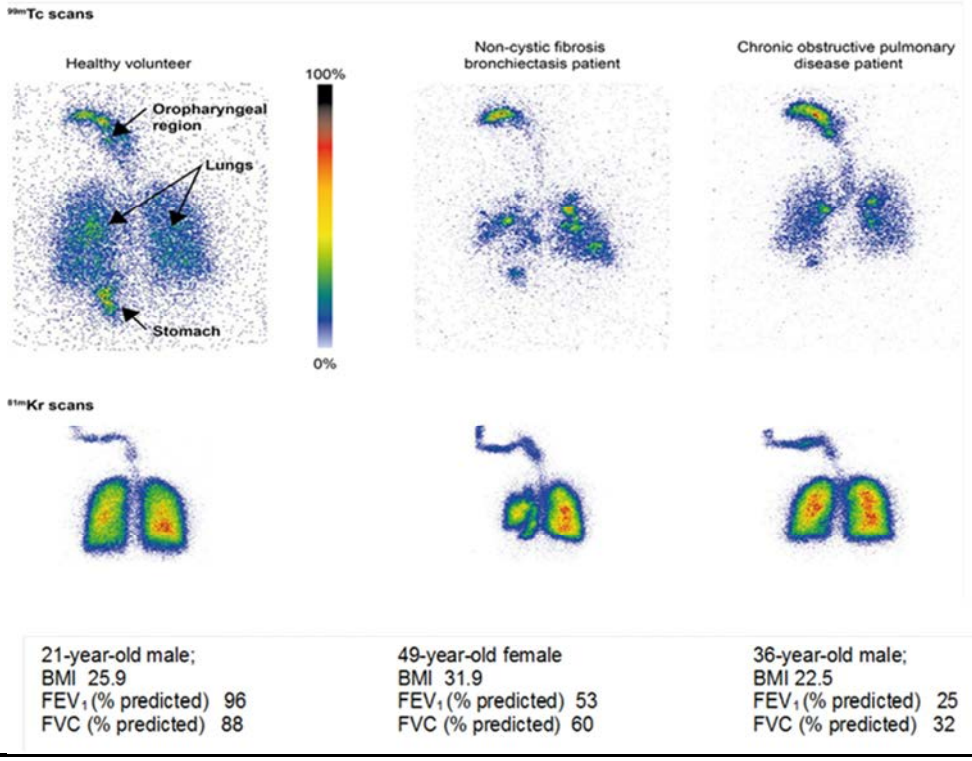

$FEV_1$=Forced expiratory volume in one second
Source: Study 17607 (CSR PH-39146)

Furthermore, the study results indicated that even patients with poor inspiratory capacity can generate the minimum peak inspiratory flow specified for the device in order to empty the capsule completely (about 1.3 L inspiratory volume needed); inhaling twice is recommendable for these patients.

Effectiveness of lung deposition

As shown by scintigraphic measurements in study No. 11523, more than 92% of the drug was aerosolized by NCFB patients with various degrees of impaired lung function, resulting in a 53% pulmonary deposition of ciprofloxacin DPI (*i.e.*, approximately 17.2 mg per inhalation) immediately after inhalation. Complete coverage of the ventilated areas of the lung was demonstrated (see Figure 4–3). This indicated the suitability of the drug-device combination to achieve high target levels in the patient population.

**Figure 4–3: Example of scintigraphic imaging to evaluate lung deposition**




BMI=Body mass index; $FEV_1$=Forced expiratory volume in one second; FVC=Forced vital capacity
Note: Gamma-scintigraphic images of a healthy volunteer *vs.* a patient with NCFB or COPD after a single dose of ciprofloxacin DPI 32.5 mg radiolabeled with $^{99M}$Tc (upper panel) or $^{81M}$Kr (lower panel, characterization of lung contours). Deposition outside of the lung (oropharyngeal region and stomach) is also indicated.
Source: Study 11523 (CSR PH-37340) and [51]

Approximately 3 to 7.5% of the nominal dose remained in the inhaler after use by patients with NCFB and chronic COPD, respectively, compared to approximately 3.5% after use by healthy volunteers. On average, <1% of the inhaled nominal dose was exhaled across all groups. Approximately 40% of the nominal dose was deposited extrathoracically in healthy subjects and in patients with NCFB or COPD.

No differences in pulmonary deposition were detected between healthy subjects and patients after single dose inhalation of ciprofloxacin DPI 32.5 mg, despite significant differences in the forced expiratory volume in one second ($FEV_1$; healthy subjects: 104%, NCFB: 49%, COPD: 54%). The powder was inhaled and distributed reproducibly in the ventilated areas of

the lung, where saturated unbound drug concentrations of ≤120 mg/L were reached in the epithelial lining fluid.

The induced sputum concentrations of ciprofloxacin, as an indicator of pulmonary drug exposure, in the various Phase I studies (see Section 4.2.3) supported the favorable findings from the two biopharmaceutical studies. These data showed that drug levels in the lung achieved with a 32.5 mg ciprofloxacin dose are far beyond those needed for antimicrobial treatment according to the PK/PD breakpoint criteria defined for systemic administration of the drug [52]. This high local exposure cannot be achieved by conventional intravenous or oral treatment using high doses (*i.e.*, 400 mg 3 times a day [TID] i.v. or 750 mg BID orally). Systemic exposure to drug associated with oral absorption of the extrathoracic part of the dose and transmission through the lungs is very low compared to standard intravenous or oral treatment.

Conclusions

From the biopharmaceutical point of view, the ciprofloxacin DPI drug-device combination as used throughout the clinical development program and proposed to be marketed is suitable for outpatient use as long-term treatment of NCFB:

- Patients can generate high exposure to ciprofloxacin in the ventilated lung while keeping systemic burden small compared with intravenous or oral treatment.
- The standard inhalation maneuver for clinical practice derived from these data consists of two deep inhalations for all patients without the need to provide special user handling instructions stratified according to lung function parameters used for diagnostic purposes (*e.g.*, $FEV_1$).

## 4.2 Clinical pharmacological evaluations

An overview of the clinical pharmacology program for ciprofloxacin DPI, including 26 NCFB patients, can be found in Appendix Table 9-1. In addition, population models for PK, PD, and PK/PD relationships were developed, with population PK models based on sparse sampling in ciprofloxacin DPI-treated patients enrolled in Phase II and III trials, in order to support interpretation of clinical results and safety/efficacy conclusions. This section describes the essential results of the studies. Appendix Figure 9–2 shows a brief overview of the most important PK data of ciprofloxacin DPI derived from the PK studies.

### 4.2.1 Methodological particularities in the assessment of lung PK/PD

The assay and PK methodology for ciprofloxacin DPI is described in Appendix 9.1.3.

The lung-targeting concept realized for ciprofloxacin DPI is based on inhalation of drug in order to achieve high target exposure with concentrations in the epithelial lining fluid of the lung at the solubility limit of ciprofloxacin (*i.e.*, the lung should be saturated). Thus, PK sampling to assess respiratory tract kinetics (*e.g.*, induced sputum collection) represents an additional "artificial" clearance process removing significant amounts of drug from the lung. This has to be thoroughly taken into consideration for the evaluation and interpretation of corresponding PK parameters. With very few exceptions (*e.g.*, maximum concentration [$C_{max}$]), the data have to be considered as potentially biased (*e.g.*, area under the curve [AUC]

and half life [$t_{1/2}$] underestimation due to rich sampling). A detailed discussion of the consequences is provided in Appendix 9.1.4.

Therefore, the PK parameters were calculated and reported without corrections for the aforementioned confounding factors. For PK/PD evaluations and dose finding, modeling approaches combined with *in vitro* PK/PD experiments based on unbound (antimicrobially active) ciprofloxacin concentration *vs.* time profiles were used and the resulting dosing predictions confirmed in the Phase II studies (for details see Appendix 9.1.4).

### 4.2.2 Systemic exposure following the inhalation of ciprofloxacin DPI

Systemic exposure to ciprofloxacin after inhalation of ciprofloxacin DPI was investigated at doses ranging from 16.25 up to 65 mg ciprofloxacin DPI (single, once daily [OD] up to TID dosing). Following the inhalation of ciprofloxacin DPI, drug deposited in the lung and ingested orally is absorbed rapidly and extensively. In adult healthy subjects, CF and COPD patients, this resulted in geometric mean peak plasma concentrations of up to approximately 0.3 mg/L and AUCs ranging between 0.4 and 0.7 mg*h/L (geometric mean). In one single dose study in NCFB patients, an AUC of 1.0 mg*h/L was observed (see Figure 4–4).

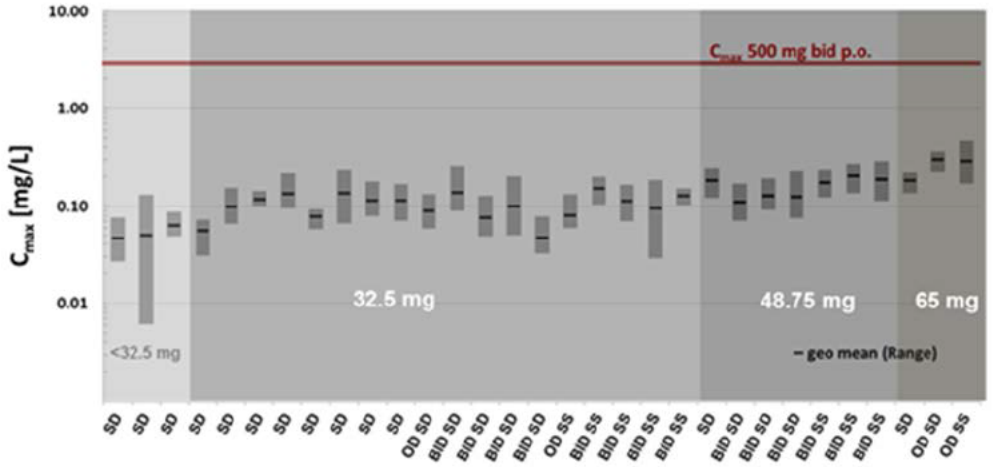
From a population PK analysis in patients receiving 32.5 mg ciprofloxacin DPI BID, medians [and 90% prediction intervals] for $AUC_{\tau,ss}$ and $C_{max}$ in plasma were 0.78 [0.41; 1.45] mg*h/L, and 0.12 [0.07; 0.20] mg/L, respectively. These results are consistent with results from individual studies shown in Figure 4–4.

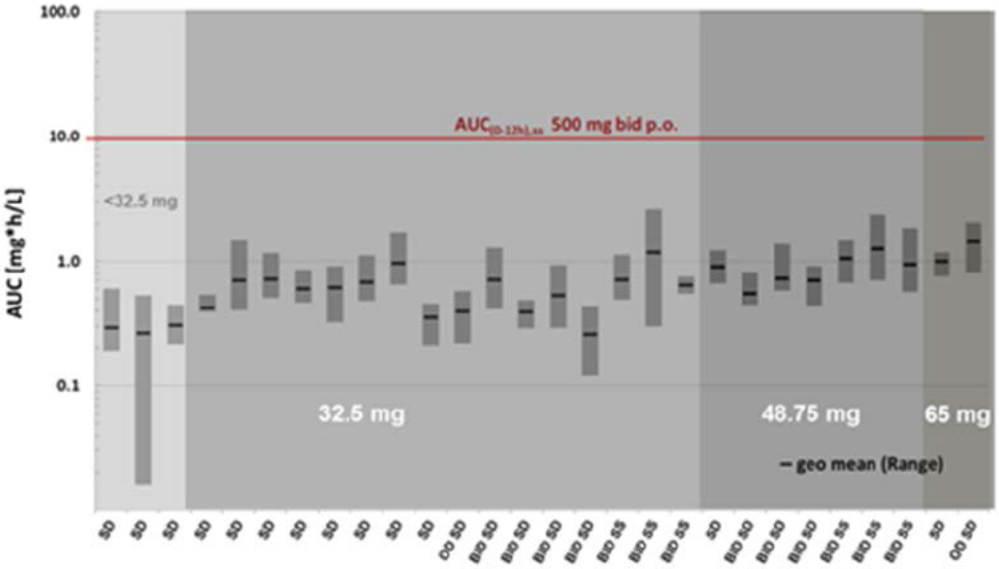
Conclusions

The systemic exposure on treatment with ciprofloxacin DPI is far lower compared with oral or intravenous administration (see Figure 4–4). When administered by inhalation BID, a plasma $AUC_{\tau,ss}$ of 0.78 mg*h/L (median) and $C_{max}$ of 0.12 mg/L (median) were determined in patients for the 32.5 mg dose, indicating that systemic exposure of ciprofloxacin is considerably lower than after standard administration with the intravenous or oral route. For example, the current US prescribing information (USPI) for ciprofloxacin reports values for plasma AUC (13.7 mg*h/L) and $C_{max}$ (2.97 mg/L) after oral administration of 500 mg ciprofloxacin BID. After i.v. administration of 400 mg ciprofloxacin BID, plasma AUC is reported in the USPI as 12.7 mg*h/L and $C_{max}$ is 4.56 mg/L [53]. Therefore, systemic exposure after ciprofloxacin DPI is about 16 to 18-fold (AUC) or 25 to 38 fold ($C_{max}$) lower compared to exposure after i.v. or oral (p.o.) administration. Based on the USPI, PK data for ciprofloxacin (500 mg orally BID) the corresponding oral dose would be approximately 20 mg.

Overall, this low systemic exposure results in a favorable safety profile especially with respect to special populations (*e.g.*, renal impairment) and drug-drug interactions (see Section 4.2.6 and Section 4.2.7).

**Figure 4–4: Peak levels / AUC in plasma reached after inhalation of ciprofloxacin DPI doses in clinical Phase I studies sorted by ascending doses (range: 16.25 to 65 mg ciprofloxacin in healthy subjects, CF, COPD, and NCFB patients)**



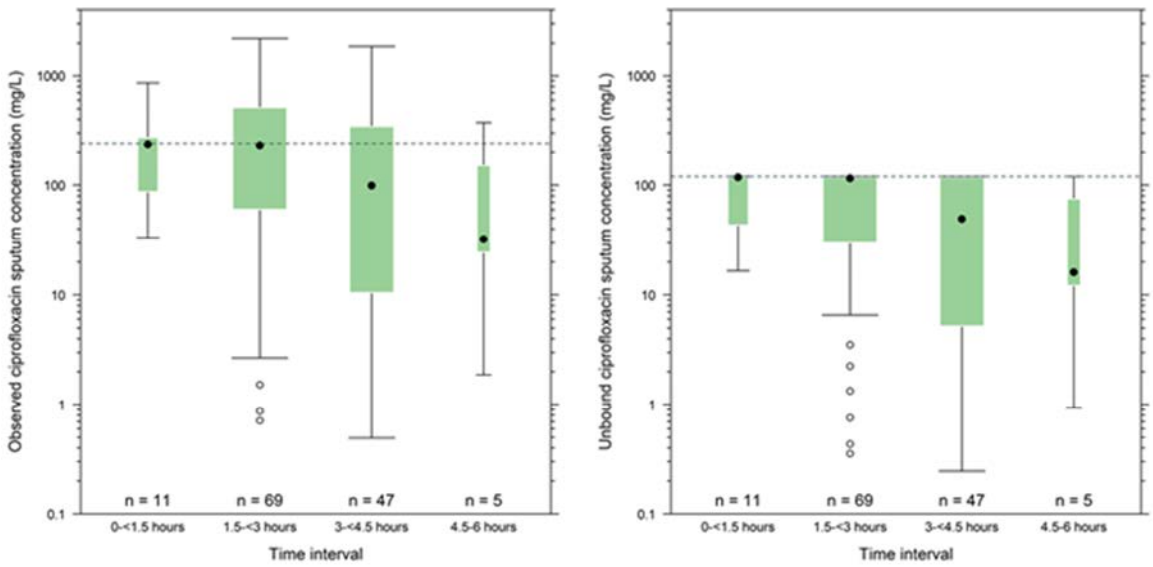

SD=single dose (first dose in case of BID and OD treatment); OD=once daily; BID=twice daily; SS=steady state
Note: The horizontal (red) reference line represents p.o. (500 mg) data for plasma according to USPI.
Source: Reports 12759, 13072, 12132, 12167, 12168, 12170, 13013, 13014, 11523, and 14019

### 4.2.3 Pulmonary (target organ) exposure

Inhalation of drug powder doses corresponding to 16.25 to 65 mg ciprofloxacin generated very high total drug concentrations in the lung. In contrast to the relatively homogenous drug deposition (see Section 4.1.2.2), sputum concentrations were markedly variable (for further discussion see Section 4.2.1 and Appendix 9.1.4). Shortly after inhalation, mean peak concentrations of up to approximately 1000 mg/L could be reached in sputum. Importantly, no dose-dependent increase of lung exposure (AUC) or peak levels ($C_{max}$) could be observed. Geometric mean AUCs and $C_{max}$ ranged from 100 to <10000 mg*h/L and approximately 100 to approximately 1,000 mg/L, respectively, and thus exhibited a very high inter-subject variability.

Corresponding concentration *vs.* time profiles in sputum derived from Phase I studies in COPD patients showed a concentration plateau lasting for up to approximately two hours. This finding is supported by sputum measurements in Phase II/III, where high concentrations were found for up to approximately 5 hours (see Figure 4–5; left panel). Since these levels are beyond the known solubility limits at physiological pH ranges for ciprofloxacin (about 200-300 mg/L; [54]), presence of deposited solid powder particles forming a drug depot has to be concluded from these findings.

**Figure 4–5: Concentration *vs.* time profiles of ciprofloxacin in NCFB patients participating in Phase II and Phase III studies (left panel: total sputum concentrations; right panel: unbound sputum concentrations)**



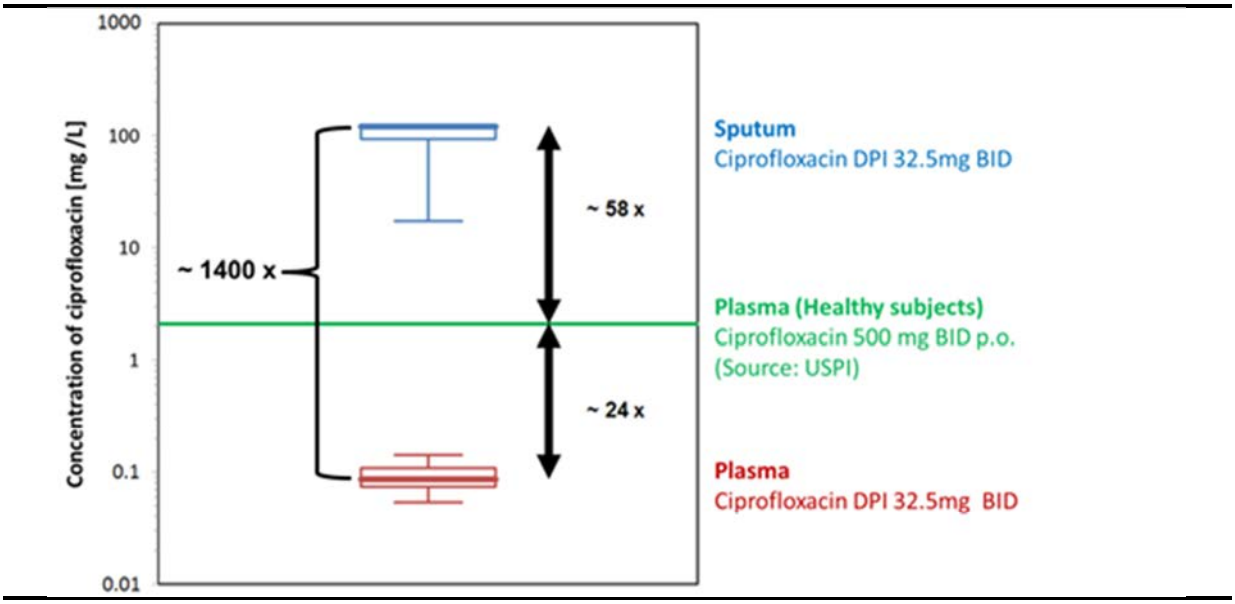

Note: The horizontal dotted lines indicate the ciprofloxacin solubility cut-off determined in sputum binding experiments.
Source: Study 19052 [PH-39230]

Determination of ciprofloxacin binding in sputum showed that active unbound drug concentrations are reaching a state of saturation at levels not exceeding approximately 120 mg/L. Below this saturation range binding amounted to approximately 53%. As a result,

bactericidal (*i.e.*, unbound) drug levels in the lung far beyond those needed for antimicrobial treatment of pathogens are achievable with a 32.5 mg ciprofloxacin DPI dose (see Figure 4–5; right panel).

The (undesired) systemic exposure is low; see Section 4.2.2 and Figure 4-6, which shows that the inhaled dose of ciprofloxacin DPI 32.5 mg BID resulted in a high local unbound concentrations in sputum (median 120 mg/L , blue box), and approx. 1400-fold lower systemic unbound exposure in plasma (median 0.086 mg/L, red box). In comparison, the concentrations in epithelial lining fluid were shown to be 1-2 fold higher compared to corresponding plasma concentrations for oral ciprofloxacin 500 mg BID treatment [55, 56]. Further, the systemic unbound plasma concentrations after oral administration (represented by the green line in Figure 4-6 as peak concentrations) are approximately 24-fold higher in comparison to those after inhalation (ratio [unbound $C_{max}$ after ciprofloxacin 500 mg p.o. BID] *vs.* [unbound $C_{max}$ after ciprofloxacin DPI 32.5mg BID]). Furthermore, the estimated ratio [unbound $C_{max}$ in sputum after ciprofloxacin DPI 32.5 mg BID] *vs.* [unbound $C_{max}$ in plasma after ciprofloxacin 500 mg BID p.o. for inhalation treatment] was ~58-fold. These findings confirm that efficient lung targeting is achieved for ciprofloxacin DPI.

**Figure 4-6: High local (lung ) *vs.* low systemic (plasma) unbound peak concentrations of ciprofloxacin DPI 32.5 mg in NCFB patients (Phase II and III)**




Source: Data on file

Conclusions

Overall, these findings show that a lung saturation concept taking advantage of a drug depot of solid particles is realized with the ciprofloxacin drug-device combination. Furthermore, one can conclude that an increase of the inhaled dose will not necessarily contribute to a higher bactericidal pressure at the target.

### 4.2.4 Metabolism

Metabolism was previously characterized for oral and intravenous ciprofloxacin (including mass balance), thus no further investigations related to metabolism were performed in the clinical development program for ciprofloxacin DPI. More details can be found in the respective USPIs for systemic ciprofloxacin.

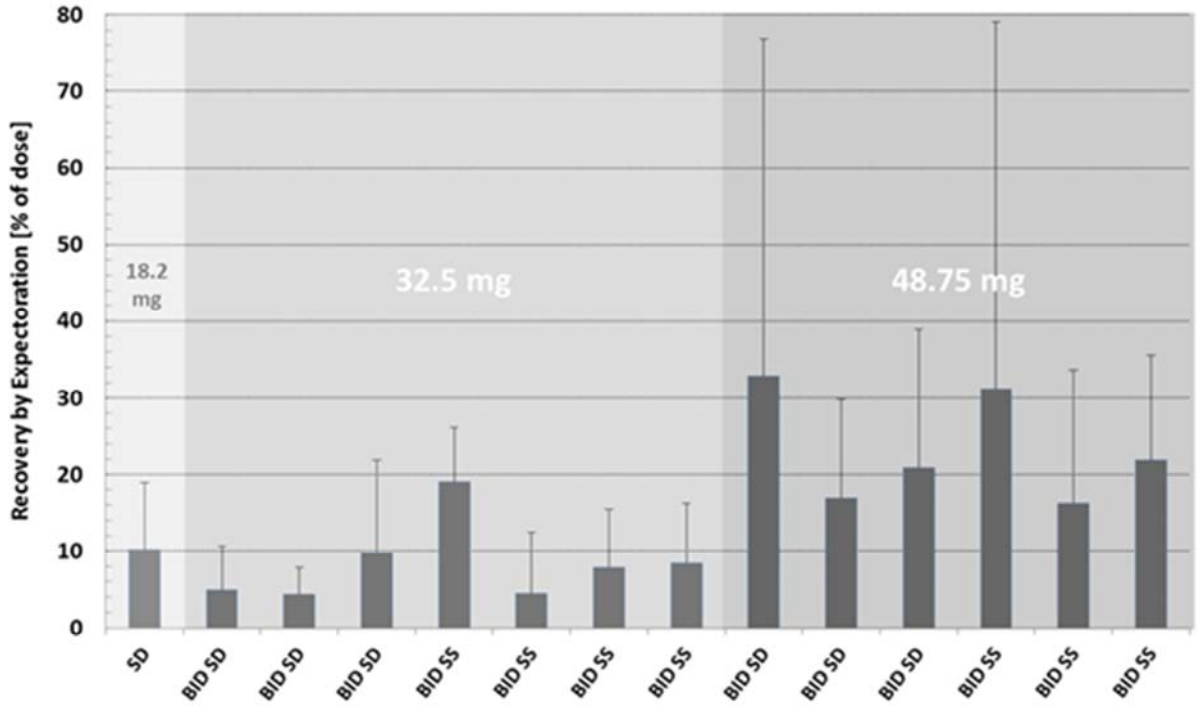
### 4.2.5 Excretion with special emphasis on drug elimination by expectoration

Since elimination pathways are well characterized for oral and intravenous ciprofloxacin administration, the characterization of elimination pathways focused mainly on the investigation of ciprofloxacin clearance from the lung. Based on lung deposition study No. 11523, the amount of drug cleared by uptake into the systemic circulation was determined to be approximately 60% of the deposited dose, while the remainder undergoes physiological elimination processes, such as mucociliary clearance and expectoration.

Quantitative drug expectoration data from Phase I studies as illustrated in Figure 4–7 and Figure 4–8 (after 32.5 *vs.* 48.75 mg ciprofloxacin DPI) clearly show that:

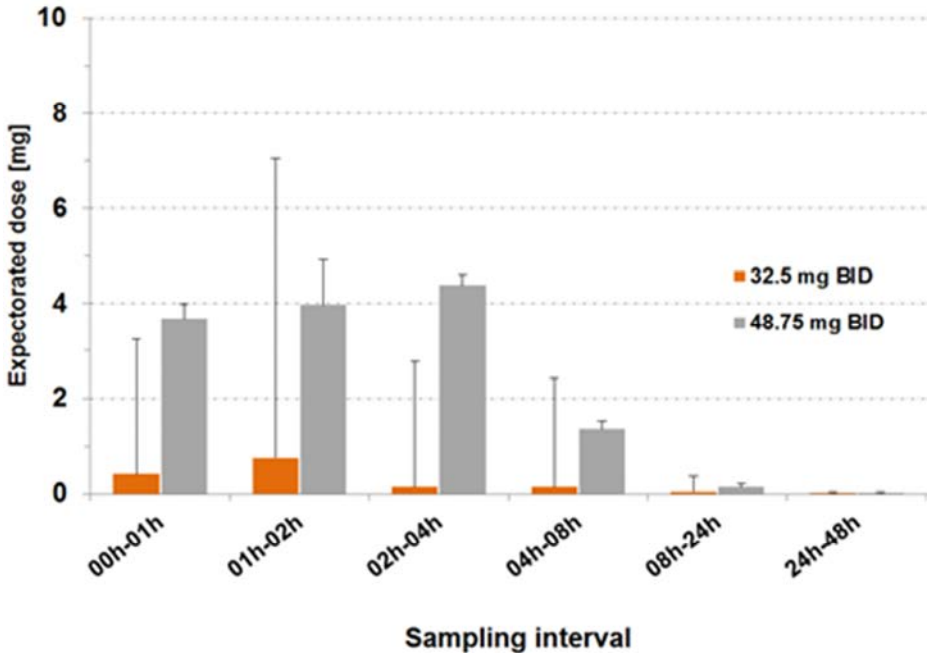
- higher doses than 32.5 mg are not needed for clinical treatment, since the excess drug administered to the lung is likely to be lost due to expectoration (see Figure 4–7). The higher powder load may cause an increased local tolerability risk; thus dosing frequency rather than dose strength is important to maintain antimicrobial pressure in the lung.
- since the drug is recovered for at least 8 hours following inhalation (see Figure 4–8), a dosing interval of 12 hours is sufficient to resupply drug into the lung, balancing safety, efficacy and compliance in clinical practice.

**Figure 4–7: Mean ciprofloxacin recovery from spontaneous sputum following inhalation of ascending single or multiple doses of ciprofloxacin DPI in CF- and COPD grade GOLD I to III patients**




BID=twice daily; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SD=single dose (first dose in case of BID and OD treatment); SS=steady state
Source: Reports 13013, 13014, 13072, 13014, 14019

**Figure 4–8: Mean fractional ciprofloxacin recovery from spontaneous sputum following inhalation 32.5 mg or 48.75 mg ciprofloxacin DPI in COPD grade GOLD II to III patients**




GOLD = Global Initiative for Chronic Obstructive Lung Disease
Source: Study 13014 (CSR PH-36495)

### 4.2.6 Intrinsic and extrinsic factors influencing PK (Special populations)

Intrinsic factors

All relevant subject covariates, such as age, sex, body weight, renal and hepatic function as well as ethnicity, have already been investigated in detail for the oral and intravenous formulations of ciprofloxacin. In addition, an evaluation of such factors was implemented via population PK methods in the Phase II and III studies.

Except renal function, no statistically significant co-variables on ciprofloxacin pharmacokinetics were found for ciprofloxacin DPI. However, although active renal elimination is the main clearance pathway for ciprofloxacin, the low systemic concentrations of ciprofloxacin following inhalation of 32.5 mg doses provide a sufficient safety margin, allowing to avoid dosing restrictions in renally impaired patients or in cases of inhibited renal transporters (*e.g.*, interaction with probenecid).

Extrinsic factors

The effect of smoking (*i.e.*, induction of CYP 1A2 activity) on plasma PK was found to be of no clinical relevance for ciprofloxacin DPI in a statistical analysis of Caucasian and Asian patients, as found in study No. 19051 (PH-39351).

Conclusions

There are no intrinsic or extrinsic factors with a clinically relevant influence on the pharmacokinetics of inhaled ciprofloxacin. Thus, no dose adjustments are required.

### 4.2.7 Drug-Drug interactions

Drug-drug interactions have previously been studied for oral and i.v. ciprofloxacin; thus no new drug-drug interaction studies were performed for ciprofloxacin DPI. The evaluation of the interaction profile based on findings from clinical trials, post marketing surveillance and case report analyses for the oral and intravenous formulations led to the following conclusions:

- Gastro-intestinal absorption interactions leading to reduced systemic bioavailability of ciprofloxacin swallowed during the inhalation maneuver are clinically not relevant, since the antimicrobial effect is achieved via local drug deposition in the lung (*i.e.*, no label statements needed for multivalent cations containing medicinal products and mineral supplements, food and dairy products).
- Ciprofloxacin is known to be a moderate inhibitor of CYP 1A2 enzymes in the liver. Although a potential inhibitory effect after inhalation of ciprofloxacin DPI is far less pronounced than after oral or intravenous doses, similar potentially clinically relevant effects cannot be excluded for substrates undergoing CYP 1A2 metabolism upon concomitant use of ciprofloxacin DPI. Hence, the known label statements for systemic ciprofloxacin should be maintained in the product information of ciprofloxacin DPI (*i.e.*, for tizanidine, theophylline, other xanthine derivatives (*e.g.*, caffeine), duloxetine, clozapine, ropinirole, lidocaine, lidocaine, sildenafil, phenytoin, agomelatine, and zolpidem).

Due to the great safety margin based on the very low systemic exposure of inhaled ciprofloxacin DPI doses, reduced renal elimination by inhibited renal transporters (*e.g.*, by probenecid) is clinically not relevant. Likewise, renal elimination of methotrexate may be inhibited to a very low extent. Although the effect is expected to be far less pronounced compared to oral or intravenous treatment, potentially increased plasma levels of methotrexate, leading to methotrexate-associated toxic reactions cannot be excluded. Therefore, in absence of complementary safety data, patients with concomitant methotrexate therapy should be carefully monitored.

### 4.2.8 PK/PD studies of ciprofloxacin DPI

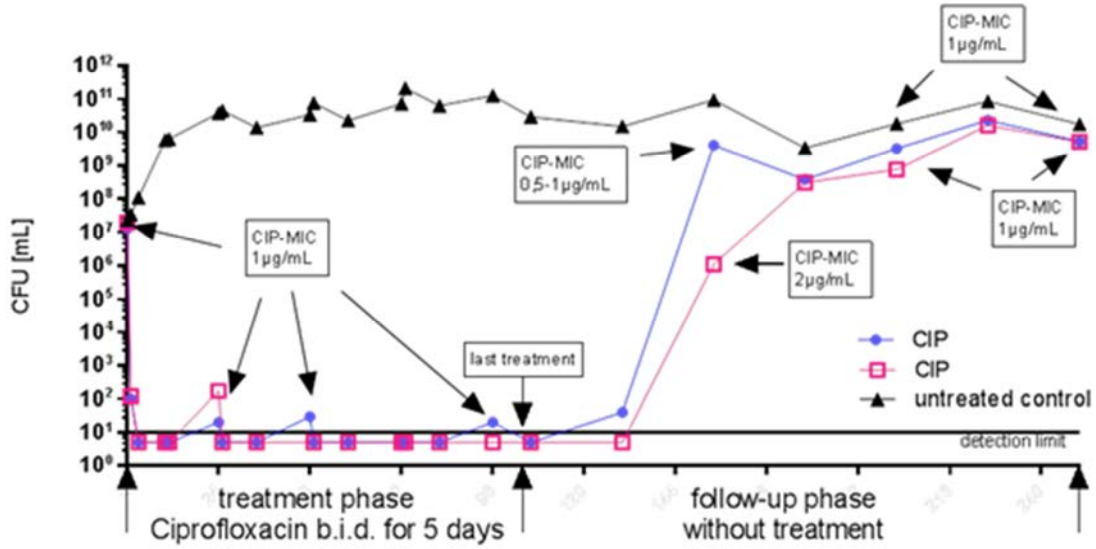
Ciprofloxacin is a synthetic, fluorinated carboxyquinolone and has *in vitro* and *in vivo* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin results from selective inhibition of bacterial type II topoisomerases (deoxyribonucleic acid [DNA] gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The inhibition of gyrase results in a pronounced and rapid bactericidal effect.

For ciprofloxacin DPI *in vitro* PK/PD studies to evaluate the antimicrobial activity of ciprofloxacin against the target respiratory pathogens under simulated *in vivo* conditions (hollow fiber system experiments) unbound concentration *vs.* time profiles were used. The

ciprofloxacin DPI 32.5 mg BID regimen was tested against recent clinical COPD isolates representing the spectrum of pathogens encountered in NCFB. The mean sputum concentration profile of patients after inhalation of ciprofloxacin DPI 32.5 mg was simulated. A 5-day BID treatment course with a subsequent 5-day untreated follow-up phase was studied. The colony-forming units (CFUs) of ciprofloxacin-susceptible *H. influenzae*, *K. pneumoniae*, *S. aureus*, and 3 representative *P. aeruginosa* isolates with minimum inhibition concentrations (MICs) of 0.12, 0.5 and 1.0 µg/mL were determined, and the susceptibilities in terms of MIC were assessed. For all tested organisms, rapid bactericidal activity was observed, with reductions of at least 5 $\log_{10}$ units achieved 10 hours after the first treatment. During the treatment cycle, all bacterial populations were reduced below the detection limit at least after the 9th treatment. In the follow-up phase, no regrowth of *H. influenzae* and *P. aeruginosa* displaying a MIC of ≤0.12 µg/mL was observed. The remaining COPD isolates showed regrowth without elevated MICs, and no changes in resistance frequency were detected compared to the untreated control population.

Figure 4–9 provides an example of the results of the PK/PD experiments using *P. aeruginosa* with an MIC of 1 µg/mL as the test organism representing the target pathogens.

**Figure 4–9: Bactericidal activity of a 5-day 32.5 mg BID ciprofloxacin DPI treatment course with a subsequent 5-day untreated follow-up phase against *P. aeruginosa* (MIC=1.0 mg/L) in a hollow fiber model simulating the concentration time courses of unbound ciprofloxacin in the lung**

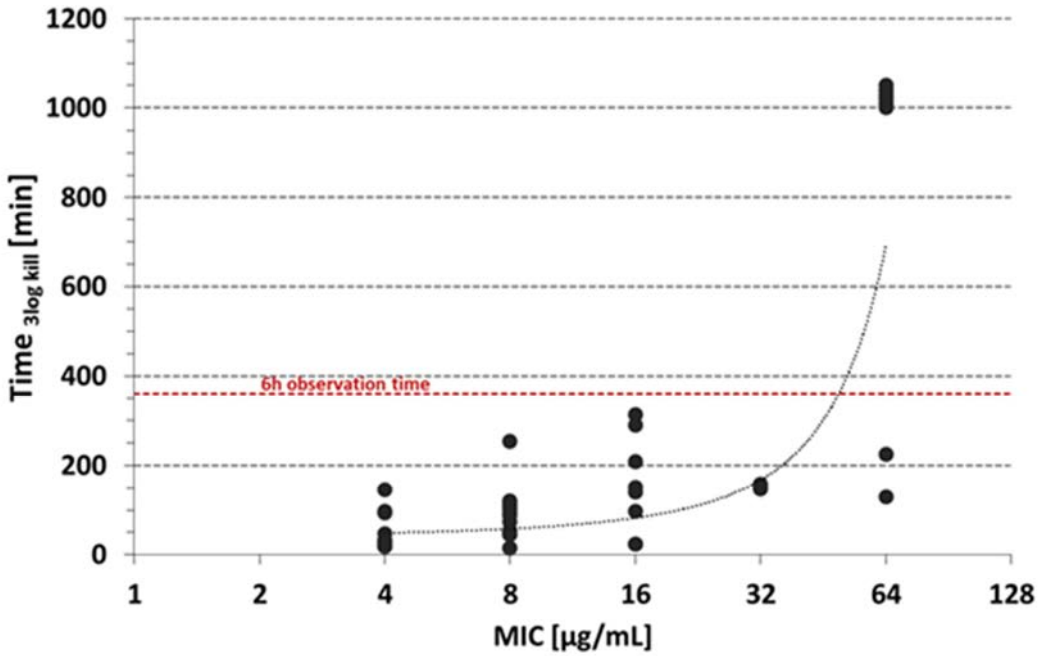



Source: Report PH-36824

Additional *in vitro* studies focusing on *P. aeruginosa* classified as resistant to ciprofloxacin according to the breakpoints defined for systemic treatment were performed with isolates, which were obtained from patients enrolled in the Phase II CF study No. 12429. These isolates were exposed for 360 minutes to static ciprofloxacin concentrations representing the maximum (120 µg/mL) or the half maximum (60 µg/mL) of unbound sputum levels of ciprofloxacin. The MIC range of used isolates was between 4 and 64 µg/mL. Within the

observation time, 3 log killing was achieved for pathogens up to a MIC of 32 µg/mL for ciprofloxacin concentrations of 120 mg/L(see Figure 4–10). The results in general showed a MIC-dependent log CFU reduction between 0.87 to 5.88 with the maximal ciprofloxacin sputum concentration and a log CFU reduction between 0.15 to 5.79 with the half-maximal ciprofloxacin sputum concentration.

**Figure 4–10: *In vitro* kill time results for clinical *P. aeruginosa* isolates**




Note: Duplicate measurements were performed for each strain. Provided are the *in vitro* kill time results for clinical *P. aeruginosa* isolates at 120 µg/mL static concentrations, representing maximum unbound concentration of ciprofloxacin in sputum after inhalation of a single 32.5 mg ciprofloxacin DPI dose (equivalent to 50 mg ciprofloxacin DPI. The observation time of 360 minutes (6 hours) is indicated with the dotted reference line, data >360 minutes were imputed to indicate lack of 3 log kill within the total observation time.
Source: Report PH-39058

In addition, a subset of the aforementioned strains were tested in an *in vitro* hollow fiber PK/PD model simulating the mean unbound ciprofloxacin sputum concentration profile of patients after inhalation of ciprofloxacin DPI 32.5 mg. MIC-independent reduction rates were observed. Time to display a 3 $\log_{10}$ CFU reduction without regrowth within 10 hours ranged from 9 to 146 minutes for isolates with ciprofloxacin MICs from 4 to 8 µg/mL. Strains with MIC of 32 µg/mL (n=1) and MIC of 64 µg/mL (n=1) against ciprofloxacin did not achieve a 3 $\log_{10}$ killing during observation time of 10 hours. A $\log_{10}$ CFU reduction of 1.6 was achieved for the strain with MIC 32 µg/mL, and for the strain with MIC 64 µg/mL, the achieved $\log_{10}$ CFU reduction was 0.89. Both strains showed a regrowth above baseline, without an increase of MICs compared to initial MIC at experimental start.

These PK/PD *in vitro* experiments, simulating the mean unbound ciprofloxacin sputum concentrations of subjects after inhalation of ciprofloxacin DPI 32.5 mg demonstrated that ciprofloxacin was highly effective, without impact on susceptibility. These results were further substantiated in acute and chronic lung infection models in rats and, eventually, also in *in vivo* based on the analyses of the microbiological endpoints in the two Phase II studies in patients with CF and NCFB (for details on the NCFB study see Section 5.2).

**Summary of Section 4 (Biopharmaceutics and clinical pharmacology of ciprofloxacin DPI):**

- The specialized formulation using the PulmoSphere™ technology results in a reliable and reproducible drug deposition in the lungs of patients with NCFB.
- With the use of the specialized formulation and inhaler, the drug reaches all ventilated parts of the lung, regardless of inhalation capacity.
- A favorably high amount of the nominal dose (about 50%) reaches the lungs.
- A ciprofloxacin DPI 32.5 mg dose is the optimal dose to achieve sustained active (*i.e.*, unbound) drug concentrations in the respiratory tract at the saturation level of approximately ≤120mg/L. Higher doses show no advantage, as the surplus is mainly expectorated. Thus, dose frequency is the most important parameter to maximize bactericidal pressure of ciprofloxacin DPI against respiratory pathogens.
- The twice daily (BID) dosing balances best the goal of a sustained, high lung exposure with a low systemic exposure and patient compliance in terms of application frequency.
- The systemic exposure upon inhalation treatment with ciprofloxacin DPI is considerably reduced compared with oral or intravenous therapy with ciprofloxacin. As a consequence, the drug-drug interaction potential is reduced. Due to the low systemic exposure, there is no need for dose adjustment in renally impaired patients.
- The pharmacokinetic characteristics of ciprofloxacin DPI have been thoroughly studied, especially with regard to the influence of drug clearance from the lung on target exposure, and thus no clinically relevant uncertainties with regard to the pharmacokinetic characteristics of ciprofloxacin DPI remain.
- *In vitro* pharmacokinetic/pharmacodynamic testing models showed that ciprofloxacin DPI 32.5 mg is active against the target pathogens, including those with reduced susceptibility to ciprofloxacin.
- The pharmacokinetic/pharmacodynamic data provided the rationale for the dosing strategy used in the subsequent Phase II/III studies: 32.5 mg BID.

# 5. Clinical efficacy of ciprofloxacin DPI in patients with NCFB

## 5.1 Introduction

The overall efficacy evaluation is based on the totality of evidence across the primary and secondary endpoints, including exacerbation-related endpoints, microbiology, and patient-reported outcomes for both treatment regimens. The overall treatment effects are consistently positive in the evaluations, even though there is heterogeneity in the individual evaluations.

The RESPIRE 1 and RESPIRE 2 trials provided meaningful data demonstrating the treatment effect, and the range of treatment effects, for ciprofloxacin DPI in NCFB patients. Ciprofloxacin DPI 14 and ciprofloxacin DPI 28 produced a range of positive treatment effects in relation to each other, and in relation to pooled placebo in RESPIRE 1 and RESPIRE 2.

Ciprofloxacin DPI 14 produced a HR of 0.53 (97.5%-CI: [0.36; 0.80]) and a p-value of p=0.0005 in RESPIRE 1. Fitting a parametric survival regression *post hoc*, a 222-day delay in median time to first exacerbation was calculated. Ciprofloxacin DPI 28 produced a positive trend for efficacy in the primary efficacy variable for increasing the time to first exacerbation event with a HR of 0.73 (97.5%-CI: [0.50; 1.07]), but missed significance with p=0.0650 and yielded a 107-day delay in median time to first exacerbation (by *post hoc* extrapolation). Positive point estimates and trends were produced by both treatment arms for the majority of secondary endpoints, including the frequency of exacerbations.

The statistically significant result in the primary efficacy endpoint was not replicated by ciprofloxacin DPI 14 in RESPIRE 2, with a HR of 0.87 (95.1%-CI: [0.62; 1.21]), a corresponding p-value of p=0.3965, and a 43-day delay in median time to first exacerbation calculated by *post hoc* extrapolation. Ciprofloxacin DPI 28 showed consistency in the primary efficacy variable with a HR of 0.71 (99.9%-CI: [0.39; 1.27]), a corresponding p-value of p=0.0511, and a 148-day delay in median time to first exacerbation calculated by *post hoc* extrapolation. Both treatment regimens produced positive point estimates in the majority of secondary endpoint analyses, including the frequency of exacerbations. Comparison of the placebo groups in RESPIRE 1 and RESPIRE 2 demonstrated a lower exacerbation rate and increased time to first event in RESPIRE 2.

The major efficacy question is to determine the treatment effect of ciprofloxacin DPI in the RESPIRE program. For the primary endpoint (time to first exacerbation), the treatment effect was highest for ciprofloxacin DPI 14 in RESPIRE 1, and lowest for ciprofloxacin DPI 14 in RESPIRE 2, while ciprofloxacin DPI 28 produced an intermediate treatment effect in both RESPIRE 1 and RESPIRE 2. For the first secondary endpoint (frequency of exacerbations), ciprofloxacin DPI 14 produced a consistent treatment effect, while ciprofloxacin DPI 28 showed both a higher and lower treatment effect across both RESPIRE 1 and RESPIRE 2.

Additional analyses were conducted to provide insights into the treatment effect of ciprofloxacin DPI. A pre-specified integrated analysis across RESPIRE 1 and RESPIRE 2 was performed to estimate the treatment effect in all patients who received ciprofloxacin DPI 14, and all patients who received ciprofloxacin DPI 28, compared to all patients who received placebo. Since both treatment regimens deliver the same amount of active drug, an additional *post hoc* analysis was also conducted on pooled ciprofloxacin DPI 14 and ciprofloxacin DPI 28, compared to pooled placebo, within RESPIRE 1, and within

RESPIRE 2. This analysis was useful for showing the overall treatment effect of ciprofloxacin DPI within each RESPIRE trial.

These additional data are provided as supportive analyses for determination of the treatment effect of ciprofloxacin DPI in a heterogeneous patient population. The efficacy evaluation is based on the totality of evidence in exacerbations, microbiology, and patient-reported outcomes for both treatment regimens.

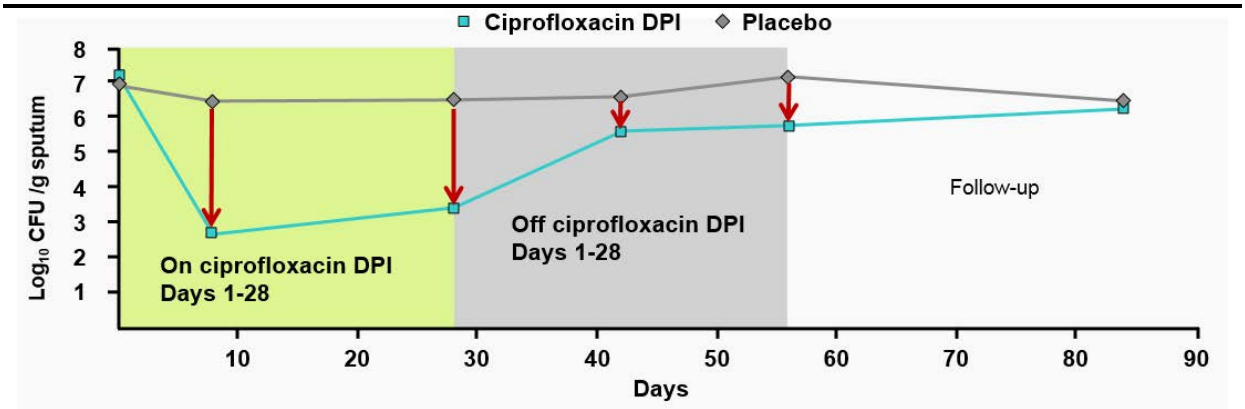
## 5.2 Main results of the Phase II NCFB study (12965) and implications for the design of the Phase III studies

Patients treated in the placebo-controlled Phase II NCFB study received 28 days of ciprofloxacin DPI 32.5 mg BID, followed by 28 days off-treatment and a further follow-up period until a total study duration of 84 days. The sample sizes and demographic characteristics of the Phase II NCFB study patients are summarized in Appendix Table 9-4. A detailed description of efficacy results (related to pathogen load, time to first exacerbation, and changes in SGRQ) can be found in Appendix Table 9-8.

Reduction in total bacterial load

The primary efficacy variable in the NCFB study was the "change in total bacteriological load from baseline to end of treatment (EOT)" considering the pre-defined species *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Klebsiella pneumoniae* or *oxytoca*, *Serratia marcescens*, *Escherichia coli* and *Proteus mirabilis*, *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans*, expressed as $\log_{10}$ CFU per g sputum. There was a significant reduction in bacterial load of -3.62 $\log_{10}$ CFU/g sputum for ciprofloxacin DPI compared with a reduction of -0.27 $\log_{10}$ CFU/g sputum for placebo ($p<0.001$; see Figure 5–1 and Appendix Table 9-8). The maximal reduction in bacterial count was achieved at Days 7-9, and was maintained throughout the 28-day treatment period. There was a regrowth of bacterial burden during the 28 day off cycle. By 8 weeks post-EOT, the mean $\log_{10}$ CFU/g sputum counts converged in the two treatment groups.

**Figure 5–1: Course of total bacterial load [$\log_{10}$CFU/g sputum] in Phase II NCFB study 12965 (ITT)**




Source: CSR of study No. 12965

Occurrence of exacerbations

The descriptive analyses showed a numerical trend in favor of ciprofloxacin DPI compared with placebo for reduction in exacerbations. This positive trend was for all 3 evaluated types of exacerbation, *i.e.*, all investigator-reported exacerbations, investigator-reported exacerbations with antibiotic intervention, and investigator-reported exacerbations with hospitalization (see Appendix Table 9-8). The Kaplan Meier plot for time to first exacerbation is additionally depicted in Appendix Figure 9–6.

Changes in Saint George's respiratory questionnaire (SGRQ) total score

The analysis of the change in SGRQ total score at EOT showed a treatment difference of -3.56 score points *vs.* placebo in favor of ciprofloxacin DPI (95%-CI: [-7.25; 0.13], p=0.059; see Appendix Table 9-8).

Impact of Phase II NCFB study data

The promising results from the NCFB Phase II study provided the rationale for the design of the Phase III development program, including the use of the ciprofloxacin DPI 14 days on/off regimen (see Section 5.3.1 for Phase III study designs). Peak reduction in bacterial burden occurred during the first measurement (Days 7-9), and a slight increase in bacterial count was noted during the second two-week period of dosing (Days 15-28). During the 4-week off-cycle (Days 29-56), the bacterial burden returned to nearly the same level as pre-treatment. These observations were the basis for the introduction of an alternative ciprofloxacin DPI dosing schedule of 14 days on/off (referred to as "14-day regimen"). The rationale of the ciprofloxacin DPI 14 regimen was to stop the treatment cycle at maximal bacterial reduction and to shorten the antibacterial treatment-free period.

## 5.3 Efficacy results in Phase III studies

### 5.3.1 Design of Phase III studies

Study setting

RESPIRE 1 and RESPIRE 2 studies were large, multicenter, randomized, placebo-controlled parallel-group studies, which were performed globally in clinical centers with expertise in the field of pulmonology. RESPIRE 1 was the first initiated study and was performed from 02-May-2013 to 09-Mar-2016, while RESPIRE 2 was performed from 30-Apr-2014 to 19-Oct-2016. Patients in RESPIRE 1 were predominantly enrolled in Western European countries, Australia/New Zealand and the US. In RESPIRE 2, there was a higher contribution from Russia, Bulgaria, and Asian countries including China. In total 60 patients (44 in RESPIRE 1 and 16 in RESPIRE 2) were randomized in the US (see Appendix Table 9-7).

A total of 902 and 1,123 patients were initially screened and 416 and 521 patients randomized in RESPIRE 1 and RESPIRE 2, respectively (see Appendix Table 9-5). No relevant change in standard of care that might have influenced the comparability of the studies are likely, since the since the two studies required less than 3.5 years to complete with an 18-month overlap in execution.

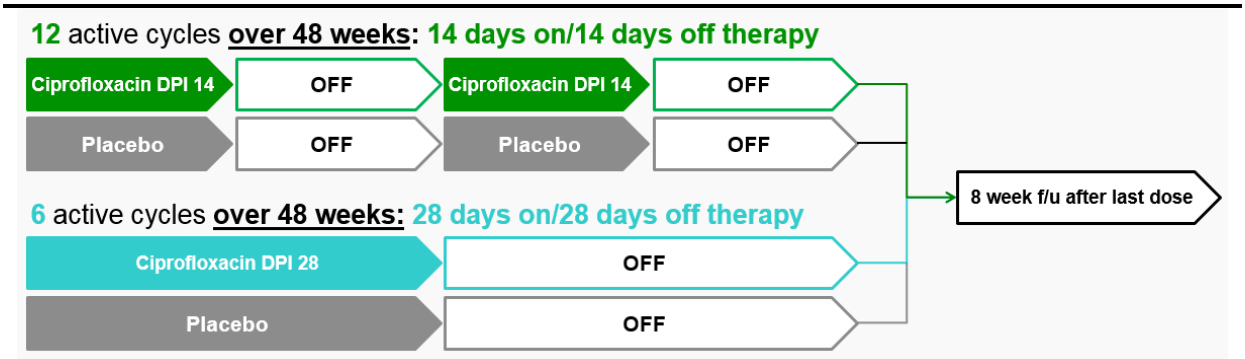
Enrollment criteria

The study eligibility criteria were defined in order to enroll a population of patients with NCFB that was considered most likely to benefit from ciprofloxacin DPI therapy. These criteria included a history of 2 or more documented exacerbations in the previous 12 months, and a positive sputum culture at baseline for at least one of 7 pre-defined respiratory pathogens (*P. aeruginosa*, *S. aureus*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. maltophilia*, and *B. cepacia*). A full list of inclusion and exclusion criteria is provided in Appendix 9.2.1.

Treatments

Eligible study patients were randomized to treatment with ciprofloxacin DPI 32.5 mg BID or matching placebo at intervals of 28 days on/off or 14 days on/off (see Figure 5–2). The treatment regimens of ciprofloxacin DPI, 32.5 mg BID 28 days on/off and 14 days on/off, were selected based on the results of the comprehensive Phase I//II clinical development program. A treatment duration of 48 weeks with a follow-up period of 8 weeks after the last dose was chosen in order to take account of the chronic nature of the disease and thus the requirement for long-term treatment. Of note, the ciprofloxacin DPI 14 and DPI 28 groups had equal drug exposure over the full course of the trial.

**Figure 5–2: Treatment regimens in Phase III studies**




Source: Data on file

Study endpoints

The efficacy evaluation of ciprofloxacin DPI treatment in NCFB patients is based primarily on the reduction of exacerbations. For the primary endpoint, a "qualifying exacerbation" in the RESPIRE studies was defined as an exacerbation that required systemic antibiotic treatment and was associated with presence of fever or malaise / fatigue and worsening of at least 3 signs/symptoms (*i.e.*, dyspnea, wheezing, cough, sputum volume [over 24 hours], and sputum purulence [color]; see Appendix 9.2.2 for more details).

The primary endpoint "time to first exacerbation" was agreed with FDA as appropriate to demonstrate long-term efficacy. The frequency of exacerbation endpoint is also an important measure to assess the performance of ciprofloxacin DPI in the proposed indication. The first secondary endpoint was the reduction of the frequency of exacerbations. Time to first exacerbation was logically thought to be related to the subsequent frequency of exacerbations.

Other secondary endpoints included the microbial endpoints eradication of pathogens present at baseline and acquisition of new pathogens. Changes in the patient-reported outcome tools SGRQ (symptoms component score) and the QOL-B (respiratory symptoms domain score) were both used to determine potential treatment effect. Finally, changes in $FEV_1$ values were measured at the end of the study (EOS).

These variables were used in both RESPIRE 1 and RESPIRE 2 for the pre-specified, statistical testing procedure in the following order (for details see Appendix 9.3.1):

| | |
|---|---|
| Primary efficacy variable: | Time to first exacerbation event. |
| Secondary efficacy variables: | Frequency of exacerbation events (≥3 signs),<br>Frequency of exacerbation events (≥1 sign),<br>Eradication of baseline pathogens,<br>Changes in SGRQ symptoms component score,<br>Occurrence of new pathogens,<br>Changes in QOL-B respiratory symptoms domain score,<br>Changes in lung function ($FEV_1$). |

Conduct of studies and assessment time points

After a maximum screening period of 4 weeks, eligible patients were randomized in a double-blind fashion to one of the 4 possible double-blinded treatment groups in a ratio of 2:1:2:1 (active: placebo: active: placebo) to receive ciprofloxacin DPI 32.5 mg BID or matching placebo either as 28 days on/off treatment or as 14 days on/off treatment. All patients were to be treated with their cyclic regimen of study medication for 48 weeks, and each patient was to be observed for a total follow-up time of 8 weeks after last dose. An EOS visit was performed after completion of the follow-up period.

The respiratory signs and symptoms as well as sputum characteristics were assessed at the randomization visit and at all subsequent scheduled study visits (as well as unscheduled visits due to assumed bronchiectasis exacerbation) according to the criteria provided in Appendix 9.2.2. Patients with an exacerbation were to be adequately treated as decided by the investigators, including the use of systemic antibiotics as needed. Study treatment could be temporarily interrupted during an exacerbation; thereafter, administration of the study drug was allowed to be continued according to the original treatment schedule, and all patients were to continue the study regularly until the EOS visit.

Patient-reported outcomes were evaluated at pre-determined time points. The SGRQ was evaluated on 4 study visits: at baseline, in the middle of the study (Day 140 in the 28-day regimen groups or Day 154 in the 14-day regimen groups), at EOT, and at EOS. The QOL-B was evaluated on 9 (28-day regimen) or 10 (14-day regimen) study visits from baseline visit until EOS. The pulmonary function tests were performed on 11 (28-day regimen) or 15 (14-day regimen) study visits, as well as at unscheduled exacerbation visits, from screening visit until EOS (see Appendix Figure 9–4). Adverse events were documented throughout the study period. Extensive sputum sampling for microbiological evaluation of baseline pathogen eradication, new pathogen acquisition, and selection of drug resistance was performed on 11 (28-day regimen) or 15 (14-day regimen) study visits as listed above for patient-reported outcomes.

Statistical methodology

Details on statistical methodology are provided in Appendix 9.3. Generally, the statistical analyses were performed using established methodology such as an analysis based on the ITT principles as stipulated by ICH-E9. The "full analysis set" (FAS) consisted of all randomized patients and was analyzed as randomized; the term "FAS" is consistently used in this document. An α-correction was applied to account for multiple testing (see Appendix 9.3.3). The primary efficacy endpoint was analyzed using a multivariate Cox regression model, in which 3 factors (baseline presence of *P. aeruginosa*, chronic macrolide use, and geographic region) that were used for stratification in the randomization were included as covariates (see Appendix 9.3.4). In accordance with FDA advice, the ciprofloxacin DPI 28 group and the ciprofloxacin DPI 14 group were separately compared with the pooled placebo group in the pre-specified efficacy analyses after confirmation that there was no statistically significant difference between the two placebo groups . The pre-defined statistical hierarchical testing sequence consisting of all efficacy endpoints is summarized in Appendix Table 9-3. In additional *post hoc* analyses, the two ciprofloxacin DPI groups were pooled for comparison *vs.* pooled placebo. An extensive array of pre-defined subgroup analyses were included in order to assess the generalizability of study results. Pre-specified sensitivity analyses to account for missing data were conducted and confirmed the results of the primary efficacy analysis (see Appendix Table 9–10).

Efficacy data presentation

Sample sizes and demographic characteristics of the patients enrolled in RESPIRE 1 and RESPIRE 2 are summarized per study in Appendix Table 9-5. The pathogens isolated from randomized patients at baseline were in similar proportions in RESPIRE 1 and RESPIRE 2, with *P. aeruginosa*, *H. influenzae*, and *S. aureus* as the 3 most prominent pathogens (see Figure 5–14).

The efficacy results are arranged by endpoint for RESPIRE 1 and RESPIRE 2. This allows for a direct comparison of efficacy results between studies for each endpoint within a single section. The exacerbation-related endpoints (see Section 5.3.2), patient-reported outcomes (see Section 5.3.3) and microbiological endpoints (see Section 5.3.4) are summarized within each section. No lung function results are discussed, since $FEV_1$ changes over time were negligibly small in each of the treatment groups.

A discussion of efficacy outcomes across studies can be found in Section 5.3.5, and an overall conclusion on efficacy is provided in Section 5.3.6.

## 5.3.2 Exacerbation-related efficacy results in RESPIRE 1 and RESPIRE 2

### 5.3.2.1 RESPIRE 1: Time to first exacerbation and frequency of exacerbations

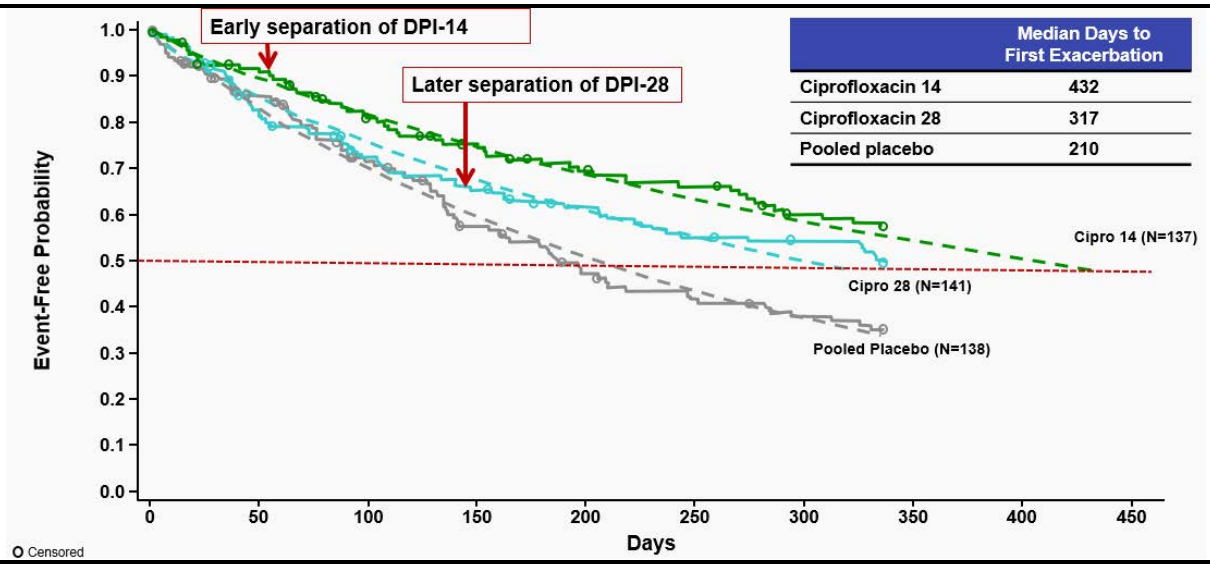
The ciprofloxacin DPI 14 regimen demonstrated a statistically significant prolongation of the time to the first exacerbation event in RESPIRE 1. The HR was 0.53 for ciprofloxacin DPI 14 (97.5%-CI: [0.34; 0.80]) associated with a highly significant p-value (p=0.0005). Treatment results on the 28-day regimen were also in favor of ciprofloxacin DPI, but the primary efficacy analysis missed statistical significance for the HR=0.73 (97.5%-CI: [0.50; 1.07]; p=0.0650). The median time to first event was 186 days in the pooled placebo group, 336 days in the ciprofloxacin DPI 28 group and could not be estimated (>336 days) using the

Kaplan Meier method for the ciprofloxacin DPI 14 group, due to the fact that too few patients had a qualifying exacerbation (38.7%). In RESPIRE 1, the two-sided, pre-specified significance level was α=0.025 for either treatment regimen, and thus corresponding 97.5%-CIs were calculated (for the hierarchical testing procedure see Appendix Table 9-3).

Since the median time to first exacerbation could not be estimated with the Kaplan Meier method in the ciprofloxacin DPI 14 group, a *post hoc* analysis using a parametric survival regression fitting a Weibull distribution was applied (for statistical details see Appendix 9.3.7). This method resulted in an (extrapolated) median time to first exacerbation of 432 days in the ciprofloxacin DPI 14 group, 317 days in the ciprofloxacin DPI 28 group, and 210 days in the pooled placebo group. Thus, the gain with ciprofloxacin DPI 14 *vs.* pooled placebo was estimated as (median) 222 days, and 107 days on treatment with ciprofloxacin DPI 28 *vs.* pooled placebo.

The Kaplan Meier plot for the time to the first exacerbation (with the Weibull survival fit) is displayed in Figure 5-3.

**Figure 5-3: Primary endpoint: Time to first exacerbation event up to Week 48 in RESPIRE 1 - Kaplan Meier plot with Weibull survival fit (FAS)**




Cipro 14=Ciprofloxacin DPI 14 days on/off; Cipro 28=Ciprofloxacin DPI 28 days on/off
Note: Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution. Kaplan Meier plots are solid lines, Weibull survival fits are dashed.
Source: CSR of Study 15625 (Kaplan Meier plot); data on file (Weibull survival fit)

Thus, the primary efficacy endpoint was met for the 14-day regimen (see Appendix Table 9–9 for an overview of the outcomes of the hierarchical test sequence in both RESPIRE 1 and RESPIRE 2).

Table 5–1 summarizes the results of the statistical analyses of the exacerbation frequency-related secondary efficacy endpoints (primary analyses as per SAP, *i.e.*, using an extrapolation approach for the exacerbation frequency in patients who did not complete the study; see Appendix 9.3.5). For the exacerbation frequency, differences between treatment

groups were expressed as "incidence rate ratio" (IRR), with estimates <1.0 indicating outcomes in favor of ciprofloxacin DPI *vs.* pooled placebo.

**Table 5–1: Results of the primary and secondary efficacy analyses related to exacerbation (primary tests as per statistical analysis plan) in RESPIRE 1 (FAS)**

| | Cipro 14 N=137 | Cipro 28 N=141 | Pooled placebo N=138 |
|---|---|---|---|
| **Time to first exacerbation** [a] | | | |
| Estimated median time | 432 | 317 | 210 |
| **Patients with exacerbation** | | | |
| n (%) | 53 (38.7) | 67 (47.5) | 79 (57.2) |
| **Time to first exacerbation** | | | |
| Median time [97.5%-CI] [b] | >336 [290; >336] | 336 [206; >336] | 186 [136; 282] |
| Hazard ratio (HR) [c] | 0.53 | 0.73 | --- |
| 97.5%-CI for HR [c] | [0.36; 0.80] | [0.50; 1.07] | --- |
| p-value [d] | 0.0005 | 0.0650 | --- |
| **No. of exacerbations** | | | |
| Mean number ± SD | 0.85 ± 1.24 | 1.01 ± 1.41 | 1.17 ± 1.27 |
| Incidence rate ratio (IRR) [e] | 0.73 | 0.86 | --- |
| 97.5%-CI for IRR [e] | [0.52; 1.03] | [0.63; 1.18] | --- |
| p-value [d] | 0.0382 | 0.2944 | --- |

CI = Confidence interval; Cipro 14 = Ciprofloxacin DPI 14 days on/off; Cipro 28 = Ciprofloxacin DPI 28 days on/off; SD = Standard deviation

Note: Exacerbations are defined as events with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of at least 3 signs/symptoms over 48 weeks. "Time to first exacerbation" was the primary efficacy analysis. For the secondary efficacy endpoint "frequency of exacerbations", a pre-specified extrapolation approach was used to take account of patients with premature study discontinuation.

a: Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution (*post hoc* analysis).

b: Median time to first exacerbation in days based on Kaplan Meier estimate.

c: Hazard ratio (HR) based on Cox Proportional Hazards model; HR for the comparison of active treatment *vs.* pooled placebo (HRs <1 indicate better outcome on active treatment).

d: Wald-type test.

e: Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment *vs.* pooled placebo (IRRs <1 indicate better outcome on active treatment).

Source: CSR of Study 15625; data on file (Weibull survival fit)

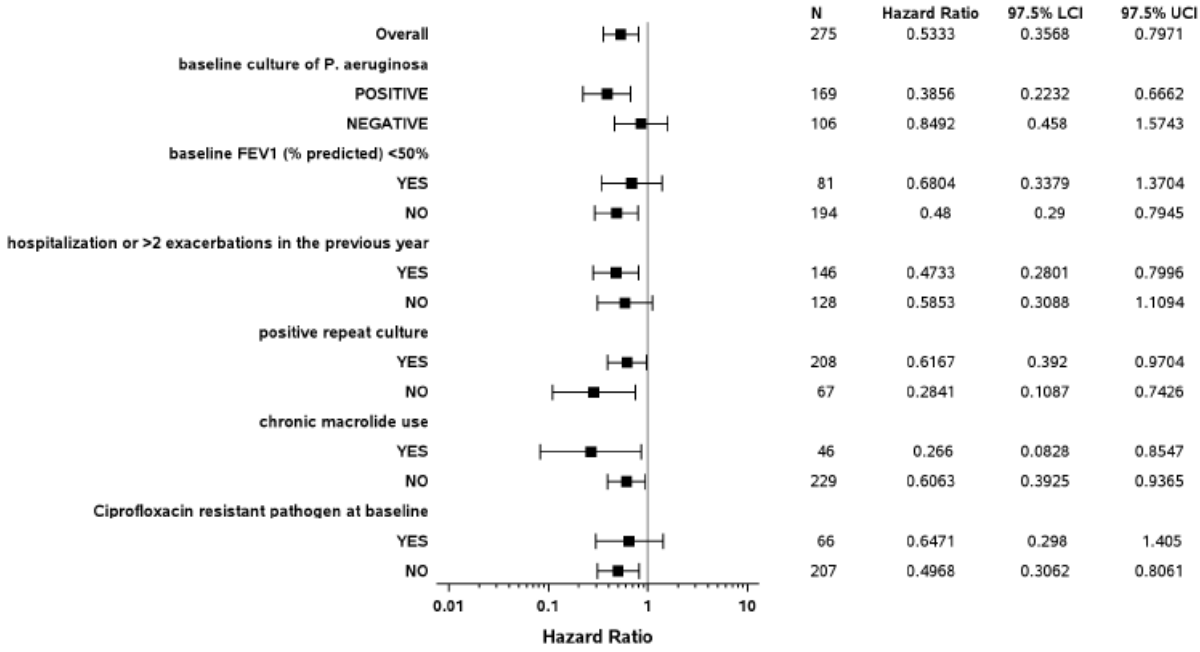
The proportion of patients who experienced an exacerbation was notably lower for ciprofloxacin DPI compared to pooled placebo (ciprofloxacin DPI 14: 38.7%, ciprofloxacin DPI 28: 47.5%, and pooled placebo: 57.2%).

The beneficial treatment effects of ciprofloxacin DPI *vs.* pooled placebo observed in both treatment groups were consistently apparent in the various, pre-specified sensitivity analyses of the time to first exacerbation, thereby confirming the robustness of the results of the primary efficacy analysis (see Appendix Table 9–10).

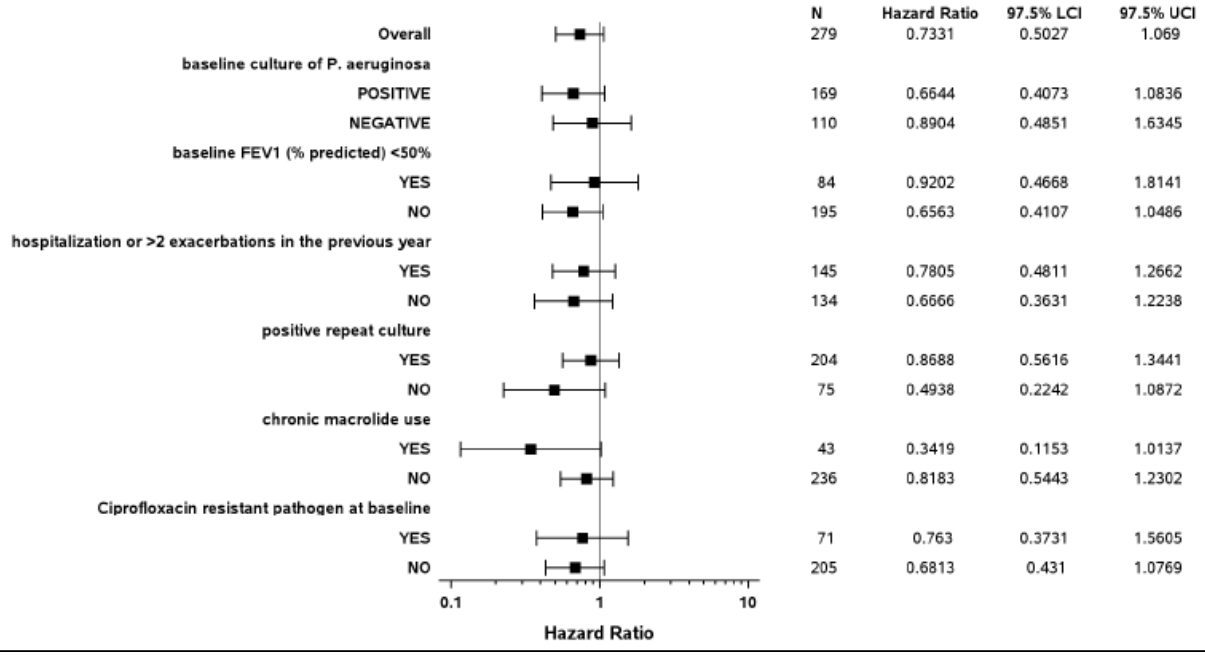
Moreover, the positive treatment effect of both treatment regimens on the time to first exacerbation event was apparent in all of the 6 pre-defined subgroups; *i.e.*, in 12/12 subgroups on treatment with ciprofloxacin DPI 14 or ciprofloxacin DPI 28 (see Figure 5-4).

**Figure 5-4: Overview of pre-defined subgroup analyses for the time to first exacerbation in RESPIRE 1 (FAS)**

**Ciprofloxacin DPI 14 *vs.* pooled placebo**




**Ciprofloxacin DPI 28 *vs.* pooled placebo**




Note: Hazard ratios <1 indicate superiority of active treatment. Source: CSR of Study 15625

According to the primary analysis presented in Table 5–1, the IRR for the first secondary efficacy endpoint (frequency of exacerbations) for the 14-day regimen (IRR=0.73) approached statistical significance, but did not meet the required significance level of α=0.025

(p=0.0382). The 14-day regimen reduced the frequency of exacerbations by 27% *vs.* pooled placebo, while the 28-day regimen reduced the frequency of exacerbations by 14%.

An alternative statistical model that was regarded as a sensitivity analysis in RESPIRE 1, but was later upgraded as main analysis model for RESPIRE 2 (as approved by the FDA, see Appendix 9.3.3) was applied. This model used a Poisson regression model with "time in study" as an offset variable instead of extrapolation. These non-extrapolated frequency data can be found in Appendix Table 9–11. In the analysis of the first secondary endpoint, the IRR for ciprofloxacin DPI 14 *vs.* placebo was 0.69 (97.5%-CI: [0.48; 0.98]; p=0.0193) and the IRR for ciprofloxacin DPI 28 *vs.* placebo was 0.86 (97.5%-CI: [0.62; 1.19]; p=0.3002).

Overall, the secondary efficacy analyses of exacerbation frequencies supported the outcome of the primary efficacy analysis. Beneficial treatment effects were observed in both ciprofloxacin DPI regimens, but were particularly pronounced among patients treated with the 14-day regimen. The IRRs (reduction in frequencies) within the 14-day treatment regimen were close to significance with the primary analysis model using extrapolation, and nominally significant with the alternative analysis model using time in study as offset variable (see Appendix Table 9–11). The frequency reduction of qualifying exacerbation events (≥3 signs) by 27% is supported by the calculated gain of 222 days in event-free days for median time to exacerbation.

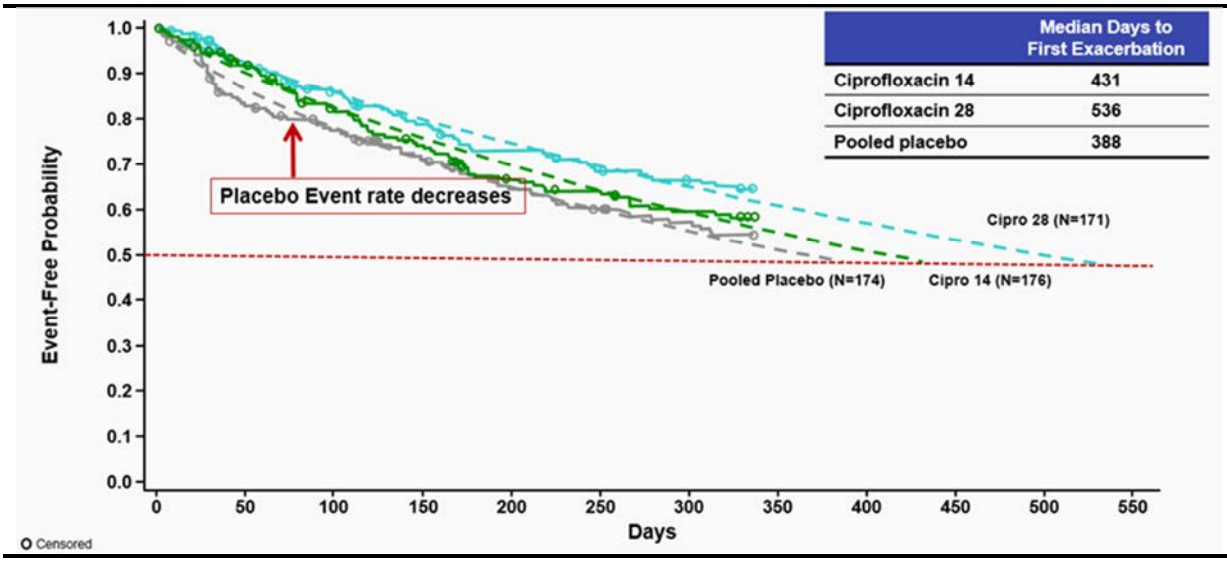
An overview of the outcomes of the entire statistical hierarchical testing sequence can be found in Appendix Table 9–9.

#### 5.3.2.2 RESPIRE 2: Time to first exacerbation and frequency of exacerbations

Neither ciprofloxacin DPI 14 nor ciprofloxacin DPI 28 demonstrated a statistically significant prolongation of the time to the first exacerbation event in the RESPIRE 2 trial. The median time to first event was >336 days and could not be estimated using the Kaplan Meier method for any group due to the fact that too few patients had an exacerbation. The HRs of 0.71 and 0.87 for the 28-day regimen and 14-day regimen, respectively, were associated with non-significant p-values (p=0.0511 and p=0.3965, respectively).

A *post hoc* analysis using a parametric survival regression fitting a Weibull distribution resulted in an (extrapolated) median time to first exacerbation event of 431 days in the ciprofloxacin DPI 14 group, 536 days in the ciprofloxacin DPI 28 group, and 388 days in the pooled placebo group. Thus, the gain of event-free days (estimated by extrapolation) on treatment with ciprofloxacin DPI 14 and ciprofloxacin DPI 28 *vs.* pooled placebo was (median) 43 days and 148 days, respectively. The Kaplan Meier plot for the time to the first exacerbation with the Weibull Survival fit is displayed in Figure 5-5.

**Figure 5-5: Primary endpoint: Time to first exacerbation event up to Week 48 in RESPIRE 2 - Kaplan Meier plot with Weibull survival fit (FAS)**




Cipro 14=Ciprofloxacin DPI 14 days on/off; Cipro 28=Ciprofloxacin DPI 28 days on/off
Note: Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution. Kaplan Meier plots are solid lines, Weibull survival fits are dashed.
Source: CSR of Study 15626 (Kaplan Meier plot); data on file (Weibull survival fit)

The analyses of exacerbation-related endpoints in RESPIRE 2 are shown in Table 5–2 (for information about the hierarchal statistical testing procure and applied α-levels in RESPIRE 2 see Appendix 9.3.1).

**Table 5–2: Results of the primary and secondary efficacy analyses related to exacerbation frequency (main tests as per statistical analysis plan) in RESPIRE 2 (FAS)**

| | Cipro 14 N=176 | Cipro 28 N=171 | Pooled placebo N=174 |
|---|---|---|---|
| **Time to first exacerbation** [a] | | | |
| Estimated median time | 431 | 536 | 388 |
| **Patients with exacerbation** | | | |
| n (%) | 68 (38.6) | 56 (32.7) | 73 (42.0) |
| **Time to first exacerbation** | | | |
| Median time [b] | >336 | >336 | >336 |
| Hazard ratio (HR) [c] | 0.87 | 0.71 | --- |
| 99.9%-CI for HR [c] | --- | [0.39; 1.27] | --- |
| 95.1%-CI for HR [c] | [0.62; 1.21] | --- | --- |
| p-value [d] | 0.3965 | 0.0511 | --- |
| **No. of exacerbations** | | | |
| Mean number ± SD | 0.58 ± 0.84 | 0.40 ± 0.64 | 0.70 ± 1.02 |
| Incidence rate ratio (IRR) [e] | 0.81 | 0.56 | --- |
| 99.9%-CI for IRR [e] | --- | [0.33; 0.95] | --- |
| 95.1%-CI for IRR [e] | [0.61; 1.08] | --- | --- |
| p-value [d] | 0.1471 | 0.0003 | --- |

CI = Confidence interval; Cipro 14 = Ciprofloxacin DPI 14 days on/off; Cipro 28 = Ciprofloxacin DPI 28 days on/off; SD = Standard deviation

Note: Exacerbations are defined as events with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of at least 3 signs/symptoms over 48 weeks. "Time to first exacerbation" was the primary efficacy analysis. For the secondary efficacy endpoint "frequency of exacerbations", no extrapolation approach was used.

a: Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution (*post hoc* analysis).

b: Median time to first exacerbation in days based on Kaplan Meier estimate.

c: Hazard ratio (HR) based on Cox Proportional Hazards model; HR for the comparison of active treatment *vs.* pooled placebo (HRs <1 indicate better outcome on active treatment).

d: Wald-type test.

e: Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment *vs.* pooled placebo (IRRs <1 indicate better outcome on active treatment). Time in study was used as an offset in the Poisson model.

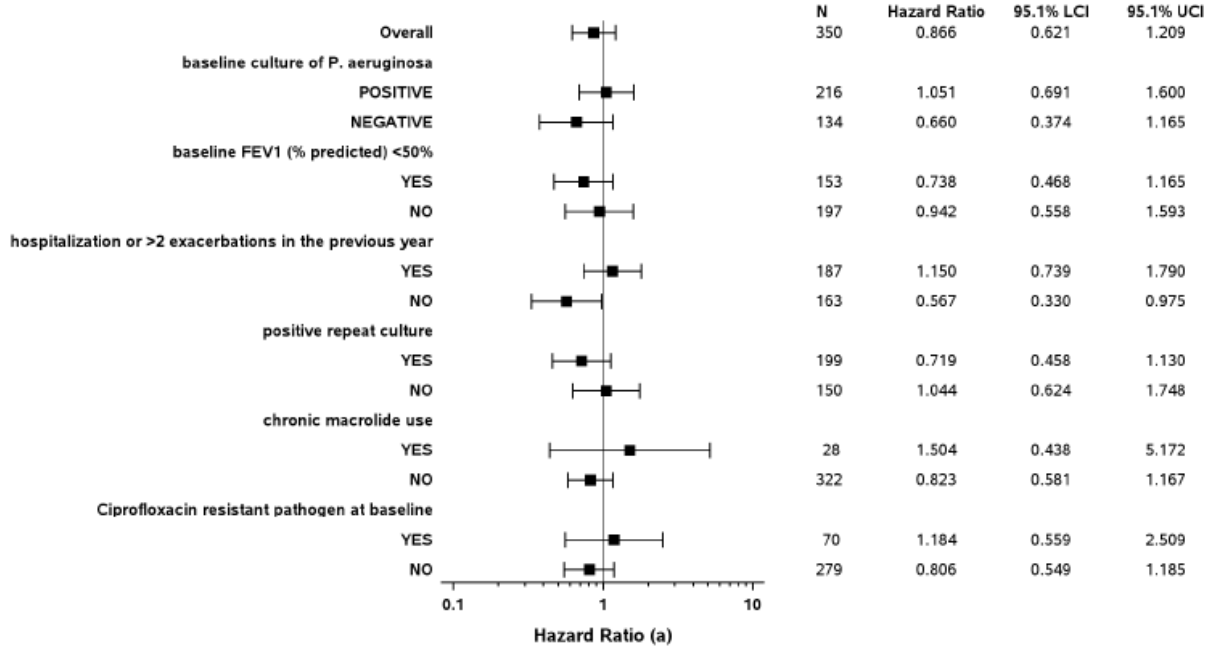
Source: CSR of Study 15626; data on file (Weibull survival fit)

The reduction in frequency of exacerbations was nominally significant for ciprofloxacin DPI 28, but not for ciprofloxacin DPI 14. The IRR of 0.56 (99.9%-CI: [0.33; 0.95]) seen for the 28-day regimen in the analysis of the frequency of exacerbations was associated with a nominally significant p-value of p=0.0003. The IRR of 0.81 (95.1%-CI: [0.61; 1.08]) seen for the 14-day regimen in the analysis of the frequency of exacerbations was not significant (p=0.1470). Overall, the analysis of the exacerbation-related study endpoints consistently showed positive treatment effects of ciprofloxacin DPI on both treatment regimens; however, these did not meet the pre-defined criteria for confirmatory statistical significance (see Appendix Table 9–9). The frequency of exacerbations was primarily analyzed with a Poisson regression model including time in study as offset variable (*i.e.*, no extrapolation approach as employed in RESPIRE 1; see Appendix 9.3.3); this approach was agreed upon with the FDA.

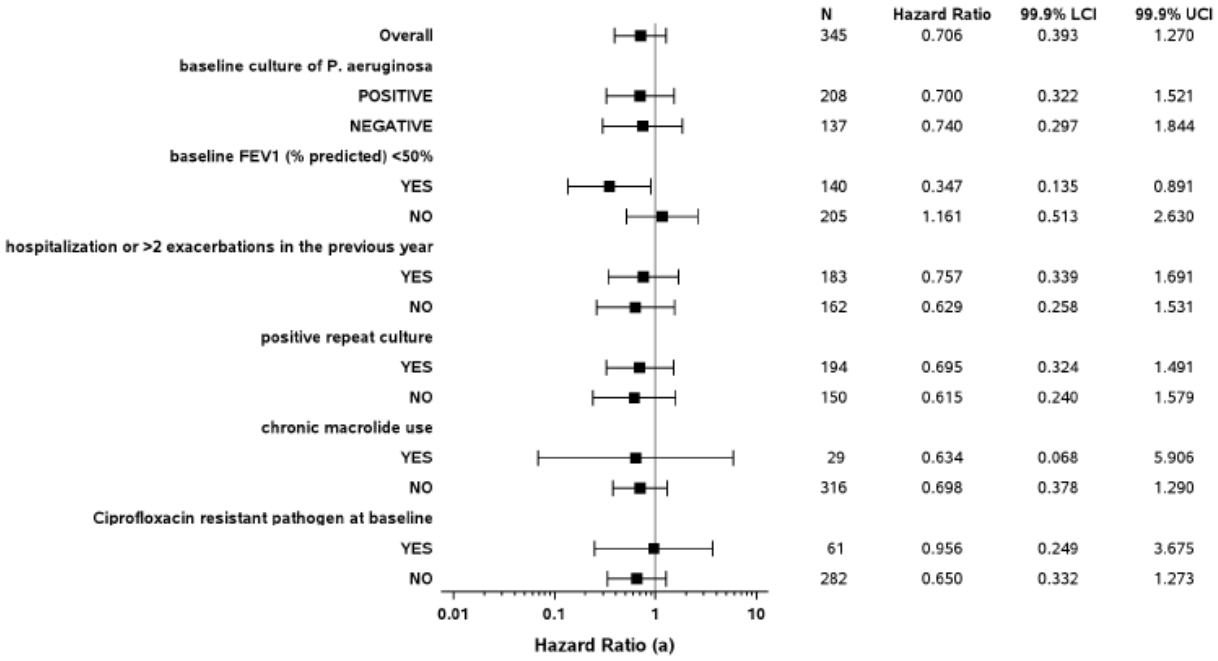
The analysis of the time to first exacerbation event by pre-defined subgroups showed HRs in favor of ciprofloxacin DPI in 7/12 subgroups on treatment with ciprofloxacin DPI 14 and in 11/12 subgroups on treatment with ciprofloxacin DPI 28 (see Figure 5-6).

**Figure 5-6: Overview of pre-defined subgroup analyses for the time to first exacerbation in RESPIRE 2 (FAS)**

**Ciprofloxacin DPI 14 *vs.* pooled placebo**




**Ciprofloxacin DPI 28 *vs.* pooled placebo**




Note: Hazard ratios <1 indicate superiority of active treatment. Source: CSR of Study 15626

### 5.3.2.3 Total number of exacerbations in RESPIRE 1 and RESPIRE 2

The overall treatment effect can also be illustrated by showing the total number of exacerbations recorded for each treatment group in RESPIRE 1 and RESPIRE 2 (see Table 5–3). This tabulation demonstrates the overall treatment effects of ciprofloxacin DPI 14 and ciprofloxacin DPI 28 across both trials. Both ciprofloxacin DPI treatment regimens were associated with a marked decrease in total number of exacerbations, and a corresponding decrease in the frequency of exacerbations per patient.

**Table 5–3: Overall number of exacerbations in RESPIRE 1 and RESPIRE 2 (FAS)**

| | | Exacerbations | |
|---|---|---|---|
| Treatment group | Total patients | Total | Mean/patient |
| Ciprofloxacin DPI 14 | 313 | 188 | 0.60 |
| Ciprofloxacin DPI 28 | 312 | 184 | 0.59 |
| Pooled placebo | 312 | 248 | 0.79 |

Note: Given is the absolute number of exacerbations and the arithmetic mean (related to patients in FAS).
Source: Integrated analysis, data on file

### 5.3.2.4 Additional analyses of exacerbations in RESPIRE 1 and RESPIRE 2

As stated previously, the major efficacy question is to determine the treatment effect of ciprofloxacin DPI in the RESPIRE program. Ciprofloxacin DPI 14 produced the highest treatment effect in RESPIRE 1, and the lowest treatment effect in RESPIRE 2. Ciprofloxacin DPI 28 produced intermediate treatment effects in both RESPIRE 1 and RESPIRE 2. Additional analyses were conducted to provide insights into the treatment effect.

A pre-planned integrated analysis across RESPIRE 1 and RESPIRE 2 was conducted to estimate the treatment effect in all patients who received ciprofloxacin DPI 14, and all patients who received ciprofloxacin DPI 28, compared to all patients who received placebo (integrated analysis across studies; see Section 5.3.2.4.1). Analyses were also conducted on pooled ciprofloxacin DPI 14 and ciprofloxacin DPI 28 (pooled ciprofloxacin group) compared to pooled placebo within RESPIRE 1, and on pooled ciprofloxacin DPI 14 and ciprofloxacin DPI 28 compared to pooled placebo within RESPIRE 2 (pooled ciprofloxacin analysis by study; see Section 5.3.2.4.2).

An overview of the full set of primary and secondary efficacy analyses based on the pooled study data can be found in Appendix Table 9–17 (descriptive results) and Appendix Table 9–18 (exploratory test results for all efficacy variables).

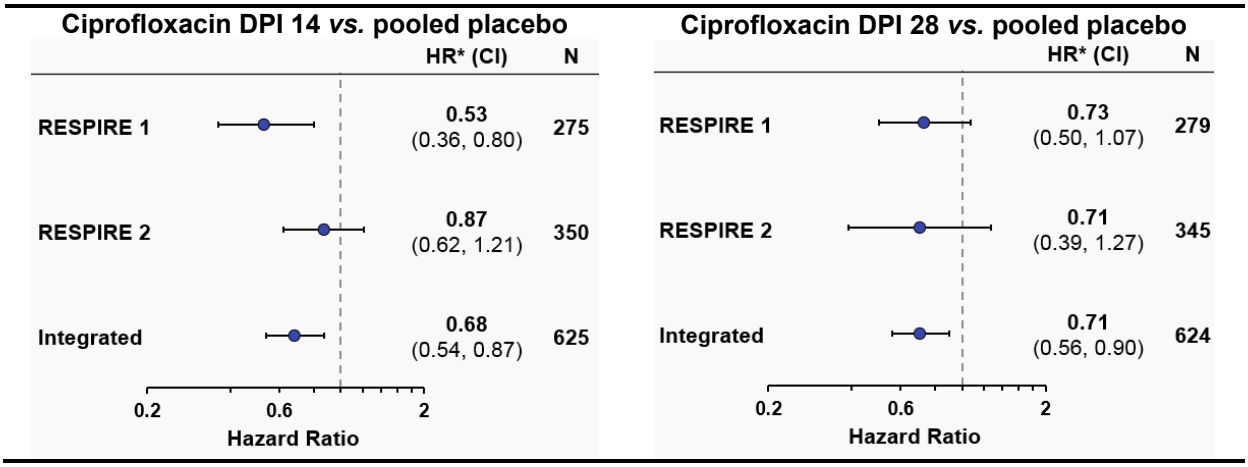
#### 5.3.2.4.1 Results of Phase III study data analysis across RESPIRE 1 and RESPIRE 2 (integrated analysis)

The treatment effect of all patients treated with ciprofloxacin DPI 14 and all patients treated with ciprofloxacin DPI 28, was compared to pooled placebo across the two RESPIRE studies for an integrated efficacy analysis. This analysis was pre-planned, though not included in the NDA, and subsequently was requested by the FDA during the NDA review. The main results are presented in this section, the methodology is described in Appendix 9.3.6.

The results should be interpreted with caution in case of statistical heterogeneity of the treatment effect across studies, especially if the heterogeneity is also clinically relevant. In contrast to the single study analyses, no confirmatory statistical significance testing was performed; all of these integrated efficacy analyses are purely exploratory in nature.

For the primary endpoint of time to first exacerbation, the estimated HRs for integrated ciprofloxacin DPI 14 across RESPIRE 1 and RESPIRE 2 against pooled placebo was 0.68 (95%-CI: [0.54, 0.87]) and the estimated HR for integrated ciprofloxacin DPI 28 against pooled placebo was 0.71 (95%-CI: [0.56, 0.90]; see Appendix Table 9–18 and Figure 5–7). Statistical heterogeneity in the treatment effect between trials (*i.e.*, p≤0.1 in the heterogeneity test) was observed for the comparison of integrated ciprofloxacin DPI 14 *vs.* pooled placebo, while the treatment effect for ciprofloxacin DPI 28 *vs.* pooled placebo was consistent between trials.

**Figure 5–7: Time to first exacerbation by single study and in the integrated analysis of RESPIRE 1 and RESPIRE 2 (FAS)**



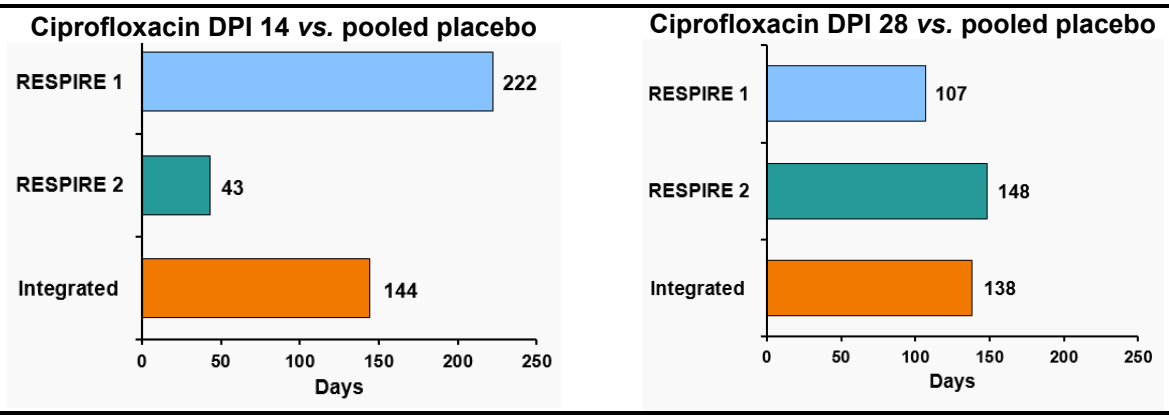

CI=Confidence interval; HR=Hazard ratio

*: HRs are based on Cox Proportional Hazards model for the comparison of active treatment *vs.* pooled placebo (HRs <1 indicate better outcome on active treatment). CIs are 97.5% for RESPIRE 1 and 95.1% (ciprofloxacin DPI 14) / 99.9% (ciprofloxacin DPI 28) for RESPIRE 2. CIs are 95.0% for integrated analysis.

Source: CSRs of Studies 15625 and 15626; integrated analysis tables, data on file

In the integrated analysis, the median time to the first exacerbation event was calculated as 431 days in the ciprofloxacin DPI 14 group, 425 days in the ciprofloxacin DPI 28 group, and 287 days in the pooled placebo group using the *post hoc* parametric survival regression fitting a Weibull distribution (see Appendix Table 9–17). Thus, the gain of event-free days (estimated by extrapolation) on treatment with ciprofloxacin DPI 14 and ciprofloxacin DPI 28 *vs*. pooled placebo was (median) 144 days and 138 days, respectively (see Figure 5–8). The heterogeneity in the ciprofloxacin DPI 14 response between RESPIRE 1 and RESPIRE 2 is illustrated by these extrapolated prolongation in median time to first exacerbation.

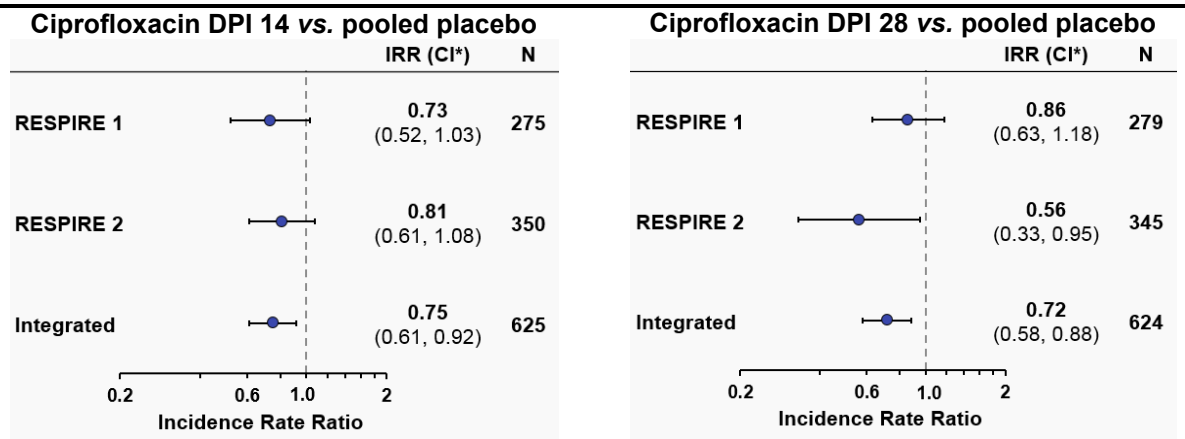
**Figure 5–8: Increase in median time to first exacerbation by single study and in the integrated analysis of RESPIRE 1 and RESPIRE 2 (FAS)**




Note: Estimates of median time to first exacerbation are based on Weibull regression model. Provided is the difference in estimated median time to event between ciprofloxacin DPI and pooled placebo.
Source: Integrated analysis tables, data on file

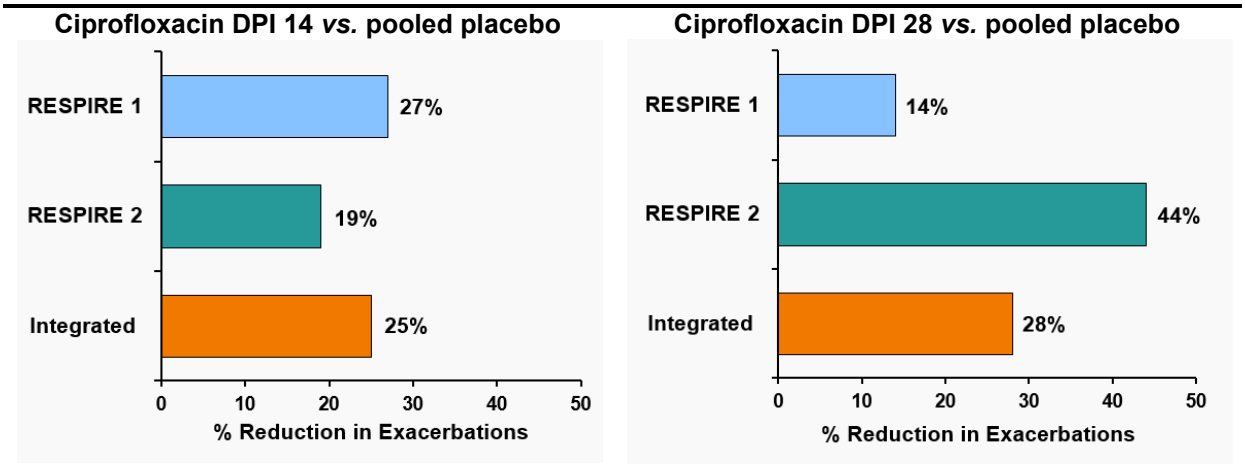
The treatment effect for integrated ciprofloxacin DPI 14 *vs.* pooled placebo and ciprofloxacin DPI 28 *vs.* pooled placebo in RESPIRE 1 and RESPIRE 2 was IRR=0.75 and IRR=0.72, respectively (see Appendix Table 9–18 and Figure 5–9). The reduction in frequency of exacerbations was calculated as 25% in the ciprofloxacin DPI 14 group, and 28% in the ciprofloxacin DPI 28 group, (see Figure 5–10). The range of treatment effects was also apparent in the two treatment arms, most especially for ciprofloxacin DPI 28 (14% and 44% in RESPIRE 1 and RESPIRE 2, compared to 27% and 19% for ciprofloxacin DPI 14).

**Figure 5–9: Frequency of exacerbations by single study and in the integrated analysis of RESPIRE 1 and RESPIRE 2 (FAS)**




CI=Confidence interval; IRR=Incidence rate ratio
*: IRRs are based on Poisson regression model for the comparison of active treatment *vs.* pooled placebo (IRRs <1 indicate better outcome on active treatment). CIs are 97.5% for RESPIRE 1 and 95.1% (ciprofloxacin DPI 14) / 99.9% (ciprofloxacin DPI 28) for RESPIRE 2. CIs are 95.0% for integrated analysis.
Source: CSRs of Studies 15625 and 15626; integrated analysis tables, data on file

**Figure 5–10: Decrease in frequency of exacerbations by single study and in the integrated analysis of RESPIRE 1 and RESPIRE 2 (FAS)**




Note: Decrease in frequency from Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment *vs.* pooled placebo.
Source: Integrated analysis tables, data on file

#### 5.3.2.4.2 Results of analyses of overall treatment effects within RESPIRE 1 and RESPIRE 2 (pooled ciprofloxacin analysis by study)

The overall treatment effect of ciprofloxacin DPI within each trial was examined by pooling ciprofloxacin DPI 14 and ciprofloxacin DPI 28 within RESPIRE 1 and RESPIRE 2. Pooling of the active treatment groups is a reasonable approach, since the ciprofloxacin DPI 14-day regimen and the 28-day regimen resulted in the same total drug administered over the 48-week treatment period, and both regimens showed a positive treatment effect. The RESPIRE studies were not designed to discriminate between the ciprofloxacin DPI 14- and 28-day regimens.

Patients treated with ciprofloxacin DPI in RESPIRE 1 showed a strong treatment effect with a HR for the time to the first exacerbation event of 0.63 (97.5%-CI: [0.45; 0.87]) and an IRR of 0.77 (97.5%-CI: [0.58; 1.03]) for a 23% reduction in the frequency of exacerbations (see Table 5–4). The median times to first exacerbation were 369 and 210 days based on survival regression using a Weibull distribution, leading to a calculated delay in median time to first exacerbation of 159 days.

Consistently, patients treated with ciprofloxacin DPI in RESPIRE 2 showed a strong treatment effect, with a HR of 0.78 (95%-CI: [0.58; 1.05]), and an IRR of 0.68 (95%-CI: [0.53; 0.87]) for a 32% reduction in the frequency of exacerbations. Numerically, the treatment effects of pooled ciprofloxacin DPI for reduction in frequency of exacerbations were stronger in RESPIRE 2 than in RESPIRE 1. The median times to first exacerbation were 480 and 388 days based on survival regression using a Weibull distribution, leading to a calculated delay in median time to first exacerbation of 92 days.

**Table 5–4: Comparison of pooled ciprofloxacin DPI *vs.* pooled placebo for exacerbation-related endpoints in RESPIRE 1 and RESPIRE 2 (FAS)**

| | Ciprofloxacin DPI (14+28) | Pooled placebo |
|---|---|---|
| **RESPIRE 1** | **N=278** | **N=138** |
| **Time to first exacerbation** [a] | | |
| Estimated median time | 369 | 210 |
| **Time to first exacerbation** | | |
| Median time [97.5%-CI] [b] | >336 [290; >336] | 186 [136; 282] |
| Hazard ratio (HR) [c] | 0.63 | --- |
| 97.5%-CI for HR [c] | [0.45; 0.87] | --- |
| p-value [d] | p=0.0014 | --- |
| **No. of exacerbations** | | |
| Mean number ± SD | 0.73 ± 1.07 | 0.91 ± 1.05 |
| Incidence rate ratio (IRR) [e] | 0.77 | --- |
| 97.5%-CI for IRR [e] | [0.58; 1.03] | --- |
| p-value [d] | p=0.0436 | --- |
| **RESPIRE 2** | **N=347** | **N=174** |
| **Time to first exacerbation** [a] | | |
| Estimated median time | 480 | 388 |
| **Time to first exacerbation** | | |
| Median time [b] | >366 | >366 |
| Hazard ratio (HR) [c] | 0.78 | --- |
| 95%-CI for HR [c] | [0.58; 1.05] | --- |
| p-value [d] | p=0.0981 | --- |
| **No. of exacerbations** | | |
| Mean number ± SD | 0.49 ± 0.75 | 0.70 ± 1.02 |
| Incidence rate ratio (IRR) [e] | 0.68 | --- |
| 95%-CI for IRR [e] | [0.53; 0.87] | --- |
| p-value [d] | p=0.0021 | --- |

CI = Confidence interval; Ciprofloxacin DPI=Ciprofloxacin DPI 14 days on/off plus Ciprofloxacin DPI 28 days on/off; SD = Standard deviation

Note: Exacerbations are defined as events with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of at least 3 signs/symptoms over 48 weeks. For the secondary efficacy endpoint "frequency of exacerbations", no extrapolation approach was used.

a: Median time to first exacerbation in days, estimates based on survival regression fitting a Weibull distribution (*post hoc* analysis).

b: Median time to first exacerbation in days based on Kaplan Meier estimate.

c: Hazard ratio (HR) based on Cox Proportional Hazards model; HR for the comparison of active treatment *vs.* pooled placebo (HRs <1 indicate better outcome on active treatment).

d: Wald-type test.

e: Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment *vs.* pooled placebo (IRRs <1 indicate better outcome on active treatment). Time in study was used as an offset in the Poisson model.

Source: Data on file

## 5.3.3 Changes in patient-reported outcomes (SGRQ, QOL-B) in RESPIRE 1 and RESPIRE 2

### 5.3.3.1 Methodology

The efficacy of ciprofloxacin DPI was evaluated using two patient-reported outcome questionnaires (PROs): the SGRQ and the QOL-B (version 3.1). Each PRO questionnaire consists of several components or domains. Changes in the respiratory symptoms part

(SGRQ symptoms component score [SGRQ SCS], and QOL-B respiratory symptoms domain score [QOL-B RSDS]) were selected as secondary outcome variables. Domain scores and the total scores are calculated to the range between 0 and 100 points according to the respective manuals; lower values in SGRQ and higher values in QOL-B correspond to a better health status.

The SGRQ SCS assesses the following symptoms:

- Frequency of cough, sputum production, and shortness of breath,
- Wheezing (frequency and worse in morning),
- Respiratory attack (frequency and duration),
- Number of "good days".

Recall period is the past 4 weeks.

The QOL-B RSDS is a recently developed NCFB-specific PRO that assesses the following symptoms:

- Degree of congestion, cough, sputum production (a lot, moderate, a little, not at all),
- Sputum color,
- Frequency of wheezing, chest pain, waking in the night with coughing, and shortness of breath with activity and while talking (always, often, sometimes, never).

Recall period is the past week.

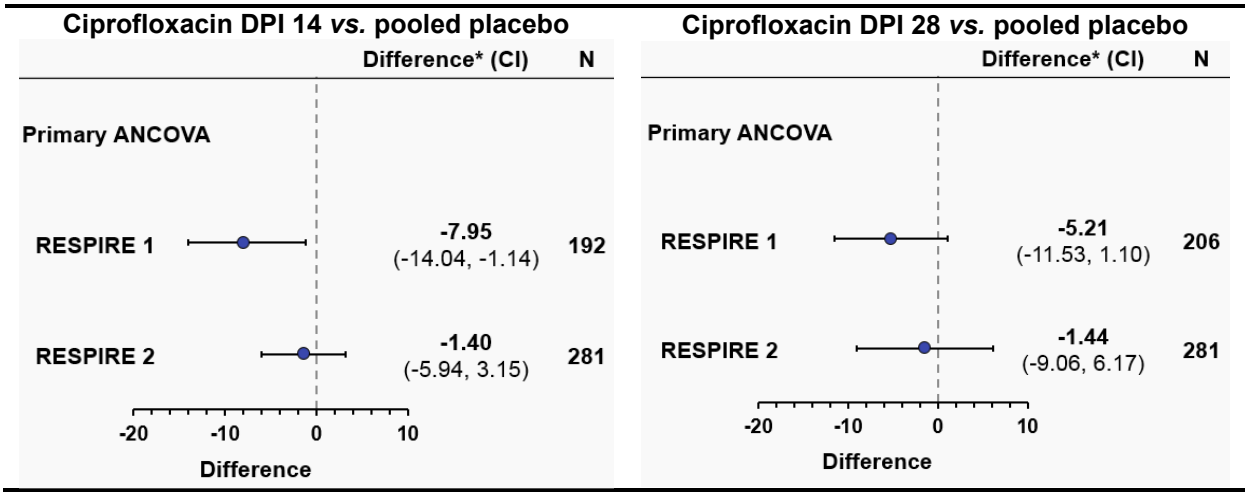
The sampling times for the SGRQ and the QOL-B are shown in Appendix Figure 9–4. The QOL-B was assessed at 10 and 9 different time points for the 14- and 28-day cycles, respectively. The SGRQ was assessed at 4 different time points for both the 14- and 28-day regimens. The primary evaluation of the PRO questionnaires was an ANCOVA model with treatment, baseline value, geographic regions, pre-therapy positive culture for *P. aeruginosa* (negative/positive), and chronic macrolide use (no/yes) as covariates. The primary analysis was based on patients with both completed baseline and EOT assessments (missing data on individual items were handled according to the respective manuals). An LOCF analysis and a mixed model for repeated measurements (MMRM) were used as sensitivity analyses (see Appendix 9.3.5).

### 5.3.3.2 Results of the SGRQ SCS analyses

The mean improvements (*i.e.*, reduction) in the SGRQ SCS *vs.* pooled placebo were stronger in RESPIRE 1 than in RESPIRE 2 for both ciprofloxacin DPI groups (see Appendix Table 9–12 and Appendix Table 9–13 for tables of pre-specified study analyses). Relative to placebo, ciprofloxacin DPI 14 produced a reduction in SGRQ SCS that was nominally significant in RESPIRE 1, and a positive point estimate in RESPIRE 2. Ciprofloxacin DPI 28 also produced a greater treatment effect in RESPIRE 1 than in RESPIRE 2, and positive point estimates for treatment effect both trials.

The primary analysis for changes from baseline based on ANCOVA is additionally displayed in Figure 5–11; descriptive mean changes from baseline within each treatment group can be found in Appendix Table 9–15.

**Figure 5–11: Change from baseline in SGRQ symptoms component score to EOT for ciprofloxacin DPI 14 and DPI 28 versus pooled placebo (FAS)**




*: Treatment differences <0 indicate superiority of ciprofloxacin DPI treatment. CIs are 97.5% for RESPIRE 1 and 99.9% (ciprofloxacin DPI 28) / 95.1% (ciprofloxacin DPI 14) for RESPIRE 2.
Source: CSRs of Studies 15625 and 15626

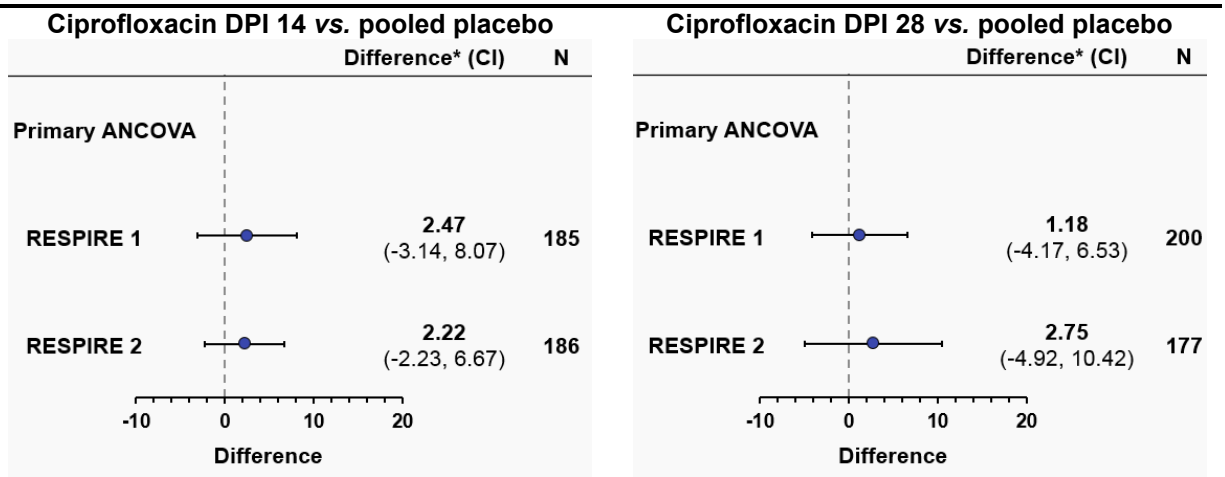
### 5.3.3.3 Results of the QOL-B RSDS analyses

Mean changes at EOT

Higher scores in QOL-B RSDS correspond to better health status. In both RESPIRE 1 and RESPIRE 2, ciprofloxacin DPI 14 and ciprofloxacin DPI 28 produced similar score increases, which were not nominally significant compared to placebo. In these QOL-B analyses, positive differences indicated positive treatment effects of ciprofloxacin DPI 14 and ciprofloxacin DPI 28 (see Appendix Table 9–12 and Appendix Table 9–13 for tables of pre-specified study analyses).

The primary analysis for changes from baseline based on ANCOVA is additionally displayed in Figure 5–12; descriptive changes from baseline within each treatment group can be found in Appendix Table 9–15.

**Figure 5–12: Change from baseline in QOL-B respiratory symptoms domain score to EOT for ciprofloxacin DPI 14 and DPI 28 versus pooled placebo (FAS)**

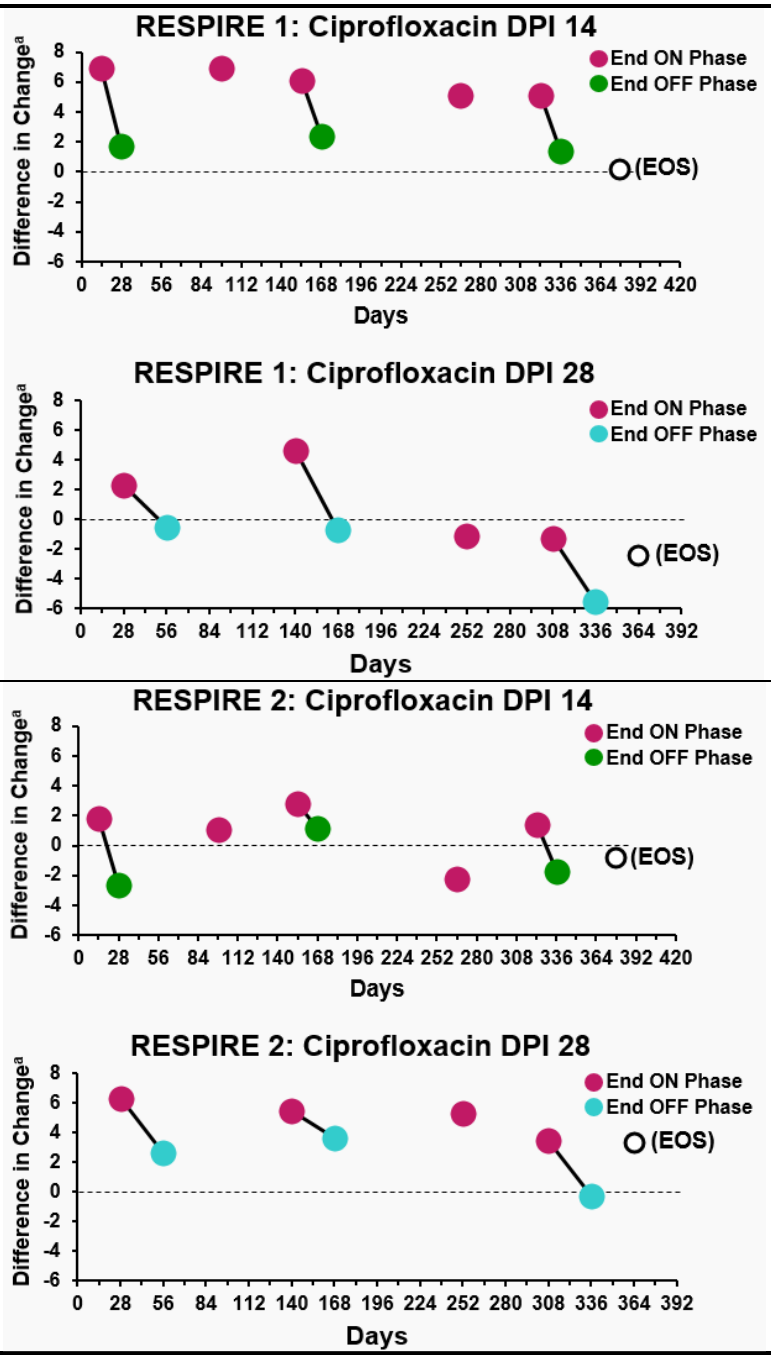



*: Treatment differences >0 indicate superiority of ciprofloxacin DPI treatment. CIs are 97.5% for RESPIRE 1 and 99.9% (ciprofloxacin DPI 28) / 95.1% (ciprofloxacin DPI 14) for RESPIRE 2.
Source: CSRs of Studies 15625 and 15626

Mean changes at multiple time points

The QOL-B RSDS was measured at multiple time points during the trial (see Appendix Figure 9–4). The overall point estimates and differences of ciprofloxacin DPI *vs.* pooled placebo for changes from baseline at EOT were positive, as shown above in Figure 5–12. However, the pattern of improvement in the detailed QOL-B RSDS over time showed a pattern of waxing and waning that appears to be related to the timing of measurement in the treatment cycle. The differential in score between ciprofloxacin DPI and placebo was consistently greater following the on-treatment cycle, and consistently narrowed during the off-cycle. This pattern held for both ciprofloxacin DPI 14 and ciprofloxacin DPI 28 and for both RESPIRE 1 and RESPIRE 2 (see Figure 5–13). These findings suggest that the treatment effect of ciprofloxacin DPI is greater at the end of the on-cycle than at the end of the off-cycle.

**Figure 5–13: Improvement in QOL-B RSDS observed during the on- and off-treatment phase with ciprofloxacin DPI 14 and ciprofloxacin DPI 28 in the RESPIRE studies (FAS)**

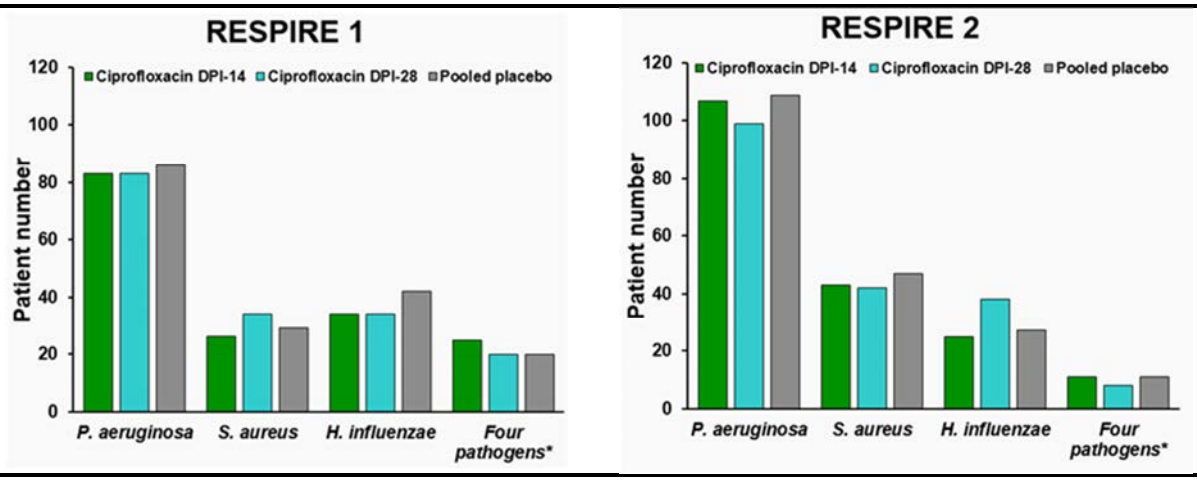



EOT=End of treatment; EOS=End of study
Note: Differences >0 indicate superiority of ciprofloxacin DPI.
a: ANCOVA adjusted for geographic region, pre-therapy positive culture for *P. aeruginosa*, and chronic macrolide use.
Source: CSRs of Studies 15625 and 15626

### 5.3.4 Analyses of microbiological endpoints in RESPIRE 1 and RESPIRE 2

All patients had to be culture-positive for at least one of 7 pre-specified respiratory pathogens at baseline. The distribution of baseline cultures by pathogen and patient is shown in Figure 5–14. *P. aeruginosa* was the most frequent baseline pathogen in both trials, and was isolated in over 180 patients in each group. *S. aureus* and *H. influenzae* were the next two most frequent pathogens, and were each isolated in a total of 50 to 60 patients per group. *S. pneumoniae* and *M. catarrhalis* were the next two most prominent pathogens (grouped for convenience), and were each isolated in 17 to 25 total patients per group. The 2 most infrequent pathogens were *S. maltophilia* (5 to 17 patients per group) and *B. cepacia* (0 to 3 patients per group).

**Figure 5–14: Distribution of baseline pathogens by patient in RESPIRE 1 and RESPIRE 2 (FAS)**

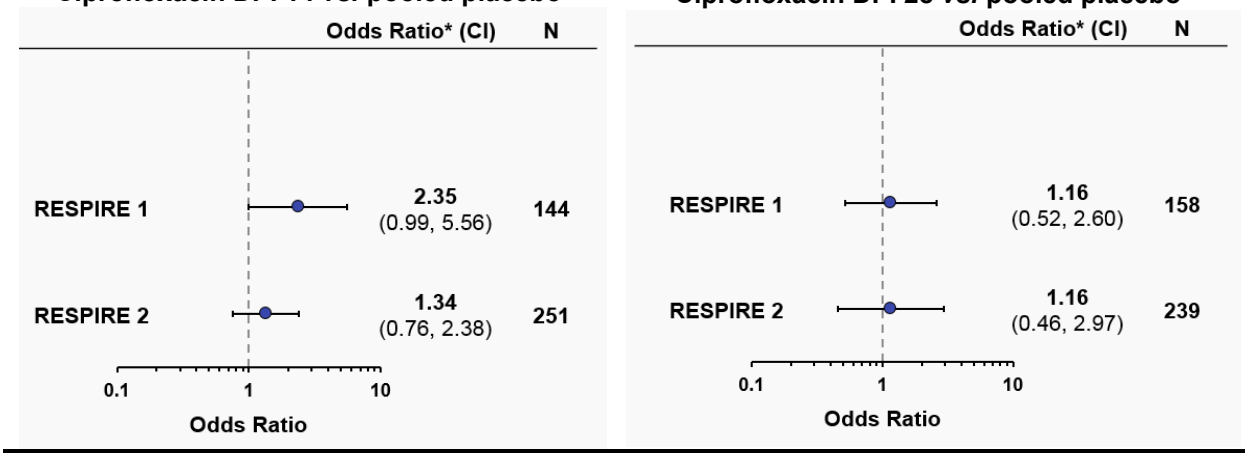



*: Includes *S. pneumoniae*, *S. maltophilia*, *H. influenzae*, and *B. cepacia*
Note: Number of patients is N=416 in RESPIRE 1 and N=521 in RESPIRE 2.
Source: CSRs of Studies 15625 and 15626

Secondary efficacy variables related to microbiological findings were the eradication of all pathogens at EOT that were identified at baseline and the occurrence of any new pathogens (not present at baseline) at EOT. A culture-negative result at EOT for a specific species found at baseline was tabulated as eradication.

Ciprofloxacin DPI achieved positive treatment effects for eradication of baseline pathogens (see Figure 5–15). The treatment effect was most prominent for ciprofloxacin DPI 14 in RESPIRE 1 (odds ratio [OR] of 2.35), but was also positive for ciprofloxacin DPI 14 in RESPIRE 2, and for ciprofloxacin DPI 28 in RESPIRE 1 and RESPIRE 2 (ORs of 1.1.6 to 1.34; see also Table 9–14 for full statistical analysis).

**Figure 5–15: Analyses of eradication of pre-specified baseline pathogens in RESPIRE 1 and RESPIRE 2 (FAS)**




*: Odds ratios >1 indicate superiority of active treatment. CIs are 97.5% for RESPIRE 1 and 99.9% (ciprofloxacin DPI 28) / 95.1% (ciprofloxacin DPI 14) for RESPIRE 2.
Source: CSRs of Studies 15625 and 15626

The proportions of patients with new pathogens at EOT in RESPIRE 1 were numerically smaller in the ciprofloxacin DPI groups (5.1% and 3.5% for ciprofloxacin DPI 14 and ciprofloxacin DPI 28, respectively) than in the pooled placebo group (8.0%), and associated ORs were in favor of ciprofloxacin DPI. In RESPIRE 2, the proportions of patients with new pathogens at EOT were numerically smaller in the two ciprofloxacin DPI groups (4.0% and 4.1%, respectively) than in the pooled placebo group (10.0%), and the associated ORs thus both in favor of ciprofloxacin DPI. However, the overall numbers of new pathogens at EOT were relatively small in all groups (see Table 5–5).

**Table 5–5: Analyses of occurrence of new pathogens (main test as per statistical analysis plan) in RESPIRE 1 and RESPIRE 2 (FAS)**

| | Cipro 14 | Cipro 28 | Pooled placebo |
|---|---|---|---|
| **RESPIRE 1** | **N=137** | **N=141** | **N=138** |
| New pathogen - YES (n, %) [a] | 7 (5.1) | 5 (3.5) | 11 (8.0) |
| Odds ratio (OR) [b] | 0.56 | 0.36 | --- |
| p-value [c] | 0.2569 | 0.0582 | --- |
| **RESPIRE 2** | **N=176** | **N=171** | **N=174** |
| New pathogen - YES (n, %) [a] | 7 (4.0) | 7 (4.1) | 18 (10.3) |
| Odds ratio (OR) [b] | 0.29 | 0.41 | --- |
| p-value [c] | p=0.0072 | p=0.0534 | --- |

Cipro 14 = Ciprofloxacin DPI 14 days on/off; Cipro 28 = Ciprofloxacin DPI 28 days on/off
a: The percentage is calculated based on the number of all randomized patients within the respective population. No imputation procedure was applied.
b: Odds ratio (OR) based on Cochran-Mantel-Haenszel (CMH method) for the comparison of active treatment *vs.* pooled placebo (ORs <1 indicate better outcome on active treatment). No imputation procedure was applied.
c: CMH test.
Source: CSRs of Studies 15625 and 15626

A *post hoc* analysis of the descriptive frequency of exacerbations by pathogen suggested that ciprofloxacin DPI was effective in reducing the frequency of exacerbations in most pathogen groups (see Table 5–6).

**Table 5–6: Integrated analysis: Frequency of exacerbations by pathogen (FAS)**

| | ***P. aeruginosa*** | ***S. aureus*** | ***H. influenzae*** | ***S. pneumoniae*, *M. catarrhalis*, *S. maltophilia*, or *B. cepacia*** |
|---|---|---|---|---|
| | **(N) mean** | **(N) mean** | **(N) mean** | **(N) mean** |
| Cipro 14 | (190) 0.58 | (69) 0.51 | (59) 0.64 | (55) 0.71 |
| Cipro 28 | (182) 0.57 | (76) 0.45 | (72) 0.75 | (48) 0.69 |
| Pooled placebo | (195) 0.78 | (76) 0.79 | (69) 0.71 | (47) 0.89 |

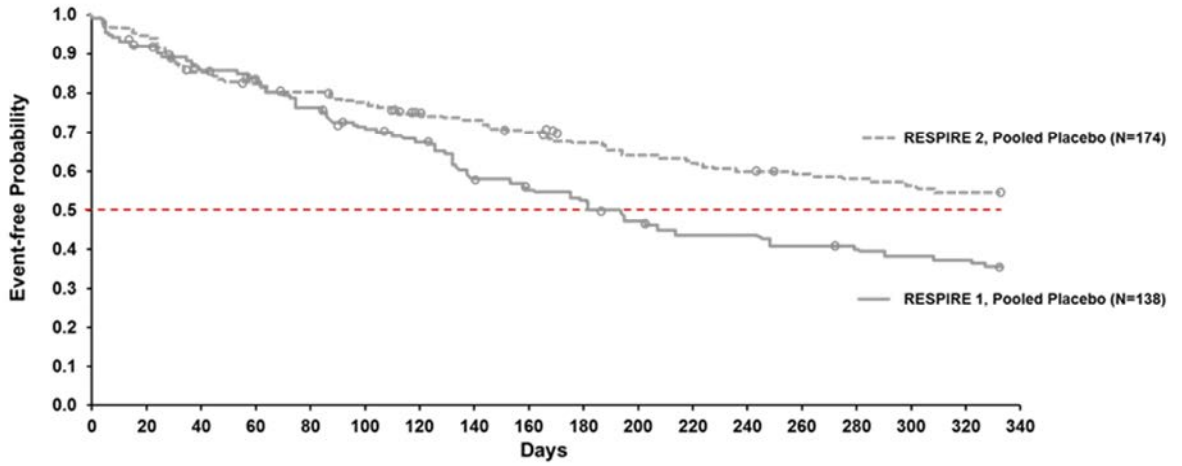
Cipro 14=Ciprofloxacin DPI 14 days on/off; Cipro 28=Ciprofloxacin DPI 28 days on/off; N=Number of patients with the indicated pathogen; mean=mean number of exacerbations per patient
Note: Exacerbations were defined as exacerbation with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of at least 3 signs/symptoms over 48 weeks (qualifying exacerbation for primary efficacy analysis).
Source: Integrated analysis, data on file

### 5.3.5 Discussion and interpretation of efficacy outcomes across studies

Nearly all of the point estimates calculated for the comparison of ciprofloxacin DPI 14 or ciprofloxacin DPI 28 *vs.* pooled placebo were numerically in favor of ciprofloxacin DPI in both studies (see Appendix Table 9–16). For the primary endpoint, ciprofloxacin DPI 14 demonstrated a highly significant level of efficacy in RESPIRE 1, but produced the lowest level of treatment effect in RESPIRE 2, while ciprofloxacin DPI 28 demonstrated a more consistent treatment effect in RESPIRE 1 and RESPIRE 2. For frequency of exacerbations (first secondary endpoint), there was a higher treatment effect for ciprofloxacin 28 in RESPIRE 2 compared to RESPIRE 1, while ciprofloxacin DPI 14 produced a more consistent treatment effect.

The overall exacerbation event rate was lower in RESPIRE 2 than in RESPIRE 1. Therefore, the sample size in RESPIRE 2 was larger. The proportion of event-free patients over time for the pooled placebo group differed considerably between the studies (see Figure 5–16).

**Figure 5–16: Kaplan Meier plot of time to first exacerbation event through Week 48 by Phase III study - pooled placebo groups (FAS)**




Note: Exacerbation events are defined as exacerbations with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of ≥ 3 signs/symptoms.
Source: Data on file

Several demographic and other baseline differences (which are summarized in Appendix 9.4.2) were identified. However, none of these differences between the trials explained the differences in treatment effect of ciprofloxacin DPI 14 and ciprofloxacin DPI 28 in RESPIRE 1 and RESPIRE 2.

RESPIRE 2 was conducted in more countries and involved a substantially higher number of centers. The majority of patients in RESPIRE 2 were enrolled in Eastern European countries (including Russia, Bulgaria and Latvia) as well as Asian countries, whereas the regional focus in RESPIRE 1 was more on Western European countries/US and Australia/New Zealand (see Appendix 9.4.2). Different standards of care for NCFB, a different level of availability of and adherence to the treatment guidelines, and more diverse patient-investigator interactions may have contributed to the different treatment effects seen between the studies (see the improvement in the SGRQ symptoms component score [see Appendix Table 9–15] or the high eradication rate [see Appendix Table 9–14] in the pooled placebo group).

Another marked difference was that placebo patients in RESPIRE 2 with *P. aeruginosa* at baseline experienced a markedly lower number of qualifying exacerbations per patient compared to those without *P. aeruginosa* at baseline (0.64 ± 0.95 *vs.* 0.80 ± 1.12 events; comparison within the pooled placebo group). In RESPIRE 1, placebo patients with *P. aeruginosa* at baseline had the highest rate of exacerbations.

In addition, some descriptive baseline differences between the RESPIRE study populations suggested that RESPIRE 2 patients were less prone to frequent exacerbations than those enrolled in RESPIRE 1. While there were demographic differences between RESPIRE 1 and RESPIRE 2, none of these factors can be correlated to differences in treatment effect. Some of these findings, which are fully summarized in Appendix 9.4.2, are additionally displayed in Table 5–7.

**Table 5–7: Integrated analysis: Frequency of exacerbations by pathogen (FAS)**

| *Characteristic* | RESPIRE 1 | RESPIRE 2 |
|---|---|---|
| Mean age of patients (years) | 64.7 | 60.1 |
| Exacerbations in previous 12 months (per patient) | 2.9 | 2.4 |
| Patients with 3 or more exacerbations in previous 12 months (%) | 45.0 | 22.1 |
| Patients with COPD as comorbidity (%) | 15.9 | 28.4 |

Source: Data on file; see also Appendix 9.4.2.2

Overall, there was a lower risk of exacerbations in RESPIRE 2:

- The proportion of study patients without a qualifying exacerbation was higher in RESPIRE 2 than in RESPIRE 1: (62.2% *vs.* 52.2%).
- The proportion of study patients with multiple (>1) qualifying exacerbations was lower in RESPIRE 2 than in RESPIRE 1 (13.4% *vs.* 18.5%).
- The mean number of qualifying exacerbations was lower in RESPIRE 2 than in RESPIRE 1 (292 episodes in 521 patients [mean: 0.56 episodes per patient] *vs.* 328 episodes in 416 patients [mean: 0.79 episodes per patient]).

Numerous demographic and other factors were analyzed to determine potential causes for the difference in exacerbation rates with no single factor or combination of factors found responsible. It is possible that the difference in exacerbation rates in the RESPIRE 1 and RESPIRE 2 placebo groups represent the normal variation in the heterogeneous NCFB patient population.

### 5.3.6 Efficacy conclusions

The treatment effect of ciprofloxacin DPI was positive but clearly variable between RESPIRE 1 and RESPIRE 2, and between the ciprofloxacin DPI 14 and ciprofloxacin DPI 28 regimens. For the primary endpoint of time to first exacerbation, ciprofloxacin DPI 14 demonstrated both the greatest treatment effect and the lowest treatment effect. Ciprofloxacin DPI 28 demonstrated consistent treatment effects that were greater than ciprofloxacin DPI 14 in RESPIRE 2, but less in RESPIRE 1. The delays in median time to first exacerbation were estimated as 222 and 43 days for ciprofloxacin DPI 14, and 107 and 148 days for ciprofloxacin DPI 28.

Ciprofloxacin DPI 14 showed a 27% and 19% reduction in the frequency of exacerbations in RESPIRE 1 and RESPIRE 2, respectively (based on the incidence rate ratios) while ciprofloxacin DPI 28 had a 14% and 44% reduction in frequency of exacerbations, respectively.

Integrated analysis across RESPIRE 1 and RESPIRE 2 showed that ciprofloxacin DPI 14 and ciprofloxacin DPI 28 produced similar overall treatment effects for decreasing the frequency of exacerbations and increasing the time to the next exacerbation. Pooled analysis within RESPIRE 1 and RESPIRE 2 showed the positive treatment effects of ciprofloxacin DPI, which were greater in RESPIRE 1.

Patient-reported outcomes showed overall positive trends for ciprofloxacin DPI 14 and ciprofloxacin DPI 28, but the treatment effect varied between trials. An analysis of QOL-B RSDS by timing of measurement suggested that the treatment effect of ciprofloxacin DPI was greater at the end of on-cycles than at the end of off-cycles. Microbiology-related endpoints showed positive treatment effects in eradication of baseline pathogens and in reducing the occurrence of new pathogens, with variance in treatment effect between trials.

The total number of exacerbations in the RESPIRE program were 188 for ciprofloxacin DPI 14, 184 for ciprofloxacin DPI 28, and 248 for the pooled placebo.

**Summary of Section 5 (Clinical efficacy of ciprofloxacin DPI in patients with NCFB):**

- The Phase II NCFB study 12965 showed that ciprofloxacin DPI administered at the clinical dose of 32.5 mg BID reduced the bacterial load and produced a trend towards reduction in exacerbation frequency and improvement in quality of life.
- The Phase III RESPIRE studies were well-designed, randomized, placebo-controlled studies with 48 weeks of treatment with a broad array of clinical, microbiological, and health-related quality of life efficacy variables.

Ciprofloxacin DPI 14 produced the following results:

- In RESPIRE 1, statistically significant superiority (HR=0.53, 97.5%-CI: [0.36; 0.80], p=0.0005) was demonstrated for prolonging the time to first exacerbation (222 days). A 27% reduction in the frequency of exacerbations was achieved.
- In RESPIRE 2, the lowest treatment effect was produced for prolonging the time to first exacerbation (HR=0.87, 95.1%-CI: [0.62; 1.21], p=0.3965), with a calculated prolongation of 43 days to first exacerbation. A 19% reduction in the frequency of exacerbations was achieved.
- Ciprofloxacin DPI 14 also showed positive trends in the microbiological and patient-reported outcome variables, some of which were nominally significant in RESPIRE 1 and RESPIRE 2.

Ciprofloxacin DPI 28 produced the following results:

- In RESPIRE 1, a moderate treatment effect was shown for prolonging the time to first exacerbation (HR=0.73, 97.5%-CI: [0.50; 1.07], p=0.0650) with a calculated prolongation of 107 days to first exacerbation. A 14% reduction in the frequency of exacerbations was achieved.
- In RESPIRE 2, a moderate treatment effect was observed for prolonging the time to first exacerbation (HR=0.71, 99.9%-CI: [0.39; 1.27], p=0.0511) with a calculated prolongation of 148 days to first exacerbation. A 44% reduction in the frequency of exacerbations was achieved.
- Ciprofloxacin DPI 28 also showed positive trends in the microbiological and patient-reported outcome variables, some of which were nominally significant in RESPIRE 1 and RESPIRE 2.

Pooled analysis within RESPIRE studies and integrated analysis across RESPIRE studies:

- Pooled analysis of ciprofloxacin DPI 14 and ciprofloxacin DPI 28 within each trial produced consistent efficacy *vs.* pooled placebo, with both prolongation of exacerbation-free days (159 days and 92 days) and reduction of frequency of exacerbations (23% and 32%) in both RESPIRE 1 and RESPIRE 2, respectively.
- Integrated analyses of ciprofloxacin DPI 14 and ciprofloxacin DPI 28 across both trials showed consistent positive treatment effects, with no meaningful overall differences between the two regimens. There was an estimated 144-day and 138-day delay in time to first exacerbation, and a 25% and 28% reduction in exacerbations for ciprofloxacin DPI 14 and ciprofloxacin DPI 28, respectively.

RESPIRE 1 and RESPIRE 2 trial responses:

- No single factor or combination of factors investigated explained the differing degrees of treatment effect for ciprofloxacin DPI 14 and ciprofloxacin DPI 28 regimens within each trial.
- Overall exacerbation totals (mean per patient) were 188 (0.60) for ciprofloxacin DPI 14, 184 (0.59) for ciprofloxacin DPI 28, and 248 (0.79) for pooled placebo.
- The results of the comprehensive efficacy analyses of exacerbation-related, microbiological, and patient-reported efficacy variables in the clinical Phase II/III program demonstrated an overall consistent positive treatment effect of ciprofloxacin DPI in patients with NCFB. The treatment effects of ciprofloxacin DPI 14 and DPI 28 are very similar.

# 6. Clinical safety of ciprofloxacin DPI in patients with NCFB

This section describes the adverse event experience in the Phase III study program based on the pooled safety data of the two RESPIRE studies (SAF, N=933 overall or FAS, N=937 overall). Data pooling of the Phase III safety data was performed in order to improve the ability to detect safety signals. An overview of the adverse event occurrence separated by single Phase III study is provided in Appendix Table 9–26.

Phase II safety results are not further detailed in this core document as they were fully consistent with the experience made in the Phase III program and did not provide any additional information about the safety profile of ciprofloxacin DPI. However, the main safety results observed in the Phase II NCFB study No. 12965 are summarized, for the interested reader, in Appendix 9.4.6.

It should be noted that the eligibility criteria of the Phase III studies were designed to reflect the target population of patients with moderate to severe NCFB, and thus no restrictions for age or renal impairment were made. However, NCFB populations excluded in the studies were patients on concomitant high-dose systemic corticosteroid use as well as pregnant patients.

## 6.1 Exposure to study medication and overall compliance in Phase III studies

The total treatment duration (from first dose to last dose; including treatment interruptions and off-cycles, given as mean ± SD) in the FAS (N=937) was 273.2 ± 98.4 days in the ciprofloxacin DPI 14 group, 267.9 ± 87.7 days in the ciprofloxacin DPI 28 group, 263.4 ± 107.2 days in the placebo 14 group, 250.2 ± 100.8 days in the placebo 28 group, (pooled placebo: 256.8 ± 104.1 days), and 266.0 ± 97.1 days in the total study population.

Appendix Table 9–24 summarizes the duration of exposure on study drug treatment in the Safety Analysis Set (SAF) (only considering the days on actual study treatment; excluding treatment interruptions and off-cycles), while Appendix Table 9–25 shows the exposure to study drug expressed as mean number of capsules taken (planned administration per patient: 2 capsules per treatment day). The mean number of treatment days ranged between 136.5 ± 53.3 days (placebo 28 group) and 146.7 ± 46.2 days (ciprofloxacin DPI 28 group), and the mean number of capsules taken ranged between 258.4 ± 106.6 capsules (placebo 28 group) and 280.9 ± 92.9 capsules (ciprofloxacin DPI 28 group). The mean exposure was lower in the placebo groups than in the active treatment groups, but overall, there were no clinically meaningful differences among the 4 treatment groups in terms of exposure.

The analysis of compliance is additionally presented (for the FAS) in Table 6–1. These data show that the mean drug compliance during the Phase III studies was >90% and well balanced across all treatment arms.

**Table 6–1: Overall treatment compliance in RESPIRE 1 and RESPIRE 2 - integrated analysis (FAS)**

| | Cipro 14 N=313 | Cipro 28 N=312 | Placebo 14 N=156 | Placebo 28 N=156 | Pooled Plc N=312 | Total N=937 |
|---|---|---|---|---|---|---|
| **Continuous data** | | | | | | |
| n | 310 | 312 | 156 | 155 | 311 | 933 |
| Nmiss | 3 | 0 | 0 | 1 | 1 | 4 |
| Mean | 95.4 | 95.1 | 94.3 | 93.5 | 93.9 | 94.8 |
| (SD) | (8.3) | (10.5) | (10.3) | (12.8) | (11.6) | (10.3) |
| Min, Max | 36, 104 | 0 a, 109 | 50, 150 | 14, 117 | 14, 150 | 0, 150 |
| Median | 98.0 | 98.5 | 97.8 | 97.9 | 97.9 | 98.2 |
| **Categorical data, n (%)** | | | | | | |
| <80% | 14 ( 4.5) | 24 ( 7.7) | 14 ( 9.0) | 14 ( 9.0) | 28 ( 9.0) | 66 ( 7.0) |
| ≥80% | 296 (94.6) | 288 (92.3) | 142 (91.0) | 141 (90.4) | 283 (90.7) | 867 (92.5) |

Max=maximum; Min=minimum; Nmiss=number of patients with missing information; Plc=Placebo; SD=Standard deviation
Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; Placebo 14=Placebo 14 on/off; Placebo 28=Placebo 28 on/off
Note: Compliance (%) is determined as number of capsules taken/number of planned capsules (*i.e.*, number of days on treatment x 2).
a: One patient used 1 capsule of ciprofloxacin DPI, withdrew afterwards from study, but did not return the remaining study medication. Therefore, the actual number of capsules used was unknown and set to zero based on pre-defined imputation algorithms.
Source: Integrated analysis tables; data on file

## 6.2 Integrated analysis of adverse events in Phase III studies

### 6.2.1 Description of safety population

Please note that all safety data provided in this section refer to the pooled safety data of RESPIRE 1 and RESPIRE 2 (SAF: N=933; 310 patients in the ciprofloxacin DPI 14 group, 312 patients in the ciprofloxacin DPI 28 group, and 311 patients in the pooled placebo group).

The demographic characteristics of the pooled FAS population (N=937) are summarized in Appendix Table 9-6. This population consisted of 350 males (37.4%) and 587 females (62.6%) aged between 18 and 91 years; the mean age was 62.1 ± 13.7 years. The 1st and 3rd quartiles of the age distribution in the total population indicate that 25% of the patients were at an age of ≤55 years and 25% of the patients were >72 years, respectively.

### 6.2.2 Overview of treatment-emergent adverse events (TEAEs)

Adverse events (AEs) were regarded as treatment-emergent (TEAEs), if they first occurred (or worsened) after start of study drug treatment through 30 days after administration of the last dose of study medication. All TEAEs were followed-up until the individual patient's EOS visit. Overall, TEAEs were reported in 239 patients (77.1%) in the ciprofloxacin DPI 14 group, 204 patients (65.4%) in the ciprofloxacin DPI 28 group, 113 patients (72.4%) in the placebo 14 group, and 117 patients (75.5%) in the placebo 28 group, (230 patients [74.0%] in the pooled placebo group).

The overall TEAE incidence was similar in the ciprofloxacin DPI 14 group compared with the two placebo groups, and the incidence was lower in the ciprofloxacin DPI 28 group than in the 2 placebo groups. Table 6–2 summarizes the overall incidences of AEs, any TEAEs, fatal TEAEs, serious TEAEs (including fatal TEAEs) and TEAEs leading to study drug discontinuation (the full overview of AEs and TEAEs can be found in Appendix Table 9–27).

Generally, the observed incidences of the various TEAE types (*i.e.*, all TEAEs, drug-related TEAEs, serious TEAEs, etc.) were similar in the two ciprofloxacin DPI regimens compared with pooled placebo. The incidence of TEAEs resulting in premature discontinuation of study drug treatment was higher in the pooled placebo group than in the two active treatment groups (9.3% in the pooled placebo group *vs.* 6.4% in the ciprofloxacin DPI 28 group and 8.7% in the ciprofloxacin DPI 14 group).

**Table 6–2: Overview of adverse events and treatment-emergent adverse events - integrated analysis (SAF)**

| | Cipro 14 N=310 | Cipro 28 N=312 | Placebo 14 N=156 | Placebo 28 N=155 | Pooled placebo N=311 | Total N=933 |
|---|---|---|---|---|---|---|
| Type of AE | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Any AE [a] | 246 (79.4) | 212 (67.9) | 115 (73.7) | 119 (76.8) | 234 (75.2) | 692 (74.2) |
| Any TEAE | 239 (77.1) | 204 (65.4) | 113 (72.4) | 117 (75.5) | 230 (74.0) | 673 (72.1) |
| TEAE with outcome death | 4 ( 1.3) | 6 ( 1.9) | 4 ( 2.6) | 1 ( 0.6) | 5 ( 1.6) | 15 ( 1.6) |
| Any serious TEAE | 68 (21.9) | 56 (17.9) | 45 (28.8) | 28 (18.1) | 73 (23.5) | 197 (21.1) |
| Discontinuation of study drug due to TEAE | 27 ( 8.7) | 20 ( 6.4) | 17 (10.9) | 12 ( 7.7) | 29 ( 9.3) | 76 ( 8.1) |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; Placebo 14=Placebo 14 on/off; Placebo 28=Placebo 28 on/off
Note: All frequency data are based on the number of patients with event.
a: Additionally selected data to show the number of patients based on all AEs.
Source: Integrated analysis tables of Studies 15625 and 15626

Incidence differences by ≥5.0%-points *vs.* pooled placebo were observed for the following TEAEs (differences [Δ] are shown as ciprofloxacin DPI value minus pooled placebo value):

- All TEAEs: 65.4% of patients in the ciprofloxacin DPI 28 group *vs.* 74.0% in the pooled placebo group (Δ= -8.6%-points).
- Serious TEAEs: 17.9% of patients in the ciprofloxacin DPI 28 group *vs.* 23.5% in the pooled placebo group (Δ= -5.6%-points).

In conclusion, there were no clinically meaningful differences in the comparisons of the active treatment groups *vs.* pooled placebo with regard to the frequencies of TEAEs, study drug-related TEAEs, severe TEAEs, serious TEAEs, and TEAEs resulting in premature discontinuation of study drug treatment. These results demonstrated that treatment with both ciprofloxacin DPI 14 and ciprofloxacin DPI 28 was safe and well tolerated.

### 6.2.3 Common TEAEs

#### 6.2.3.1 All common TEAEs

The reported TEAE pattern covered a broad spectrum of medical conditions. The 3 most commonly reported system organ classes (SOCs) in the total SAF population were "respiratory, thoracic and mediastinal disorders" (39.1% of all SAF patients), "infections and infestations" (34.2%), and "gastrointestinal disorders" (20.2%; see Appendix Table 9–28, which displays all TEAEs at SOC level).

Only a few TEAEs occurred at a frequency of ≥5.0% in at least one of the treatment groups at preferred term level (see Table 6–3), and no incidence differences by ≥5.0%-points between treatment groups were observed. The events "bronchiectasis" and "bronchospasm" occurred more frequently in the pooled placebo group than in the two active treatment groups, while "dyspnoea" was more frequently reported in patients on active treatment. In addition, headache was reported more frequently on active treatment than on treatment with placebo. Another preferred term event that contributed to the numerical incidence difference in the SOC "nervous system disorders" was "dysgeusia", which occurred in 4.2% of patients in the ciprofloxacin DPI 14 group and in 4.8% of patients in the ciprofloxacin DPI 28 group *vs.* 1.3% in the pooled placebo group (*i.e.*, incidence <5%, therefore not listed as most common TEAE).

**Table 6–3: Most common TEAEs (≥5.0% of patients affected in at least one of the treatment groups at preferred term level) by primary SOC and preferred term - integrated analysis (SAF)**

| MedDRA 19.0<br>Primary SOC<br>Preferred term | Cipro 14<br>N=310<br>n (%) | Cipro 28<br>N=312<br>n (%) | Pooled placebo [a]<br>N=311<br>n (%) | Total<br>N=933<br>n (%) |
|---|---|---|---|---|
| Any TEAE | 239 (77.1) | 204 (65.4) | 230 (74.0) | 673 (72.1) |
| **Respiratory, thoracic and mediastinal disorders** | **134 (43.2)** | **104 (33.3)** | **127 (40.8)** | **365 (39.1)** |
| Bronchiectasis | 32 (10.3) | 33 (10.6) | 38 (12.2) | 103 (11.0) |
| Haemoptysis | 33 (10.6) | 27 ( 8.7) | 32 (10.3) | 92 ( 9.9) |
| Cough | 20 ( 6.5) | 20 ( 6.4) | 20 ( 6.4) | 60 ( 6.4) |
| Dyspnoea | 26 ( 8.4) | 20 ( 6.4) | 12 ( 3.9) | 58 ( 6.2) |
| Bronchospasm | 14 ( 4.5) | 10 ( 3.2) | 19 ( 6.1) | 43 ( 4.6) |
| **Infections and infestations** | **99 (31.9)** | **114 (36.5)** | **106 (34.1)** | **319 (34.2)** |
| Nasopharyngitis | 32 (10.3) | 25 ( 8.0) | 24 ( 7.7) | 81 ( 8.7) |
| Upper respiratory tract infection | 17 ( 5.5) | 14 ( 4.5) | 15 ( 4.8) | 46 ( 4.9) |
| **Gastrointestinal disorders** | **70 (22.6)** | **56 (17.9)** | **62 (19.9)** | **188 (20.2)** |
| Diarrhoea | 16 ( 5.2) | 8 ( 2.6) | 10 ( 3.2) | 34 ( 3.6) |
| **Nervous system disorders** | **59 (19.0)** | **58 (18.6)** | **30 ( 9.6)** | **147 (15.8)** |
| Headache | 24 ( 7.7) | 21 ( 6.7) | 9 ( 2.9) | 54 ( 5.8) |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off
Note: All frequency data are based on the number of patients with event. SOCs and preferred terms within SOCs are sorted in order of decreasing frequency in the total study population.
[a] The incidence cut was applied to any of the treatment groups (active treatment groups or pooled placebo group).
Source: Integrated analysis tables of Studies 15625 and 15626

### 6.2.3.2 Severity and outcome of most common TEAEs

The TEAEs reported in the two Phase III studies were mostly mild or moderate in intensity (see Appendix Table 9–27). Severe TEAEs were reported in 48 patients (15.5%) in the ciprofloxacin DPI 14 group, 38 patients (12.2%) in the ciprofloxacin DPI 28 group, and 51 patients [16.4%] in the pooled placebo group. Thus, proportions of patients with severe TEAEs were small and similarly distributed between the active treatment groups and the pooled placebo group. Fatal events were infrequent in all treatment groups (1.6% of patients overall; see Section 6.2.5).

Most of the study patients with TEAEs in each treatment group recovered from the TEAE, and only a minority of patients with TEAEs experienced TEAEs that remained "not recovered/not resolved" (fatal events excluded): 46 patients (14.8%) in the ciprofloxacin DPI 14 group, 46 patients (14.7%) in the ciprofloxacin DPI 28 group, and 52 patients (16.7%) in the pooled placebo group. Also within the SOC "respiratory, thoracic and mediastinal disorders" the proportion of patients with "not recovered/not resolved" events was small in each treatment group and similar across treatment groups: 6 patients (1.9%) in the ciprofloxacin DPI 14 group, 9 patients (2.9%) in the ciprofloxacin DPI 28 group, and 9 patients (2.9%) in the pooled placebo group.

### 6.2.3.3 Common drug-related TEAEs

The relationship to study drug was assessed by site investigators. Generally, the incidence of drug-related TEAEs was small and similar across the treatment groups. Appendix Table 9–29 summarizes all drug-related TEAEs by primary SOC and additionally by preferred term, if ≥1.0% of patients in at least one of the treatment groups were affected (*i.e.*, at least 3 patients). The 3 most frequently reported SOCs for drug-related TEAEs were "respiratory, thoracic and mediastinal disorders" (9.3% of SAF patients overall), "nervous system disorders" (4.8%), and "gastrointestinal disorders" (4.1%). Drug-related TEAEs pertaining to the SOC "respiratory, thoracic and mediastinal disorders" were more frequent in the pooled placebo group than in the active treatment groups (9.0% in the ciprofloxacin DPI 14 group and 6.1% in the ciprofloxacin DPI 28 group *vs.* 12.9% in the pooled placebo group). This difference was driven by the higher incidence of "bronchospasm" and "cough" in the pooled placebo group compared with the active treatment groups. However, the absolute numbers of events in all treatment groups as well as the incidence differences were rather small.

The incidence differences seen for the SOC "nervous disorders" (6.1% in either active treatment group *vs.* 2.3% in the pooled placebo group) were driven by the higher occurrence of "dysgeusia" on active treatment, while the incidence of "headache" was similar across the treatment groups. No noteworthy incidence differences were seen with regard to the remaining SOCs containing the drug-related TEAEs.

As with all TEAEs, most of the drug-related TEAEs were either mild or moderate in intensity; 15 patients experienced at least one severe drug-related TEAE. Overall, severe drug-related TEAEs were infrequent, and no apparent, clinically meaningful treatment group differences were observed (see Appendix Table 9–31).

Most of the study patients with drug-related TEAEs in each treatment group recovered from the TEAE, and only a minority of patients with TEAEs experienced drug-related TEAEs that

remained "not recovered/not resolved" until the individual patient's EOS visit (no fatal drug-related TEAEs were reported): 4 patients (1.3%) in the ciprofloxacin DPI 14 group, 4 patients (1.3%) in the ciprofloxacin DPI 28 group, and 6 patients (1.9%) in the pooled placebo group.

### 6.2.4 Procedure- and device-related TEAEs

The relationship to study procedures or device were assessed by site investigators. TEAEs related to procedures required by the protocol were reported in 7 patients (2.3%) in the ciprofloxacin DPI 14 group, 5 patients (1.6%) in the ciprofloxacin DPI 28 group, and 8 patients (2.6%) in the pooled placebo group. Two of these events occurring in one patient in the ciprofloxacin DPI 14 group (pathogen resistance and pneumonia) were considered serious.

Device-related TEAEs were reported in 3 patients (1.0%) in the ciprofloxacin DPI 14 group, 3 patients (1.0%) in the ciprofloxacin DPI 28 group, and 5 patients (1.6%) in the pooled placebo group (see Appendix Table 9–30, in which all device-related TEAEs are summarized by SOC and preferred term). Most of the events pertained to the SOC "respiratory, thoracic and mediastinal disorders. One of the device-related events occurring in one patient in the placebo 14 group (haemoptysis) was considered serious. Generally, device-related TEAEs were infrequent in each treatment group, and no apparent treatment group differences were observed. Thus, these data did not point to relevant issues associated with the inhaler device.

### 6.2.5 Deaths and other serious TEAEs

**Fatal serious adverse events**

A total of 23 deaths overall were documented in the RESPIRE studies (see Appendix Table 9–27), and 15 patients (1.6%) thereof experienced fatal TEAEs: 4 patients (1.3%) in the ciprofloxacin DPI 14 group, 6 patients (1.9%) in the ciprofloxacin DPI 28 group, 4 patients (2.6%) in the placebo 14 group, and one patient (0.6%) in the placebo 28 group (5 patients [1.6%] in the pooled placebo group). Thus, no differences in mortality were observed across the treatment groups.

At preferred term level, the 15 fatal adverse events in the 15 involved patients were:

- Ciprofloxacin DPI 14 group (n=4): "Bronchiectasis" (n=1), "gastrointestinal haemorrhage" (n=1), "oesopharyngeal carcinoma" (n=1), and "pneumonia aspiration" (n=1).
- Ciprofloxacin DPI 28 group (n=6): "Bronchiectasis" (n=2), "cor pulmonale" (n=2), "congestive cardiomyopathy" (n=1), and "pneumonia" (n=1).
- Pooled placebo group (n=5): "Bronchiectasis" (n=2), "complications of transplant surgery" (n=1), "pneumonia" (n=1), and "pulmonary haemorrhage" (n=1).

None of the treatment-emergent deaths were rated as drug-, device- or procedure-related.

## All serious adverse events

Serious TEAEs (including deaths) were reported in 68 patients (21.9%) in the ciprofloxacin DPI 14 group, 56 patients (17.9%) in the ciprofloxacin DPI 28 group, and 73 patients (23.5%) in the pooled placebo group (see Table 6–4). Also the serious TEAEs covered a broad range of various medical conditions, and only a few TEAEs occurred in more than one patient in a given treatment group at preferred term level. Most of the serious TEAEs belonged to the SOC "respiratory, thoracic and mediastinal disorders" (13.1% of SAF patients), with "bronchiectasis" reported most frequently as serious TEAE in this SOC (11.0% of SAF patients). No clinically meaningful differences across treatment groups at SOC level or at preferred term level were observed in the integrated analysis of serious TEAEs.

**Table 6–4: All serious TEAEs by SOC and additionally by preferred term, if at least 2 patients in at least one treatment group were affected - integrated analysis (SAF)**

| MedDRA 19.0<br>Primary SOC<br>Preferred term | Cipro 14<br>N=310<br>n (%) | Cipro 28<br>N=312<br>n (%) | Pooled placebo [a]<br>N=311<br>n (%) | Total<br>N=933<br>n (%) |
|---|---|---|---|---|
| Any serious TEAE | 68 (21.9) | 56 (17.9) | 73 (23.5) | 197 (21.1) |
| **Respiratory, thoracic and mediastinal disorders** | **40 (12.9)** | **38 (12.2)** | **44 (14.1)** | **122 (13.1)** |
| Bronchiectasis | 32 (10.3) | 33 (10.6) | 38 (12.2) | 103 (11.0) |
| Haemoptysis | 4 ( 1.3) | 4 ( 1.3) | 6 ( 1.9) | 14 ( 1.5) |
| Chronic obstructive pulmonary disease | 3 ( 1.0) | 0 | 1 ( 0.3) | 4 ( 0.4) |
| Respiratory failure | 2 ( 0.6) | 0 | 1 ( 0.3) | 3 ( 0.3) |
| **Infections and infestations** | **10 ( 3.2)** | **14 ( 4.5)** | **18 ( 5.8)** | **42 ( 4.5)** |
| Pneumonia | 6 ( 1.9) | 7 ( 2.2) | 7 ( 2.3) | 20 ( 2.1) |
| Infective exacerbation of bronchiectasis | 4 ( 1.3) | 2 ( 0.6) | 3 ( 1.0) | 9 ( 1.0) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | **3 ( 1.0)** | **2 ( 0.6)** | **6 ( 1.9)** | **11 ( 1.2)** |
| **Cardiac disorders** | **3 ( 1.0)** | **4 ( 1.3)** | **3 ( 1.0)** | **10 ( 1.1)** |
| Cardiac failure | 1 ( 0.3) | 0 | 2 ( 0.6) | 3 ( 0.3) |
| Atrial flutter | 0 | 2 ( 0.6) | 0 | 2 ( 0.2) |
| Cor pulmonale | 0 | 2 ( 0.6) | 0 | 2 ( 0.2) |
| **Gastrointestinal disorders** | **3 ( 1.0)** | **2 ( 0.6)** | **4 ( 1.3)** | **9 ( 1.0)** |
| **Injury, poisoning and procedural complications** | **4 ( 1.3)** | **1 ( 0.3)** | **3 ( 1.0)** | **8 ( 0.9)** |
| **Nervous system disorders** | **2 ( 0.6)** | **3 ( 1.0)** | **3 ( 1.0)** | **8 ( 0.9)** |
| **Musculoskeletal and connective tissue disorders** | **2 ( 0.6)** | **1 ( 0.3)** | **3 ( 1.0)** | **6 ( 0.6)** |
| **Renal and urinary disorders** | **2 ( 0.6)** | **0** | **2 ( 0.6)** | **4 ( 0.4)** |
| **Vascular disorders** | **2 ( 0.6)** | **0** | **2 ( 0.6)** | **4 ( 0.4)** |
| **Eye disorders** | **1 ( 0.3)** | **1 ( 0.3)** | **1 ( 0.3)** | **3 ( 0.3)** |
| **General disorders and administration site conditions** | **2 ( 0.6)** | **1 ( 0.3)** | **0** | **3 ( 0.3)** |
| **Hepatobiliary disorders** | **1 ( 0.3)** | **0** | **2 ( 0.6)** | **3 ( 0.3)** |
| **Blood and lymphatic system disorders** | **0** | **0** | **2 ( 0.6)** | **2 ( 0.2)** |

*table continued...*

**Table 6–4: All serious TEAEs by SOC and additionally by preferred term, if at least 2 patients in at least one treatment group were affected - integrated analysis (SAF)**

| MedDRA 19.0<br>Primary SOC<br>Preferred term | Cipro 14<br>N=310<br>n (%) | Cipro 28<br>N=312<br>n (%) | Pooled placebo [a]<br>N=311<br>n (%) | Total<br>N=933<br>n (%) |
|---|---|---|---|---|
| **Metabolism and nutrition disorders** | **1 ( 0.3)** | **0** | **1 ( 0.3)** | **2 ( 0.2)** |
| **Reproductive system and breast disorders** | **2 ( 0.6)** | **0** | **0** | **2 ( 0.2)** |
| **Ear and labyrinth disorders** | **1 ( 0.3)** | **0** | **0** | **1 ( 0.1)** |
| **Immune system disorders** | **0** | **1 ( 0.3)** | **0** | **1 ( 0.1)** |
| **Investigations** | **0** | **1 ( 0.3)** | **0** | **1 ( 0.1)** |
| **Pregnancy, puerperium and perinatal conditions** | **0** | **1 ( 0.3)** | **0** | **1 ( 0.1)** |
| **Psychiatric disorders** | **1 ( 0.3)** | **0** | **0** | **1 ( 0.1)** |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off
Note: All frequency data are based on the number of patients with event. SOCs and preferred terms within SOCs are sorted in order of decreasing frequency in the total study population.
[a] The incidence cut was applied to any of the treatment groups (active treatment groups or pooled placebo group).
Source: Integrated analysis tables of Studies 15625 and 15626

Study drug-related serious TEAEs as assessed by the investigator were infrequent and were reported in 7 patients overall (see Appendix Table 9–32). Six of the patients were treated with ciprofloxacin DPI, but the absolute event number was too small to draw reliable conclusions on potential group differences. Apart from the patients with "retinal vasculitis" and "atrial flutter" (both events were "not recovered/not resolved") the remaining patients recovered from the events.

### 6.2.6 TEAEs of special interest

**Pre-specified treatment-emergent adverse events of special interest (AESIs)**

Four pre-specified treatment-emergent AESIs were analyzed in the integrated analysis: "bronchospasm" (single preferred term), "haemoptysis" (single preferred term), hypersensitivity (standardized MedDRA query [SMQ] "hypersensitivity"; narrow search), and "tendon disorder" (SMQ "tendinopathies and ligament disorders"; narrow search). Table 6–5 summarizes the overall incidence of treatment-emergent AESIs and serious AESIs (both all and drug-related) and shows that the incidences of all tabulated events were similar (or even smaller in the active treatment groups than in the pooled placebo group).

Bronchospasm was less frequent in the ciprofloxacin DPI groups than in the pooled placebo group, but is known to be a risk with other inhaler devices.

Hemoptysis incidences were similar across the treatment groups; this condition might be caused by the underlying disease, or can be the result of local irritation due to powder particle inhalation.

The occurrence of hypersensitivity was quite similar across the treatment groups. Except for one patient in the ciprofloxacin DPI 28 group with serious bronchospasm, all other cases

referring to hypersensitivity were non-serious. Most of the included events in all treatment groups belonged to the SOCs "respiratory, thoracic and mediastinal disorders" (5.0% of study patients; reported preferred terms were "allergic sinusitis", "bronchospasm", and "rhinitis allergic") and "skin and subcutaneous tissue disorders" (4.3% of study patients; "rash" was the most common preferred term with 20 patients [2.1%] involved). Rarer cases of hypersensitivity included "periorbital oedema" (1 patient in the ciprofloxacin DPI 28 group), "mouth swelling" (1 patient in the placebo 28 group), "swollen tongue" (1 patient in the ciprofloxacin DPI 28 group), and "swelling face" (1 patient in the ciprofloxacin DPI 28 group).

Tendon disorders were infrequent in all treatment groups, and no TEAEs involving the Achilles tendon were reported. Thus, the integrated analysis of tendon disorders did not indicate an increased risk of tendon disorders on active treatment compared with placebo.

Serious treatment-emergent AESIs were too infrequent to draw reliable conclusions on potential differences between treatment groups.

**Table 6–5: Patients with pre-defined, treatment-emergent AESIs and serious AESIs (all or drug-related AESIs) - integrated analysis (SAF)**

| | Cipro 14 N=310 | | Cipro 28 N=312 | | Pooled placebo N=311 | |
|---|---|---|---|---|---|---|
| | All n (%) | Related n (%) | All n (%) | Related n (%) | All n (%) | Related n (%) |
| **TEAEs** | | | | | | |
| Bronchospasm | 14 ( 4.5) | 8 ( 2.6) | 10 ( 3.2) | 5 ( 1.6) | 19 ( 6.1) | 12 ( 3.9) |
| Haemoptysis | 33 (10.6) | 5 ( 1.6) | 27 ( 8.7) | 3 ( 1.0) | 32 (10.3) | 3 ( 1.0) |
| Hypersensitivity | 32 (10.3) | 9 ( 2.9) | 21 ( 6.7) | 8 ( 2.6) | 40 (12.9) | 16 ( 5.1) |
| Tendon disorder | 5 ( 1.6) | 0 | 3 ( 1.0) | 1 ( 0.3) | 3 ( 1.0) | 0 |
| **Serious TEAEs** | | | | | | |
| Bronchospasm | 0 | 0 | 1 ( 0.3) | 1 ( 0.3) | 0 | 0 |
| Haemoptysis | 4 ( 1.3) | 0 | 4 ( 1.3) | 1 ( 0.3) | 6 ( 1.9) | 1 ( 0.3) |
| Hypersensitivity | 0 | 0 | 1 ( 0.3) | 1 ( 0.3) | 0 | 0 |
| Tendon disorder | 0 | 0 | 0 | 0 | 0 | 0 |

Cipro 14=Ciprofloxacin DPI 14 days on/off; Cipro 28=Ciprofloxacin DPI 28 days on/off
Note: All frequency data are based on the number of patients with event. Drug-relatedness is based on investigator's assessment.
Source: Integrated analysis tables of Studies 15625 and 15626

Other potential inhalation-associated TEAEs include cough and dyspnea. Cough incidences were similar across treatment groups (6.5% in the ciprofloxacin DPI 14 group, 6.4% in the ciprofloxacin DPI 28 group, and 6.4% in the pooled placebo group), while dyspnea was slightly more frequent in the two ciprofloxacin DPI group than in the pooled placebo group (8.4% in the ciprofloxacin DPI 14 group and 6.4% in the ciprofloxacin DPI 28 group *vs.* 3.9% in the pooled placebo group; see Table 6–3).

**TEAEs pertaining to the pharmacological class**

Potential pharmacological class effects and adverse drug reactions (ADRs) known to be associated with systemically administered fluoroquinolones (*e.g.*, anaphylaxis, QT interval prolongation, seizures, depression or psychiatric reactions, polyneuropathy, pseudo-

membranous colitis, liver failure, tendinopathies) occurred infrequently or were even absent in the active treatment groups. Overall, no increased risk of fluoroquinolone class effects was seen on active treatment compared with placebo.

Due to the low systemic exposure observed with inhalation treatment with ciprofloxacin DPI 32.5 mg BID and the safety profile as observed in the clinical trials, the risk of systemic side effects is regarded as low.

## 6.3 Development of treatment-emergent resistance in Phase III - pooled data from RESPIRE 1 and RESPIRE 2

Resistance to ciprofloxacin was analyzed in both Phase III studies in the FAS according to pre-defined systemic breakpoints based on an extensive sputum sampling schedule and tracked on both a patient level and on an isolate level. In addition, genotyping of resistant pathogens isolated from sputum using pulse-field gel electrophoresis was performed. Due to the congruence of the individual study results in terms of resistance results, the pooled study data are presented in this section.

**Main results on a patient level**

The key parameters were "baseline resistance" (number of patients with at least one resistant isolate at baseline), "development of resistance at end of study (EOS)" (number of patients with the same species susceptible before start of treatment and resistant at time point EOS), and "any development of resistance" (number of patients with the same species susceptible before start of treatment and resistant at any other time point during the course of the study until/including EOS).

Two approaches were chosen to calculate the percentages of patients with resistance: In the first approach, the denominator for calculation was the number of FAS patients within each treatment group with the specific bacterial genus/species present for analysis (meaning the specific baseline pathogen must be present). In the second approach, the denominator for calculation was the total number of FAS patients within each treatment group (meaning that the baseline pathogen could be present or absent post-baseline).

Based on the first approach (see Table 6–6) resistance rates at baseline were similar for ciprofloxacin DPI 14 (22.8%), ciprofloxacin DPI 28 (21.6%), and pooled placebo (20.0%). During the trial, resistance at any time point in the study was noted in 40.9% (ciprofloxacin DPI 14 group), 39.2% (ciprofloxacin DPI 28 group), and 13.4% (pooled placebo group). Many of the patients showed transient resistance. At the end of study, the resistance rates were similar to baseline with 25.9% (ciprofloxacin DPI 14 group), 26.7% (ciprofloxacin DPI 28 group), and 8.0% (pooled placebo group) of patients showing resistant isolates. This likely reflects the selective pressure of long-term ciprofloxacin DPI administration.

**Table 6–6: Number of patients with any ciprofloxacin-resistant * pathogens in sputum samples - percentages based on patients with the specific bacterial genus/species present for analysis (FAS)**

| | Cipro 14 n (%) | Cipro 28 n (%) | Pooled placebo [a] n (%) | Total n (%) |
|---|---|---|---|---|
| Resistance at baseline | | | | |
| N | 312 | 310 | 310 | 932 |
| No | 241 (77.2) | 243 (78.4) | 248 (80.0) | 732 (78.5) |
| Yes [a] | 71 (22.8) | 67 (21.6) | 62 (20.0) | 200 (21.5) |
| Development of resistance: from pre-treatment at any time | | | | |
| N | 159 | 166 | 201 | 526 |
| No | 94 (59.1) | 101 (60.8) | 174 (86.6) | 369 (70.2) |
| Yes [b] | 65 (40.9) | 65 (39.2) | 27 (13.4) | 157 (29.8) |
| Development of resistance: from pre-treatment at EOS | | | | |
| N | 85 | 86 | 88 | 259 |
| No | 63 (74.1) | 63 (73.3) | 81 (92.0) | 207 (79.9) |
| Yes [c] | 22 (25.9) | 23 (26.7) | 7 ( 8.0) | 52 (20.1) |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; EOS=End of study
Note: All frequency data are patient-based (denominator [N] is the number of FAS patients with the specific bacterial genus/species present for analysis within each treatment group).
*: Resistance defined by breakpoints for systemic therapy
[a] Number of patients with at least one resistant isolate at baseline.
[b] Number of patients with same species susceptible before start of treatment and resistant at any post-baseline time point.
[c] Number of patients with same species susceptible before start of treatment and resistant at end of study.
Source: Integrated analysis tables of Studies 15625 and 15626

According to the second approach (see Appendix Table 9–33), the proportions of patients with treatment-emergent development of resistance at any time were numerically higher in the ciprofloxacin DPI groups than in the pooled placebo group (20.8% of patients in both the ciprofloxacin DPI 14 group and the ciprofloxacin DPI 28 group compared with 8.7% in the pooled placebo group). The proportions of patients with treatment-emergent development of resistance at the time point EOS (7.0% of patients in the ciprofloxacin DPI 14 group, 7.4% in the ciprofloxacin DPI 28 group, and 2.2% in the pooled placebo group) were lower than cumulative resistance. This result might reflect the inherent lower sensitivity of a single sputum sample at EOS compared to the multiple sputum samples analyzed during the course of the study as well as potential regression of ciprofloxacin-resistant isolates due to a variety of factors, including removal of antimicrobial pressure during the several week period between end of treatment and the EOS visit.

**Main results on an isolate level**

On an isolate level, *P. aeruginosa* was both the most common pathogen and the pathogen most often associated with ciprofloxacin resistance. Baseline resistance to ciprofloxacin was noted in 71/326 (21.8%), 71/332 (21.4%), and 73/344 (21.2%) *P. aeruginosa* isolates in the ciprofloxacin DPI 14, ciprofloxacin DPI 28, and pooled placebo groups, respectively. The

incidence of resistance tabulated at any time point post-baseline in *P. aeruginosa* approximately doubled in the ciprofloxacin DPI groups (571/1327 isolates [43.0%] for ciprofloxacin DPI 14 and 436/1038 isolates [42.0%] for ciprofloxacin DPI 28), and remained stable in the pooled placebo group (328/1319 isolates [24.9%]). Some cases of ciprofloxacin resistance in the ciprofloxacin DPI groups were also noted in *H. influenzae*, *S. aureus*, and *S. pneumoniae*, and also for *S. pneumoniae* in the placebo group. No resistance development was noted in *M. catarrhalis*. These results indicated that *P. aeruginosa* was both the most common pathogen, and the pathogen most likely to demonstrate resistance to ciprofloxacin during therapy.

**Main results of genotyping analyses**

Genotyping of resistant pathogens was primarily performed based on isolates from sputum samples from baseline and the first visit closest to the baseline visit that demonstrated resistance (subsequent resistant isolates of the same pathogen were not intended to be genotyped). This analysis indicated a genotyping match in 47/65 (72.3%) of cases in the ciprofloxacin DPI 14 group, 45/66 (68.2%) of cases in the ciprofloxacin DPI 28 group, and in 16/27 (59.3%) of cases in the pooled placebo group. This analysis demonstrated genetic relationship between the susceptible baseline isolate and the resistant post-baseline isolate in about 70% of cases in the active treatment groups, which implies selection of resistance under antibiotic pressure. The relatively high genotyping match rate of about 60% in the pooled placebo group could be due to concomitant antibiotic use, acquisition of a resistant isolate that is genetically related to the baseline isolate, or due to undetected resistance at baseline.

**Appraisal of resistance findings**

Resistance development is an inherent concern with any antibiotic treatment, including inhaled antibiotics. The RESPIRE program thus included extensive sputum sampling (15 and 11 sampling points on the 14-days and 28-day regimen, respectively) in order to study the development of ciprofloxacin resistance on chronic-intermittent treatment with ciprofloxacin DPI. The overall resistance at any time point, *i.e.*, the number of patients with at least one resistant isolate at any time point (including baseline) until the end of study was 53.0% in the ciprofloxacin DPI 14 group, 46.2% in the ciprofloxacin DPI 28 group, and 32.4% in the pooled placebo group (FAS).

Baseline resistance had the largest impact on the reductions in frequency of resistance achieved by ciprofloxacin DPI. The effects of resistance first detected at baseline, post baseline, or never present are shown in Table 6–7. Treatment effect for ciprofloxacin DPI was minimal for patients with baseline resistance. Treatment effect was partially preserved when resistance was first detected post baseline, and treatment effect was maximal in patients who never showed resistance. The treatment effects in terms of both the time to first exacerbation and frequency of exacerbations were minimal in patients with ciprofloxacin-resistant pathogens at baseline compared to those without resistance. Overall, the anticipated clinical benefit of long-term treatment with ciprofloxacin DPI is expected to outweigh the potential risks associated with resistance development in the individual patient. Effects of resistance are part of risk management in the NCFB patient.

**Table 6–7: Frequency of exacerbations by timing of resistance detection (FAS)**

| First detection of resistance at: | Cipro 14 N=313 n (mean ± SD) [a] | Cipro 28 N=312 n (mean ± SD) [a] | Pooled placebo N=312 n (mean ± SD) [a] |
|---|---|---|---|
| **First detection of resistance at:** | | | |
| baseline | 71 (0.85 ± 1.08) | 67 (0.75 ± 0.86) | 62 (0.84 ± 1.01) |
| post-baseline | 82 (0.59 ± 0.77) | 72 (0.56 ± 0.85) | 34 (0.79 ± 1.12) |
| never | 160 (0.50 ± 0.88) | 173 (0.54 ± 0.97) | 216 (0.78 ± 1.03) |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off
Note: Exacerbations are defined as exacerbation with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of at least 3 signs/symptoms over 48 weeks (qualifying exacerbation for primary efficacy analysis).
a: Given is the number of patients within the respective resistance group and the mean number of exacerbation events within that group.
Source: Integrated analysis tables of Studies 15625 and 15626

Resistance, as defined by systemic MIC breakpoints, do not necessarily correlate with clinical efficacy outcomes with aerosol delivery for pulmonary infections, since significantly higher lung concentrations are achieved with local delivery (see Section 4.2.3). Generally, it should be taken into account that the systemic MIC breakpoints for ciprofloxacin, which were used for the definition of resistance, are not necessarily equated with actual efficacy outcomes in aerosol delivery for chronic infections. The very high sputum concentrations up to saturation, together with the depot effect that results from the undissolved ciprofloxacin in sputum (see Section 4.2.3), can potentially overcome MIC values of 4 µg/mL.

**Summary of Section 6 (Clinical safety of ciprofloxacin DPI in patients with NCFB):**

- Data pooling of the Phase III safety data was performed in order to improve the ability to detect safety signals. Thus, the total safety analysis population for the integrated analysis comprised 933 patients, with 622 SAF patients exposed to ciprofloxacin DPI (310 in the ciprofloxacin DPI 14 group 312 in the ciprofloxacin DPI 28 group).
- The Phase III studies were reflective of the target population, and there were no restrictions for age or renal impairment.
- Drug compliance during the studies was high with >90% and well balanced across the treatment groups.
- The TEAE incidences were similar across the treatment groups, and the most frequent TEAEs were mostly mild to moderate and reversible.
- The incidences of all treatment-emergent SAEs (21.9% of SAF patients in the ciprofloxacin DPI 14 group, 17.9% in the ciprofloxacin DPI 28 group, and 23.5% in the pooled placebo group) and treatment-emergent fatal SAEs (1.3% in the ciprofloxacin DPI 14 group, 1.9% in the ciprofloxacin DPI 28 group, and 1.6% in the pooled placebo group) were similar across the groups.
- TEAEs of special interest and potential inhalation-associated TEAEs included local events (bronchospasm, hemoptysis, cough, dyspnea), hypersensitivity, and those typically related to the fluoroquinolone class (*e.g.*, tendinopathies).
    - In general, local effects were seen with similar incidence. Dyspnea was numerically slightly more frequent in the ciprofloxacin DPI treatment groups than in the pooled placebo group, whilst the bronchospasm incidence was numerically lower on active treatment *vs.* pooled placebo.
    - No increased risk of hypersensitivity and systemic fluoroquinolone class effects were observed compared to placebo treatment.
- Rates of resistance development were higher in the two active treatment groups compared with placebo, but the overall resistance rates at the end of the studies were similar to those seen at baseline for ciprofloxacin DPI.
- Resistance had the most impact on treatment efficacy when present at baseline. Treatment effect was maximal in the patient population that never showed the development of resistance.
- Overall, ciprofloxacin DPI demonstrated a favorable safety profile throughout the development program exposure of up to 48 weeks. This finding is supported by the PK profile, which shows that ciprofloxacin DPI has only low systemic exposure.

# 7. Overall summary of benefit/risk evaluation

The following overall conclusions can be made based on the evidence presented in this briefing document:

Unmet medical need

- NCFB is a chronic, progressive, and heterogeneous disease characterized by a vicious cycle of impaired mucociliary clearance, mucus plugs, chronic bacterial infection, airway inflammation, and tissue destruction. The result is debilitating symptoms including severe coughing, excessive purulent sputum production, fatigue, and frequent exacerbations. Exacerbations can persist for two to 4 or more weeks, and may result in hospitalizations.
- There is a major unmet medical need in NCFB patients. NCFB is an understudied, neglected disease, and existing treatment guidelines must rely on limited evidence, with physicians often utilizing off-label therapies. There are no approved drugs for reduction of exacerbations in NCFB patients.
- There is clear evidence that NCFB patients who have more frequent exacerbations have worse quality of life and worse prognosis. In addition, exacerbations are an important prognostic factor for additional exacerbations. The reduction of exacerbations has to be a central goal of long-term management.

Demonstrated benefit

- The rationale of ciprofloxacin DPI therapy is to decrease the incidence of exacerbations by reducing the bacterial load in the lung through the direct delivery of high local concentrations of ciprofloxacin. Inhalation of ciprofloxacin DPI routinely provides bactericidal ciprofloxacin concentrations in sputum, with sustained unbound concentrations of 120 µg/mL and a 58-fold higher sputum concentration compared to what can be achieved with systemic treatment.
- Ciprofloxacin DPI 14 days on/off therapy over 48 weeks produced the following effects:
    - The median time to first exacerbation was extended 222 days in RESPIRE 1 and 43 days in RESPIRE 2, with the resulting point estimates of RESPIRE 1: HR=0.53 (97.5%-CI: [0.36; 0.80]); RESPIRE 2: HR=0.87 (95.1%-CI: [0.62; 1.21]).
    - A 27% and 19% reduction in the frequency of exacerbations was achieved in the two trials.
    - Positive treatment effects were also seen in the microbiological (pathogen eradication and acquisition of new pathogens) and patient-reported outcome (SGRQ SCS and QOL-B RSDS) variables.

- Ciprofloxacin DPI 28 days on/off therapy over 48 weeks produced the following effects:
    - The median time to first exacerbation was delayed by 107 and 148 days in RESPIRE 1 and RESPIRE 2. A moderate treatment effect was observed for prolonging the time to first exacerbation in both RESPIRE 1 (HR=0.73; 97.5%-CI: [0.50; 1.07]) and in RESPIRE 2 (HR=0.71; 99.9%-CI: [0.39; 1.27]).
    - A 14% and 44% reduction in the frequency of exacerbations was shown in the two trials.
    - Positive treatment effects were also seen in the microbiological (pathogen eradication and acquisition of new pathogens) and patient-reported outcome (SGRQ SCS and QOL-B RSDS) variables.
- Pooled analyses (ciprofloxacin DPI 14 plus ciprofloxacin DPI 28) supported the positive treatment effect of ciprofloxacin DPI within each individual trial. According to protocol, patients in both ciprofloxacin DPI treatment arms received the same total dose during the course of the studies.
    - In RESPIRE 1, pooled ciprofloxacin DPI achieved a 159-day increase in time to first exacerbation, and a 23% reduction of frequency of exacerbations.
    - In RESPIRE 2, pooled ciprofloxacin DPI increased time to first exacerbation by 92 days and reduced exacerbation frequency by 32%.
- Integrated analysis of ciprofloxacin DPI 14 across RESPIRE 1 and RESPIRE 2, and ciprofloxacin DPI 28 across RESPIRE 1 and RESPIRE 2 confirmed the overall efficacy of both treatment regimens. There was a 144-day and 138-day delay in time to first exacerbation, and a 25% and 28% reduction in exacerbations for ciprofloxacin DPI 14 and ciprofloxacin DPI 28, respectively.
- The range of treatment effects of ciprofloxacin DPI observed in RESPIRE 1 and RESPIRE 2 might reflect the heterogeneity of patients with NCFB.

<u>Manageable risk</u>

- The Phase III studies were designed to reflect the adult target population of patients with NCFB. No restrictions for advanced age or renal impairment were made.
- Ciprofloxacin DPI showed a favorable safety profile. The majority of adverse events under treatment were non-serious, mild to moderate, and reversible.
- The risks identified during the development program were hemoptysis and bronchospasm, which are considered factors also associated with the inhalation of the vehicle powder, and also occurred in similar frequencies in patients treated with placebo. No increased risk of the class effects of systemic fluoroquinolones were observed with ciprofloxacin DPI.
- Resistance development was numerically higher with ciprofloxacin DPI than with placebo, but the resistance rates at the end of the trial were similar to those at the beginning. The ciprofloxacin DPI treatment effect for exacerbation-related endpoints

was reduced in patients with ciprofloxacin-resistant pathogens identified at baseline and at post-baseline, compared to patients without resistance.

- Risks are considered to be manageable via appropriate labeling and established pharmacovigilance processes.

Favorable benefit/risk

- The positive treatment effects of ciprofloxacin DPI were variable across the Phase III studies, but there was a consistent positive treatment benefit of ciprofloxacin DPI across the exacerbation-related, patient-reported, and microbiological efficacy variables. There is heterogeneity of the NCFB study population, which contributed to the variability in positive treatment effects. The safety profile of ciprofloxacin DPI was favorable.
- The RESPIRE program generated variable, but multiple lines of evidence that ciprofloxacin DPI produces a positive treatment effect. Ciprofloxacin DPI can be an important treatment option for reducing the occurrence of exacerbations in NCFB patients. The risk profile is overall favorable and acceptable against the background of a severe medical illness. The overall benefit-risk balance of ciprofloxacin DPI for treatment of NCFB is favorable.

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# 9. Appendices

## 9.1 Additional information about biopharmaceutics and clinical pharmacology of ciprofloxacin DPI

### 9.1.1 Overview of the Phase I program for ciprofloxacin DPI

**Table 9-1: Overview of the Phase I program for ciprofloxacin DPI (multipage table)**

| Study | Dose* | Objective | Design | Report / CTD |
|---|---|---|---|---|
| **Studies to assess biopharmaceutical aspects** | | | | |
| 11523 | 32.5 mg | Single dose, lung deposition, pharmaco-kinetics in healthy subjects, COPD-, and bronchiectasis patients | Randomized, crossover for healthy subject group, Group comparison for patient groups | PH-37340 / 5.3.1.1.2 |
| 17607 | Not applicable | Peak inspiratory flow measurement in NCFB patients | Open label, multi center, group comparison according to FEV1 categories | PH-39146 / 5.3.1.1.1 |
| **Studies using human biomaterials** | | | | |
| 11841 | Not applicable | Penetration of ciprofloxacin through CF mucus | *In vitro* trial | R-9290 / 5.3.2.3.1 |
| 19052 | Not applicable | Binding and Solubility of ciprofloxacin in sputum of CF patients | *In vitro* trial | PH-39230 / 5.3.2.3.2 |
| **Studies in healthy subjects** | | | | |
| 12132 | 32.5 mg | Single-dose pharmacokinetics in healthy volunteers | Randomized, single-blind, placebo-controlled, cross-over | PH-35078 / 5.3.3.1.1 |
| **Studies in patients with CF** | | | | |
| 12167 | 32.5, 65 mg | Single-dose pharmacokinetics in CF patients | Partially randomized, partially single-blinded, placebo-controlled | PH-35853 / 5.3.3.2.1 |
| 12168 | 32.5 mg once daily and bid, 65 mg once daily for 7 days | Multiple-dose pharmacokinetics in CF patients | Randomized, single-blinded, placebo-controlled | PH-36004/ 5.3.3.2.2 |
| 12170 | 32.5 mg | Single-dose pharmacokinetics in CF patients age 12 to 17 y | Non-randomized, non-blinded, non-controlled | PH-35669 / 5.3.3.2.3 |
| 12759 | 16.25 mg | Single-dose pharmacokinetics in CF patients age 6 to 12 y | Non-randomized, non-blinded, non-controlled | PH-36996 / 5.3.3.2.4 |
| 13072 | 18.2 mg | Single-dose pharmacokinetics in CF patients | Randomized, single-blinded, placebo-controlled | PH-36102 / 5.3.3.2.7 |

[a] refers to the amount of ciprofloxacin

**Table 9-1: Overview of the Phase I program for ciprofloxacin DPI (multipage table)**

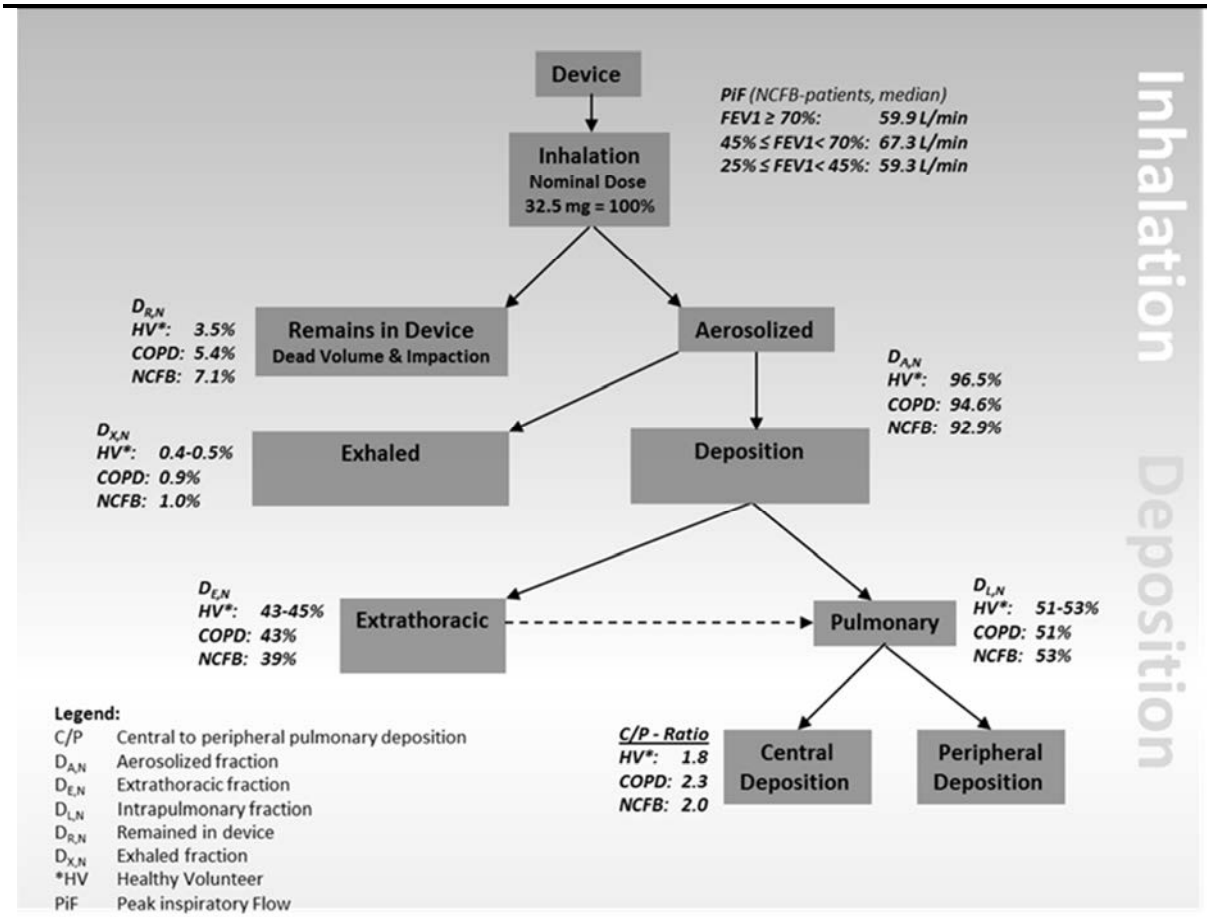
| Study | Dose* | Objective | Design | Report / CTD |
|---|---|---|---|---|
| **Studies in patients with COPD and bronchiectasis** | | | | |
| **Caucasian** | | | | |
| 11523 | 32.5 mg | Single dose, lung deposition, pharmaco-kinetics in healthy subjects, COPD-, and bronchiectasis patients | Randomized, crossover for healthy subject group, Group comparison for patient groups | PH-37340 / 5.3.1.1.2 |
| 14972 | 32.5 mg / 48.75 mg | Single-dose pharmacokinetics in COPD patients for new 48.75 mg dose strength | Randomized, double-blind, crossover | PH-36599 / 5.3.3.2.10 |
| 13013 | 32.5 mg / 48.75 mg | Single-dose/multiple-dose pharmacokinetics in COPD (GOLD I to II) patients | Randomized, single-blinded, placebo-controlled | PH-36381 / 5.3.3.2.6 |
| 13014 | 32.5 mg / 48.75 mg | Single-dose/multiple-dose pharmacokinetics in COPD (GOLD II to III) patients | Randomized, single-blinded, placebo-controlled | PH-36495 / 5.3.3.2.5 |
| **Asian** | | | | |
| 14018 | 32.5 mg | Single-dose pharmacokinetics in **Japanese** COPD (GOLD I to II) patients | Randomized, single-blinded, placebo-controlled | A47728 / 5.3.3.2.8 |
| 14019 | 32.5 mg / 48.75 mg | Multiple-dose pharmacokinetics in **Japanese** COPD (GOLD II to III) patients | Randomized, single-blinded, placebo-controlled | A49613 / 5.3.3.2.9 |
| **Population pharmacokinetic investigations including pooled analyses** | | | | |
| **CF patients** | | | | |
| 13016 | Various doses | Exploratory population pharmacokinetics for data from studies 12132, 12167, 12168 and 12170 (healthy volunteers and CF patients) | Not applicable | PH-36434 / 5.3.3.5.2 |
| **COPD patients** | | | | |
| 13822 | Various doses | Exploratory population pharmacokinetics for data from studies 13013 and 13014 (healthy volunteers and COPD patients) | Not applicable | PH-36653 / 5.3.3.5.1 |
| **NCFB patients** | | | | |
| 13823 | 32.5 mg | Exploratory population pharmacokinetics for data from clinical efficacy trials in NCFB | Not applicable | R-11182 / 5.3.3.5.3 |
| **Pooled statistical analyses** | | | | |
| 19051 | 32.5 mg | Impact of smoking on Ciprofloxacin PK in plasma | Not applicable | PH-39351 / 5.3.3.4.1 |

**Table 9-1: Overview of the Phase I program for ciprofloxacin DPI (multipage table)**

| Study | Dose* | Objective | Design | Report / CTD |
|---|---|---|---|---|
| **Physiology-based pharmacokinetic studies** | | | | |
| 18914 | Various doses | Exploratory PBPK modeling | Not applicable | PH-39140<br>PH-39143<br>PH-39141<br>PH-39142<br>5.3.3.5.5 |
| 13793 | Various doses | Building physiological-based model for adult healthy volunteers and CF patients, extrapolation to pediatric population | Not applicable | PH-37473 / 5.3.3.5.4 |
| 18915 | Various doses | Exploratory PBPK study to assess secretion into the GI tract | Not applicable | PH-39112 / 5.3.3.5.6. |
| 18916 | Various doses | Exploratory PBPK study to compare inhalative with oral/i.v. PK /renal impairment | Not applicable | PH-39111/ 5.3.3.5.7 |

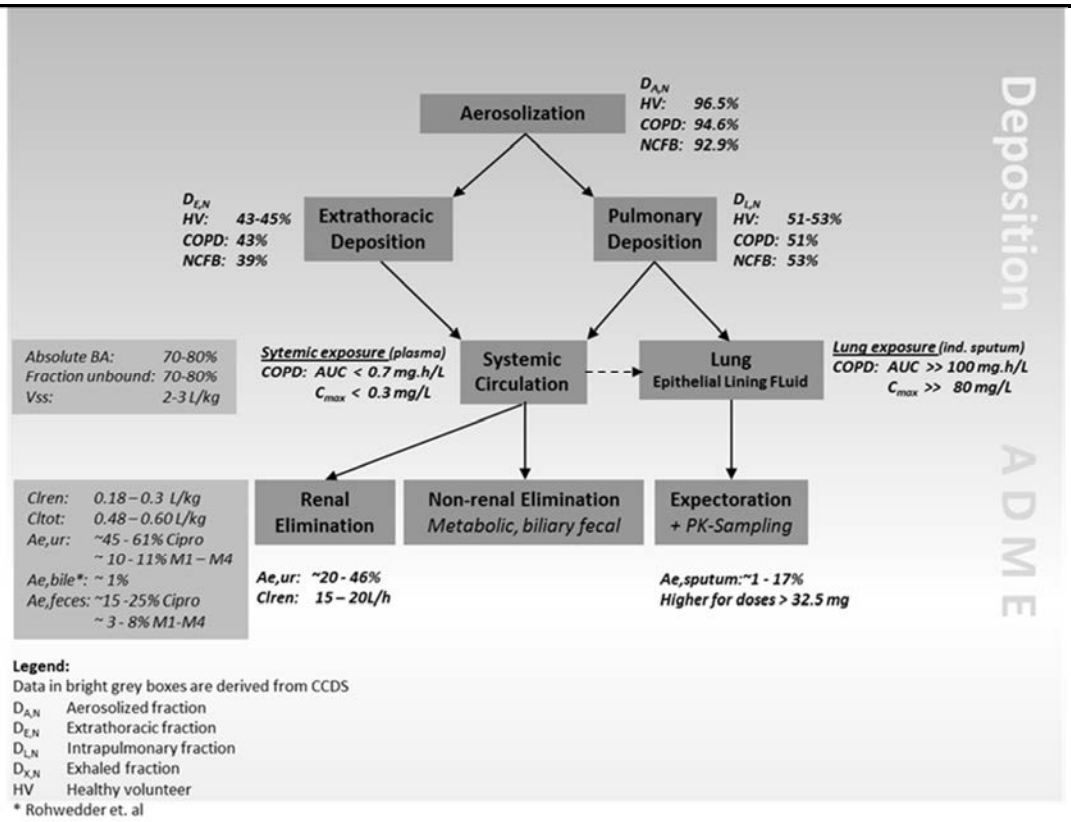
## 9.1.2 Overview of the device characteristics, deposition pattern, and clinical pharmacology profile of ciprofloxacin DPI

**Figure 9–1: Summary of device characteristics and ciprofloxacin inhalation pattern including mass balance in man, based on study Nos. 11523 and 17607**




Source: Studies 11523 (CSR PH-37340) and 17607 (CSR PH-39146)

**Figure 9–2: Summary of the clinical pharmacology profile of ciprofloxacin after drug inhalation including mass balance in man, based on deposition studies**




Source: Data on file

## 9.1.3 Bioanalytical methodology

Different high performance liquid chromatography (HPLC)-fluorescence and HPLC-tandem mass spectrometry (MS/MS) assays with different working ranges were developed and validated, depending on the requirements of the specific studies for the determination of ciprofloxacin in oral rinsing fluid, sputum, induced sputum, bronchoalveolar lavage cells, bronchoalveolar lavage fluid, and urine. The assays were fully validated according to pertinent guidelines, and were found to be appropriate with respect to limit of quantification, specificity, accuracy and precision to deliver valid analytical data of ciprofloxacin for subsequent pharmacokinetic investigations. [1,2]

Pharmacokinetic evaluations were performed using non-compartmental methods population PK approaches (via NON-linear mixed-effect modeling [NONMEM]) and physiology-based PK studies and were adequate to describe the clinical pharmacokinetic profile of ciprofloxacin.

1. Forrest A, Nix DE, Ballow CH, et al. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother. 1993; 37(5):1073-81.

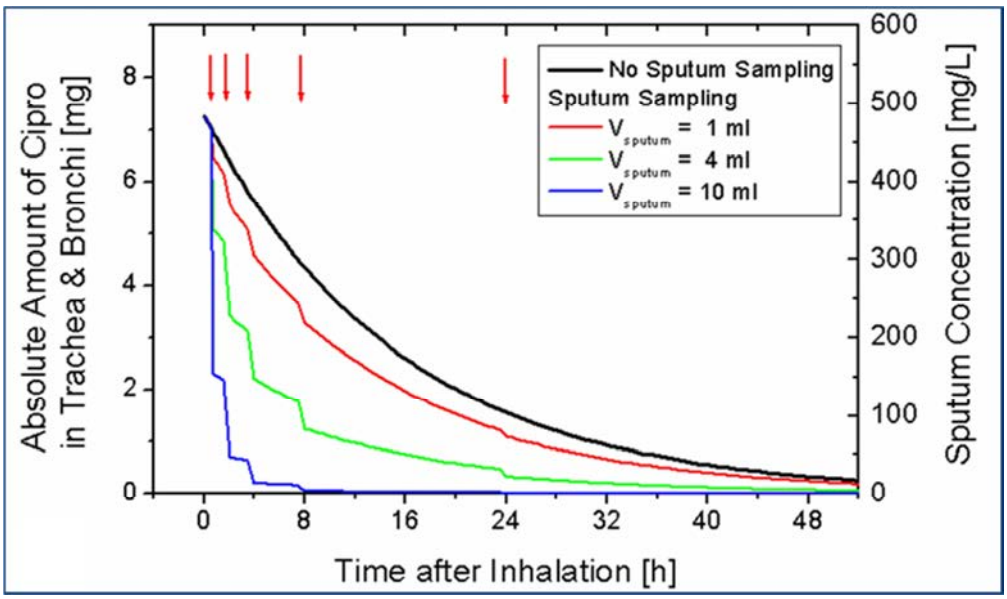
2. EMA guideline on bioanalytical method validation, 2011. (EMEA/CHMP/EWP/192217/2009, Rev. 1, Corr. 2).

### 9.1.4 PK sampling to assess pharmacokinetics in the lung

In the clinical program, predominantly collection of induced sputum and sputum were the preferred procedures to obtain samples representing the mucosa of the lung. They were the basis to assess pharmacokinetics of ciprofloxacin in the respiratory tract and to derive PK and PK/PD estimates. Special aspects of these methods, which were investigated in mechanistic PBPK studies are:

- PK sample collection of specimen from the respiratory tract is associated with inherent methodological shortcomings which need to be taken into consideration when interpreting lung kinetics, especially the associated high variability in the results describing lung exposure.
- In view of the low dose of ciprofloxacin directly targeted to the respiratory tract sample collection as well as sputum recovered from expectoration both represent an additional clearance process removing significant amounts of drug from the lung; mean amounts of 5 to 30% of the total dose can be expectorated, see Appendix Figure 9–3). This will lead inevitably to systematically underestimated lung concentrations and hence get pharmacokinetic estimates, which are lower than the unbiased "true" data.

**Figure 9–3: Simulated amounts of ciprofloxacin present in the trachea/bronchi**




Note: Simulated amounts of ciprofloxacin present in the trachea/bronchi of healthy volunteers and plasma concentration as a function of time under the assumption of drug loss due to expectorations (time points indicated by the red arrows). The right y-axis displays the resulting sputum concentration assuming a sputum volume of 15 mL.
Source: Study 18914 ([PH-39142)

Therefore, in contrast to PK and PK/PD parameters (*i.e.*, AUC/MIC ratios) derived from urine and plasma, evaluation of PK and PK/PD parameters calculated from epithelial lining fluid,

induced sputum or sputum which is spontaneously brought up by patients have to be considered as too low and associated with high variability (due to the different sampling schedules in the various studies and the impact of spontaneous expectoration, which depends on a plethora of different factors (*e.g.*, severity of impaired lung function, stimulation by external factors) with corresponding consequences for PK and PK/PD evaluations in Phase I:

- PK/PD surrogate parameters (*e.g.*, AUC/MIC values) to determine microbiological breakpoints indicative of antimicrobial efficacy were not calculated from the PK parameter estimates reported in the individual studies.
- No pooling of PK parameters (*e.g.*, $C_{max}$) was performed for additional statistical analyses of PK parameters derived from samples collected from the respiratory tract.
- For *in vitro* PK/PD experiments unbound concentrations were derived from measured total lung concentration time profiles using information on linearity of binding to and solubility in lung mucus based on ex-vivo investigations. Concentrations above the solubility limit were capped to the highest measured unbound concentrations (120 mg/L).

No correction of lung concentration *vs.* time profiles or PK parameter estimates accounting for the factors described above were performed assuming that the sampling schedules used to obtain the concentration time profiles would “mimic” expectoration happening in clinical practice.

## 9.2 Additional Information on design of Phase III studies RESPIRE 1 and RESPIRE 2

### 9.2.1 Inclusion and exclusion criteria in RESPIRE 1 and RESPIRE 2

The following inclusion and exclusion criteria were stipulated in both RESPIRE 1 and RESPIRE 2:

**Inclusion criteria**

- 1) Age ≥18 years;
- 2) Proven and documented diagnosis of non-CF idiopathic or post-infectious BE by CT scan (conventional high resolution CT is considered the standard) including 2 or more lobes and dilated airways compatible with BE at initial diagnosis;
- 3) Positive culture from an adequate sputum sample for *Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Streptococcus pneumoniae, Stenotrophomonas maltophilia* or *Burkholderia cepacia* obtained at screening and with history ≥2 documented exacerbations in the past 12 months;
- 4) Stable pulmonary status as indicated by $FEV_1$ (percent of predicted) ≥30% and <90% (post-bronchodilator, if used as standard of treatment);
- 5) Stable regimen of standard treatment with:
  - Bronchodilators, anticholinergics, inhaled corticosteroids, or mucolytics, if used as chronic treatment for BE, at least for the past 4 weeks prior to screening. Subjects on maintenance therapy with low-dose systemic corticosteroids should be receiving ≤10 mg/day prednisolone equivalent at least for the past 4 weeks before the screening visit;

  and/or

  - Macrolides if used as chronic treatment for BE for at least 6 months prior to screening;
- 6) Sputum production on the majority of days;
- 7) Ability to follow the inhaler device instructions;
- 8) Ability to complete questionnaires;
- 9) Written informed consent;
- 10) Negative urine pregnancy test result for women of childbearing potential before first dose of study drug;
- 11) Women of childbearing potential and men must agree to use adequate contraception when sexually active. This applies from the time of signing of the informed consent form (ICF) until 3 months after the last study drug administration. Adequate methods of contraception include vasectomy, or condom use, diaphragm

with spermicidal gel, coil (intrauterine device), surgical sterilization, or oral contraceptives.

**Exclusion criteria**

- 1) $FEV_1$ <30% or ≥90% predicted (post-bronchodilator);
- 2) Active allergic bronchopulmonary aspergillosis (ABPA);
- 3) Active and actively-treated non-tuberculosis mycobacterial (NTM) infection or tuberculosis;
- 4) Diagnosis of common variable immunodeficiency (CVID);
- 5) Recent significant hemoptysis (≥300 mL or requiring blood transfusion) in the preceding 4 weeks before screening (and during the screening period);
- 6) Primary diagnosis of COPD;
- 7) Known CF and / or documented chronic bronchial asthma;
- 8) Administration of any investigational drug within 4 weeks before screening;
- 9) Medical history of allergies to quinolones or fluoroquinolones;
- 10) Women who are pregnant, lactating, or in whom pregnancy cannot be excluded;
- 11) History of tendon disorders related to quinolone treatment;
- 12) History of myasthenia gravis;
- 13) Concomitant administration of tizanidine while on study drug;
- 14) Systemic or inhaled antibiotic treatment for any indication within 4 weeks prior to the administration of study drug; except for chronic macrolide use;
- 15) Systemic corticosteroids at >10 mg/day prednisolone equivalent for >14 days within 4 weeks prior to the administration of study drug;
- 16) If participating in or has participated in other investigational interventional studies within the previous 4weeks before screening;
- 17) Subjects with any other conditions (specifically those which are addressed in the warnings and precautions section of the IB) or clinically relevant laboratory findings that the investigator defines as not appropriate for enrollment of a subject into the study;
- 18) Previous assignment to treatment in the current study (randomized in RESPIRE 1 and RESPIRE 2, respectively); previous participation in RESPIRE 1 (applicable only for patients planned to be enrolled in RESPIRE 2).

### 9.2.2 Criteria for exacerbation in RESPIRE 1 and RESPIRE 2

Table 9–2 shows the respiratory signs and symptoms as well as sputum characteristics that were assessed at the baseline visit (Visit 2) and all scheduled visits (exacerbation criteria at unscheduled visits). The definition of a "qualifying" exacerbation as per protocol in RESPIRE 1 and RESPIRE 2 is subsequently provided.

**Table 9–2: Respiratory signs and symptoms as well as sputum characteristics to be assessed and graded at the baseline visit (Visit 2) and all scheduled visits (exacerbation criteria at unscheduled visits)**

| Signs and symptoms | Grading |
|---|---|
| Cough | None<br>Mild<br>Moderate<br>Severe |
| Dyspnea | None<br>Mild<br>Moderate<br>Severe |
| Wheezing | no<br>yes |
| Fever >38°C | no<br>yes |
| Malaise / Fatigue | no<br>yes |
| Sputum volume# | ___mL |
| Sputum purulence (color)* | Mucoid (clear)<br>Mucopurulent (pale yellow / pale green)<br>Purulent (dark yellow / dark green)<br>Purulent (dark yellow / dark green with rusty spots/colors) |

* Color chart will be available
# Sputum volume from 24 hour sputum collection, if available

At unscheduled visits due to suspected exacerbations, the signs and symptoms of non-CF bronchiectasis were assessed as displayed in Table 9–2.

In the RESPIRE studies, a "qualifying" exacerbation requires that:

- **≥3** of the following signs or symptoms have worsened (beyond normal day-to-day variations) for at least 2 consecutive days after the start of worsening, irrespective of whether any intervention was necessary:
    - Dyspnea
    - Wheezing
    - Cough
    - Sputum volume (24 hour)
    - Sputum purulence (color)

and

- the presence of
    - Fever (body temperature >38.0°C)

  or
    - Malaise / fatigue

and

- Systemic antibiotic treatment.

If a minimum of 4 weeks occurs between one exacerbation onset and the next, these will be considered separate exacerbations. Only exacerbations requiring systemic antibiotic treatment will qualify for the primary endpoint definition of exacerbation.

**Definitions of severity of symptoms:**

**Dyspnea:**

It is recommended to follow the definitions for dyspnea grades below:

**None**: Not significantly troubled by breathlessness;

**Mild:** Breathlessness with no disruption of normal activities;

**Moderate:** Breathlessness with some disruption of normal activities;

**Severe:** Breathlessness with marked disruption of normal activities.

**Cough:**

It is recommended to follow the definitions for cough grades as below:

**None**: Not significantly troubled by cough;

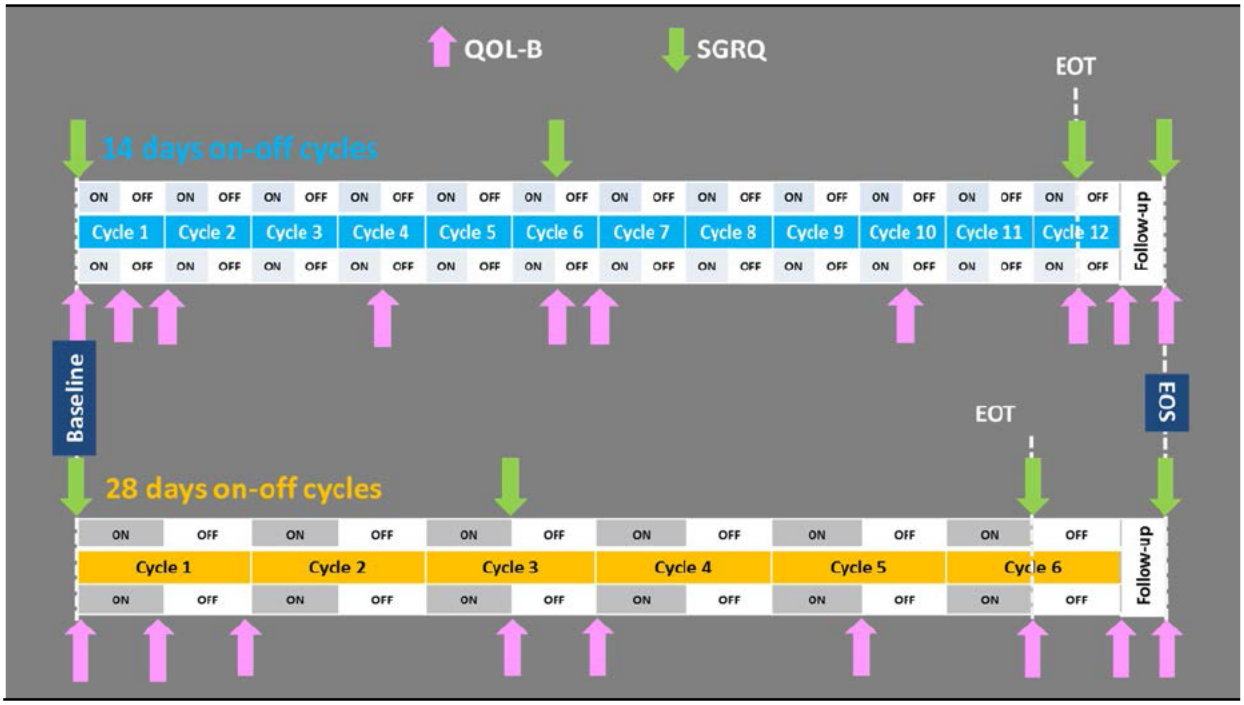
**Mild:** Frequent coughing, not interfering with usual daily activities;

**Moderate**: Frequent coughing, interfering with usual daily activities;

**Severe:** Distressing coughs for most of the day.

### 9.2.3 Assessment time points for patient-reported outcomes (SGRQ; QOL-B)

**Figure 9–4: Patient-reported outcome assessments points for SGRQ and QOL-B**



## 9.3 Statistical methodology for Phase III study analyses

### 9.3.1 Overview of hierarchical test procedure in the RESPIRE studies for FDA submission

**Table 9-3: Planned hierarchical test procedure in RESPIRE studies**

| **Ciprofloxacin DPI *vs.* pooled placebo** | |
|---|---|
| **14 days on/off**<br>**α-level=0.025 (2-sided) for RESPIRE 1;**<br>**α-level=0.049 (2-sided) for RESPIRE 2** | **28 days on/off**<br>**α-level=0.025 (2-sided) for RESPIRE 1;**<br>**α-level=0.001 (2-sided) for RESPIRE 2** |
| **Primary endpoint**<br>**Time to first exacerbation event (up to Week 48)**<br>defined as exacerbation with systemic antibiotic use and presence of fever or malaise / fatigue and worsening of at least three signs/symptoms up to Week 48 | |
| **Secondary efficacy endpoint**<br>**Frequency of exacerbation events (during 48 weeks)**<br>defined as exacerbations with systemic antibiotic use and presence of fever or malaise / fatigue and worsening of at least three signs/symptoms<br>*(for RESPIRE 1 with extrapolation of the number of exacerbation events for patients who did not complete Week 48, for RESPIRE 2: time in study as offset in Poisson regression model)* | |
| **Frequency of exacerbation events (during 48 weeks)**<br>defined as exacerbations with systemic antibiotic use and worsening of at least one/ sign symptom<br>*(for RESPIRE 1 with extrapolation of the number of exacerbation events for patients who did not complete Week 48, for RESPIRE 2: time in study as offset in Poisson regression model)* | |
| **Baseline pathogen eradication**<br>at EOT of last cycle | |
| **Quality of Life measured by SGRQ symptoms component score**<br>changes from baseline at EOT of last cycle | |
| **Occurrence of new pathogens not present at baseline**<br>at EOT of last cycle | |
| **Quality of Life measured by QOL-B respiratory symptoms domain score**<br>changes from baseline at EOT of last cycle | |
| **Change in lung function measured by $FEV_1$**<br>changes from baseline at EOT of last cycle | |

EOT: end of treatment

Note: Based on the outcomes observed in RESPIRE 1, where a stronger positive effect of the 14-day regimen was observed, particular emphasis was put in RESPIRE 2 on the test of the 14-day regimen by implementing weighted Bonferroni adjustment of α=0.049 for the 14-day

regimen (95.1%-CIs) and α=0.001 for the 28-day regimen (99.9%-CIs; see Appendix 9.3.3). This change was introduced prior to data base lock with a formal amendment to the study protocol.

### 9.3.2 Study planning and sample size estimation

Sample size planning for the RESPIRE studies was based on the primary endpoint "time to first exacerbation", assuming a hazard ratio of 0.6 for each of the ciprofloxacin DPI regimens compared to pooled placebo. The study was to be considered successful, if at least one of the two comparisons gave a significant result in favor of ciprofloxacin DPI. With a two-sided α -level of 0.025 for each of the two comparisons and 200 events in total (*i.e.*, 200 events in any of the 4 treatment groups), the power for each comparison was 75% (nQuery Advisor version 6.01).

To account for dependencies between the test statistics, a Monte-Carlo simulation was conducted. The choice of a sample size that resulted on an average in 200 events with 10,000 repetitions confirmed this power of about 75% for each of the individual tests, and gave a disjunctive power of approximately 90%, *i.e.*, a chance of approximately 90% that any of the two tests was significant.

Planning assumptions were:

- Exponentially distributed event times,
- Patients in the placebo groups would on average experience 2 exacerbations per year (corresponding to a median time to first exacerbation of 126 days),
- HR of 0.6. The resulting expected mean number of exacerbations per year in the ciprofloxacin DPI treatment groups was therefore 1.2 (corresponding median time to first exacerbation of 211 days).

Based on these assumptions, and accounting for a drop-out rate of approximately 20%, approximately 300 patients would have been to be included in the study to achieve 200 events, 100 patients in each of the ciprofloxacin DPI arms and 50 patients in each of the two placebo arms.

To ensure that the required number of 200 qualifying first exacerbations was reached in this study, the blinded drop-out rate and blinded event rate were monitored. Recruitment was terminated, when it was expected that the required number of qualifying exacerbation would be reached with the enrolled patients within the planned treatment period of the enrolled patients.

### 9.3.3 Methodological differences in the analysis of RESPIRE 1 and RESPIRE 2

**Correction for multiple testing**

In RESPIRE 1, an unweighted Bonferroni adjustment using a two-sided α of 0.025 for each test was applied, as no prior knowledge regarding the superiority of any treatment regimen over the other was available. In RESPIRE 2, the procedure was adapted to a weighted Bonferroni adjustment after the results of RESPIRE 1 were available. To increase the power for the 14-day regimen, and thus increasing the probability to show superiority over pooled

placebo for the same regimen in both studies, α=0.049 was used for the tests regarding the 14-day regimen, and the remaining α=0.001 was spent on tests regarding the 28-day regimen. Under the original assumption of a HR of 0.6, the power for the primary test of ciprofloxacin DPI 14 *vs.* pooled placebo was thereby increased from about 75% to approximately 82%, while the power for the test of ciprofloxacin DPI 28 *vs.* pooled placebo was reduced to approximately 32%. The power for any significant result in RESPIRE 2 was thereby reduced from nearly 90% to about 84%.

**Poisson regression**

The secondary efficacy endpoint ”frequency of exacerbations” was analyzed using a Poisson regression in both RESPIRE 1 and RESPIRE 2. However, different approaches to account for drop-outs were used for the primary analysis in the two studies. Based on a request from the FDA, the time under risk (t) was not included in the statistical model in RESPIRE 1. Nonetheless, to account for drop-outs, the number of exacerbations of subjects who prematurely discontinued the study was extrapolated on an individual level based on a pre-specified algorithm (see Appendix 9.3.5). In RESPIRE 2, the primary analysis was changed to a Poisson regression, adjusting for different times under risk by including log(t) as offset in the model. This change in the primary analysis was agreed with the FDA prior to unblinding RESPIRE 2 study data.

### 9.3.4 Confirmatory analysis of the primary efficacy endpoint

A Cox Proportional Hazards model was used as confirmatory analysis to test for differences in the primary efficacy variable “time to first exacerbation event up to week 48” between the ciprofloxacin DPI groups and pooled placebo.

In the Cox model, the independent variables were treatment group, geographic region, pre-therapy positive culture for *P. aeruginosa*, and chronic macrolide use, *i.e.*, the following model for the hazard function λ(t) was used:

$\lambda_{jkln}(t) = \lambda_0(t) \exp(\tau_j + f_{1k} + f_{2l} + region_n)$

where $\lambda_{jkln}(t)$: Hazard at time t for subjects in treatment group j and stratum kln
$\lambda_0(t)$: Common hazard function
$\tau_j$: Treatment effect
1: Ciprofloxacin DPI 28 on/off
2: Matching placebo 28 on/off
3: Ciprofloxacin DPI 14 on/off
4: Matching placebo 14 on/off
$f_{1k}$: Effect of positive culture for *P. aeruginosa* at baseline (negative/positive)
$f_{2l}$: Effect of chronic macrolide use (no/yes)
$region_n$: Effect of the geographic region

The following null hypotheses ($H_0$) were tested by a Wald-type test:

$$\mathbf{H_{01}: \tau_1 = 0.5*(\tau_2 + \tau_4)} \quad \mathbf{vs.} \quad \mathbf{H_{A1}: \tau_1 < 0.5*(\tau_2 + \tau_4)}$$

$$\mathbf{H_{02}: \tau_3 = 0.5*(\tau_2 + \tau_4)} \quad \mathbf{vs.} \quad \mathbf{H_{A2}: \tau_3 < 0.5*(\tau_2 + \tau_4).}$$

The following sensitivity analyses were performed to assess the robustness of the results and the impact of missing data:

- Cox model without adjustment for covariates,
- Unstratified log-rank test,
- Patients censored prior to Day 336 were considered as having an event at time of censoring,
- Tipping point analysis.

### 9.3.5 Confirmatory analysis of the secondary efficacy endpoints

**Frequency of exacerbation events**

The same analysis was performed for the two different definitions of exacerbation events used to calculate the frequency of exacerbations (*i.e.*, qualifying exacerbation event and exacerbation event with systemic antibiotic use and worsening of at least one sign/symptom).

A Poisson regression with adjustment for over-/underdispersion was used to analyze the number of exacerbation events over 48 weeks. The model included the variables treatment group, pre-therapy positive culture for *P. aeruginosa*, chronic macrolide use, and geographic region.

The following model was applied in RESPIRE 1:

$Y_{ijkln}$ has a Poisson distribution with parameter $\lambda_{jkln}$,

where $\log(\lambda_{jkln}) = \mu + \tau_j + f_{1k} + f_{2l} + \text{region}_n$

with $Y_{ijkln}$ : Number of acute exacerbation events up to end of week 48 in subject i in treatment group j, and stratum kln

$\lambda_{jkln}$: Expected number of exacerbation events for subjects in treatment group j and stratum kln

$\mu$: Intercept

$\tau_j$: Treatment effect

1: Ciprofloxacin DPI 28 on/off
2: Matching placebo 28 on/off
3: Ciprofloxacin DPI 14 on/off
4: Matching placebo 14 on/off

$f_{1k}$: Effect of positive culture for *P. aeruginosa* at baseline (negative/positive)

$f_{2l}$: Effect of chronic macrolide use (no/yes)

$\text{region}_n$: Effect of the geographic region

The following null hypotheses ($H_0$) were tested by a Wald-type test:

$$\mathbf{H_{01}: \tau_1 = 0.5*(\tau_2 + \tau_4)} \quad \textbf{vs.} \quad \mathbf{H_{A1}: \tau_1 < 0.5*(\tau_2 + \tau_4)}$$

$$\mathbf{H_{02}: \tau_3 = 0.5*(\tau_2 + \tau_4)} \quad \textbf{vs.} \quad \mathbf{H_{A2}: \tau_3 < 0.5*(\tau_2 + \tau_4).}$$

In RESPIRE 1, the number of exacerbations for subjects who did not complete 48 weeks was extrapolated linearly for subjects who experienced at least one exacerbation. In subjects who discontinued without an exacerbation, the average rate of exacerbations across all treatment groups of subjects who completed 48 weeks was used as basis to impute the rate of exacerbations for the unobserved time period.

In RESPIRE 2, the model was changed to $\log(\lambda_{jkln}) = \log(t) + \mu + \tau_j + f_{1k} + f_{2l} + \text{region}_n$ with t = min(time until discontinuation from study, 336 days).

The following sensitivity analyses were performed to assess the robustness of the results and the impact of missing data:

- The primary analysis of RESPIRE 1 was used as sensitivity analysis in RESPIRE 2, and vice versa,
- Poisson regression without adjustment for covariates,
- Unstratified Cochran-Mantel-Haenszel test for ordinal data.

**Pathogen eradication and occurrence of new pathogens**

These endpoints were analyzed using Cochran-Mantel-Haenszel tests stratified by regions, pre-therapy positive culture for *P. aeruginosa*, and chronic macrolide use. The primary analysis was based on complete cases only. A "last observation carried forward" (LOCF) analysis and a tipping point analysis were performed as sensitivity analyses.

**Changes from baseline in PROs (SGRQ symptoms component score, QoL-B respiratory symptoms domain score) and $FEV_1$**

The PRO endpoints were analyzed using an ANCOVA with treatment, baseline value, geographic regions, pre-therapy positive culture for *P. aeruginosa* (negative/positive), and chronic macrolide use (no/yes) as covariates. The primary analysis was based on complete cases only. An LOCF analysis and a mixed model for repeated measurements (MMRM) were used as sensitivity analyses.

### 9.3.6 Methodology of the Phase III integrated efficacy analysis

Meta-analysis methods for individual patient data including forest plots as well as descriptive methods were used in the integrated efficacy analysis. One of the main differences between the RESPIRE 1 and RESPIRE 2 studies were the geographical regions in which they were conducted (see Appendix 9.4.2). For the integrated analysis it was therefore necessary to harmonize the definitions used in the two single studies by merging selected geographical regions. This is of importance because "geographical region" was a stratification variable in the randomization to be taken into account in the model based analyses.

The same or similar statistical models as used for the RESPIRE 1 and RESPIRE 2 studies were implemented and extended for the integrated analysis, which included the following 3 model steps:

1) The same model as applied in the single studies was repeated for both studies separately, however, using the harmonized definition of geographical regions, so that there might be slight numerical differences compared to the single study results.
2) The model above was extended to an integrated analysis by running it on the pooled studies and adding the factor "study" as an independent variable or as a stratification variable, as appropriate.
3) Heterogeneity tests were performed by including a "study-by-treatment" interaction term, to investigate whether the treatment effects are homogeneous between RESPIRE 1 and RESPIRE 2. An α-level of 10% was used to give a first orientation when assessing statistical heterogeneity.

Different α-levels were used in RESPIRE 1 and RESPIRE 2 (see Appendix 9.3.3). For the integrated analysis it was decided to show the conventional two-sided 95%-CI for single and pooled studies in light of the exploratory character. These CIs were displayed in forest plots for HRs and IRRs.

In contrast to the single study analyses, no confirmatory statistical significance testing was performed, *i.e.*, all integrated efficacy analyses are purely exploratory in nature. They do not compensate any non-significant confirmatory results, and should be used only as supportive information. The statistical models used for the integrated efficacy analysis assume that the treatment effect for the respective treatment comparison is the same in both studies. In case of statistical heterogeneity, especially if also clinically relevant, the results should be interpreted with caution, because the underlying model assumptions are not fulfilled, potentially leading to too small confidence intervals and p-values.

### 9.3.7 Estimation of time to first exacerbation event

To estimate the median time to first exacerbation in all treatment groups, a parametric survival regression was fitted using a Weibull distribution. The Weibull survival model (intercept only, no covariates) was fitted for each combination of treatment group and study. Estimates for the parameter of the fitted Weibull distribution and according 95%-CIs were obtained. The median and corresponding 95%-CIs were derived as quantiles from the estimated Weibull distribution and its confidence interval. It has to be noted that the estimated medians from the parametric survival regression are often outside the time frame where actually observed survival times are available, and the estimated results from that model should therefore be interpreted with caution.

## 9.4 Additional tabulated summaries, listings and descriptions of Phase II and Phase III studies

### 9.4.1 Sample sizes, demographic and other baseline characteristics of patients enrolled in the Phase II / III studies

**Table 9-4: Sample sizes and demographic characteristics in the Phase II NCFB study 12965 (FAS)**

| | Ciprofloxacin 32.5 mg BID | Placebo 32.5 mg BID | Total |
|---|---|---|---|
| **Sample size, n** | | | |
| Randomized | 60 | 64 | 124 |
| SAF | 60 | 64 | 124 |
| FAS | 60 | 64 | 124 |
| PPS | 37 | 45 | 82 |
| **Sex; n (%)** | | | |
| Male | 21 (35.0) | 21 (32.8) | 42 (33.9) |
| Female | 39 (65.0) | 43 (67.2) | 82 (66.1) |
| **Age (years)** | | | |
| Mean ± SD | 64.7 ± 11.8 | 61.4 ± 11.9 | 63.0 ± 11.9 |
| Range | 26 to 84 | 26 to 86 | 26 to 86 |
| **Age groups** | | | |
| <65 years; n (%) | 25 (41.7) | 37 (57.8) | 62 (50.0) |
| ≥65 years; n (%) | 35 (58.3) | 27 (42.2) | 62 (50.0) |
| **BMI ($kg/m^2$)** | | | |
| Mean ± SD | 25.64 ± 5.46 | 25.07 ± 5.59 | 25.35 ± 5.51 |
| Range | 15.3 to 39.2 | 15.3 to 47.3 | 15.3 to 47.3 |
| **Race; n (%)** | | | |
| White | 60 (100.0) | 63 (98.4) | 123 (99.2) |
| Black/African American | 0 | 0 | 0 |
| Asian | 0 | 1 ( 1.6) | 1 ( 0.8) |
| American Indian/Alaska Native | 0 | 0 | 0 |

BMI=Body mass index; FAS=Full analysis set; PPS=Per protocol set; SAF=Safety analysis set; SD=Standard deviation
Source: CSR of Study 12965

**Table 9-5: Sample sizes and demographic characteristics (FAS) in the Phase III studies RESPIRE 1 and RESPIRE 2**

| | RESPIRE 1 (15625) | | | | | RESPIRE 2 (15626) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cipro 14 | Cipro 28 | Placebo 14 | Placebo 28 | Total | Cipro 14 | Cipro 28 | Placebo 14 | Placebo 28 | Total |
| **Sample size, n** | | | | | | | | | | |
| Screened | | | | | 902 | | | | | 1123 |
| Randomized | 137 | 141 | 68 | 70 | 416 | 176 | 171 | 88 | 86 | 521 |
| SAF | 136 | 141 | 68 | 69 | 414 | 174 | 171 | 88 | 86 | 519 |
| FAS | 137 | 141 | 68 | 70 | 416 | 176 | 171 | 88 | 86 | 521 |
| PPS | 117 | 124 | 58 | 58 | 357 | 162 | 146 | 81 | 75 | 464 |
| **Sex; n (%)** | | | | | | | | | | |
| Male | 49 (35.8) | 40 (28.4) | 24 (35.3) | 18 (25.7) | 131 (31.5) | 80 (45.5) | 79 (46.2) | 26 (29.5) | 34 (39.5) | 219 (42.0) |
| Female | 88 (64.2) | 101 (71.6) | 44 (64.7) | 52 (74.3) | 285 (68.5) | 96 (54.5) | 92 (53.8) | 62 (70.5) | 52 (60.5) | 302 (58.0) |
| **Age (years)** | | | | | | | | | | |
| Mean ± SD | 65.2 ± 13.5 | 64.2 ± 12.1 | 65.5 ± 12.9 | 64.0 ± 13.5 | 64.7 ± 12.9 | 60.4 ± 13.7 | 59.3 ± 14.2 | 60.4 ± 15.0 | 60.6 ± 13.7 | 60.1 ± 14.0 |
| Range | 23 to 89 | 22 to 88 | 32 to 89 | 23 to 88 | 22 to 89 | 26 to 91 | 18 to 84 | 21 to 88 | 25 to 83 | 18 to 91 |
| **Age (years)** | | | | | | | | | | |
| <65; n (%) | 55 (40.1) | 59 (41.8) | 26 (38.2) | 26 (37.1) | 166 (39.9) | 98 (55.7) | 99 (57.9) | 54 (61.4) | 48 (55.8) | 299 (57.4) |
| ≥65; n (%) | 82 (59.9) | 82 (58.2) | 42 (61.8) | 44 (62.9) | 250 (60.1) | 78 (44.3) | 72 (42.1) | 34 (38.6) | 38 (44.2) | 222 (42.6) |
| **BMI ($kg/m^2$)** | | | | | | | | | | |
| Mean ± SD | 24.95 ± 5.73 | 24.86 ± 5.20 | 25.30 ± 4.55 | 24.66 ± 5.60 | 24.93 ± 5.34 | 24.04 ± 4.56 | 24.31 ± 4.88 | 24.05 ± 4.70 | 23.67 ± 5.09 | 24.07 ± 4.77 |
| Range | 15.1 to 45.4 | 16.0 to 40.4 | 15.4 to 35.2 | 15.0 to 45.7 | 15.0 to 45.7 | 13.3 to 38.8 | 15.1 to 41.9 | 14.6 to 34.5 | 11.0 to 44.6 | 11.0 to 44.6 |
| **Race; n (%)** | | | | | | | | | | |
| White | 115 (83.9) | 124 (87.9) | 60 (88.2) | 64 (91.4) | 363 (87.3) | 133 (75.6) | 135 (78.9) | 68 (77.3) | 67 (77.9) | 403 (77.4) |
| Black/African American | 2 ( 1.5) | 1 ( 0.7) | 1 ( 1.5) | 0 | 4 ( 1.0) | 2 ( 1.1) | 2 ( 1.2) | 1 ( 1.1) | 0 | 5 ( 1.0) |
| Asian | 12 ( 8.8) | 12 ( 8.5) | 4 ( 5.9) | 6 ( 8.6) | 34 ( 8.2) | 41 (23.3) | 33 (19.3) | 18 (20.5) | 19 (22.1) | 111 (21.3) |
| American Indian/Alaska Native | 0 | 1 ( 0.7) | 0 | 0 | 1 ( 0.2) | 0 | 0 | 0 | 0 | 0 |
| Native Hawaiian / Other Pacific Islander | 5 ( 3.6) | 2 ( 1.4) | 1 ( 1.5) | 0 | 8 ( 1.9) | 0 | 0 | 0 | 0 | 0 |
| Not reported | 3 ( 2.2) | 1 ( 0.7) | 2 ( 2.9) | 0 | 6 ( 1.4) | 0 | 0 | 0 | 0 | 0 |
| Multiple | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 0.6) | 1 ( 1.1) | 0 | 2 (0.4) |

BMI=Body mass index; Cipro 14=Ciprofloxacin DPI 14 days on/off; Cipro 28=Ciprofloxacin DPI 28 days on/off; FAS=Full analysis set; Placebo 14=Placebo 14 days on/off; Placebo 28=Placebo 28 days on/off; PPS=Per protocol set; SAF=Safety analysis set; SD=Standard deviation
Source: CSRs of Studies 15625 and 15626

**Table 9-6: Sample sizes and demographic characteristics (FAS) in the pooled RESPIRE studies**

| | Cipro 14 | Cipro 28 | Placebo 14 | Placebo 28 | Total |
|---|---|---|---|---|---|
| **Sample size, n** | | | | | |
| Randomized | 313 | 312 | 156 | 156 | 937 |
| SAF | 310 | 312 | 156 | 155 | 933 |
| FAS | 313 | 312 | 156 | 156 | 937 |
| PPS | 279 | 270 | 139 | 133 | 821 |
| **Sex; n (%)** | | | | | |
| Male | 129 (41.2) | 119 (38.1) | 50 (32.1) | 52 (33.3) | 350 (37.4) |
| Female | 184 (58.8) | 193 ( 61.9) | 106 (67.9) | 104 (66.7) | 587 (62.6) |
| **Age (years)** | | | | | |
| Mean ± SD | 62.5 ± 13.8 | 61.5 ± 13.5 | 62.6 ± 14.3 | 62.1 ± 13.7 | 62.1 ± 13.7 |
| Range | 23 to 91 | 18 to 88 | 21 to 89 | 23 to 88 | 18 to 91 |
| Median | 65.0 | 64.0 | 64.0 | 65.0 | 65.0 |
| Q1; Q3 | 55.0; 73.0 | 54.0; 71.0 | 56.0; 73.0 | 54.0; 72.0 | 55.0; 72.0 |
| **Age (years)** | | | | | |
| <65; n (%) | 153 (48.9) | 158 (50.6) | 80 (51.3) | 74 (47.4) | 465 (49.6) |
| ≥65; n (%) | 160 (51.1) | 154 (49.4) | 76 (48.7) | 82 (52.6) | 472 (50.4) |
| **BMI (kg/m$^2$)** | | | | | |
| Mean ± SD | 24.44 ± 5.12 | 24.56 ± 5.03 | 24.60 ± 4.67 | 24.11 ± 5.33 | 24.45 ± 5.05 |
| Range | 13.3 to 45.4 | 15.1 to 41.9 | 14.6 to 35.2 | 11.0 to 45.7 | 11.0 to 45.7 |
| **Race; n (%)** | | | | | |
| White | 248 (79.2) | 259 (83.0) | 128 (82.1) | 131 (84.0) | 766 (81.8) |
| Black/African American | 4 ( 1.3) | 3 ( 1.0) | 2 ( 1.3) | 0 | 9 ( 1.0) |
| Asian | 53 (16.9) | 45 (14.4) | 22 (14.1) | 25 (16.0) | 145 (15.5) |
| American Indian/Alaska Native | 0 | 1 ( 0.3) | 0 | 0 | 1 ( 0.1) |
| Native Hawaiian / Other Pacific Islander | 5 ( 1.6) | 2 ( 0.6) | 1 ( 0.6) | 0 | 8 ( 0.9) |
| Not reported | 3 ( 1.0) | 1 ( 0.3) | 2 ( 1.3) | 0 | 6 ( 0.6) |
| Multiple | 0 | 1 ( 0.3) | 1 ( 0.6) | 0 | 2 ( 0.2) |

BMI=Body mass index; Cipro 14=Ciprofloxacin DPI 14 days on/off; Cipro 28=Ciprofloxacin DPI 28 days on/off; FAS=Full analysis set; Placebo 14=Placebo 14 days on/off; Placebo 28=Placebo 28 days on/off; PPS=Per protocol set; Q=Quartile; SAF=Safety analysis set; SD=Standard deviation
Source: Integrated analysis data set of Studies 15625 15626

## 9.4.2 Overview of differences between RESPIRE 1 and RESPIRE 2 in terms of geographical regions and demographic and other baseline characteristics

### 9.4.2.1 Geographical regions

Patients in RESPIRE 1 were predominantly enrolled in European countries, Australia/New Zealand and the US. In RESPIRE 2, there was a higher contribution from Russia, Bulgaria, and Asian countries, including China (see Appendix Table 9-7).

**Table 9-7: Number of patients randomized by study and geographical region**

| Study | Geographical region used for stratification (included countries [a]) | No. of randomized patients (%) |
|---|---|---|
| **RESPIRE 1** | **Total** | 416 (100.0) |
| | **Southern Europe** (Israel, Italy, Spain) | 123 (29.6) |
| | **Northern Europe** (Denmark, France, Germany, Latvia, Slovakia, United Kingdom) | 107 (25.7) |
| | **Australia/New Zealand** | 103 (24.8) |
| | **Japan** | 33 ( 7.9) |
| | **Northern US** [b] | 25 ( 6.0) |
| | **Southern US** [b] | 19 ( 4.6) |
| | **Latin America** (Argentina) | 6 ( 1.4) |
| **RESPIRE 2** | **Total** | 521 |
| | **Northern Europe** (Austria, Czech Republic, Germany, Latvia, Lithuania, Netherlands, Poland, Russian Federation) | 193 (37.0) |
| | **Southern Europe** (Bulgaria, Portugal, Romania, Serbia, Turkey) | 163 (31.3) |
| | **Asia except China** (Hong Kong, South Korea, Philippines, Taiwan, Thailand) | 75 (14.4) |
| | **Latin America, South Africa, Australia** (Argentina, Brazil, South Africa, Australia) | 41 ( 7.9) |
| | **China** | 33 ( 6.3) |
| | **US/Canada** (US) | 16 ( 3.1) |

[a] Countries with randomized patients only.
[b] 44 patients randomized in the US overall in RESPIRE 1.
Source: Data on file.

In RESPIRE 1, countries that contributed at least 10% to the overall study population were Israel (12.7%), Australia (12.5%), New Zealand (12.3%), Spain (11.8%), Germany (11.3%), and the United States of America (10.6%). In RESPIRE 2, countries that contributed at least 10% to the overall study population were the Russian Federation (11.5%) and Bulgaria (10.4%; see Appendix Figure 9–5).

**Figure 9–5: Number of patients enrolled by participating country in the Phase III studies**

| | RESPIRE 1 N=416 n (%) | RESPIRE 2 N=521 n (%) |
|---|---|---|
| Argentina | 6 (1.4) | 13 (2.5) |
| **Australia** | 52 (12.5) | 21 (4.0) |
| Austria | | 1 (0.2) |
| **Bulgaria** | | 54 (10.4) |
| Brazil | | 5 (1.0) |
| China | | 33 (6.3) |
| Czech Republic | | 4 (0.8) |
| **Germany** | 47 (11.3) | 19 (3.6) |
| Denmark | 1 (0.2) | |
| **Spain** | 49 (11.8) | |
| France | 14 (3.4) | |
| United Kingdom | 27 (6.5) | |
| Hong Kong | | 9 (1.7) |
| **Israel** | 53 (12.7) | |
| Italy | 21 (5.0) | |
| Japan | 33 (7.9) | |

| | RESPIRE 1 N=416 n (%) | RESPIRE 2 N=521 n (%) |
|---|---|---|
| South Korea | | 34 (6.5) |
| Lithuania | | 6 (1.2) |
| Latvia | 16 (3.8) | 45 (8.6) |
| Netherlands | | 19 (3.6) |
| **New Zealand** | 51 (12.3) | |
| Philippines | | 10 (1.9) |
| Poland | | 39 (7.5) |
| Portugal | | 14 (2.7) |
| Romania | | 32 (6.1) |
| **Russian Federation** | | 60 (11.5) |
| Serbia | | 33 (6.3) |
| Slovakia | 2 (0.5) | |
| Thailand | | 13 (2.5) |
| Turkey | | 30 (5.8) |
| Taiwan | | 9 (1.7) |
| **United States** | 44 (10.6) | 16 (3.1) |
| South Africa | | 2 (0.4) |

#### 9.4.2.2 Differences in demographic and other baseline characteristics

Potentially relevant numerical differences between study populations (FAS) randomized in RESPIRE 1 and RESPIRE 2 at baseline were seen for:

- Sex distribution (females: 68.5% in RESPIRE 1 *vs.* 58.0% in RESPIRE 2);
- Proportion of Asians (8.2% in RESPIRE 1 *vs.* 21.3% in RESPIRE 2);
- Mean age (64.7 ± 12.9 years [median: 67.0 years] in RESPIRE 1 *vs.* 60.1 ± 14.0 years [median: 62.0 years] in RESPIRE 2);
- Etiology of NCFB (54.3% idiopathic and 44.2% post-infective in RESPIRE 1 *vs.* 33.2% idiopathic and 66.2% post-infective in RESPIRE 2);
- Number of patients with at least one sputum sample tested positive for a pathogen in sputum culture history (79.1% in RESPIRE 1 [with *P. aeruginosa*: 50.7%, with *H. influenzae*: 22.4%] *vs.* 68.1% in RESPIRE 2 [with *P. aeruginosa*: 39.7%, with *H. influenzae*: 12.9%]);
- Number of patients with >2 exacerbations in the previous 12 months (187/416 [45.0%] in RESPIRE 1 *vs.* 115/521 [22.1%] in RESPIRE 2);
- Mean number of exacerbations in the previous 12 months (1,200 episodes in 416 patients [mean: 2.9 episodes per patient] in RESPIRE 1 *vs.* 1,225 episodes in 521 patients [mean: 2.4 episodes per patient] in RESPIRE 2);
- Presence of *H. influenzae* at baseline (26.4% of patients in RESPIRE 1 *vs.* 17.3% in RESPIRE 2);
- Number of patients with standard medication for NCFB at baseline (335/416 [80.5%] in RESPIRE 1 *vs.* 354/521 [67.9%] in RESPIRE 2);
- Number of patients with any medical history findings - excluding NCFB (97.4% in RESPIRE 1 *vs.* 84.1% in RESPIRE 2);
- Proportion of patients with COPD in medical history (15.9% in RESPIRE 1 *vs.* 28.4% in RESPIRE 2).

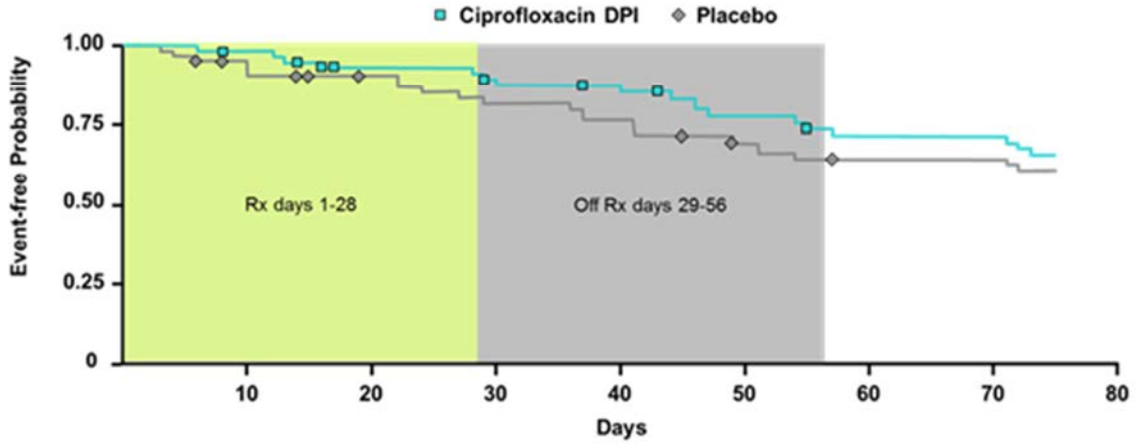
## 9.4.3 Selected efficacy results in Phase II NCFB study 12965

**Table 9-8: Selected efficacy results in Phase II NCFB study 12965 (FAS)**

| | | | | |
|---|---|---|---|---|
| Treatment duration / regimen | 28 days / 32.5 mg BID (Ciprofloxacin DPI or placebo) | | | |
| Duration of observation | EOT visit on Day 29 ± 1; EOS visit (last study visit) on Day 84 ± 2 | | | |
| Primary efficacy analysis | Variable: Changes in bacterial load ($log_{10}$ CFU/g sputum) at EOT (FAS) | | | |
| | *Descriptive statistics (no imputation)* | | | |
| | Baseline mean value: | Cipro DPI: | 7.19 ± 1.94 | |
| | | Placebo: | 6.92 ± 1.90 | |
| | EOT mean value: | Cipro DPI: | 3.38 ± 2.99 | |
| | | Placebo: | 6.47 ± 2.68 | |
| | Mean change: | Cipro DPI: | -3.62 ± 3.46 | |
| | | Placebo: | -0.27 ± 2.29 | |
| | *ANCOVA test (LOCF, no interaction model)* | | | |
| | Bacterial load (LS mean) at EOT: | Cipro DPI: | 4.048 | |
| | | Placebo: | 6.416 | |
| | LS mean treatment difference (Cipro DPI minus placebo): | | | -2.368 |
| | 95%-CI for LS mean treatment difference: | | | [-3.350; -1.386] |
| | P-value for factor treatment: | | | p<0.001 |
| Time to first exacerbation: All reported exacerbations [a] | Patients with event until EOT (Day 30): | Cipro DPI: | 6/60 (10.0%) | |
| | | Placebo: | 11/64 (17.2%) | |
| | Patients with event until study end: | Cipro DPI: | 22/60 (36.7%) | |
| | | Placebo: | 25/64 (39.1%) | |
| | Hazard ratio for events until study end [95%-CI]: | | 0.802 [0.443; 1.454] | |
| Time to first exacerbation: Exacerbations with antibiotic intervention [a] | Patients with event until EOT (Day 30): | Cipro DPI: | 5/60 (8.3%) | |
| | | Placebo: | 7/64 (10.9%) | |
| | Patients with event until study end: | Cipro DPI: | 14/60 (23.3%) | |
| | | Placebo: | 18/64 (28.1%) | |
| | Hazard ratio for events until study end [95%-CI]: | | 0.674 [0.324; 1.401] | |
| Time to first exacerbation: Exacerbations requiring hospitalization [a] | Patients with event until EOT (Day 30): | Cipro DPI: | 1/60 (1.7%) | |
| | | Placebo: | 3/64 (4.7%) | |
| | Patients with event until study end: | Cipro DPI: | 2/60 (3.3%) | |
| | | Placebo: | 5/64 (7.8%) | |
| | Hazard ratio for events until study end [95%-CI]: | | 0.171 [0.023; 1.276] | |
| SGRQ total score | *Descriptive statistics (no imputation)* | | | |
| | Baseline mean value: | Cipro DPI: | 43.79 ± 20.33 | |
| | | Placebo: | 44.72 ± 18.06 | |
| | EOT mean value: | Cipro DPI: | 41.47 ± 21.03 | |
| | | Placebo: | 44.79 ± 19.81 | |
| | Mean change: | Cipro DPI: | -2.52 ± 11.61 | |
| | | Placebo: | 0.38 ± 7.52 | |
| | Responder rate [b]: | Cipro DPI: | 21/60 (35.0%) | |
| | | Placebo: | 18/64 (28.1%) | |
| | *ANCOVA test (no imputation, no interaction model)* | | | |
| | Total score (LS mean) at EOT: | Cipro DPI: | 41.738 | |
| | | Placebo: | 45.299 | |
| | LS mean treatment difference (Cipro DPI minus placebo): | | | -3.561 |
| | 95%-CI for LS mean treatment difference: | | | [-7.254; 0.131] |
| | P-value for factor treatment: | | | p=0.059 |
| SGRQ symptoms component score (no imputation) | Baseline mean value: | Cipro DPI: | 56.91 ± 20.73 | |
| | | Placebo: | 56.61 ± 20.85 | |
| | EOT mean value: | Cipro DPI: | 53.00 ± 23.28 | |
| | | Placebo: | 56.08 ± 21.00 | |
| | Mean change: | Cipro DPI: | -4.26 ± 18.19 | |
| | | Placebo: | 0.47 ± 14.09 | |
| | Responder rate [b]: | Cipro DPI: | 26/60 (43.3%) | |
| | | Placebo: | 16/64 (25.0%) | |

a: Based on Kaplan Meier estimates and Cox proportional hazard model.
b: Patients with improvement (reduction) by more than 4 score points.
Source: CSR of Study 12965

**Figure 9–6: Kaplan Meier plot for time to first exacerbation (any exacerbation) in NCFB study 12965 (ITT)**




Source: CSR of study No. 12965

## 9.4.4 Efficacy results in Phase III studies - by single studies

### 9.4.4.1 Hierarchical test procedure in the RESPIRE studies for FDA submission - actual qualitative outcomes

**Table 9–9: Overview of confirmatory *vs.* exploratory statistical tests within the framework of the pre-specified hierarchical testing in RESPIRE 1 and RESPIRE 2**

| | RESPIRE 1 | | RESPIRE 2 | |
|---|---|---|---|---|
| **Variable** | 14 days | 28 days | 14 days | 28 days |
| **Primary efficacy variable** | | | | |
| Time to first exacerbation event | Conf. (+) | Conf. (-) † | Conf. (-) † | Conf. (-) † |
| **Secondary efficacy variables** | | | | |
| Frequency of exacerbation events (≥3 signs) | Conf. (-) † | Expl. (-) | Expl. (-) | Expl. (+) |
| Frequency of exacerbation events (≥1 sign) | Expl. (+) | Expl. (-) | Expl. (-) | Expl. (-) |
| Eradication of baseline pathogens | Expl. (+) | Expl. (-) | Expl. (-) | Expl. (-) |
| Changes in SGRQ SCS | Expl. (+) | Expl. (-) | Expl. (-) | Expl. (-) |
| Occurrence of new pathogens | Expl. (-) | Expl. (-) | Expl. (+) | Expl. (-) |
| Changes in QOL-B RSDS | Expl. (-) | Expl. (-) | Expl. (-) | Expl. (-) |
| Changes in lung function ($FEV_1$) | Expl. (-) | Expl. (-) | Expl. (-) | Expl. (-) |

Conf.=Confirmatory test; Expl.=Exploratory test; RSDS=Respiratory symptoms domain score; SCS=Symptoms component score
Note: The columns 14 days / 28 days include the primary statistical tests according to SAP in the respective active treatment regimen group *vs.* pooled placebo.
(+) : Statistically (nominally) significant test outcome based on the group-specific α-level.
(-) : No statistically (nominally) significant test outcome based on the group-specific α-level.
† : Abandonment of the hierarchical testing procedure after this step.
Source: Clinical Overview of NDA

### 9.4.4.2 Sensitivity analyses of the primary endpoint in RESPIRE 1 and RESPIRE 2

**Table 9–10: Overview of selected sensitivity analyses of time to first exacerbation in RESPIRE 1 and RESPIRE 2 (FAS)**

| | | *RESPIRE 1* | | *RESPIRE 2* | |
|---|---|---|---|---|---|
| **Analysis** | | **Cipro 14** | **Cipro 28** | **Cipro 14** | **Cipro 28** |
| **Primary analysis - Cox model** | | | | | |
| | HR | 0.53 | 0.73 | 0.87 | 0.71 |
| | CI | [0.36; 0.80] | [0.50; 1.07] | [0.62; 1.21] | [0.39; 1.27] |
| | p-value | 0.0005 | 0.0650 | 0.3965 | 0.0511 |
| **Cox model without adjustment for covariates** | | | | | |
| | HR | 0.54 | 0.71 | 0.87 | 0.70 |
| | CI | [0.36; 0.81] | [0.49; 1.04] | [0.62; 1.21] | [0.39; 1.26] |
| | p-value | 0.0006 | 0.0431 | 0.3985 | 0.0475 |
| **Unstratified log-rank test** | | | | | |
| | p-value | 0.0004 | 0.0429 | 0.4025 | 0.0452 |
| **Censored patients regarded as having an event (Cox model)** [a] | | | | | |
| | HR | 0.58 | 0.70 | 0.89 | 0.75 |
| | CI | [0.41; 0.82] | [0.50; 0.98] | [0.66; 1.19] | [0.45; 1.25] |
| | p-value | 0.0004 | 0.0167 | 0.4209 | 0.0630 |

CI = Confidence interval; Cipro 14 = Ciprofloxacin DPI 14 days on/off; Cipro 28 = Ciprofloxacin DPI 28 days on/off; HR = Hazard ratio

Note: The columns Cipro 14 / Cipro 28 include the tests according to SAP in the respective active treatment regimen group *vs.* pooled placebo. CIs are 97.5% for RESPIRE 1, and 95.1% (14 day-regimen) / 99.9% (28-days regimen) for RESPIRE 2

a: Patients censored prior to Day 336 were considered as having an event at time of censoring.

Source: CSRs of Studies 15625 and 15626

### 9.4.4.3 Sensitivity analysis of frequency of exacerbations in RESPIRE 1 (without extrapolation)

**Table 9–11: Results of the secondary efficacy analyses related to exacerbation frequency (sensitivity analysis without extrapolation) in RESPIRE 1 (FAS)**

| | Cipro 14 N=137 | Cipro 28 N=141 | Pooled placebo N=138 |
|---|---|---|---|
| **No. of exacerbations (≥3 signs) †** | | | |
| Mean number ± SD | 0.63 ± 0.99 | 0.82 ± 1.14 | 0.91 ± 1.05 |
| Incidence rate ratio (IRR) [a] | 0.69 | 0.86 | --- |
| 97.5%-CI for IRR [a] | [0.48; 0.98] | [0.62; 1.19] | --- |
| p-value [b] | p=0.0193 | 0.3002 | --- |
| **No. of exacerbations (≥1 sign) ‡** | | | |
| Mean number ± SD | 0.89 ± 1.26 | 1.14 ± 1.40 | 1.22 ± 1.18 |
| Incidence rate ratio (IRR) [a] | 0.73 | 0.88 | --- |
| 97.5%-CI for IRR [a] | [0.53; 1.00] | [0.65; 1.18] | --- |
| p-value [b] | 0.0243 | 0.3348 | --- |

CI = Confidence interval; Cipro 14 = Ciprofloxacin DPI 14 days on/off; Cipro 28 = Ciprofloxacin DPI 28 days on/off; SD = Standard deviation

Note: This mode of analysis was the primary mode for the analysis of exacerbation frequency in RESPIRE 2.

†: Defined as exacerbation with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of at least 3 signs/symptoms over 48 weeks (qualifying exacerbation for primary efficacy analysis).

‡: Defined as exacerbation with systemic antibiotic use and worsening of at least one sign/symptom over 48 weeks.

a: Incidence rate ratio (IRR) based on Poisson regression for the comparison of active treatment *vs.* pooled placebo (IRRs <1 indicate better outcome on active treatment). No extrapolation approach (but time in study as offset).

b: Wald-type test.

Source: CSR of Study 15625

### 9.4.4.4 Results of the primary analyses of patient-reported outcomes in RESPIRE 1 and RESPIRE 2

**Table 9–12: Treatment differences at EOT and ANCOVA test results for SGRQ and QOL-B in RESPIRE 1 (FAS)**

| | SGRQ SCS [a] | QOL-B RSDS [b] |
|---|---|---|
| **Cipro 14 *vs.* pooled placebo** | | |
| Treatment difference [c] | -7.59 | 2.47 |
| 97.5%-CI for difference [c] | [-14.04; -1.14] | [-3.14; 8.07] |
| p-value [d] | 0.0085 | 0.3219 |
| **Cipro 28 *vs.* pooled placebo** | | |
| Treatment difference [c] | -5.21 | 1.18 |
| 97.5%-CI for difference [c] | [-11.53; 1.10] | [-4.17; 6.53] |
| p-value [d] | 0.0636 | 0.6187 |

Cipro 14 = Ciprofloxacin DPI 14 days on/off; Cipro 28 = Ciprofloxacin DPI 28 days on/off; EOT=End of treatment; RSDS=Respiratory symptoms domain score; SCS=Symptoms component score

Note: Baseline is defined as the last non-missing measurement before the first study drug inhalation. EOT is defined as Cycle 6, end ON phase, Day 28 for the 28-day regimen and Cycle 12, end ON phase, Day 14 for the 14-dayas regimen. No data imputation in addition to the handling of missing data as per PRO manuals was performed.

a: Lower score values indicate better clinical conditions, and a negative treatment difference is in favor of ciprofloxacin DPI.

b: Higher score values indicate better clinical conditions, and a positive treatment difference is in favor of ciprofloxacin DPI.

c: From ANCOVA for the treatment difference (*i.e.*, the difference between treatment groups in LS mean change from baseline) of active treatment *vs.* pooled placebo.

d: t-test.

Source: CSRs of Study 15625 and 15626

**Table 9–13: Treatment differences at EOT and ANCOVA test results for SGRQ and QOL-B in RESPIRE 2 (FAS)**

| | SGRQ SCS [a] | QOL-B RSDS† [b] |
|---|---|---|
| **Cipro 14 *vs.* pooled placebo** | | |
| Treatment difference [c] | -1.40 | 2.22 |
| CI for difference [c] | [-5.94; 3.15] | [-2.23; 6.67] |
| p-value [d] | 0.5446 | 0.3247 |
| **Cipro 28 *vs.* pooled placebo** | | |
| Treatment difference [c] | -1.44 | 2.75 |
| CI for difference [c] | [-9.06; 6.17] | [-4.92; 10.42] |
| p-value [d] | 0.5302 | 0.2340 |

Cipro 14 = ciprofloxacin DPI 14 days on/off; Cipro 28 = ciprofloxacin DPI 28 days on/off; EOT=End of treatment; RSDS=Respiratory symptoms domain score; SCS=Symptoms component score

Note: Baseline is defined as the last non-missing measurement before the first study drug inhalation. EOT is defined as Cycle 6, end ON phase, Day 28 for the 28-day regimen and Cycle 12, end ON phase, Day 14 for the 14-dayas regimen. No data imputation in addition to the handling of missing data as per PRO manuals was performed.

†: This questionnaire was not available for Latvia, Philippines, Portugal, Romania, Serbia, Thailand, Turkey (177 patients [34%]), because of a lack of linguistically validated versions.

a: Lower score values indicate better clinical conditions, and a negative treatment difference is in favor of ciprofloxacin DPI.

b: Higher score values indicate better health status, and a positive treatment difference is in favor of ciprofloxacin DPI.

c: From ANCOVA for the treatment difference (*i.e.*, the difference between treatment groups in LS mean change from baseline) of active treatment *vs.* pooled placebo. Confidence intervals are 99.9% for the 28-day regimen and 95.1% for the 14-day regimen.

d: t-test.

Source: CSR of Study 15626

### 9.4.4.5 Results of the primary analyses of eradication of pathogens in RESPIRE 1 and RESPIRE 2

**Table 9–14: Overview of analysis results of eradication of baseline pathogens (main tests as per statistical analysis plan) in RESPIRE 1 and RESPIRE 2 (FAS)**

| | Cipro 14 | Cipro 28 | Pooled placebo |
|---|---|---|---|
| **RESPIRE 1** | **N=137** | **N=141** | **N=138** |
| Eradication - YES (n, %) [a] | 39 (28.5) | 34 (24.1) | 23 (16.7) |
| Odds ratio (OR) [b] | 2.35 | 1.16 | --- |
| p-value [c] | 0.0182 | 0.6723 | --- |
| **RESPIRE 2** | **N=176** | **N=171** | **N=174** |
| Eradication - YES (n, %) [a] | 63 (35.8) | 54 (31.6) | 55 (31.6) |
| Odds ratio (OR) [b] | 1.34 | 1.16 | --- |
| p-value [c] | p=0.3162 | p=0.6019 | --- |

BL = Baseline; CI = Confidence interval; Cipro 14 = Ciprofloxacin DPI 14 days on/off; Cipro 28 = Ciprofloxacin DPI 28 days on/off; SD = Standard deviation

a: The percentage is calculated based on the number of all randomized patients within the respective population. No imputation procedure was applied.

b: Odds ratio (OR) based on Cochran-Mantel-Haenszel (CMH method) for the comparison of active treatment *vs.* pooled placebo (ORs >1 indicate better outcome on active treatment). No imputation procedure was applied.

c: CMH test.

Source: CSRs of Studies 15625 and 15626

### 9.4.4.6 Overview of efficacy results in the RESPIRE studies by study

**Table 9–15: Summary of descriptive efficacy results by Phase III study (FAS)**

| | Cipro 14 | Cipro 28 | Pooled Placebo |
|---|---|---|---|
| **Time to first exac. (median time) [a]** | | | |
| RESPIRE 1 | >336 days | 336 days | 186 days |
| RESPIRE 2 | >336 days | >336 days | >336 days |
| **Time to first exac. (median time) [b]** | | | |
| RESPIRE 1 | 432 | 317 | 210 |
| RESPIRE 2 | 431 | 536 | 388 |
| **Freq. of exac. (≥3) [c] (mean ± SD)** | | | |
| RESPIRE 1 [d] | 0.63 ± 0.99 | 0.82 ± 1.14 | 0.91 ± 1.05 |
| RESPIRE 2 [d] | 0.58 + 0.84 | 0.40 ± 0.64 | 0.70 + 1.02 |
| **Freq. of exac. (≥1) [e] (mean ± SD)** | | | |
| RESPIRE 1 [d] | 0.89 ± 1.26 | 1.14 ± 1.40 | 1.22 ± 1.18 |
| RESPIRE 2 [d] | 0.72 ± 0.98 | 0.54 ± 0.77 | 0.85 ± 1.13 |
| **Pathogen eradication, Yes - %** | | | |
| RESPIRE 1 | 28.5 | 24.1 | 16.7 |
| RESPIRE 2 | 35.8 | 31.6 | 31.6 |
| **Occur. of new pathogens, Yes - %** | | | |
| RESPIRE 1 | 5.1 | 3.5 | 8.0 |
| RESPIRE 2 | 4.0 | 4.1 | 10.3 |
| **Mean changes in SGRQ-SCS [f] (units; mean ± SD)** | | | |
| RESPIRE 1 | -7.2 ± 20.4 | -8.2 ± 22.9 | -0.8 ± 18.2 |
| RESPIRE 2 | -9.0 ± 20.1 | -8.9 ± 21.1 | -7.3 ± 22.0 |
| **Mean changes in QOL-B-RSDS [g] (units; mean ± SD)** | | | |
| RESPIRE 1 | 6.7 ± 17.9 | 7.7 ± 18.5 | 6.4 ± 17.3 |
| RESPIRE 2 | 10.9 ± 18.1 | 11.6 ± 17.5 | 9.0 ± 16.3 |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; exac:=exacerbation(s); Freq.=Frequency; Occur.=Occurrence; RSDS=Respiratory symptoms domain score; SCS=Symptoms component score

a: Kaplan Meier estimates.
b: Estimates based on survival regression fitting a Weibull distribution.
c: Defined as exacerbations with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of ≥ 3 signs/symptoms.
d: Non-extrapolated data.
e: Defined as exacerbations with systemic antibiotic use and worsening of ≥1 sign/symptom.
f: Only patients with documented values for both baseline and end of treatment; negative changes indicate improvement.
g: Only patients with documented values for both baseline and end of treatment; positive changes indicate improvement.

Source: CSRs of Studies 15625 and 15626

**Table 9–16: Overview of treatment benefits (primary statistical test results in order of hierarchical testing) by Phase III study (FAS)**

| | Cipro 14 *vs.* pooled placebo Estimate / p-value | Cipro 28 *vs.* pooled placebo Estimate / p-value |
|---|---|---|
| **Time to first exacerbation** | **Hazard ratio (HR)** | **Hazard ratio (HR)** |
| RESPIRE 1 | 0.53 / p=0.0005 ** | 0.73 / p=0.0650 |
| RESPIRE 2 | 0.87 / p=0.3965 | 0.71 / p=0.0511 |
| **Freq. of exac. (≥3 signs) [a]** | **Incidence rate ratio (IRR)** | **Incidence rate ratio (IRR)** |
| RESPIRE 1 [b] | 0.73 / p=0.0382 | 0.86 / p=0.2944 |
| RESPIRE 1 [c] | 0.69 / p=0.0193 * | 0.86 / p=0.3002 |
| RESPIRE 2 [c] | 0.81 / p=0.1471 | 0.56 / p=0.0003 * |
| **Freq. of exac. (≥1 sign) [d]** | **Incidence rate ratio (IRR)** | **Incidence rate ratio (IRR)** |
| RESPIRE 1 [b] | 0.74 / p=0.0231 * | 0.87 / p=0.2761 |
| RESPIRE 1 [c] | 0.73 / p=0.0243 * | 0.88 / p=0.3348 |
| RESPIRE 2 [c] | 0.84 / p=0.1811 | 0.63 / p=0.0014 |
| **Pathogen eradication** | **Odds ratio (OR)** | **Odds ratio (OR)** |
| RESPIRE 1 | 2.35 / p=0.0182 * | 1.16 / p=0.6723 |
| RESPIRE 2 | 1.34 / p=0.3162 | 1.16 / p=0.6019 |
| **Changes (units) in SGRQ-SCS** | **LS mean difference** | **LS mean difference** |
| RESPIRE 1 | -7.59 / p=0.0085 * | -5.21 / p=0.0636 |
| RESPIRE 2 | -1.40 / p=0.5446 | -1.44 / p=0.5302 |
| **Occur. of new pathogens** | **Odds ratio (OR)** | **Odds ratio (OR)** |
| RESPIRE 1 | 0.56 / p=0.2569 | 0.36 / p=0.0582 |
| RESPIRE 2 | 0.29 / p=0.0072 * | 0.41 / p=0.0534 |
| **Changes (units) in QOL-B-RSDS** | **LS mean difference** | **LS mean difference** |
| RESPIRE 1 | 2.47 / p=0.3219 | 1.18 / p=0.6187 |
| RESPIRE 2 | 2.22 / p=0.3247 | 2.75 / p=0.2340 |
| **Changes (L) in $FEV_1$** | **LS mean difference** | **LS mean difference** |
| RESPIRE 1 | -0.05 / p=0.1936 | -0.03 / p=0.3700 |
| RESPIRE 2 | -0.04 / p=0.2657 | 0.04 / p=0.3100 |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; exac:=exacerbation(s); Freq.=Frequency; LS=Least squares; Occur.=Occurrence; RSDS=Respiratory symptoms domain score; SCS=Symptoms component score
Note: This table serves as a condensed overview and shows the results of the primary analyses. Pre-specified α-evels were ≤0.025 in RESPIRE 1, ≤0.001 for the 28-day regimen and ≤0.049 for the 14-day regimen in RESPIRE 2.
HR, IRR, and OR estimates <1 indicate outcomes in favor of active treatment (apart from "pathogen eradication", where OR estimates >1 indicate a better outcome on active treatment). Positive differences (>0) in QOL-B and $FEV_1$ and negative differences (<0) in SGRQ indicate better outcome on active treatment.
*: Indicates nominally significant test outcomes.
**: Indicates statistically significant (confirmatory) test outcomes.
a: Defined as exacerbations with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of ≥ 3 signs/symptoms.
b: Based on imputed data using an extrapolation approach (primary analysis in RESPIRE 1).
c: Based on non-extrapolated data (primary analysis in RESPIRE 2).
d: Defined as exacerbations with systemic antibiotic use and worsening of ≥1 sign/symptom.
Source: CSRs of Studies 15625 and 15626

## 9.4.5 Efficacy results in Phase III studies - description of integrated analysis results based on pooled data from RESPIRE 1 and RESPIRE 2

**Table 9–17: Summary of descriptive efficacy results in Phase III integrated analysis (FAS)**

| | | Cipro 14 N=313 | Cipro 28 N=312 | Pooled Placebo N=312 |
|---|---|---|---|---|
| **Time to first exac. (median time)** [a] | | | | |
| | N days | 431 | 425 | 287 |
| **Time to first exac. (median time)** [b] | | | | |
| | N days | >336 | >336 | 284 |
| **Freq. of exac. (≥3)** [c, d] | | | | |
| | Mean ± SD | 0.60 ± 0.91 | 0.59 ± 0.92 | 0.79 ± 1.03 |
| **Freq. of exac. (≥1)** [e, d] | | | | |
| | Mean ± SD | 0.80 ± 1.11 | 0.81 ± 1.14 | 1.01 ± 1.16 |
| **Pathogen eradication: Yes** | | | | |
| | n (%) | 102 (32.6) | 88 (28.2) | 78 (25.0) |
| **Occur. of new pathogens: Yes** | | | | |
| | n (%) | 14 (4.5) | 12 (3.8) | 29 (9.3) |
| **Mean changes (units) in SGRQ-SCS** [f] | | | | |
| | Mean ± SD | -8.3 ± 20.2 | -8.6 ± 21.9 | -4.7 ± 20.8 |
| **Mean changes (units) in QOL-B-RSDS** [g] | | | | |
| | Mean ± SD | 8.9 ± 18.1 | 9.4 ± 18.1 | 7.7 ± 16.8 |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; exac:=exacerbation(s); Freq.=Frequency; Occur.=Occurrence; RSDS=Respiratory symptoms domain score; SCS=Symptoms component score

a: Estimates based on survival regression fitting a Weibull distribution.

b: Kaplan Meier estimates.

c: Defined as exacerbations with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of ≥ 3 signs/symptoms.

d: Based on non-extrapolated data (primary analysis in RESPIRE 2).

e: Defined as exacerbations with systemic antibiotic use and worsening of ≥1 sign/symptom.

f: Only patients with documented values for both baseline and end of treatment; negative changes indicate improvement.

g: Only patients with documented values for both baseline and end of treatment; positive changes indicate improvement.

Source: Integrated analysis tables of Studies 15625 and 15626

**Table 9–18: Overview of all treatment benefits in Phase III integrated analysis (FAS)**

| | Cipro 14 *vs.* pooled placebo | Cipro 28 *vs.* pooled placebo |
|---|---|---|
| **Time to first exacerbation** | | |
| Hazard ratio [95%-CI] | 0.68 [0.54; 0.87] ‡ | 0.71 [0.56; 0.90] |
| **Freq. of exac. (≥3 signs) [a]** | | |
| Incidence rate ratio [b] [95%-CI] | 0.75 [0.61; 0.92] | 0.72 [0.58; 0.88] ‡ |
| **Freq. of exac. (≥1 sign) [c]** | | |
| Incidence rate ratio [b] [95%-CI] | 0.78 [0.64; 0.94] | 0.77 [0.64; 0.93] ‡ |
| **Pathogen eradication** | | |
| Odds ratio [95%-CI] | 1.65 [1.06; 2.59] | 1.20 [0.78; 1.86] |
| **Changes (units) in SGRQ-SCS** | | |
| LS mean difference [95%-CI] | -3.87 [-7.38; -0.36] ‡ | -2.70 [-6.17; 0.77] |
| **Occur. of new pathogens** | | |
| Odds ratio [95%-CI] | 0.39 [0.20; 0.77] | 0.38 [0.19; 0.79] |
| **Changes (units) in QOL-B-RSDS** | | |
| LS mean difference [95%-CI] | 2.46 [-0.79; 5.72] | 1.82 [-1.41; 5.05] |
| **Changes (L) in $FEV_1$** | | |
| LS mean difference [95%-CI] | -0.04 [-0.09; 0.01] | 0.01 [-0.04; 0.06] |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; exac:=exacerbation(s); Freq.=Frequency; LS=Least squares; Occur.=Occurrence; RSDS=Respiratory symptoms domain score; SCS=Symptoms component score

Note: The single study results are summarized in Appendix Table 9–16. This table serves as a condensed overview and shows the results of the primary analyses. No confirmatory α-level was defined for the exploratory integrated analysis. HR, IRR, and OR estimates <1 indicate outcomes in favor of active treatment (apart from "pathogen eradication", where OR estimates >1 indicate a better outcome on active treatment). Positive differences (>0) in QOL-B and $FEV_1$ and negative differences (<0) in SGRQ indicate better outcome on active treatment.

‡: Results of the heterogeneity test (test for the null hypothesis that treatment contrasts between RESPIRE 1 and RESPIRE 2 are equal) are p<0.1.

a: Defined as exacerbations with systemic antibiotic use and presence of fever or malaise/fatigue and worsening of ≥ 3 signs/symptoms.

b: Based on non-extrapolated data (primary analysis in RESPIRE 2).

c: Defined as exacerbations with systemic antibiotic use and worsening of ≥1 sign/symptom.

Source: Integrated analysis tables of Studies 15625 and 15626

## 9.4.6 Description of safety results in Phase II NCFB study 12965

### 9.4.6.1 Common adverse events

Overall, the incidences of treatment-emergent AEs (TEAEs) were equally distributed between the ciprofloxacin DPI and placebo groups (see Appendix Table 9–19).

**Table 9–19: Overview of patients with TEAEs in NCFB study 12965 (SAF)**

| MedDRA Version 13.0 | Ciprofloxacin DPI 32.5 mg N=60 n (%) | Placebo 32.5 mg N=64 n (%) |
|---|---|---|
| Any TEAE | 41 (68.3) | 42 (65.6) |
| Any drug-related TEAE [a] | 21 (35.0) | 17 (26.6) |
| Any treatment-emergent SAE [b] | 2 ( 3.3) | 3 ( 4.7) |
| Any drug-related serious adverse event [a] | 0 ( 0.0) | 0 ( 0.0) |
| Premature discontinuation due to adverse event | 7 (11.7) | 5 ( 7.8) |

[a] Classification of "drug-related" based on investigator's assessment.
[b] All serious TEAEs were drug-related.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = Serious adverse event
Note: The definition of "treatment-emergent" in this study included the period of up to 7 days after the EOT visit.
Source: CSR of Study 12965

The highest incidences of TEAEs in both groups (ciprofloxacin DPI: 21.7%; placebo: 35.9%) referred to the MedDRA system organ class "infections and infestations" (see Appendix Table 9–20). These were primarily exacerbations of bronchiectasis, which were markedly more frequent in the placebo group (21.9% *vs.* 11.7% in the ciprofloxacin DPI group). In 3 patients of the placebo group, the exacerbations of bronchiectasis were serious, as they led to the patients' hospitalization; see Appendix 9.4.6.2). In 1 of these patients, this was additionally assessed as a medically important event.

The frequency of AEs at SOC level was similar in both treatment groups apart from gastro-intestinal disorders (15.0% in the ciprofloxacin DPI group *vs.* 1.6% in the placebo group), infections and infestations (21.7% *vs.* 35.9%), and musculoskeletal and connective tissue disorders (8.3% *vs.* 1.6%). At preferred term (PT) level, dysgeusia and nausea occurred more frequently in the ciprofloxacin DPI group, while cough and (exacerbation of) bronchiectasis were more frequently reported in the placebo group (see Appendix Table 9–20).

No TEAEs associated with abnormalities in liver enzymes were reported within the SOC "investigations" apart from one patient in the placebo group with "gamma-glutamyltrans-ferase increased".

Most of the AEs in both groups were either mild or moderate in intensity. In 4 patients (6.7%) of the ciprofloxacin DPI group and 3 patients (4.7%) of the placebo group, at least 1 AE was severe. These were most frequently exacerbations of bronchiectasis (3.3% in the ciprofloxacin DPI group and 4.7% in the placebo group).

**Table 9–20: Incidence of common (≥5%) treatment-emergent adverse events in NCFB study 12965 (population: ITT / safety)**

| MedDRA version 13.0<br>Primary system organ class<br>Preferred term | Ciprofloxacin DPI<br>N=60 (100%)<br>n (%) | Placebo<br>N=64 (100%)<br>n (%) |
|---|---|---|
| **Any TEAE** | **41 (68.3)** | **42 (65.6)** |
| **Gastrointestinal disorders** | **9 (15.0)** | **1 ( 1.6)** |
| Nausea | 3 ( 5.0) | 0 ( 0.0) |
| **General disorders and administration site conditions** | **10 (16.7)** | **14 (21.9)** |
| Product taste abnormal | 8 (13.3) | 7 (10.9) |
| **Infections and infestations** | **13 (21.7)** | **23 (35.9)** |
| Bronchiectasis | 7 (11.7) | 14 (21.9) |
| **Investigations** | **4 ( 6.7)** | **4 ( 6.3)** |
| **Musculoskeletal and connective tissue disorders** | **5 ( 8.3)** | **1 ( 1.6)** |
| **Nervous system disorders** | **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** | **8 (13.3)** | **10 (15.6)** |
| Bronchospasm | 3 ( 5.0) | 2 ( 3.1) |
| Cough | 0 ( 0.0) | 5 ( 7.8) |
| **Renal and urinary disorders** | **3 ( 5.0)** | **0 ( 0.0)** |

Note: All data are patient-based.
Source: CSR of Study 12965

The incidence of drug-related TEAEs was higher on ciprofloxacin DPI treatment (35.0% *vs.* 26.6% on placebo; see Appendix Table 9–21).

Most reports were taste related (preferred terms: “product taste abnormal” and “dysgeusia”):in the ciprofloxacin DPI group, 13.3% of patients reported “product taste abnormal” and 6.7% “dysgeusia”; in the placebo group, 10.9% reported “product taste abnormal” and 1.6% “dysgeusia”.

Drug-related coughing was more frequent in the placebo group (7.8% *vs.* 0.0% in the ciprofloxacin DPI group). There was a low risk of patient-reported bronchospasm in both groups. There were numerically more drug-related gastrointestinal disorders with ciprofloxacin DPI (n=4) than with placebo (n=1).

The incidences of other drug-related adverse events were overall comparable.

None of the treatment-emergent, drug-related AEs was severe). All but 2 events of “product taste abnormal” (1 in each treatment group) had resolved by the end of the study.

**Table 9–21: Incidence of drug-related a adverse events by primary system organ class and preferred term in NCFB study 12965 (population: ITT / safety)**

| Primary system organ class<br>Preferred term | Ciprofloxacin DPI<br>N=60 (100%)<br>n (%) | Placebo<br>N=64 (100%)<br>n (%) |
|---|---|---|
| **Any system organ class** | **21 (35.0)** | **17 (26.6)** |
| **Gastrointestinal disorders** | **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** | **8 (13.3)** | **11 (17.2)** |
| Product taste abnormal | 8 (13.3) | 7 (10.9) |
| **Infections and infestations** | **0 ( 0.0)** | **2 ( 3.1)** |
| Bronchiectasis [b] | 0 ( 0.0) | 1 ( 1.6) |
| Candidiasis | 0 ( 0.0) | 1 ( 1.6) |
| **Nervous system disorders** | **6 (10.0)** | **2 ( 3.1)** |
| Dysgeusia | 4 ( 6.7) | 1 ( 1.6) |
| **Respiratory, thoracic, and mediastinal disorders** | **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: All data are patient-based.
a Classification of “drug-related” based on investigator’s assessment.
b Refers to exacerbations of bronchiectasis.
Source: CSR of Study 12965

### 9.4.6.2 Deaths and other serious adverse events

No patients died in study No. 12965.

Two patients (3.3%) of the ciprofloxacin DPI group and 3 patients (4.7%) of the placebo groups reported treatment-emergent SAEs (see Appendix Table 9–22). All of the treatment-emergent SAEs were severe, but none of the SAEs were assessed as drug-related. With the exception of “complex regional pain syndrome”, all treatment-emergent SAEs had resolved by the end of the study.

**Table 9–22: Incidence of patients with treatment-emergent serious adverse events by SOC and preferred term in NCFB study 12965 (population: ITT / safety)**

| System organ class<br>Preferred term | Ciprofloxacin DPI<br>N=60 (100%)<br>n (%) | Placebo<br>N=64 (100%)<br>n (%) |
|---|---|---|
| **Number of patients (%) with ≥1 SAE** | **2 (3.3)** | **3 (4.7)** |
| **Infections and infestations** | **0** | **3 (4.7)** |
| Bronchiectasis [a] | 0 | 3 (4.7) |
| Sepsis | 0 | 1 (1.6) |
| **Nervous system disorders** | **1 (1.7)** | **0** |
| Complex regional pain syndrome | 1 (1.7) | 0 |
| **Psychiatric disorders** | **1 (1.7)** | **0** |
| Hallucination | 1 (1.7) | 0 |

Note: All data are patient-based.
a Refers to exacerbations of bronchiectasis.
Source: CSR of Study 12965

### 9.4.6.3 Adverse Events Leading to Premature Treatment Discontinuation

Nine patients (15.0%) in the ciprofloxacin DPI groups and 9 patients (14.1%) in the placebo groups had AEs, which resulted in premature discontinuation of study drug treatment.

In the ciprofloxacin DPI group, AEs resulting in premature discontinuation were mild (n=1) and moderate (n=2) exacerbation of bronchiectasis, mild (n=1) and moderate (n=1) bronchospasm, moderate vertigo (n=1), mild headache (n=1), mild gingival abscess (n=1), and mild ear infection (n=1). Bronchospasm and headache were assessed as drug-related by the investigators.

In the placebo group, AEs resulting in premature discontinuation were mild (n=2), moderate (n=2; one drug-related), and severe (n=1) exacerbation of bronchiectasis as well as severe exacerbation of bronchiectasis and severe H1N1 influenza (both AEs in the same patient), severe sepsis (n=1), moderate bronchospasm (n=1; drug-related), and moderate pyrexia, moderate candidiasis, moderate throat irritation, and mild headache (all 4 AEs in the same patient; pyrexia, candidiasis, and throat irritation assessed as drug-related).

### 9.4.6.4 Adverse events of special interest

Twenty-two patients (36.7%) on ciprofloxacin DPI and 26 patients (40.6%) 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 patients (11.7%) on ciprofloxacin DPI (worst severity of event: mild, n=3; moderate, n=2; severe, n=2) and 14 patients (21.9%) 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 (see Appendix Table 9–21). Only 1 patient on placebo experienced moderate exacerbation of bronchiectasis assessed as drug-related by the investigator (see Appendix Table 9–21). In 3 patients of the placebo group, severe treatment-emergent exacerbation of bronchiectasis was also considered an SAE (see Appendix Table 9–22).

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 patients 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 patients of the placebo group. In 1 patient of the ciprofloxacin DPI group, severe exacerbation of bronchiectasis occurring >7 days after EOT was also assessed as an SAE. In 3 patients 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.

### Bronchospasm

Appendix Table 9–23 presents patients with bronchospasm. None of the 6 investigator-reported AEs of bronchospasm matched the study-specific definition of bronchospasm, *i.e.*, a decline in $FEV_1$ ≥15%.

**Table 9–23: Patients with events reported by the investigator as "bronchospasm" in NCFB study 12965 (population: safety)**

| Patient Identifier | Treatment duration (days) | Start (Day)[a] | Severity | Relation-ship[b] | Duration of AE (days) | Outcome | Action taken |
|---|---|---|---|---|---|---|---|
| **Ciprofloxacin DPI** | | | | | | | |
| 100110002 | 11 | 1 | Moderate | Yes | 11 | Resolved | Study drug discontinued |
| 240010009 | 17 | 15 | Mild | Yes | 16 | Resolved | Study drug discontinued |
| 240020014 | 31 | +5 | Mild | No | 1 | Resolved | None |
| **Placebo** | | | | | | | |
| 140130001 | 8 | 2 | Moderate | Yes | 1 | Resolved | Other |
| 240010002 | 15 | 12 | Moderate | Yes | 5 | Resolved | Study drug discontinued |
| 400050009 | 29 | +18 | Mild | No | 9 | Resolved | Remedial drug therapy |

a "+" indicates days after end of treatment
b Relationship to study drug as assessed by the investigators
Source: CSR of Study 12965

There were 3 patients with AEs of bronchospasm in each of the two treatment groups and in one patient per treatment group, bronchospasm occurred after EOT. All AEs of bronchospasm during study drug treatment were assessed as drug-related.

### Cough

Two patients of the ciprofloxacin DPI group and 5 patients of the placebo group reported at least 1 AE of cough during any time of the study. No AE of cough occurred before the first administration of study drug.

No patient on ciprofloxacin DPI and 5 patients 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 (see Appendix Table 9–21). In all 5 patients on placebo, cough was assessed as drug-related by the investigator (see Appendix Table 9–21).

Two late events of mild cough, *i.e.*, events occurring >7 days after EOT, occurred in 2 patients of the ciprofloxacin DPI group and none in the placebo group.

**Hemoptysis**

One patient of the ciprofloxacin DPI group and 3 patients 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 patient on ciprofloxacin DPI and 2 patients 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 the 1 patient on ciprofloxacin DPI, hemoptysis was assessed as drug-related by the investigator (see Appendix Table 9–21).

One late event of mild hemoptysis, *i.e.*, events occurring >7 days after EOT, occurred in 1 patient of the placebo group.

## 9.4.7 Exposure to study drug in Phase III studies - integrated analysis

**Table 9–24: Extent of exposure: Overall number of days on treatment - integrated analysis (SAF)**

| | Cipro 14 N=310 | Cipro 28 N=312 | Placebo 14 N=156 | Placebo 28 N=155 | Pooled Plc N=311 | Total N=933 |
|---|---|---|---|---|---|---|
| **Continuous data** | | | | | | |
| Nmiss | 0 | 0 | 0 | 0 | 0 | 0 |
| Mean | 144.1 | 146.7 | 139.3 | 136.5 | 137.9 | 142.9 |
| (SD) | (51.5) | (46.2) | (55.5) | (53.3) | (54.3) | (50.9) |
| Min, Max | 4, 273 | 1, 183 | 1, 214 | 3, 178 | 1, 214 | 1, 273 |
| Median | 168.0 | 167.5 | 168.0 | 166.0 | 167.0 | 168.0 |
| **Categorical data, n (%)** | | | | | | |
| <85 days | 53 (17.1) | 43 (13.8) | 32 (20.5) | 33 (21.3) | 65 (20.9) | 161 (17.3) |
| 85 to 168 days | 136 (43.9) | 159 (51.0) | 59 (37.8) | 76 (49.0) | 135 (43.4) | 430 (46.1) |
| 169 to 252 days | 120 (38.7) | 110 (35.3) | 65 (41.7) | 46 (29.7) | 111 (35.7) | 341 (36.5) |
| >252 days | 1 ( 0.3) | 0 | 0 | 0 | 0 | 1 ( 0.1) |

Max=maximum; Min=minimum; Nmiss=number of patients with missing information; Plc=Placebo; SD=Standard deviation
Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; Placebo 14=Placebo 14 on/off; Placebo 28=Placebo 28 on/off
Source: Integrated analysis tables of Studies 15625 and 15626

**Table 9–25: Extent of exposure: Number of capsules taken - integrated analysis (SAF)**

| | Cipro 14 N=310 | Cipro 28 N=312 | Placebo 14 N=156 | Placebo 28 N=155 | Pooled Plc N=311 | Total N=933 |
|---|---|---|---|---|---|---|
| **Continuous data** | | | | | | |
| Nmiss | 0 | 0 | 0 | 0 | 0 | 0 |
| Mean | 276.0 | 280.9 | 264.9 | 258.4 | 261.7 | 272.8 |
| (SD) | (100.6) | (92.9) | (108.3) | (106.6) | (107.3) | (100.6) |
| Min, Max | 6, 359 | 0 [a], 380 | 1, 372 | 6, 356 | 1, 372 | 0, 380 |
| Median | 328.0 | 327.0 | 322.0 | 318.0 | 320.0 | 325.0 |
| **Categorical data, n (%)** | | | | | | |
| <29 | 14 ( 4.5) | 9 ( 2.9) | 11 ( 7.1) | 6 ( 3.9) | 17 ( 5.5) | 40 ( 4.3) |
| 29-56 | 12 ( 3.9) | 11 ( 3.5) | 6 ( 3.8) | 8 ( 5.2) | 14 ( 4.5) | 37 ( 4.0) |
| 57-112 | 13 ( 4.2) | 14 ( 4.5) | 7 ( 4.5) | 12 ( 7.7) | 19 ( 6.1) | 46 ( 4.9) |
| 113-224 | 28 ( 9.0) | 23 ( 7.4) | 12 ( 7.7) | 14 ( 9.0) | 26 ( 8.4) | 77 ( 8.3) |
| 225-336 | 188 (60.6) | 206 (66.0) | 92 (59.0) | 96 (61.9) | 188 (60.5) | 582 (62.4) |
| >336 | 55 (17.7) | 49 (15.7) | 28 (17.9) | 19 (12.3) | 47 (15.1) | 151 (16.2) |

Max=maximum; Min=minimum; Nmiss=number of patients with missing information; Plc=Placebo; SD=Standard deviation

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; Placebo 14=Placebo 14 on/off; Placebo 28=Placebo 28 on/off

a: One patient used 1 capsule of ciprofloxacin DPI, withdrew afterwards from study, but did not return the remaining study medication. Therefore, the actual number of capsules used was unknown and set to zero based on pre-defined imputation algorithms.

Source: Integrated analysis tables of Studies 15625 and 15626

## 9.4.8 Overview of adverse events in Phase III - by single study

**Table 9–26: Overview of adverse events and treatment-emergent adverse events in RESPIRE 1 and RESPIRE 2 by single study (SAF)**

| Type of AE | | Cipro 14 R1: N=136 R2: N=174 n (%) | Cipro 28 R1: N=141 R2: N=171 n (%) | Plc 14 R1: N=68 R2: N=88 n (%) | Plc 28 R1: N=69 R2: N=86 n (%) | Pooled Plc R1: N=137 R2: N=174 n (%) | Total R1: N=414 R2: N=519 n (%) |
|---|---|---|---|---|---|---|---|
| Any AE [a] | R1 | 115 (84.6) | 111 (78.7) | 61 (89.7) | 56 (81.2) | 117 (85.4) | 343 (82.9) |
| | R2 | 131 (75.3) | 101 (59.1) | 54 (61.4) | 63 (73.3) | 117 (67.2) | 349 (67.2) |
| Any TEAE | R1 | 112 (82.4) | 110 (78.0) | 60 (88.2) | 54 (78.3) | 114 (83.2) | 336 (81.2) |
| | R2 | 127 (73.0) | 94 (55.0) | 53 (60.2) | 63 (73.3) | 116 (66.7) | 337 (64.9) |
| Any study drug-related TEAE [b] | R1 | 33 (24.3) | 35 (24.8) | 20 (29.4) | 16 (23.2) | 36 (26.3) | 104 (25.1) |
| | R2 | 28 (16.1) | 19 (11.1) | 9 (10.2) | 15 (17.4) | 24 (13.8) | 71 (13.7) |
| Any protocol-related TEAE | R1 | 5 ( 3.7) | 3 ( 2.1) | 1 ( 1.5) | 3 ( 4.3) | 4 ( 2.9) | 12 ( 2.9) |
| | R2 | 2 ( 1.1) | 2 ( 1.2) | 2 ( 2.3) | 2 ( 2.3) | 4 ( 2.3) | 8 ( 1.5) |
| Any device-related TEAE | R1 | 2 ( 1.5) | 3 ( 2.1) | 3 ( 4.4) | 2 (2.9) | 5 ( 3.6) | 10 ( 2.4) |
| | R2 | 1 (0.6) | 0 | 0 | 0 | 0 | 1 ( 0.2) |
| Max. intensity (any TEAE) | | | | | | | |
| Mild | R1 | 35 (25.7) | 33 (23.4) | 23 (33.8) | 22 (31.9) | 45 (32.8) | 113 (27.3) |
| | R2 | 48 (27.6) | 36 (21.1) | 17 (19.3) | 23 (26.7) | 40 (23.0) | 124 (23.9) |
| Moderate | R1 | 55 (40.4) | 54 (38.3) | 23 (33.8) | 23 (33.3) | 46 (33.6) | 155 (37.4) |
| | R2 | 53 (30.5) | 43 (25.1) | 18 (20.5) | 30 (34.9) | 48 (27.6) | 144 (27.7) |
| Severe | R1 | 22 (16.2) | 23 (16.3) | 14 (20.6) | 9 (13.0) | 23 (16.8) | 68 (16.4) |
| | R2 | 26 (14.9) | 15 ( 8.8) | 18 (20.5) | 10 (11.6) | 28 (16.1) | 69 (13.3) |
| Max. intensity - study drug-related TEAE [b] | | | | | | | |
| Mild | R1 | 15 (11.0) | 10 ( 7.1) | 9 (13.2) | 10 (14.5) | 19 (13.9) | 44 (10.6) |
| | R2 | 19 (10.9) | 12 (7.0) | 4 ( 4.5) | 10 (11.6) | 14 ( 8.0) | 45 ( 8.7) |
| Moderate | R1 | 16 (11.8) | 19 (13.5) | 8 (11.8) | 6 ( 8.7) | 14 (10.2) | 49 (11.8) |
| | R2 | 7 ( 4.0) | 6 ( 3.5) | 5 ( 5.7) | 4 ( 4.7) | 9 ( 5.2) | 22 ( 4.2) |
| Severe | R1 | 2 ( 1.5) | 6 ( 4.3) | 3 ( 4.4) | 0 | 3 ( 2.2) | 11 ( 2.7) |
| | R2 | 2 ( 1.1) | 1 ( 0.6) | 0 | 1 ( 1.2) | 1 ( 0.6) | 4 ( 0.8) |
| AE with outcome death [a] | R1 | 1 ( 0.7) | 3 ( 2.1) | 4 ( 5.9) | 1 ( 1.4) | 5 ( 3.6) | 9 ( 2.2) |
| | R2 | 5 ( 2.9) | 4 ( 2.3) | 4 ( 4.5) | 1 ( 1.2) | 5 ( 2.9) | 14 ( 2.7) |
| TEAE with outcome death | R1 | 1 ( 0.7) | 2 ( 1.4) | 2 ( 2.9) | 1 ( 1.4) | 3 ( 2.2) | 6 ( 1.4) |
| | R2 | 3 ( 1.7) | 4 ( 2.3) | 2 ( 2.3) | 0 | 2 ( 1.1) | 9 ( 1.7) |
| Any SAE [a] | R1 | 27 (19.9) | 33 (23.4) | 23 (33.8) | 14 (20.3) | 37 (27.0) | 97 (23.4) |
| | R2 | 49 (28.2) | 30 (17.5) | 26 (29.5) | 17 (19.8) | 43 (24.7) | 122 (23.5) |
| Any serious TEAE | R1 | 23 (16.9) | 28 (19.9) | 20 (29.4) | 12 (17.4) | 32 (23.4) | 83 (20.0) |
| | R2 | 45 (25.9) | 28 (16.4) | 25 (28.4) | 16 (18.6) | 41 (23.6) | 114 (22.0) |
| Any study drug-related serious TEAE [b] | R1 | 2 ( 1.5) | 3 ( 2.1) | 1 ( 1.5) | 0 | 1 ( 0.7) | 6 ( 1.4) |
| | R2 | 0 | 1 ( 0.6) | 0 | 0 | 0 | 1 ( 0.2) |
| Any protocol-related serious TEAE | R1 | 1 ( 0.7) | 0 | 0 | 0 | 0 | 1 ( 0.2) |
| | R2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Any device-related serious TEAE | R1 | 0 | 0 | 1 ( 1.5) | 0 | 1 ( 0.7) | 1 ( 0.2) |
| | R2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Discontinuation of study drug due to TEAE | R1 | 17 (12.5) | 14 ( 9.9) | 12 (17.6) | 7 (10.1) | 19 (13.9) | 50 (12.1) |
| | R2 | 10 ( 5.7) | 6 ( 3.5) | 5 ( 5.7) | 5 ( 5.8) | 10 ( 5.7) | 26 ( 5.0) |
| Discontinuation of study drug due to serious TEAE | R1 | 3 ( 2.2) | 4 ( 2.8) | 5 ( 7.4) | 2 ( 2.9) | 7 (5.1) | 14 ( 3.4) |
| | R2 | 2 ( 1.1) | 2 ( 1.2) | 1 ( 1.1) | 0 | 1 ( 0.6) | 5 ( 1.0) |

AE=Adverse event; SAE=Serious Adverse Event; Max.=Maximum; Plc=Placebo; R1=RESPIRE 1; R2=RESPIRE 2

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; Placebo 14=Placebo 14 on/off; Placebo 28=Placebo 28 on/off

Note: All frequency data are based on the number of patients with event.

[a] Additionally selected data to show the number of patients based on all AEs.

[b] Classification of “drug-related” based on investigator’s assessment.

Source: CSRs of Studies 15625 and 15626

## 9.4.9 Additional adverse event tables in Phase III - integrated analysis

**Table 9–27: Overview of adverse events and treatment-emergent adverse events - integrated analysis (SAF)**

| Type of AE | Cipro 14 N=310 n (%) | Cipro 28 N=312 n (%) | Placebo 14 N=156 n (%) | Placebo 28 N=155 n (%) | Pooled placebo N=311 n (%) | Total N=933 n (%) |
|---|---|---|---|---|---|---|
| Any AE [a] | 246 (79.4) | 212 (67.9) | 115 (73.7) | 119 (76.8) | 234 (75.2) | 692 (74.2) |
| Any TEAE | 239 (77.1) | 204 (65.4) | 113 (72.4) | 117 (75.5) | 230 (74.0) | 673 (72.1) |
| Any drug-related TEAE [b] | 61 (19.7) | 54 (17.3) | 29 (18.6) | 31 (20.0) | 60 (19.3) | 175 (18.8) |
| Any protocol-related TEAE | 7 ( 2.3) | 5 ( 1.6) | 3 ( 1.9) | 5 ( 3.2) | 8 ( 2.6) | 20 ( 2.1) |
| Any device-related TEAE | 3 ( 1.0) | 3 ( 1.0) | 3 ( 1.9) | 2 ( 1.3) | 5 ( 1.6) | 11 ( 1.2) |
| Max. intensity (any TEAE) | | | | | | |
| Mild | 83 (26.8) | 69 (22.1) | 40 (25.6) | 45 (29.0) | 85 (27.3) | 237 (25.4) |
| Moderate | 108 (34.8) | 97 (31.1) | 41 (26.3) | 53 (34.2) | 94 (30.2) | 299 (32.0) |
| Severe | 48 (15.5) | 38 (12.2) | 32 (20.5) | 19 (12.3) | 51 (16.4) | 137 (14.7) |
| Max. intensity - drug-related TEAE [b] | | | | | | |
| Mild | 34 (11.0) | 22 ( 7.1) | 13 ( 8.3) | 20 (12.9) | 33 (10.6) | 89 ( 9.5) |
| Moderate | 23 ( 7.4) | 25 ( 8.0) | 13 ( 8.3) | 10 ( 6.5) | 23 ( 7.4) | 71 ( 7.6) |
| Severe | 4 ( 1.3) | 7 ( 2.2) | 3 ( 1.9) | 1 ( 0.6) | 4 ( 1.3) | 15 ( 1.6) |
| AE with outcome death [a] | 6 ( 1.9) | 7 ( 2.2) | 8 ( 5.1) | 2 ( 1.3) | 10 ( 3.2) | 23 ( 2.5) |
| TEAE with outcome death | 4 ( 1.3) | 6 ( 1.9) | 4 ( 2.6) | 1 ( 0.6) | 5 ( 1.6) | 15 ( 1.6) |
| Any SAE [a] | 76 (24.5) | 63 (20.2) | 49 (31.4) | 31 (20.0) | 80 (25.7) | 219 (23.5) |
| Any serious TEAE | 68 (21.9) | 56 (17.9) | 45 (28.8) | 28 (18.1) | 73 (23.5) | 197 (21.1) |
| Any study drug-related serious TEAE [b] | 2 ( 0.6) | 4 ( 1.3) | 1 ( 0.6) | 0 | 1 ( 0.3) | 7 ( 0.8) |
| Any protocol-related serious TEAE | 1 ( 0.3) | 0 | 0 | 0 | 0 | 1 ( 0.1) |
| Any device-related serious TEAE | 0 | 0 | 1 ( 0.6) | 0 | 1 ( 0.3) | 1 ( 0.1) |
| Discontinuation of study drug due to TEAE | 27 ( 8.7) | 20 ( 6.4) | 17 (10.9) | 12 ( 7.7) | 29 ( 9.3) | 76 ( 8.1) |
| Discontinuation of study drug due to serious TEAE | 5 ( 1.6) | 6 ( 1.9) | 6 ( 3.8) | 2 ( 1.3) | 8 ( 2.6) | 19 ( 2.0) |

Max.=Maximum
Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; Placebo 14=Placebo 14 on/off; Placebo 28=Placebo 28 on/off
Note: All frequency data are based on the number of patients with event.
[a] Additionally selected data to show the number of patients based on all AEs.
[b] Classification of “drug-related” based on investigator’s assessment.
Source: Integrated analysis tables of Studies 15625 and 15626

**Table 9–28: All TEAEs by primary SOC - integrated analysis (SAF)**

| MedDRA 19.0 | Cipro 14 N=310 n (%) | Cipro 28 N=312 n (%) | Pooled placebo N=311 n (%) | Total N=933 n (%) |
|---|---|---|---|---|
| Any TEAE | 239 (77.1) | 204 (65.4) | 230 (74.0) | 673 (72.1) |
| Respiratory, thoracic and mediastinal disorders | 134 (43.2) | 104 (33.3) | 127 (40.8) | 365 (39.1) |
| Infections and infestations | 99 (31.9) | 114 (36.5) | 106 (34.1) | 319 (34.2) |
| Gastrointestinal disorders | 70 (22.6) | 56 (17.9) | 62 (19.9) | 188 (20.2) |
| Nervous system disorders | 59 (19.0) | 58 (18.6) | 30 ( 9.6) | 147 (15.8) |
| Musculoskeletal and connective tissue disorders | 46 (14.8) | 43 (13.8) | 26 ( 8.4) | 115 (12.3) |
| General disorders and administration site conditions | 45 (14.5) | 38 (12.2) | 28 ( 9.0) | 111 (11.9) |
| Investigations | 39 (12.6) | 21 ( 6.7) | 20 ( 6.4) | 80 ( 8.6) |
| Skin and subcutaneous tissue disorders | 28 ( 9.0) | 23 ( 7.4) | 28 ( 9.0) | 79 ( 8.5) |
| Injury, poisoning and procedural complications | 28 ( 9.0) | 21 ( 6.7) | 28 ( 9.0) | 77 ( 8.3) |
| Metabolism and nutrition disorders | 24 ( 7.7) | 12 ( 3.8) | 17 ( 5.5) | 53 ( 5.7) |
| Vascular disorders | 19 ( 6.1) | 13 ( 4.2) | 14 ( 4.5) | 46 ( 4.9) |
| Psychiatric disorders | 14 ( 4.5) | 9 ( 2.9) | 14 ( 4.5) | 37 ( 4.0) |
| Cardiac disorders | 12 ( 3.9) | 10 ( 3.2) | 11 ( 3.5) | 33 ( 3.5) |
| Surgical and medical procedures | 8 ( 2.6) | 11 ( 3.5) | 6 ( 1.9) | 25 ( 2.7) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 9 ( 2.9) | 5 ( 1.6) | 9 ( 2.9) | 23 ( 2.5) |
| Renal and urinary disorders | 10 ( 3.2) | 4 ( 1.3) | 9 ( 2.9) | 23 ( 2.5) |
| Blood and lymphatic system disorders | 9 ( 2.9) | 5 ( 1.6) | 8 ( 2.6) | 22 ( 2.4) |
| Ear and labyrinth disorders | 6 ( 1.9) | 8 ( 2.6) | 7 ( 2.3) | 21 ( 2.3) |
| Eye disorders | 5 ( 1.6) | 11 ( 3.5) | 3 ( 1.0) | 19 ( 2.0) |
| Immune system disorders | 7 ( 2.3) | 4 ( 1.3) | 4 ( 1.3) | 15 ( 1.6) |
| Reproductive system and breast disorders | 3 ( 1.0) | 5 ( 1.6) | 5 ( 1.6) | 13 ( 1.4) |
| Hepatobiliary disorders | 2 ( 0.6) | 4 ( 1.3) | 2 ( 0.6) | 8 ( 0.9) |
| Product issues | 1 ( 0.3) | 2 ( 0.6) | 0 | 3 ( 0.3) |
| Endocrine disorders | 1 ( 0.3) | 1 ( 0.3) | 0 | 2 ( 0.2) |
| Congenital, familial and genetic disorders | 0 | 0 | 1 ( 0.3) | 1 ( 0.1) |
| Pregnancy, puerperium and perinatal conditions | 0 | 1 ( 0.3) | 0 | 1 ( 0.1) |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off
Note: All frequency data are based on the number of patients with event. SOCs are sorted in order of decreasing frequency in the total SAF population.
Source: Integrated analysis tables of Studies 15625 and 15626

**Table 9–29: All drug-related TEAEs [a] by primary SOC and additionally by preferred term, if ≥1.0% of patients in at least one of the treatment groups were affected - integrated analysis (SAF)**

| MedDRA 19.0<br>Primary SOC<br>Preferred term | Cipro 14<br>N=310<br>n (%) | Cipro 28<br>N=312<br>n (%) | Pooled placebo<br>N=311<br>n (%) | Total<br>N=933<br>n (%) |
|---|---|---|---|---|
| Any drug-related [a] TEAE | 61 (19.7) | 54 (17.3) | 60 (19.3) | 175 (18.8) |
| **Respiratory, thoracic and mediastinal disorders** | **28 ( 9.0)** | **19 ( 6.1)** | **40 (12.9)** | **87 ( 9.3)** |
| Bronchospasm | 8 ( 2.6) | 5 ( 1.6) | 12 ( 3.9) | 25 ( 2.7) |
| Cough | 4 ( 1.3) | 6 ( 1.9) | 11 ( 3.5) | 21 ( 2.3) |
| Dyspnoea | 7 ( 2.3) | 6 ( 1.9) | 5 ( 1.6) | 18 ( 1.9) |
| Haemoptysis | 5 ( 1.6) | 3 ( 1.0) | 3 ( 1.0) | 11 ( 1.2) |
| Dysphonia | 1 ( 0.3) | 2 ( 0.6) | 3 ( 1.0) | 6 ( 0.6) |
| Oropharyngeal pain | 3 ( 1.0) | 0 | 2 ( 0.6) | 5 ( 0.5) |
| Dyspnoea exertional | 3 ( 1.0) | 0 | 1 ( 0.3) | 4 ( 0.4) |
| **Nervous system disorders** | **19 ( 6.1)** | **19 ( 6.1)** | **7 ( 2.3)** | **45 ( 4.8)** |
| Dysgeusia | 13 ( 4.2) | 15 ( 4.8) | 4 ( 1.3) | 32 ( 3.4) |
| Headache | 3 ( 1.0) | 1 ( 0.3) | 2 ( 0.6) | 6 ( 0.6) |
| **Gastrointestinal disorders** | **13 ( 4.2)** | **14 ( 4.5)** | **11 ( 3.5)** | **38 ( 4.1)** |
| Nausea | 4 ( 1.3) | 4 ( 1.3) | 2 ( 0.6) | 10 ( 1.1) |
| Diarrhoea | 2 ( 0.6) | 3 ( 1.0) | 1 ( 0.3) | 6 ( 0.6) |
| **General disorders and administration site conditions** | **9 ( 2.9)** | **4 ( 1.3)** | **5 ( 1.6)** | **18 ( 1.9)** |
| Chest discomfort | 2 ( 0.6) | 0 | 4 ( 1.3) | 6 ( 0.6) |
| Fatigue | 4 ( 1.3) | 2 ( 0.6) | 0 | 6 ( 0.6) |
| **Skin and subcutaneous tissue disorders** | **3 ( 1.0)** | **6 ( 1.9)** | **5 ( 1.6)** | **14 ( 1.5)** |
| Rash | 1 ( 0.3) | 3 ( 1.0) | 2 ( 0.6) | 6 ( 0.6) |
| **Infections and infestations** | **3 ( 1.0)** | **6 ( 1.9)** | **1 ( 0.3)** | **10 ( 1.1)** |
| **Investigations** | **6 ( 1.9)** | **2 ( 0.6)** | **2 ( 0.6)** | **10 ( 1.1)** |
| **Musculoskeletal and connective tissue disorders** | **1 ( 0.3)** | **3 ( 1.0)** | **3 ( 1.0)** | **7 ( 0.8)** |
| **Eye disorders** | **2 ( 0.6)** | **1 ( 0.3)** | **0** | **3 ( 0.3)** |
| **Product issues** | **1 ( 0.3)** | **2 ( 0.6)** | **0** | **3 ( 0.3)** |
| **Psychiatric disorders** | **3 ( 1.0)** | **0** | **0** | **3 ( 0.3)** |
| **Cardiac disorders** | **1 ( 0.3)** | **1 ( 0.3)** | **0** | **2 ( 0.2)** |
| **Metabolism and nutrition disorders** | **1 ( 0.3)** | **1 ( 0.3)** | **0** | **2 ( 0.2)** |
| **Injury, poisoning and procedural complications** | **0** | **0** | **1 ( 0.3)** | **1 ( 0.1)** |
| **Renal and urinary disorders** | **0** | **1 ( 0.3)** | **0** | **1 ( 0.1)** |
| **Surgical and medical procedures** | **0** | **1 ( 0.3)** | **0** | **1 ( 0.1)** |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off

Note: All frequency data are based on the number of patients with event. SOCs and preferred terms within SOCs are sorted in order of decreasing frequency in the total SAF population.

[a] Classification of "drug-related" based on investigator's assessment.

Source: Integrated analysis tables of Studies 15625 and 15626

**Table 9–30: All device-related [a] TEAEs by primary system organ class and preferred term - integrated analysis (SAF)**

| MedDRA 19.0<br>Primary SOC<br>Preferred term | Cipro 14<br>N=310<br>n (%) | Cipro 28<br>N=312<br>n (%) | Pooled placebo<br>N=311<br>n (%) | Total<br>N=933<br>n (%) |
|---|---|---|---|---|
| Any device-related TEAE | 3 ( 1.0) | 3 ( 1.0) | 5 ( 1.6) | 11 ( 1.2) |
| **Respiratory, thoracic and mediastinal disorders** | **2 ( 0.6)** | **2 ( 0.6)** | **4 ( 1.3)** | **8 ( 0.9)** |
| Haemoptysis | 0 | 1 ( 0.3) | 2 ( 0.6) | 3 ( 0.3) |
| Bronchospasm | 1 ( 0.3) | 0 | 1 ( 0.3) | 2 ( 0.2) |
| Dyspnoea | 1 ( 0.3) | 0 | 0 | 1 ( 0.1) |
| Hiccups | 0 | 0 | 1 ( 0.3) | 1 ( 0.1) |
| Pleuritic pain | 0 | 0 | 1 ( 0.3) | 1 ( 0.1) |
| Sputum increased | 0 | 0 | 1 ( 0.3) | 1 ( 0.1) |
| Upper respiratory tract inflammation | 0 | 1 ( 0.3) | 0 | 1 ( 0.1) |
| **Gastrointestinal disorders** | **0** | **1 ( 0.3)** | **0** | **1 ( 0.1)** |
| Cheilitis | 0 | 1 ( 0.3) | 0 | 1 ( 0.1) |
| **Immune system disorders** | **1 ( 0.3)** | **0** | **0** | **1 ( 0.1)** |
| Seasonal allergy | 1 ( 0.3) | 0 | 0 | 1 ( 0.1) |
| **Musculoskeletal and connective tissue disorders** | **0** | **0** | **1 ( 0.3)** | **1 ( 0.1)** |
| Osteopenia | 0 | 0 | 1 ( 0.3) | 1 ( 0.1) |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off
Note: All frequency data are based on the number of patients with event. SOCs and preferred terms within SOCs are sorted in order of decreasing frequency in the total study population.
a: Classification of “device-related” is based on investigator’s assessment.
Source: Integrated analysis tables of Studies 15625 and 15626

**Table 9–31: All severe drug-related TEAEs by primary SOC and preferred term - integrated analysis (SAF)**

| MedDRA 19.0<br>Primary SOC<br>Preferred term | Cipro 14<br>N=310<br>n (%) | Cipro 28<br>N=312<br>n (%) | Pooled placebo<br>N=311<br>n (%) | Total<br>N=933<br>n (%) |
|---|---|---|---|---|
| *Any drug-related TEAE (maximum intensity)* | | | | |
| *total* | *61 (19.7)* | *54 (17.3)* | *60 (19.3)* | *175 (18.8)* |
| *mild* | *34 (11.0)* | *22 ( 7.1)* | *33 (10.6)* | *89 ( 9.5)* |
| *moderate* | *23 ( 7.4)* | *25 ( 8.0)* | *23 ( 7.4)* | *71 ( 7.6)* |
| *severe* | *4 ( 1.3)* | *7 ( 2.2)* | *4 ( 1.3)* | *15 ( 1.6)* |
| **Respiratory, thoracic and mediastinal disorders** | **2 ( 0.6)** | **6 ( 1.9)** | **2 ( 0.6)** | **10 ( 1.1)** |
| Bronchospasm | 1 ( 0.3) | 2 ( 0.6) | 0 | 3 ( 0.3) |
| Cough | 0 | 2 ( 0.6) | 1 ( 0.3) | 3 ( 0.3) |
| Dyspnoea | 0 | 1 ( 0.3) | 0 | 1 ( 0.1) |
| Haemoptysis | 0 | 1 ( 0.3) | 0 | 1 ( 0.1) |
| Respiratory disorder | 0 | 0 | 1 ( 0.3) | 1 ( 0.1) |
| Throat irritation | 1 ( 0.3) | 0 | 0 | 1 ( 0.1) |
| **Gastrointestinal disorders** | **0** | **0** | **2 ( 0.6)** | **2 ( 0.2)** |
| Abdominal pain | 0 | 0 | 1 ( 0.3) | 1 ( 0.1) |
| Nausea | 0 | 0 | 1 ( 0.3) | 1 ( 0.1) |
| **Cardiac disorders** | **0** | **1 ( 0.3)** | **0** | **1 ( 0.1)** |
| Atrial flutter | 0 | 1 ( 0.3) | 0 | 1 ( 0.1) |
| **Eye disorders** | **1 ( 0.3)** | **0** | **0** | **1 ( 0.1)** |
| Retinal vasculitis | 1 ( 0.3) | 0 | 0 | 1 ( 0.1) |
| **Nervous system disorders** | **1 ( 0.3)** | **0** | **0** | **1 ( 0.1)** |
| Dysgeusia | 1 ( 0.3) | 0 | 0 | 1 ( 0.1) |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off
Note: All frequency data are based on the number of patients with event. SOCs and preferred terms within SOCs are sorted in order of decreasing frequency in the total SAF population. Classification of “drug-related” is based on investigator’s assessment.
Source: Integrated analysis tables of Studies 15625 and 15626

**Table 9–32: All drug-related serious TEAEs (investigators' assessment) by primary SOC and preferred term - integrated analysis (SAF)**

| MedDRA 19.0<br>Primary SOC<br>Preferred term | Cipro 14<br>N=310<br>n (%) | Cipro 28<br>N=312<br>n (%) | Pooled placebo<br>N=311<br>n (%) | Total<br>N=933<br>n (%) |
|---|---|---|---|---|
| Any drug-related TEAE | 2 (0.6) | 4 (1.3) | 1 (0.3) | 7 (0.8) |
| **Respiratory, thoracic and mediastinal disorders** | **0** | **2 (0.6)** | **1 (0.3)** | **3 (0.3)** |
| Haemoptysis | 0 | 1 (0.3) | 1 (0.3) | 2 (0.2) |
| Bronchospasm | 0 | 1 (0.3) | 0 | 1 (0.1) |
| **Infections and infestations** | **1 (0.3)** | **1 (0.3)** | **0** | **2 (0.2)** |
| Bronchiolitis | 0 | 1 (0.3) | 0 | 1 (0.1) |
| Pathogen resistance | 1 (0.3) | 0 | 0 | 1 (0.1) |
| **Eye disorders** | **1 (0.3)** | **0** | **0** | **1 (0.1)** |
| Retinal vasculitis | 1 (0.3) | 0 | 0 | 1 (0.1) |
| **Cardiac disorders** | **0** | **1 (0.3)** | **0** | **1 (0.1)** |
| Atrial flutter | 0 | 1 (0.3) | 0 | 1 (0.1) |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off
Note: All frequency data are based on the number of patients with event. SOCs and preferred terms within SOCs are sorted in order of decreasing frequency in the total SAF population.
Source: Integrated analysis tables of Studies 15625 and 15626

## 9.4.10 Analyses of patients with ciprofloxacin-resistant pathogens in the Phase III studies (integrated analysis on a patient level)

**Table 9–33: Number of patients with any ciprofloxacin-resistant * pathogens in sputum samples - percentages based on total FAS population (FAS)**

| | Cipro 14 N=313 n (%) | Cipro 28 N=312 n (%) | Pooled placebo N=312 n (%) | Total N=937 n (%) |
|---|---|---|---|---|
| Resistance at baseline | | | | |
| Yes [a] | 71 (22.7) | 67 (21.5) | 62 (19.9) | 200 (21.3) |
| Development of resistance: from pre-treatment at any time | | | | |
| Yes [b] | 65 (20.8) | 65 (20.8) | 27 ( 8.7) | 157 (16.8) |
| Development of resistance: from pre-treatment at EOS | | | | |
| Yes [c] | 22 ( 7.0) | 23 ( 7.4) | 7 ( 2.2) | 52 ( 5.5) |

Cipro 14=Ciprofloxacin DPI 14 on/off; Cipro 28=Ciprofloxacin DPI 28 on/off; EOS=End of study
Note: All frequency data are patient-based (denominator [N] is the number of all randomized patients within the respective population).

*: Resistance defined by breakpoints for systemic therapy

[a] Number of patients with at least one resistant isolate at baseline.

[b] Number of patients with same species susceptible before start of treatment and resistant at any post-baseline time point.

[c] Number of patients with same species susceptible before start of treatment and resistant at end of study.

Source: Integrated analysis tables of Studies 15625 and 15626