Systemic Exposure to Fluticasone Propionate (FP) With an Intranasal Exhalation Delivery System With FP (EDS-FLU) 186 µg Versus Observed, Dose-Normalized and Reported Orally Inhaled Flovent® HFA 220 µg

**BACKGROUND**

- EDS-FLU contains FP in a novel exhalation delivery system (EDS) that has been shown to deliver drug more deeply and broadly in the nasal cavity (Figure 1) with less loss of drug to drip-out and swelling than conventional nasal sprays.
- FP is a highly lipophlic, second-generation androstane glucocorticoid with high selectivity and affinity for the glucocorticoid receptor.
- The systemic exposure produced after use of FP is highly dependent on route of administration.
  - The majority of the FP delivered to the lung after oral inhalation is systemically absorbed. However, intranasally administered FP is associated with much lower systemic absorption.
- Second-generation intranasal corticosteroids (INS) are distinguished from first-generation INS by notably lower systemic absorption and bioavailability. Examples of the bioavailability of commonly used first-generation INS include beclomethasone (34%), budesonide (44%), and triamcinolone (46%). By comparison, the intranasal bioavailability of FP is estimated at <2%.
- The superior/posterior regions of the nasal cavity are the targets for treating chronic rhinosinusitis (CRS). These areas are typically lined with respiratory epithelium that is highly vascularized. The anterior part of the nose where standard INS sprays typically deposit medication is lined with squamous/transitional epithelium and is less vascularized. The difference in deposition characteristics between EDS and standard INS delivery systems, thus, is likely to impact systemic absorption.
- We previously reported that EDS-FLU 372 µg produces higher systemic FP exposure than Flovent® 400 µg and substantially lower FP exposure than Flovent® 440 µg. This is consistent with the greatly improved superior/posterior intranasal drug deposition needed to improve treatment of CRS compared with conventional steroid nasal sprays.
- The objective of this population pharmacokinetic (PK) analysis was to compare the simulated peak (Cmax) and extent of exposure (AUC) following multiple, twice-daily (BID) intranasal doses of EDS-FLU 186 µg to the observed data following a single, orally inhaled dose of Flovent HFA 440 µg and to the 220 µg dose-dosed-normalized exposure of Flovent HFA. Comparisons with published data for multiple, twice daily orally inhaled doses of Flovent 220 µg and 440 µg were also conducted.

**METHODS**

- A population PK model was developed using previously reported FP concentration-time data following single intranasal doses of EDS-FLU 186 µg and 372 µg in healthy subjects (Part 1) and patients with mild to moderate asthma (Part 1). See Figure 2.
- The population PK model included a structural PK model with appropriate interindividual and residual error models. Population PK parameter estimates and their associated variability were generated with the PK model.
- Phoenix® Version 1.3 NLME® Version 1.2 (nonlinear mixed-effect [NLME]) was used to perform the modeling and simulations.
- A normal distribution was assumed for plasma concentrations. No outliers were identified. All available data were used for model construction and covariate selection.
- Simulations were performed to generate a virtual population of individuals receiving single and multiple doses of EDS-FLU. Multidose regimens were simulated on a BID basis for 7 consecutive doses to achieve steady-state concentrations of FP.

**RESULTS**

- Simulated values for Cmax and AUC if following multiple BID intranasal doses of EDS-FLU 186 µg were compared with observed FP exposures following a single, orally inhaled dose of Flovent 440 µg and with the dose-normalized exposure of Flovent 220 µg. Dose-normalization of Flovent 440 µg to 220 µg was considered reasonable based on published data in which AUC of the Fluticasone propionate metered-dose inhaler (MDI) was demonstrated to be proportional from doses of 44 µg to 1760 µg in healthy subjects. ²
- Simulated geometric mean (GMR) values for Cmax and AUC if following repeat-dose EDS-FLU 186 µg were substantially lower than the steady-state exposure reported for Flovent 220 µg (Cmax 22.71 vs 45.8-80.6 pg/mL; GMR = 28.2-49.6%); AUC if 123.8 vs 191.0-463.6 h·pg/mL (GMR = 26.7-64.8%) (Tables 3 and 4).

**CONCLUSIONS**

- FP is a second-generation steroid with low nasal absorption; it acts topically where delivered. Using an EDS-FLU to substantially improve superior/posterior delivery may be a means of greatly improving anti-inflammatory effects at the key superior/posterior sites targeted for treatment in CRS with and without nasal polyps.
- This study shows that EDS-FLU 186 µg produces much lower systemic FP exposure than Flovent 220 µg following single doses.
- Simulated FP Cmax values at steady state for EDS-FLU 186 µg are less than the observed Cmax following a single dose of Flovent 440 µg.
- Exposure estimates following intranasal doses of EDS-FLU 186 µg BID for at least 7 consecutive doses generally result in exposure profiles below those that would be observed for marketed, orally inhaled FP products within the labeled range deemed to be safe.
- Overall conclusion: EDS-FLU is not bioequivalent to Flonase or Flovent. It produces higher systemic exposure than Flovent and substantially lower exposure than Flovent 220 µg. This is consistent with the greatly improved superior/posterior intranasal drug deposition needed to improve treatment of CRS compared with conventional steroid nasal sprays.

**REFERENCES**

3. Messina J, et al. A randomized comparison of bioavailability using an exhalation delivery system with fluticasone propionate (EDS-FLU) versus Flonase® nasal spray and Flovent® HFA. Poster presented at: Annual Meeting of the American Academy of Allergy, Asthma, & Immunology; March 3-6, 2017; Atlanta, GA.