## Clinical Study Synopsis

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

Bayer HealthCare

# Clinical Trial Results Synopsis

| Study Design Description | | |
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| Study Sponsor: | Bayer HealthCare AG | |
| Study Number: | 12170 | |
| Study Phase: | I | |
| Official Study Title: | Study to evaluate the safety and pharmacokinetics of ciprofloxacin following inhalation of ciprofloxacin dry powder for inhalation administered to pediatric patients with cystic fibrosis aged 12 - 17 years | |
| Therapeutic Area: | Anti-Infectives | |
| Test Product | | |
| Name of Test Product: | Ciprofloxacin (Cipro Inhale, BAYQ3939) | |
| Name of Active Ingredient: | Ciprofloxacin | |
| Dose and Mode of Administration: | Single inhalational dose of 50 mg Ciprofloxacin PulmoSphere® inhalation powder corresponding to 32.5 mg ciprofloxacin betaine | |
| Reference Therapy/Placebo | | |
| Reference Therapy: | Not applicable | |
| Dose and Mode of Administration: | Not applicable | |
| Duration of Treatment: | Single inhalative dose | |
| Studied period: | Date of first subjects' first visit: | 15 NOV 2007 |
| | Date of last subjects' last visit: | 03 APR 2008 |
| Premature Study Suspension / Termination: | No | |
| Substantial Study Protocol Amendments: | Amendment no. 1 (dated 23 OCT 2007), specified the following changes:<br>• Regular inhalative and systemic antibiotic treatment was to be interrupted at least 5 days (instead of 3 days) before administration of Ciprofloxacin PulmoSphere® inhalation powder<br>• Planned sample size of completed subjects per dose level and number of valid subjects per dose level were increased to 8 subjects<br>• FEV1 <50%, smoking and use of medication within the 5 days preceding the study which could have interfered with the investigational drug were added as additional exclusion criteria. | |
| Study Centre(s): | The study was conducted at a single site in Germany. | |
| Methodology: | This was a non-randomized, non-blinded, non-controlled single-dose design with an option to perform an exposure-guided dose escalation. Inhalations were performed in the morning after an overnight fast and after completion of the subjects' regular cystic fibrosis (CF) treatment. After completion of study drug treatment, subjects continued their standard CF treatment. Assessments (physical examination [including | |

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| | oral body temperature, body weight, and height], vital parameters [heart rate and blood pressure], lung function test, ECG, safety laboratory panel, and pregnancy test [if applicable] were done at screening, during the treatment period (in-house phase) and out-patient phase, and during follow up. About 1 hour before study drug administration, a baseline lung function measurement and a physical examination were performed. Lung function test was then performed on dosing day till 24h post dosing, and during follow up. Blood and urine sampling for pharmacokinetic (PK) evaluation was done on dosing day from 00h to 24h post dosing. The follow up period was approximately 2 weeks. The follow-up period for adverse events (AEs) was at least seven days for all AEs with active follow-up, another 23 days thereafter the investigator was required to report every serious adverse event (SAE) of which he or she became aware. |
| Indication/<br>Main Inclusion Criteria: | Indication:<br>Cystic fibrosis<br><br>Main inclusion criteria:<br>Adolescents with CF aged 12 - 17 years (BMI between 15 and 30 $kg/m^2$) with stable pulmonary status, i.e., forced expiratory volume in 1 s (FEV1) ≥50% |
| Study Objectives: | Primary:<br>To investigate the safety and tolerability of inhaled ciprofloxacin given as single inhalation dose to pediatric CF subjects.<br><br>Secondary:<br>To investigate the pharmacokinetics of ciprofloxacin in plasma, urine, and sputum after inhalative administration in order to show that an exposure needed for an assumed effective treatment of *P. aeruginosa* can be reached in the lung of pediatric CF subjects. |
| Evaluation Criteria: | Primary:<br>Not applicable<br><br>Secondary:<br>Not applicable<br><br>Safety:<br>AEs, vital signs, ECG, laboratory parameters and subjective well-being were assessed during the in-house phase. Lung function parameters FEV1, forced mid-expiratory flow in the time interval between 25% and 75% of the forced vital capacity (FEF25-75), and forced vital capacity (FVC) were also assessed. |
| | Pharmacokinetics:<br>For investigation of PK parameters, plasma, urine, and induced sputum concentrations of ciprofloxacin were determined. Based on concentration vs time data, the following pharmacokinetic parameters of ciprofloxacin were calculated:<br><br>• Primary parameters: AUC, AUC(0-tn) [AUC(0-tn) primary if AUC(tn-∞) >20% of AUC], $C_{max}$, $t_{max}$, $t_{1/2}$, MRT |

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| | • Secondary parameters: $AUC_{norm}$, AUC(0-tn) [AUC(0-tn) primary if AUC(tn-∞) >20% of AUC], AUC/D, $C_{max}$/D, $C_{max,norm}$, CL/f, $CL_R$, $V_z$/f, C(24), $Ae_{ur}$<br>• Other parameters: AUC(tn-∞), points terminal |
| Statistical Methods: | Primary:<br>Not applicable<br><br>Secondary:<br>Not applicable<br><br>Safety:<br>Demographic and safety data were described in summary tables and graphics.<br><br>Descriptive statistics for the lung function parameters were calculated relative to their reference values and displayed graphically. |
| | Pharmacokinetics :<br>The concentration vs time courses of ciprofloxacin in plasma, urine, and sputum as well as the concentration-ratios 'sputum/plasma' were summarized. The following statistics were calculated for the concentration vs time courses of ciprofloxacin in plasma, urine, and sputum as well as the concentration-ratios 'sputum/plasma': arithmetic mean, standard deviation and coefficient of variation (CV), geometric mean, geometric standard deviation (re-transformed standard deviation of the logarithms) and CV, minimum, median, maximum value and the number of measurements. Means at any time were only calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value, a data point below LLOQ was substituted by one half of this limit. Individual and mean plasma-and sputum-concentrations versus time curves were plotted using both linear and semi-logarithmic scales.<br><br>The amount (mg) of drug excreted into urine was graphically illustrated for each sampling interval (bar-charts for the individual data and for the arithmetic means including standard deviation) as well as for the whole sampling period.<br><br>Pharmacokinetic characteristics ($t_{max}$ excluded) as well as the ratios 'sputum/plasma' of the parameters AUC and $C_{max}$ were summarized by the statistics mentioned above. $T_{max}$ was described utilizing minimum, maximum and median as well as frequency counts. |
| Number of Subjects: | A total of 9 (5 male and 4 female) adolescents with CF were enrolled and completed the study according to protocol. Thus, all subjects were valid for PK and safety analyses. |

| Study Results |
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| Results Summary — Subject Disposition and Baseline |
| All 9 subjects were White with arithmetic mean age of 14.8 years (range 11 – 17), and mean BMI of 17.8 $Kg/m^2$ (range 14.7 – 23.4). |

None of the 9 subjects had any relevant finding on medical history or physical examination, which were likely to interfere with the study objectives. None of the concomitant medications during the study were likely to interfere with the study objectives.

Results Summary — Efficacy

Not applicable

Results Summary — Safety

Table 1 displays the incidence of subjects with treatment-emergent AEs.

**Table 1: Incidence of subjects with treatment-emergent AEs (all subjects valid for safety, n=9)**

| MedDRA Primary System Organ Class<br>Preferred Term | Ciprofloxacin 32.5 mg<br>(n=9) |
|---|---|
| ANY CLASS | |
| Any event | 9 (100%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | |
| Orthostatic intolerance | 1 (11%) |
| NERVOUS SYSTEM DISORDERS | |
| Dysgeusia | 9 (100%) |

All 9 subjects experienced drug-related dysgeusia of mild (n=8) or moderate intensity (n=1). There were no severe, serious, or significant AEs reported in this study. There were no clinically relevant changes in any laboratory parameter, lung function parameter or any other vital sign including ECG parameters such as QT and QTc.

Results Summary — Pharmacokinetics

PK analysis was performed in 2 study populations: all subjects valid for PK (n=9) and all subjects valid for PK without 1 subject (n=8), who was only 11 years old at study start. Table 2 and Table 3 summarize the results as geometric means, CV, and range of the PK parameters of ciprofloxacin for plasma, urine, and sputum for the 2 study populations.

Following a single inhalational dose of 32.5 mg ciprofloxacin betaine as Ciprofloxacin PulmoSphere® inhalation powder, the geometric mean AUC and $C_{max}$ in sputum were nearly 3-times higher in adolescents compared with adult subjects with CF (study 12167). Therefore, no further dose-escalation in adolescents was deemed necessary to reach a microbiologically relevant ciprofloxacin exposure in the lung. After inhalation of a single 32.5 mg dose, ciprofloxacin was rapidly absorbed (median $t_{max}$ in sputum: less than 1 hour; median $t_{max}$ in plasma 1.5 hours). The geometric mean terminal half-life in plasma was 4.5 hours; this was within the range of the known half-life for ciprofloxacin following oral or intravenous administration ($t_{1/2}$ = 3 - 5 hours).

Relative to the exposure observed after systemic administration of clinical doses (e.g., a 500 mg oral dose in adults leads to mean concentration in plasma of 2000 µg/L 2 hours after administration, AUC approximately 11 mg*h/L vs geometric mean $C_{max}$ of 141 µg/L and geometric mean AUC of 0.706 mg*h/L for inhalative administration of 32.5 mg), systemic exposure following a single inhalative dose was minimal.

In accordance with the differences in lung function (FEV1) the sputum concentrations showed high variability. Overall, ciprofloxacin exposure in sputum was >100 times higher than in plasma. Forty-five minutes after inhalation was started, the geometric mean ratio of sputum to plasma concentrations was >500. Eight hours after inhalation was started, this ratio was still >60. Mean $\%Ae_{ur}$ within 24 hours was 45% (range: 25 - 61%).

Comparing these results in adolescents with the results in adult subjects with CF, geometric mean $AUC_{norm}$ and $C_{max,norm}$ in plasma were about 20 - 30% higher in adolescents (0.916 kg*h/L and 0.183 kg/L in adolescents vs 0.754 kg*h/L and 0.140 kg/L in adults). In contrast, geometric mean AUC and $C_{max}$ in sputum were nearly 3-times higher in adolescents compared with adults (205 mg*h/L and 91.1 mg/L in adolescents vs 72.5 mg*h/L and 33.0 mg/L in adults).

**Table 2: Pharmacokinetic parameters of ciprofloxacin in plasma, urine, and sputum in all subjects valid for PK (n=9)**

| Matrix | Parameter | Unit | n | Ciprofloxacin 32.5 mg (n=9) |
|---|---|---|---|---|
| Plasma | AUC | mg*h/L | 9 | 0.7062/39.2 (0.4065-1.460) |
| | $AUC_{norm}$ | kg*h/L | 9 | 0.9162/38.3 (0.4628-1.437) |
| | AUC/D | h/L | 9 | 0.02173/39.2 (0.01251-0.04492) |
| | AUC(0-tn) | mg*h/L | 9 | 0.6888/39.5 (0.3932-1.438) |
| | AUC(0-24) | mg*h/L | 9 | 0.6932/39.8 (0.3932-1.438) |
| | $C_{max}$ | mg/L | 9 | 0.1413/40.5 (0.06730-0.2388) |
| | $C_{max,norm}$ | kg/L | 9 | 0.1833/38.3 (0.07662-0.2748) |
| | $C_{max}/D$ | 1/L | 9 | 0.004347/40.5 (0.002071-0.007348) |
| | C(24) | mg/L | 9 | 0.00178/60.8 (< LLOQ - 0.0037) |
| | $t_{1/2}$ | h | 9 | 4.463/20.4 (2.783-5.724) |
| | MRT | h | 9 | 5.374/11.4 (4.257-6.006) |
| | $V_Z/f$ | L | 9 | 296.3/54.5 (135.9-660.2) |
| | CL/f | L/h | 9 | 46.02/39.2 (22.26-79.95) |
| | $t_{max}$ [a] | h | 9 | 1.500 (0.7500-1.500) |
| Urine | $Ae_{ur}$ [b] | mg | 9 | 14.67/3.633 (8.098-19.74) |
| | $\%Ae_{ur}$ [b] | % | 9 | 45.13/11.18 (24.92-60.74) |
| | $CL_R$ | L/h | 9 | 20.49/31.3 (12.63-33.79) |
| Sputum | AUC | mg*h/L | 4 | 204.9/102.8 (76.61-528.7) |
| | $AUC_{norm}$ | kg*h/L | 4 | 283.1/125.4 (87.22-911.1) |
| | AUC/D | h/L | 4 | 6.305/102.8 (2.357-16.27) |
| | AUC(0-tn) | mg*h/L | 7 | 163.8/110.7 (40.52-520.4) |
| | $C_{max}$ | mg/L | 7 | 91.07/133.9 (19.44-322.3) |
| | $C_{max,norm}$ | kg/L | 7 | 120.3/133.1 (28.72-457.2) |
| | $C_{max}/D$ | 1/L | 7 | 2.802/133.9 (0.5983-9.916) |
| | $t_{1/2}$ | h | 4 | 3.047/68.9 (1.834-6.921) |
| | MRT | h | 4 | 2.820/51.9 (1.367-3.880) |
| | $V_Z/f$ | L | 4 | 0.6971/101.9 (0.2807-2.164) |
| | CL/f | L/h | 4 | 0.1586/102.8 (0.06147-0.4242) |
| | $t_{max}$ [a] | h | 7 | 0.8333 (0.000-1.000) |

a Median (range)
b Arithmetic mean/SD (range)

**Table 3: Pharmacokinetic parameters of ciprofloxacin in plasma, urine, and sputum in all subjects valid for PK without 1 subject (n=8)**

| Matrix | Parameter | Unit | n | Ciprofloxacin 32.5 mg (n=8) |
|---|---|---|---|---|
| Plasma | AUC | mg*h/L | 8 | 0.7059/42.1 (0.4065-1.460) |
| | $AUC_{norm}$ | kg*h/L | 8 | 0.9478/39.4 (0.4628-1.437) |
| | AUC/D | h/L | 8 | 0.02172/42.1 (0.01251-0.04492) |
| | AUC(0-tn) | mg*h/L | 8 | 0.6876/42.5 (0.3932-1.438) |
| | AUC(0-24) | mg*h/L | 8 | 0.6926/42.8 (0.3932-1.438) |
| | $C_{max}$ | mg/L | 8 | 0.1357/41.2 (0.06730-0.2388) |
| | $C_{max,norm}$ | kg/L | 8 | 0.1822/41.1 (0.07662-0.2748) |
| | $C_{max}/D$ | 1/L | 8 | 0.004174/41.2 (0.002071-0.007348) |
| | C(24) | mg/L | 8 | 0.00181/65.5 (< LLOQ - 0.0037) |
| | $t_{1/2}$ | h | 8 | 4.453/21.8 (2.783-5.724) |
| | MRT | h | 8 | 5.454/11.3 (4.257-6.006) |
| | $V_Z/f$ | L | 8 | 295.8/58.8 (135.9-660.2) |
| | CL/f | L/h | 8 | 46.04/42.1 (22.26-79.95) |
| | $t_{max}$ [a] | h | 8 | 1.500 (0.7500-1.500) |
| Urine | $Ae_{ur}$ [b] | mg | 8 | 14.66/3.883 (8.098-19.74) |
| | $\%Ae_{ur}$ [b] | % | 8 | 45.12/11.95 (24.92-60.74) |
| | $CL_R$ | L/h | 8 | 20.42/33.5 (12.63-33.79) |
| Sputum | AUC | mg*h/L | 4 | 204.9/102.8 (76.61-528.7) |
| | $AUC_{norm}$ | kg*h/L | 4 | 283.1/125.4 (87.22-911.1) |
| | AUC/D | h/L | 4 | 6.305/102.8 (2.357-16.27) |
| | AUC(0-tn) | mg*h/L | 6 | 166.5/126.7 (40.52-520.4) |
| | $C_{max}$ | mg/L | 6 | 91.80/155.8 (19.44-322.3) |
| | $C_{max,norm}$ | kg/L | 6 | 127.3/151.8 (28.72-457.2) |
| | $C_{max}/D$ | 1/L | 6 | 2.825/155.8 (0.5983-9.916) |
| | $t_{1/2}$ | h | 4 | 3.047/68.9 (1.834-6.921) |
| | MRT | h | 4 | 2.820/51.9 (1.367-3.880) |
| | $V_Z/f$ | L | 4 | 0.6971/101.9 (0.2807-2.164) |
| | CL/f | L/h | 4 | 0.1586/102.8 (0.06147-0.4242) |
| | $t_{max}$ [a] | h | 6 | 0.7917 (0.000-1.000) |

a Median (range)
b Arithmetic mean/SD (range)

Conclusion(s)

In this study, a single inhalational dose of 32.5 mg ciprofloxacin betaine as dry powder formulation was safe and well tolerated in male and female adolescents with CF aged 11 - 17 years.

Following a single inhalational dose of 32.5 mg ciprofloxacin betaine as dry powder formulation, ciprofloxacin was rapidly absorbed. Systemic exposure following these single inhalative doses was minimal compared with a 500 mg oral dose of ciprofloxacin.

Ciprofloxacin exposure in sputum was >100 times higher than in plasma. Forty-five min after inhalation was started, the geometric mean ratio of sputum to plasma concentrations was >500. Eight hours after inhalation was started, this ratio was still >60 suggesting microbiologically relevant ciprofloxacin exposure in the lung with minimum systemic exposure. Ciprofloxacin exposure in sputum of the adolescents treated in this trial was similar to results in adult subjects with CF.

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| Publication(s): | None | | |
| Date Created or Date Last Updated: | 20 APR 2012 | Date of Clinical Study Report: | 27 NOV 2008 |