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

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BACKGROUND

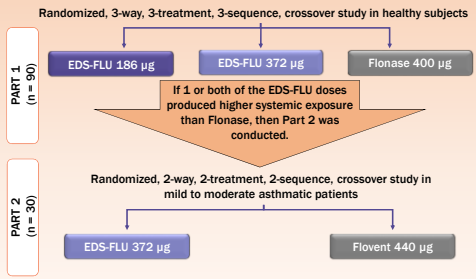
- EDS-FLU contains FP in a novel exhalation delivery system (EDS) that has been shown to deliver drug more deeply and broadly in the nasal cavity **(Figure 1)**,[1] with less loss of drug to drip-out and swallowing than conventional nasal sprays.[2]
- FP is a highly lipophilic, second-generation androstane 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.[3] 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 budesonide (34%), beclomethasone (44%), and triamcinolone (46%).[4-6] 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 Flonase® 400 µg and substantially lower FP exposure than Flovent® 440 µg.[7] 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 (C_{max}) 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-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.

Figure 1. EDS-FLU MOA; Gamma Scintigraphy Nasal Deposition[1]

METHODS

- A population PK model was developed using previously reported[7] 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 2)**. 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 outlier data 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. Multiple-dose regimens were simulated on a BID basis for 7 consecutive doses to achieve steady-state concentrations of FP.
- Simulated C_{max} and AUC 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 Flovent propellant metered-dose inhaler (MDI) was demonstrated to be proportional from doses of 44 µg to 1760 µg in healthy subjects.[8]

Figure 2. Study Design



RESULTS

Observed data (Parts 1 and 2)

- **Table 1** illustrates FP PK parameters from Study Part 1.
  - EDS-FLU 186 µg produced ≈37% higher peak exposure (C_{max}) and similar total exposure ($AUC_{0-\infty}$) compared with Flonase 400 µg.

Table 1. Statistical Comparisons of Plasma FP PK Parameters in Healthy Subjects

Parameter	Treatment Geometric LS Means		% Geometric Mean Ratio	UL of 90% CI of the Geometric Mean Ratio	% Intra-subject CV
	EDS-FLU 186 µg	Flonase 400 µg			
$AUC_{0-\infty}$ (pg · h/mL)	97.3	99.6	97.7	110.3	33.1
AUC_{0-t} (pg · h/mL)	83.6	82.1	101.9	111.2	35.7
C_{max} (pg/mL)	16.0	11.7	137.4	148.5	31.4

$AUC_{0-\infty}$, area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to time of the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; LS, least squares; UL, upper limit.

- Single doses of EDS-FLU 186 µg produced lower FP C_{max} (geometric mean ratio [GMR] = 80.6%) and substantially lower FP $AUC_{0-\infty}$ (GMR = 50.2%) in healthy subjects compared with single doses of Flovent 220 µg (dose normalized from 440 µg) in mild to moderate asthmatics **(Table 2)**.

Table 2: Observed Systemic FP Exposure Following Single Doses of EDS-FLU Compared with Single Doses of Flovent HFA MDI

Product	EDS-FLU		Flovent			
Dosing Regimen	186 µg		440 µg		DN 220 µg	
	C_{max}	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$
N	89	89	29	28	29	28
Mean	17.2	111.0	43.7	452.4	21.8	226.2
SD	7.3	49.6	18.7	268.4	9.3	9.4
Minimum	6.6	27.7	12.3	139.0	6.2	6.2
Median	16.2	104.4	42.5	411.7	21.3	205.9
Maximum	54.1	287.0	95.7	1580.0	47.9	790
CV%	42.2	44.7	42.8	59.3	42.8	59.3
GEO mean	16.0	100.5	39.8	400.1	19.9	200.1
GEO CV%	39.0	48.9	47.9	51.9	47.9	51.9
CI GEO 95% lower	7.6	39.7	15.7	146.9	7.8	73.5
CI GEO 95% upper	33.8	254.3	100.9	1089.7	50.5	544.9

Units: C_{max} (pg/mL) and AUC (h · pg/mL); $AUC_{0-\infty}$,total exposure; CI, confidence interval; CV, coefficient of variation; DN, dose normalized; GEO, geometric; SD, standard deviation

Simulated steady-state exposure of EDS-FLU 186 µg compared with observed Flovent data from Part 2:

- FP exposure (AUC_{0-12}) derived from simulations of multiple BID intranasal doses of EDS-FLU 186 µg **(Table 3)** were lower than the exposure ($AUC_{0-\infty}$) following a single, orally inhaled dose of Flovent 440 µg **(Table 2)**.

Simulated exposure of EDS-FLU 186 µg BID compared with published Flovent data:

- Simulated values for C_{max} and AUC_{0-12} of EDS-FLU 186 µg fell below the reported 95% geometric CI of multiple, BID, orally inhaled doses of Flovent 440 µg **(Tables 3 and 4)**.
- Simulated geometric mean (GM) values for C_{max} and AUC_{0-12} following repeat-dose EDS-FLU 186 µg BID were substantially lower than the steady-state exposure reported for Flovent 220 µg BID (C_{max} 22.71 vs 45.8-80.6 pg/mL [GMR = 28.2-49.6%]); AUC_{0-12} 123.8 versus 191.0-463.6 h · pg/mL (GMR = 26.7-64.8%) **(Tables 3 and 4)**.

Table 3. Simulated and Observed Systemic FP Exposure Following Multiple Doses of EDS-FLU Compared with Single Doses of Flovent HFA MDI

Product	EDS-FLU			
Dosing Regimen	186 µg BID · 7 Doses			
Source: Simulated	C_{max}	AUC_{D4_0-12}	AUC_{D4_0-24}	AUC_{last}
N	100	100	100	100
Mean	24.2	138.0	221.7	292.0
SD	8.6	65.9	116.7	168.2
Minimum	9.5	40.9	60.7	56.2
Median	22.8	120.2	193.4	249.6
Maximum	49.5	367	605	872
CV%	35.6	47.8	52.6	57.6
GEO mean	22.7	123.8	194.3	248.6
GEO CI%	37.5	50.0	55.9	63.6
CI GEO 95% lower	11.1	48.5	69.0	78.2
CI GEO 95% upper	46.6	315.8	546.9	790.7

Units: C_{max} (pg/mL) and AUC (h · pg/mL); AUC_{D4_0-12}, AUC on day 4 from 0 to 12 hours; AUC_{D4_0-24}, AUC on day 4 from 0 to 24 hours; BID, twice daily (every 12 hours); CI, confidence interval; CV, coefficient of variation; GEO, geometric; SD = standard deviation

Table 4. Observed 95% Geometric Mean CI of FP Exposure in Escalating Doses of Flovent HFA MDI After 4 Weeks of Multiple, BID Doses in Asthmatic Patients[8]

Parameter	Flovent 88 µg BID	Flovent 220 µg BID	Flovent 440 µg BID
AUC_{last} (pg · h/mL)	33.2-174.7	191.0-436.6	430.7-838.2
C_{max} (pg/mL)	17.6-36.1	45.8-80.6	73.2-145.1

AUC_{last} = AUC_{0-12h} on last day of dosing

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 C_{max} values at steady state for EDS-FLU 186 µg are less than the observed C_{max} 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 Flonase 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:

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