

Supplementary Material

Dose-ranging and cumulative dose studies of albuterol sulfate MDI in Co-suspension Delivery™ Technology (AS MDI; PT007) in patients with asthma: the ASPEN and ANTORA trials

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Protocol deviations: ANTORA

In the ANTORA study, protocol deviations documenting improper priming procedures at one site (site 10) were identified. At this site, 1 to 2 inhalations were mistakenly used to prime all metered dose inhaler (MDI) devices instead of the 4 required inhalations. Priming ensures delivery of the appropriate dose of study drug, so these deviations could have resulted in inappropriate dose delivery for patients at this site (n=12). There is evidence to suggest that if Proventil is not primed properly, the delivered dose can be higher than the label claim.

A pre-planned sensitivity analysis, excluding data from site 10, was conducted to determine the effect of improper priming procedures. This analysis was compared to the primary Modified Intent-to-Treat (mITT) analyses (incorporating data from all sites). Historical *in vitro* data on the loss of prime were available for albuterol sulfate pressurized inhalation suspension via metered dose inhaler (AS MDI), from which the mean drug delivery across 5 non-primed MDIs was within $\pm 15\%$ of the label claim beginning at the first and third inhalations for the valve-down and valve-up MDI orientations, respectively. However, as no such historical data was available for Proventil, *in vitro* tests of delivered dose were conducted to determine the potential impact of these protocol deviations after single-dose administration. The first 8 individual MDI inhalations were collected from 5 non-primed Proventil MDIs (valve-down orientation) to determine when the inhalation weight and delivered dose stabilized. Mean drug delivery across non-primed Proventil MDIs was within 75–125% of the label claim beginning at the second and within $\pm 15\%$ of the label claim beginning at the third inhalation.

The results of the sensitivity analyses were consistent with the primary analyses for the primary (forced expiratory volume in 1 second area under the curve from 0–6 hours [FEV₁ AUC₀₋₆]) and secondary (FEV₁ area under the curve from 0–4 hours [AUC₀₋₄]; peak change from baseline in FEV₁) endpoints, though the difference between AS MDI and Proventil was reduced in the sensitivity analyses. Nevertheless, the consistency between the two analyses was such that protocol deviations related to priming were considered not to have affected the interpretation of the study's results or conclusions; the results from subjects treated at Site 10 were retained in the mITT Analysis Set.

Subjects from the ITT Analysis Set with protocol deviations leading to subject-level exclusions from the mITT Analysis Set are summarized in Supplementary Table S1.

Pharmacokinetic parameters: ASPEN

Pharmacokinetic sample collection occurred prior to dosing and 15 minutes post-dose following doses 1 through 4. Additional pharmacokinetic samples were collected following Dose 5 at 15, 30, 60, 120, 180, 240, 300, 360, 480, 600, and 720 minutes post-dose. Plasma concentration data falling outside the following time windows were excluded: Pre-dose (within 30 minutes prior), 15 minutes (+/- 5 minute) post any of the cumulative doses, and 30 minutes (+/- 5 minutes), 60 minutes (+/- 5 minutes), 120 minutes (+/- 15 minutes), 180 minutes (+/- 15 minutes), 240 minutes (+/- 15 minutes), 300 minutes (+/- 15 minutes), 360 minutes (+/- 15 minutes), 480 minutes (+/- 15 minutes), 600 minutes (+/- 15 minutes), and 720 minutes (+/- 15 minutes) post the last cumulative dose.

Descriptive statistics for plasma concentrations of albuterol by study drug and nominal timepoint were summarized using the Pharmacokinetic Analysis Set. Pharmacokinetic parameters were estimated by noncompartmental analysis (NCA) using the software Phoenix[®] WinNonlin[®] (Certara, US). Plasma concentration values below the lower limit of quantification (LLOQ) were marked as missing in the NCA, with the exception of those values reported at pre-dose. Pre-dose concentrations that were below the limit of quantification were recorded as zero. Missing values (e.g., no blood sample collected, no value obtained at analysis) were treated as missing and excluded from the NCA. If there were ≥ 2 consecutive missing concentration values, the estimation of pharmacokinetic parameters was evaluated on a case-by-case basis. For descriptive statistics of concentration-time data and for the concentration figures, all values below LLOQ were assigned a value of $\frac{1}{2}$ LLOQ except for pre-dose which was assigned a value of 0 (no geometric mean was calculated for pre-dose).

Supplementary Tables and Figures

Supplementary Table S1. Reasons for exclusion from the mITT analysis set (ITT analysis set)

Parameter	Placebo (n=82)	AS MDI		Proventil	
		90 µg (n=81)	180 µg (n=81)	90 µg (n=82)	180 µg (n=79)
Exclusion of a subject from mITT Analysis Set (n, %)	4 (4.9)	2 (2.5)	2 (2.5)	4 (4.9)	2 (2.5)
Spirometry acceptability and repeatability (n, %)	2 (2.4)	2 (2.5)	2 (2.5)	2 (2.4)	2 (2.5)
Subject did not have post-treatment efficacy data from at least 2 Treatment Periods (n, %)	2 (2.4)	0	0	2 (2.4)	0

AS, albuterol sulfate; MDI, metered dose inhaler; mITT, Modified Intent-to-Treat.

Supplementary Figure S1. Study design for a) ASPEN and b) ANTORA.

