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Ciprofloxacin DPI (BAY q3939)

Erratum

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for FDA Advisory Committee Meeting
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Abbreviations and definition of terms

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AE	Adverse event
BID	*Bis in die* (2 times a day)
SAF	Safety analysis set
SOC	System organ class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event

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. Objective of erratum

A previously unreported treatment-emergent serious adverse event (TESAE) was detected in a patient treated with ciprofloxacin DPI 32.5 mg BID days at cycles of 28 days on/off. This new TESAE is addressed with the present erratum.

2. Case description

This report refers to an 79-year old female patient (patient ID: 390100018) who was treated with ciprofloxacin DPI 28 in the RESPIRE 1 study. The previously undetected new TESAE was reported to local Bayer Pharmacovigilance on 16-Oct-2017.

The patient had a medical history of a femur fracture, anorexia, deafness, osteoporosis, cellulitis, tuberculosis, and cataract extract. No other adverse events (AEs) were reported in this patient during the course of the study. The TESAE "pyometra" (preferred term, pertaining to primary system organ class [SOC]: "infections and infestations") occurred in (b) (6) between Visit 7 and Visit 8 during an on-cycle. The patient presented with purulent vaginal excretion and was hospitalized (reason for seriousness) for "pyometra" in (b) (6). The Patient was treated in hospital with intravenous antibiotic therapy (Rocephin® and Flagyl®) and was discharged after 3 days in a good condition with additional oral antibiotic therapy (Augmentin®) for one week (outcome: "recovered/resolved"). The site investigator assessed the TESAE as unrelated to study drug and inhalation device and confirmed that study treatment would not have been affected, if the SAE would have been reported in time (*i.e.*, no change of dose, no treatment interruption).

As a consequence of this newly reported TESAE in a patient without any other AEs, the overall incidences of AEs, TEAEs and TESAEs in the integrated safety analysis of RESPIRE 1 and RESPIRE 2 slightly increase in both the ciprofloxacin DPI 28 group and in the total safety population. These changes are exemplarily shown for briefing document Table 6-2 (please note that all other involved safety tables would change accordingly).

Table 6–2: 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)~~ 213 (68.3)	115 (73.7)	119 (76.8)	234 (75.2)	~~692 (74.2)~~ 693 (74.3)
Any TEAE	239 (77.1)	~~204 (65.4)~~ 205 (65.7)	113 (72.4)	117 (75.5)	230 (74.0)	~~673 (72.1)~~ 674 (72.2)
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)~~ 57 (18.3)	45 (28.8)	28 (18.1)	73 (23.5)	~~197 (21.1)~~ 198 (21.2)
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; manually corrected

Overall, the company agrees with the investigator's causality assessment that this event is unrelated to study drug and device. Both the incidence changes and the nature of the event are considered not to alter the overall safety conclusions in the studies. The benefit risk assessment of inhalation therapy with ciprofloxacin DPI in the target population of patients with non-cystic fibrosis bronchiectasis to reduce the frequency of pulmonary exacerbations remains unchanged.