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Title: Safety and pharmacokinetics of two dose strengths of ciprofloxacin dry powder for inhalation (DPI) in patients with moderate to severe COPD

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Body: Introduction Ciprofloxacin dry powder for inhalation (DPI), formulated using Novartis' PulmoSphere™ technology for pulmonary delivery via a T-326 inhaler, is under investigation in various respiratory tract disorders. Aim To compare the safety and PK of two dose strengths of ciprofloxacin DPI in patients with COPD. Methods In a randomized, phase I, double-blind, crossover study, 12 (8m/4f) adults with GOLD stage II or III COPD received a single dose of 32.5 mg and 48.75 mg ciprofloxacin DPI (corresponding to 50 mg and 75 mg dry powder, respectively). The washout period was 7–14 days between doses. Results There were no severe or serious AEs nor clinically relevant differences in incidence or severity of AEs between the doses, most being mild. Drug-related AEs (bitter taste) occurred in 7 and 6 patients after 32.5 mg and 48.75 mg ciprofloxacin DPI, respectively. The PK (Table) was similar to previous studies, showing high and variable lung exposure at low systemic exposure. Conclusions Ciprofloxacin DPI was well tolerated in patients with moderate to severe COPD with no clinically relevant differences between the two dose strengths. Increased systemic exposure from the 48.75 mg dose was not matched by increased lung exposure. PK data indicate that the lower dose produced similar drug concentrations in the lung, with less powder inhaled.

Table*

		Plasma		Induced sputum	
		32.5mg (n=12)	48.75mg (n=12)	32.5mg (n=11)	48.75mg (n=11)
AUC	mg•h/l	0.600/16.0#	0.901/16.2#	552/119.3§	505/132.5§
C_{max}	mg/l	0.114/26.8	0.183/26.3	409/89.9	454/141.3
$t_{½}$	h	6.00/23.2	4.99/17.9	-	-
t_{max}^{II}	h	0.875	1.00	0.550	0.583

*Geometric means/%CV; #AUC(0–∞); §AUC(0–t_{last}); ||median