Data analysis plan

Pharmacokinetic Comparison of Locally Acting Orally Inhaled Drug Products ('DPI study', FDA BAA-16-00122)

1. Purpose

This document describes the non-compartmental data analysis plan for the above mentioned clinical trial. This clinical pharmacokinetic (PK) study assessed three fluticasone propionate DPI formulations (formulation 1, 2, 3) which have been characterized through *in vitro* methods. These formulations were compared in the present double-blind, randomized 4-way cross-over study; one formulation was repeated to evaluate intra-subject variability; this replicated formulation is named 3a and 3b.

2. Objectives

The primary aim of this research study is to aid the FDA in finding methods to ensure that the versions of generic drugs that are inhaled (for example, drugs used to treat asthma) are bioequivalent to the trade name drug. As a part of the research study, pharmacokinetic (PK) studies (studies measuring drug levels in the blood over time after inhalation) will be done using three different versions of fluticasone propionate (FP, a drug routinely used in asthmatic patients) administered using a dry powder inhaler (DPI, an inhalation device that delivers the drug as a dry powder).

3. Available *in vitro* data and proposed normalization

We will use the formulation with the largest Median Mass Aerodynamic Diameter (MMAD) as reference (**Table 1**).

Table 1: Summary of FPD data averaged over the 12 and 20 month time points

Formulation	FPD (<5 µm) (µg)	FPD (<3 µm) (µg)	MMAD (µm)
15-mm-016	18.707	9.977	**3.77**
15-mm-017	12.230	5.274	**4.53**
15-mm-015	15.869	8.599	**3.73**

We expect that the c/p ratio is determined by the MMAD with larger particles being deposited more centrally compared to smaller particles.

We will use three approaches of normalizing the PK parameters:

1) Normalization based on the ex-throat data

2) Normalization based on fine particle dose (FPD <3 µm) data

3) Normalization based on fine particle dose (FPD <5 µm) data

Normalization factors for the ex-throat data will be calculated separately for the VCU, AIT and OPC throats. The average normalization factors over the three throats will be used for the normalization using this approach. The normalization factors from this ex-throat approach will be used for the **primary analysis**.

For the FPD <3 µm and FPD <5 µm normalization, we will average the respective FPD data at the 12 and 20 month stability time-points. These two time-points include the time of the clinical trials performance. The 15-mm-017 formulation will be used as reference (i.e. normalization factor is defined as 1.0). Normalization factors using the FPD approach will be used as secondary analyses.

4. Methods

4.1. Non-compartmental pharmacokinetic analysis

Non-compartmental analysis (NCA) will be performed as described previously.[1] The NCA PK parameters will be calculated for each subject and study period using the formulas implemented in the Phoenix / WinNonlin Professional software. Whenever possible, at least three observations above the quantification limit will be used to estimate the terminal slope. The ANOVA statistics will be calculated for Cmax, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$. Descriptive statistics will be calculated and reported for all PK parameters.

The NCA PK parameters will be calculated and NCA PK results sent to the FDA colleagues **before unblinding**. Summary statistics will be calculated after subsequent unblinding.

4.2. Statistical analysis to address objective I

For bioequivalence statistics, the formulation with the larger MMAD will be treated as the reference formulation in each pairwise comparison (**Table 2**).

Table 2: Pairwise comparisons while treating the replicates of formulation 15-mm-015 separately

Comparison	Test formulation	Reference formulation
1	15-mm-016	15-mm-017
2	15-mm-015 (3a)	15-mm-017
3	15-mm-015 (3b)	15-mm-017
4	15-mm-015 (3a)	15-mm-016
5	15-mm-015 (3b)	15-mm-016
6	15-mm-015 (3a)	15-mm-015 (3b)

Bioequivalence statistics: Following the FDA guidelines [2], ANOVA statistics will be performed based on ln-transformed data. For each comparison, the ratio of geometric means and the 90% confidence interval for this ratio will be calculated. We will include effects for treatment, period, sequence and subject within sequence in the ANOVA. Equivalence statistics will be performed using the equations implemented in Phoenix / WinNonlin Professional or SAS.

Reference

1. Bulitta JB, Holford NHG. An Introductory Guide to Non-Compartmental Analysis. In: D'Agostino RB, Sullivan L, Massaro J, eds. *Wiley Encyclopedia of Clinical Trials*. Hoboken, NJ: John Wiley & Sons, Inc, 2008; 1-28.

2. Food and Drug Administration; Center for Drug Evaluation and Research (CDER). Guidance for Industry Statistical Approaches to Establishing Bioequivalence. *FDA Guideline* 2001: 1-48.