A Randomized Comparison of the Pharmacokinetics and Bioavailability of Fluticasone Propionate Delivered via Xhance Exhalation Delivery System Versus Flonase Nasal Spray and Flovent HFA Inhalational Aerosol

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ABSTRACT

Purpose: The exhalation delivery system with fluticasone propionate (Xhance®) has been shown to deliver drug substantially more broadly in the nasal cavity (particularly into superior/posterior regions), with less off-target loss of drug to drip-out and swallowing, than conventional nasal sprays. This open-label study evaluated the systemic bioavailability of Xhance® by comparing the pharmacokinetic (PK) properties of a single dose of fluticasone from 3 products administering the drug using 3 different devices: Xhance®, Flonase® (fluticasone propionate inhalational nasal spray), and Flovent® HFA (fluticasone propionate inhalational aerosol).

Methods: This open-label study was conducted in 2 parts. Study part 1 compared systemic exposure with a single dose of Xhance® 186 or 372 μg versus Flonase® 400 μg (3-way, 3-treatment, 3-sequence, randomized crossover in healthy subjects; n = 90). A separate study, part 2, under the same umbrella protocol, compared systemic exposure with Xhance® 372 μg versus Flovent® HFA 440 μg (2-way, 2-treatment, 2-sequence, randomized crossover in patients with mild to moderate asthma; n = 30).

Findings: With Xhance® 186 μg, the geometric least squares mean (LSM) C_{max} was higher than with Flonase® 400 μg (16.02 vs 11.66 pg/mL, respectively; geometric mean ratio [GMR], 137.42%) and the geometric LSM $AUC_{0-\infty}$ values were similar (97.30 vs 99.61 pg · h/mL; GMR, 97.78%). With Xhance® 372 μg, the geometric LSM C_{max} and $AUC_{0-\infty}$ were higher than with Flonase® 400 μg (C_{max}, 23.50 vs 11.66 pg/mL [GMR, 201.53%]; $AUC_{0-\infty}$, 146.61 vs 99.61 pg · h/mL [GMR, 147.19%]). In part 2, the geometric LSM C_{max} and $AUC_{0-\infty}$ values were lower with Xhance® 372 μg than with Flovent® HFA 440 μg (C_{max}, 25.28 vs 40.02 pg/mL [GMR, 63.18%]; $AUC_{0-\infty}$, 205.78 vs 415.16 pg · h/mL [GMR, 49.57%]).

Implications: Similar intranasal doses of Xhance® (372 μg) and Flonase® (400 μg) are clearly not bioequivalent. Systemic exposure is very low with all products. Systemic exposure is higher with Xhance® than with Flonase® and substantially lower than with Flovent® HFA 440 μg and, based on dose normalization, Flovent® HFA 220 μg. ClincalTrials.gov identifier: NCT02266927. (*Clin Ther*. 2019;41:2343–2356)

Key words: bioavailability, chronic rhinosinusitis, fluticasone propionate, intranasal corticosteroids, nasal polyps, pharmacokinetics.

INTRODUCTION

Antiinflammatory therapy with corticosteroids is an important tool in the treatment of inflammatory conditions of the upper and lower respiratory tract,

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such as allergic rhinitis, chronic rhinosinusitis (CRS), and asthma. Short courses of oral corticosteroids usually reduce inflammation and relieve symptoms; however, symptoms may recur soon after discontinuation, and even relatively short courses of systemic steroids, especially when repeated multiple times a year, are associated with serious potential risks, including hypothalamic-pituitary-adrenal (HPA)-axis suppression, sepsis, venous thromboembolism, varicella-zoster, ulcers, aseptic necrosis, psychiatric effects, and others.[1–6] Thus, topical treatment with locally acting corticosteroids (administered by oral or nasal inhalation) is generally recommended for such conditions, allowing long-term treatment of these chronic conditions while mitigating the risk for serious adverse events associated with systemic corticosteroids.[3,7–9] Although nasally administered, topically acting corticosteroids, particularly those with very low bioavailability, have been primarily associated with local adverse events rather than systemic effects, the potential for harmful, steroid-related systemic effects remains a consideration.[9–11]

CRS is a common heterogenous syndrome characterized by persistent inflammation of mucosal surfaces in the nasal and paranasal sinus cavities, including most notably the posterior and superior regions (the middle meatus and ostiomeatal complex) where sinuses normally drain and ventilate. Edema, impaired mucociliary clearance, the production of inflammatory cytokines, and, occasionally, the development of polypoid changes contribute to cardinal symptoms, including nasal congestion/obstruction, mucopurulent rhinorrhea, facial pain/pressure, and loss of sense of smell, lasting for >3 months. Locally acting antiinflammatory treatment ideally would target the posterior/superior regions of the sinonasal cavities; however, it has long been recognized that outcomes with locally acting corticosteroid treatment for CRS are often poor despite the appropriate molecular activity of the drug, and that a key reason is that conventional nasal spray is poor in achieving delivery of the drug to the targeted anatomic regions.[7,9,12–16] Simply, topical drugs are effective only at the site of delivery, and conventional nasal sprays deliver drug primarily to inferior and anterior regions, such as the nasal vestibule and inferior turbinate, which are not the primary targets in CRS.

Fluticasone propionate (FP) is a second-generation (ie, low bioavailability) androstane glucocorticoid with low bioavailability but high selectivity and affinity for the glucocorticoid receptor. The low oral bioavailability limits systemic exposure if it is swallowed and makes FP a suitable choice for local application by different routes. US Food and Drug Administration approvals of the use of various formulations include those for creams and ointments (for dermatologic conditions), oral pulmonary inhalers (for asthma and other respiratory conditions), and conventional inhaled nasal sprays (for rhinitis). Systemic exposure following FP use is affected by formulation and is highly dependent on the route of administration. For example, bioavailability following oral inhalation is ≈ 30% with Flovent® HFA (FP inhalational aerosol; GlaxoSmithKline, Research Triangle Park, North Carolina) and ≈18% with Flovent Diskus® (FP dry-powder inhaler; GlaxoSmithKline), whereas bioavailability following oral administration is <1%.[17–19] The FP bioavailability following nasal inhalation using conventional nasal spray (Flonase/Flixonase® aqueous nasal spray or Flixonase® nasule drops [both, GlaxoSmithKline]) is <2%.[20,21]

In an effort to achieve effective treatment of inflammation in the posterior/superior sinonasal spaces, a new mechanism for intranasal steroid delivery was recently developed, the OptiNose® exhalation delivery system (EDS; OptiNose Inc, Yardley, Pennsylvania). Exhalation delivery using an EDS has been shown to achieve broad intranasal distribution of drug with substantially more deposition in the superior/posterior nasal regions affected by inflammation in CRS, and with substantially less off-target loss of drug such as by swallowing and drip-out (Figure 1).[13,22] An EDS with FP (EDS-FLU; Xhance®[23] [OptiNose Inc]) is now available in the United States. In addition to using an EDS to target drug delivery to a different anatomic region, the formulation is new, does not include alcohol or fragrance, and has a higher concentration of fluticasone than do previously available products such as Flonase® and its generic equivalents. Notably, the ciliated, columnar respiratory epithelium in the superior/posterior nasal regions is highly vascularized in comparison to the nonciliated squamous epithelium located in the anterior regions of the nasal cavity, such as the nasal vestibule, where medication from conventional nasal sprays and pressurized metered-dose nasal aerosols is largely deposited. The more superior/posterior anatomic region of deposition, larger surface area of drug

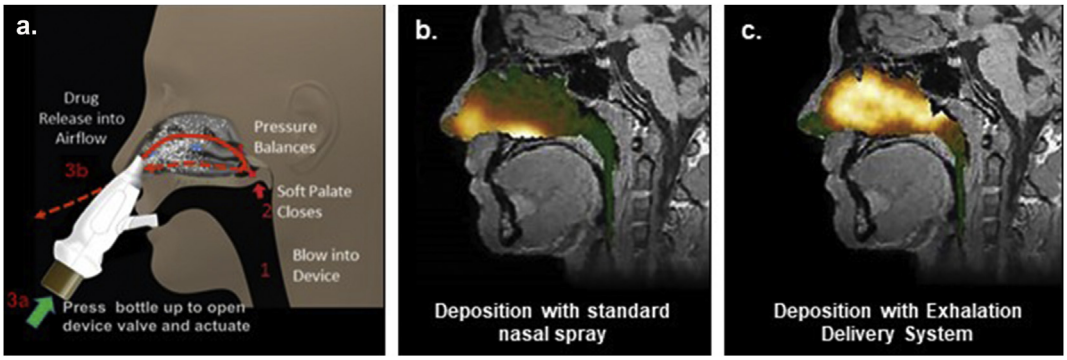

Figure 1. A, Exhalation delivery system (EDS) mechanism. Nasal deposition with convention device (B) and with the EDS device (C) by γ scintigraphy. γ Camera images after using a nasal spray without exhalation (B) or an Optinose EDS with exhalation (C). Both images are from the same healthy subject, taken 2 min after administration of radiolabeled solution and are representative of the overall findings from 211 images and 56 subjects. B and C, Reprinted with permission.[13,22]

distribution, differences in mucosal surface characteristics, and differences in formulation between exhalation delivery with Xhance® and conventional inhaled nasal spray products delivering FP all have the potential to influence the systemic absorption of FP.[13–16,24,25]

The purpose of this open-label, randomized, 2-part, pharmacokinetic (PK) study was to compare peak plasma concentrations and overall systemic exposure to FP with the use of Xhance® and 2 other, different FP-containing products: Flonase® nasal spray and Flovent® HFA inhalational aerosol.

SUBJECTS AND METHODS

Design and Objectives

This study was of a Phase I, 2-part adaptive system design (ClinicalTrials.gov identifier: NCT02266927). Each part was conducted as a separate randomized, open-label, single-dose bioavailability study. The primary objective of part 1 was to compare maximal concentration (C_{max}) and overall systemic exposure (AUC) of FP with single-dose administration of Xhance® at 2 doses (186 and 372 μg) versus Flonase® conventional nasal spray at a dose of 400 μg, in healthy subjects. If one or both Xhance® doses produced higher systemic exposure than Flonase® 400 μg (defined as an upper bound of the 90% CI of the geometric mean ratio [GMR] of >125.00%), then part 2 was to be conducted with the primary objective of comparing systemic exposure to FP after single-dose administration of Xhance® (372 μg) versus Flovent® HFA inhalational aerosol (440 μg) in patients with asthma (Figure 2).

Subjects

This study was conducted in accordance with the accepted version of the Declaration of Helsinki and in compliance with the Good Clinical Practice guideline. All subjects were required to give written informed consent prior to participation in the study. This study was conducted at 2 sites: part 1, at Celerion (Tempe, Arizona); and part 2, at Celerion UK (Belfast, Ireland). Two different institutional review boards (part 1, Chesapeake IRB [Columbia, Maryland]; and part 2, Office for Research Ethics Committees Northern Ireland [Lisburn, Ireland]) reviewed and approved the protocol and informed consents.

Inclusion criteria included: (1) male or female, aged 18 to 55 years; and (2) healthy (part 1) or mild to moderate asthma (part 2), with no clinically relevant abnormalities in the opinion of the investigator. Exclusion criteria included any condition that, in the opinion of the investigator, might have complicated or compromised the study objectives or the well-being of the subject. Additional exclusion criteria were history of smoking or use of nicotine-containing substances within the 3 months prior to screening;

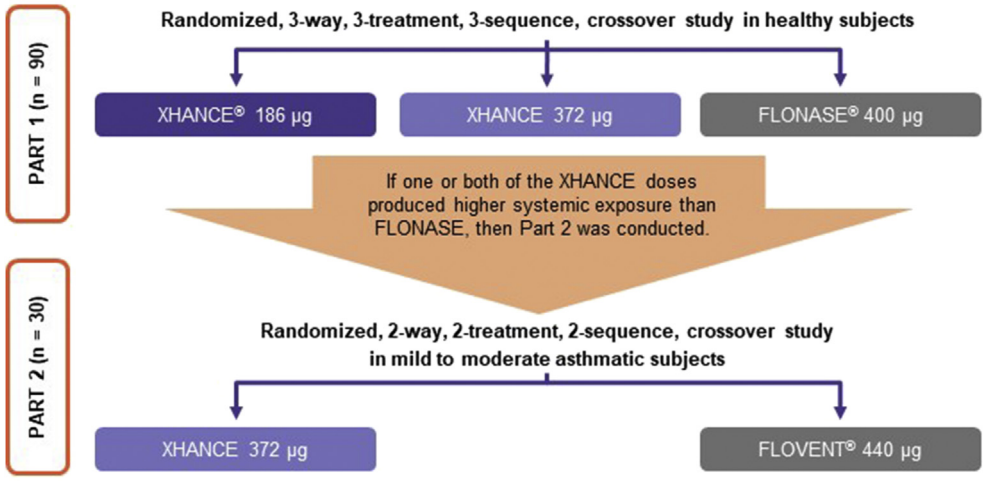

Figure 2. Study design. Trademarks: Xhance® (fluticasone propionate exhalation delivery system; OptiNose Inc, Yardley, Pennsylvania); Flonase® (fluticasone propionate nasal spray; GlaxoSmithKline, Research Triangle Park, North Carolina); Flovent® (fluticasone propionate inhalational aerosol; GlaxoSmithKline).

hypersensitivity to FP or any excipients found in the Xhance® drug formulation (parts 1 and 2), in Flonase® (part 1), or in Flovent® HFA (part 2); history of extensive nasal and/or sinus surgery; and/or known nasal obstruction. Documents and procedures were approved by the appropriate institutional review boards and ethics committees; patients provided written informed consent before participation.

Procedures

In part 1, healthy subjects were randomized to 3-way-crossover, 3-formulation, 3-sequence administration of the following treatments: (1) Xhance® 186 µg (1 metered 93-µg spray to each nostril); (2) Xhance® 372 µg (2 metered 93-µg sprays to each nostril); and (3) Flonase® 400 µg (4 × 50 µg sprays to each nostril). A total of 90 subjects were enrolled. Following the completion of part 1, data were analyzed to determine whether the study would be terminated or continued to part 2.

In part 2, subjects with mild to moderate asthma were randomized to 2-way-crossover, 2-formulation, 2-sequence treatment. Patients with asthma were studied in part 2 because previous studies establishing the systemic tolerability profile of FP (1500 µg/d) after orally inhaled administration to the lungs were performed in asthmatic patients.[26] Nonasthmatic patients were expected to experience different drug exposures with pulmonary administration and thus their inclusion would not have allowed for an appropriate benchmark for comparison with Xhance®. Part 2 single-dose administration treatments were: (1) Xhance® 372 µg (as in part 1); and (2) Flovent® HFA 440 µg inhalational aerosol (2 × 220 µg). A total of 30 subjects were enrolled.

Subjects in both parts of the study received a single dose of study drug, in accordance with the randomization scheme, on separate PK visits between 7 and 9 AM, with a washout period of not less than 7 days between treatments. Subjects were housed for a minimum of 10 h before dosing until after the 24-h blood draw (part 1) or until after the 36-h blood draw (part 2). Subjects were fasted for at least 10 h prior to dosing and for at least 4 h after dosing but were permitted to have water for thirst up to 1 h before dosing and from 1 h after dosing. Standardized meals were provided at ~4 and 10 h after dosing and at appropriate times thereafter, when applicable. Subjects returned to the facility 3 to 10 days after the last study procedures, for a follow-up visit.

Blood samples (7 mL) were collected in K_2EDTA tubes (Vacutainer; Fisher Scientific, Waltham, Massachusetts) for the measurement of plasma FP concentrations at predose (up to 10 min prior to dose administration at time 0) and at 10, 20, 30, 45, 60, 80, and 100 min and 2, 2.5, 3, 4, 6, 9, 12, 16, and 24 h after dose administration. Blood samples were also collected at 36 h after administration in part 2 only.

Measurements

The following PK parameters for plasma FP were assessed: AUC_{0-t} (pg · h/mL), calculated using the linear trapezoidal rule; $AUC_{0-\infty}$ (pg · h/mL), calculated by the linear trapezoidal rule to the last measurable plasma concentration (C_p), with additional area calculated from C_p/λ_z; percentage of $AUC_{0-\infty}$ extrapolated from Cp to infinity (AUC_{ex} [%]), reflecting the adequacy of the sampling duration, calculated as $100 \times (1 - [AUC_{0-t}/AUC_{0-\infty}])$; λ_z; C_{max} (pg/mL); T_{max} (h); and $t_{1/2}$ (h), calculated from the relationship $t_{1/2} = 0.693/\lambda_z$.

A highly sensitive assay was used for measuring plasma FP in this study, with a lower limit of detection of 1 pg/mL, which is lower than the limit of detection available in older published research.[27,28] FP concentrations in human plasma K_2EDTA were determined using HPLC-MS/MS detection. This analytical method was developed at Celerion Inc (Lincoln, Nebraska) and was validated according to standard operating procedures. The analytical range of the method was 1.00−150 pg/mL. The PK properties of FP in plasma (parts 1 and 2) were calculated using a noncompartmental approach with Phoenix WinNonlin version 6.3 (Certara LP [formerly, Pharsight], St. Louis, Missouri). Actual sampling times were used for the following PK parameter calculations: AUC_{0-t}, $AUC_{0-\infty}$, AUC_{ex}, C_{max}, T_{max}, λ_z, and $t_{1/2}$.

Statistical Analysis

For the final analysis, parameter values were imported and descriptive statistics were calculated in SAS version 9.3 (SAS Inc, Cary, North Carolina). Descriptive statistics (sample size [N]; arithmetic mean, SD, and SEM; %CV; and geometric mean, median, and range) were calculated for plasma FP concentrations and PK properties (geometric mean for AUC and C_{max} only). Data were summarized by treatment and study part. The Figures display mean and individual FP concentration−time curves on linear and semilogarithmic scales.

Tolerability

Adverse events (AEs) were coded using the *Medical Dictionary for Regulatory Activities* version 16.0. An AE that started or worsened with, or following, study drug administration was considered a treatment-emergent AE (TEAE). Clinical tolerability data were listed by subject, and continuous variables were summarized using descriptive statistics (N, mean [SD], median [range]). No inferential statistical analysis of the tolerability data was performed.

Only TEAEs and AEs experienced by $\geq 3\%$ in part 1 and $\geq 7\%$ in part 2 are reported in this article. We chose to highlight those AEs that were experienced by more than 1 subject. The 7% cutoff in part 2 represents at least 2 subjects having a given AE. Events reported include the number and percentage of subjects reporting the AE, the percentage of subjects dosed by treatment and overall in each study part, TEAE severity and relationship to study drug, and relationship to device by treatment and overall in each study part.

RESULTS

Of 90 subjects who participated in part 1, 61 were female and 29 were male, 2 were black or African American, and 88 were white. The mean age was 39.7 years (range, 20−55 years), and the mean body mass index was 27.37 kg/m^2 (range, 20.71−32.04 kg/m^2). A total of 86 subjects completed part 1.

Plasma FP exposure was generally low in part 1 (Table I and Figure 3). The mean plasma FP C_{max} in the Xhance® 186- and 372-μg and Flonase® 400-μg groups were 17.22, 25.25, and 13.37 pg/mL, respectively, with a similar T_{max} with all 3 treatments (1.332 h postdose), resulting in similar concentration−time profiles. While the mean $t_{1/2}$ was slightly shorter, by ~1 h and 0.5 h with Xhance® 186 and 372 μg, respectively, compared with Flonase® 400 μg, mean half-life estimates fell within 1 SD of the mean estimate of the treatment of comparison. The mean residual area (AUC_{ex}) ranged from 16.53% to 24.18%.

Statistical comparisons of the PK properties of FP in plasma are summarized in Table II. With the 186-μg dose of Xhance®, the total systemic FP exposure ($AUC_{0-\infty}$) was comparable to that of the significantly higher 400-μg dose of Flonase® (geometric least

Table I. Study part 1: pharmacokinetic properties of plasma fluticasone propionate (FP) with single-dose administration by Xhance® exhalation delivery system 372 and 400 μg and Flonase® nasal spray 186 μg.* Data are given as mean (SD) unless otherwise noted.

Property	Xhance® 186 μg†	Xhance® 372 μg‡	Flonase® 400 μg§
C_{max}, pg/mL	17.22 (7.4011) (n = 86)	25.25 (10.385) (n = 86)	13.37 (8.0081) (n = 85)
T_{max}, h‖	1.332 (0.333–4.00) (n = 86)	1.331 (0.499–2.52) (n = 86)	1.333 (0.499–12.0) (n = 85)
AUC_{0-t}, pg · h/mL	91.94 (41.038) (n = 86)	144.4 (65.604) (n = 86)	94.66 (46.556) (n = 85)
$AUC_{0-\infty}$, pg · h/mL	111.7 (49.746) (n = 56)	171.7 (85.547) (n = 55)	126.0 (70.507) (n = 42)
AUC_{ex}, %	18.68 (6.0132) (n = 56)	16.53 (5.8436) (n = 55)	24.18 (7.0370) (n = 42)
λ_z, 1/h	0.10107 (0.0587089) (n = 56)	0.090389 (0.0471482) (n = 55)	0.088200 (0.0547092) (n = 42)
$t_{1/2}$, h	8.436 (3.0323) (n = 56)	8.828 (2.5401) (n = 55)	9.503 (3.1609) (n = 42)

AUC_{ex}, percentage of $AUC_{0-\infty}$ extrapolated from Cp to infinity.
* Subjects 6, 26, 37, and 46 did not complete the study and, therefore, their data were excluded from the descriptive statistics. Subject 55 in period 2 (treatment C) had a measurable predose plasma fluticasone propionate concentration that was >5% of the C_{max} in this subject, and therefore the data from that subject were excluded from the descriptive statistics for the nasal spray.
† Trademark of OptiNose Inc (Yardley, Pennsylvania); 186 μg = 1 × 93 μg to each nostril (test).
‡ 372 μg = 1 × 186 μg to each nostril (test).
§ Trademark of GlaxoSmithKline (Research Triangle Park, North Carolina); 400 μg = 4 × 50 μg to each nostril (reference).
‖ T_{max} is expressed as median (range).

squares mean [LSM], 97.30 vs 99.61 pg/mL), with a GMR of 97.78% and an upper bound of 90% CI of 110.34%. The FP peak exposure (C_{max}) GMR was 37% greater with Xhance® 186 μg compared with Flonase® 400 μg. The increase in FP exposure with the 372-μg dose of Xhance® was less than proportional to that of the lower dose (186 μg), as measured by both $AUC_{0-\infty}$ and C_{max}, with ~50% greater FP exposure resulting from a 2-fold increase in dose. Consequently, the $AUC_{0-\infty}$ was ~50% greater with Xhance® 372 μg than with Flonase® 400 μg (geometric LSM, 146.61 vs 99.61 pg/mL; GMR, 147.19%; upper limit of 90% CI, 166.09%), and the C_{max} was ~2-fold higher (geometric LSM, 23.50 vs 11.66 pg/mL; GMR, 201.53%; 90% upper limit CI, 217.84%).

Because systemic exposure was higher with Xhance® 372 μg than with Flonase® 400 μg, part 2 of the study was conducted. The sample size (26) was calculated assuming a 1-tailed test using a power of at least 79% and an α error of 10%. In order to have at least 26 subjects complete the study, the statistical plan called for at least 28 subjects to be enrolled. Of 30 subjects who entered part 2, 26 completed it. Five subjects were female and 25 were male; 1 was Asian, and 29 were white. The mean age was 31.6 years (range, 18–54 years), and the mean body mass index was 25.21 kg/m^2 (range, 19.29–31.48 kg/m^2).

A summary of the mean (SD) PK properties of FP in plasma from part 2 is listed in Table III. The concentration–time profile of plasma FP with Xhance® 372 μg showed a considerably lower peak concentration compared with that with Flovent® HFA 440 μg (28.65 and 44.00 pg/mL, respectively) (Table III and Figure. 4). The T_{max} values with both

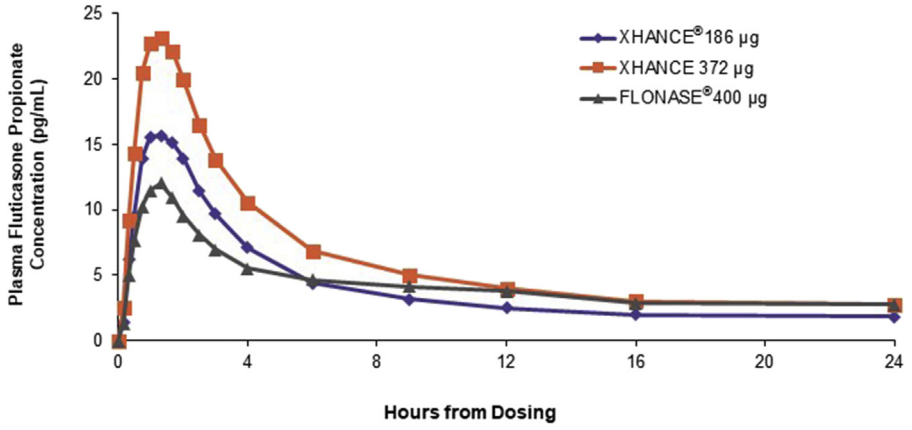

Figure 3. Study part 1: Mean plasma–time concentrations of fluticasone propionate. Trademarks: Xhance® (fluticasone propionate exhalation delivery system; OptiNose Inc, Yardley, Pennsylvania); Flonase® (fluticasone propionate nasal spray; GlaxoSmithKline, Research Triangle Park, North Carolina).

treatments were similar, ~1.0 h. The $t_{1/2}$ with Xhance® 372 µg was longer, by ~2.8 h, compared with that with Flovent® HFA 440 µg. The mean residual area (AUC_{ex}) was ~17.19% with Xhance® 372 µg compared with 11.00% with Flovent® HFA 440 µg (Table III).

Statistical comparisons of the properties of FP in plasma with Xhance® 372 µg and Flovent® HFA 440 µg are summarized in Table IV. Both total exposure ($AUC_{0-\infty}$) and peak exposure (C_{max}) were substantially lower following treatment with Xhance® 372 µg compared with Flovent® HFA 440

Table II. Study part 1: statistical comparisons of the pharmacokinetic properties of plasma fluticasone propionate (FP) with single-dose administration by Xhance® exhalation delivery system 372 and 400 µg or Flonase® nasal spray 186 µg.*

Parameter	Flonase® 400 µg,† Geometric LSM	Xhance® 186 µg‡				Xhance® 372 µg§			
		Geometric LSM	GMR, %	Upper Limit of 90% CI of GMR	Intrasubject %CV	Geometric LSM	GMR, %	Upper Limit of 90% CI of GMR	Intrasubject %CV
$AUC_{0-\infty}$, pg · h/mL	99.61	97.30	97.78	110.34	33.07	146.61	147.19	166.09	33.07
$AUC_{0-\tau}$, pg · h/mL	82.05	83.58	101.87	111.23	35.69	131.32	160.04	174.75	35.69
C_{max}, pg/mL	11.66	16.02	137.42	148.54	31.39	23.50	201.53	217.84	31.39

GMR = geometric mean ratio; LSM = least squares mean.
* Subjects 6, 26, 37, and 46 did not complete the study, and therefore, their data were excluded from the descriptive statistics. Subject 55 in period 2 (treatment C) had a measurable predose plasma fluticasone propionate concentration that was >5% of the C_{max} in this subject, and therefore the data from that subject were excluded from the descriptive statistics for nasal spray.
‡ Trademark of OptiNose Inc (Yardley, Pennsylvania); 186 µg = 1 × 93 µg to each nostril (test).
§ 372 µg = 1 × 186 µg to each nostril (test).
† Trademark of GlaxoSmithKline (Research Triangle Park, North Carolina); 400 µg = 4 × 50 µg to each nostril (reference).

Table III. Study part 2: pharmacokinetic properties of plasma fluticasone propionate (FP) with singe-dose administration by Xhance® exhalation delivery system 372 μg and Flovent® HFA inhalational aerosol 440 μg.* Data are given as mean (SD) unless otherwise noted.

Parameter	Xhance® 372 μg†	Flovent® HFA 440 μg‡
C_{max}, pg/mL	28.65 (18.724) (n = 26)	44.00 (19.115) (n = 26)
T_{max}, h§	1.001 (0.501–4.00) (n = 26)	1.033 (0.500–4.00) (n = 26)
AUC_{0-t}, pg · h/mL	188.0 (84.554) (n = 26)	408.3 (265.79) (n = 26)
$AUC_{0-\infty}$, pg · h/mL	222.6 (84.599) (n = 21)	468.7 (278.17) (n = 25)
AUC_{ex}, %	17.19 (8.0136) (n = 21)	11.00 (5.7150) (n = 25)
λ_z, 1/h	0.050852 (0.0199946) (n = 21)	0.059210 (0.0170294) (n = 25)
$t_{1/2}$, h	15.54 (5.6609) (n = 21)	12.73 (3.9630) (n = 25)

AUC_{ex} = percentage of $AUC_{0-\infty}$ extrapolated from C_p to infinity.
* Subjects 95, 107, 110, and 1095 did not complete the study, and therefore, their data were excluded from the descriptive statistics.
† Trademark of OptiNose Inc (Yardley, Pennsylvania); 372 μg = 1 × 186 μg to each nostril (test).
‡ Trademark of GlaxoSmithKline (Research Triangle Park, North Carolina); 440 μg = 2 × 220 μg to each nostril (reference).
§ T_{max} is presented as median (range).

μg ($AUC_{0-\infty}$: geometric LSM, 205.78 vs 415.16 pg • h/mL; GMR, 49.57% [upper limit of the 90% CI, 60.68%]; C_{max}: geometric LSM, 25.28 vs 40.02 pg • h/mL; GMR, 63.18% [upper limit of the 90% CI, 78.83%]), with the upper limit of the 90% CIs falling well below the threshold of 125.00% used in bioequivalence evaluations. This indicates that Xhance® 372 μg does not have a higher systemic exposure compared with Flovent® HFA 440 μg.

There were no subject discontinuations due to AEs in part 1 of the study. In part 2 of the study, 1 subject discontinued due to an unrelated AE (upper respiratory tract infection), which occurred after treatment with Flovent® HFA prior to crossover to Xhance®. There were 35 TEAEs experienced by 22 subjects (24%) in part 1 of the study; 9 subjects with Xhance® 186 μg, 10 with Xhance® 372 μg, and 6 with Flonase® 400 μg. Of these, 7 (20%) were considered by investigators to have been possibly related to study drug. The most common AE in part 1 was headache, which occurred in 5 subjects (6%), 2 occurred with Xhance® 186 μg, 2 with Xhance® 372 μg, and 1 with Flonase® 400 μg; all remaining AEs were experienced by ≤3% of subjects. In part 2, there were 30 TEAEs reported in 14 subjects (47%); 10 subjects with Xhance® 372 μg, and 8 subjects with Flovent® HFA 440 μg. None of the TEAEs were considered by investigators to have been possibly related to study drug. Wheezing was the most frequently reported TEAE in part 2 of the study, experienced 15 times by 7 (23%) subjects, with 6 subjects following Xhance® 372 μg and 4 subjects following Flovent® HFA 440 μg. Of note, 5 of these subjects also experienced wheezing prior to dosing. All remaining AEs were experienced by ≤7% of subjects. There were no deaths or serious/severe AEs reported in either part 1 or part 2 of the study.

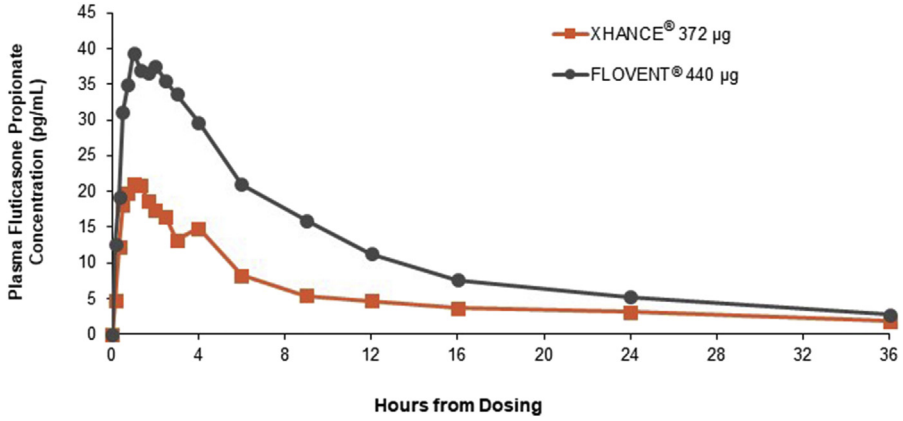

Figure 4. Study part 2: Mean plasma–time concentrations of fluticasone propionate. Trademarks: Xhance® (fluticasone propionate exhalation delivery system; OptiNose Inc, Yardley, Pennsylvania); Flovent® HFA (fluticasone propionate inhalational aerosol; GlaxoSmithKline, Research Triangle Park, North Carolina).

Table IV. Study part 2: statistical comparisons of the pharmacokinetic properties of plasma fluticasone propionate (FP) with singe-dose administration by Xhance® exhalation delivery system 372 µg and Flovent® HFA inhalational aerosol 440 µg.*

Parameter	Xhance® 372 µg,† Geometric LSM	Flovent® HFA 440 µg,‡ Geometric LSM	GMR, %	Upper Limit of 90% CI of the GMR	Intrasubject %CV
$AUC_{0-\infty}$, pg · h/mL	205.78	415.16	49.57	60.68	39.75
$AUC_{0-\tau}$, pg · h/mL	171.16	347.38	49.27	60.67	45.91
C_{max}, pg/mL	25.28	40.02	63.18	78.83	49.15

GMR = geometric mean ratio; LSM = least squares mean.
* Subjects 95, 107, 110, and 1095 did not complete the study, and therefore, were excluded from descriptive statistics.
† Trademark of OptiNose Inc (Yardley, Pennsylvania); 372 µg = 1 × 186 µg to each nostril (test).
‡ Trademark of GlaxoSmithKline (Research Triangle Park, North Carolina); 440 µg = 2 × 220 µg to each nostril (reference).

DISCUSSION

EDS delivery was developed to improve drug deposition to high and deep regions of the nasal anatomy, which play a critical role in chronic nasal inflammatory diseases. Xhance® uses a new delivery system concept, EDS, which has been shown to deliver drug substantially more broadly into the nasal cavity, with less off-target loss of drug to drip-out or swallowing than with conventional nasal sprays.[29] Given the large differences in delivery and deposition of drug, in combination with the differences in FP concentration, Xhance® could not be assumed to be bioequivalent to, or interchangeable with, conventional nasal sprays, including those delivering FP (eg, Flonase®).

In this context, it is important to examine the systemic exposure to FP with the use of products that use different modes of delivery in similar patient populations, so that the potential for systemic effects, such as HPA-axis suppression, can

be assessed, and to ensure that the systemic tolerability of Xhance® is established by reference to FP regimens previously considered well-tolerated. This protocol was designed in light of prior data establishing that the comparators (Flonase® and Flovent® HFA) were not associated with a significant risk for HPA-axis suppression in healthy volunteers and in patients with asthma at the doses studied.

Although healthy subjects are typically enrolled in most Phase I PK studies, asthmatic patients were selected for study in part 2. Systemic exposure to FP occurs through the nasal mucosa when administered via EDS-FLU, while absorption occurs through the lungs with a metered-dose or dry-powder inhaler. Systemic exposure of FP (1000 μg) with multiple inhalations via dry-powder and metered-dose inhalers is 2- to 3-fold lower in patients with asthma than it is healthy volunteers.[30] As absorption through the nasal mucosa is not known to change in asthmatic patients, enrolling these patients rather than healthy volunteers made for a more challenging PK comparison between Xhance® and Flovent® HFA.

Reference treatment doses (Flonase® 400 μg and Flovent® HFA 440 μg) were also selected based on the availability of data from previous studies characterizing PK and effects on the HPA axis.[17,19,20] Over a 4-week course, Flonase® at doses up to 400 μg BID (equivalent to 4-fold the daily dose recommended for allergic rhinitis) did not affect the adrenal response to 6-h cosyntropin stimulation.[20,31] Similarly, Flovent® HFA at doses up to and including 220 μg BID did not result in dose-related or generally significant differences in 24-h urinary cortisol excretion (n = 47) or serum cortisol (n = 65) compared with placebo when administered to patients with asthma for at least 4 weeks, indicating that a 440-μg daily dose is not associated with HPA-axis suppression and is a well-tolerated reference point.[17] It was also intended to definitively inform, in a controlled fashion, whether Xhance® was bioequivalent to the comparators.

A previously published PK/pharmacodynamics model, constructed using data from subjects treated with inhaled, oral, and IV FP, established that the effects of FP on plasma and urine cortisol concentrations are related to systemic exposure.[32] The systemic exposure (AUC_{0-24h}) to FP that resulted in 1/2(E_{max}) in plasma cortisol levels (AUC_{50}) was 3.2 μg/L · h (95% CI, 2.8−3.7); this value equates approximately to the systemic FP exposure obtained after the administration of a 1000-μg, orally inhaled dose to the lungs.[32] The present study showed that the total systemic exposure to FP (geometric LSM $AUC_{0-\infty}$) obtained with the highest recommended dose of Xhance® (372 μg) was almost 20-fold lower than the systemic exposure that resulted in half-maximal suppression of plasma cortisol.

The bioavailability with nasal administration of second-generation corticosteroids such as FP (<2%) is notably less than that with first-generation corticosteroids such as budesonide (34%), beclomethasone dipropionate (44%), or flunisolide (49%), which is advantageous when treating localized conditions such as CRS because it reduces systemic exposure.[19,33,34] However, the nasal bioavailability of corticosteroids is dependent on multiple factors, including not only drug and formulation properties (eg, molecular weight, hydrophilicity/lipophilicity, particle size), but also the surface area treated and the anatomic location and physiology of the site of deposition within the complex nasal labyrinth.[35] For example, in a 2001 study conducted by Daley-Yates et al,[36] a comparison of FP aqueous nasal spray (50 μg/100 μL) and nasal drop (100 μg/μL) formulations showed that the bioavailability was substantially lower with the nasal drops than the nasal spray (0.06% and 0.51%, respectively) despite the nasal drops having double the medication concentration. With conventional nasal steroid inhaler spray pumps, a substantial amount of drug is delivered to the anterior and inferior portions of the nasal cavities, which are lined with squamous epithelium and are less vascularized and porous than are the more posterior and superior regions, which are lined with respiratory epithelium. Moreover, the area of distribution of drug is notably less with conventional inhaled liquid nasal spray use, and a substantial fraction of delivered drug is lost to drip-out or swallowing.[36]

The systemic effects of FP with Flovent® HFA have been studied extensively. For example, a 2-year study of treatment with Flovent® HFA 440 μg BID found no significant effects on bone mineral density and a statistically significant, but not clinically relevant, temporary reduction in cortisol production.[37]

Another 2-year study found that the use of orally inhaled FP in the form of the Flovent Diskhaler® 500 μg BID had no significant effects on bone mineral density; minimal HPA axis effects; no alterations in morning plasma cortisol concentrations; and minor, but statistically significant, decreases in poststimulation cortisol C_{max} and 8-h plasma cortisol AUC values.[38] Previous studies have demonstrated the AUC of FP with orally inhaled Flovent® HFA to be proportional to those with doses of 44–440 μg in healthy subjects.[17] Therefore, after dose normalization, Flovent® HFA 220 μg (orally inhaled into the lungs) can be predicted to produce a C_{max} of 45.8–80.6 pg/mL and an AUC of 191.0–436.6 pg · h/mL; these values are substantially higher than the C_{max} and AUC demonstrated with the use of Xhance® 186 μg nasally administered by EDS in the present study, but not the 372-μg dose.[29]

Unlike conventional nasal sprays, Xhance® primarily targets the superior/posterior regions of the nasal labyrinth for drug delivery. The therapeutic intent is to substantially shift the pattern of drug delivery to place locally acting drug in the anatomic region primarily affected by disease in CRS; however, due to the comparatively high surface area, vascularity, and permeability, delivery of FP with an EDS is also expected to result in a unique PK profile. Indeed, a PK profile showing higher exposure was previously observed with the delivery of another drug by EDS versus conventional nasal spray.[39]

In the present PK study, although absolute levels of peak and overall systemic FP exposure were very low (C_{max} <30 pg/mL) with both intranasally delivered products, drug delivered by exhalation using Xhance® exhibited a clearly distinct exposure profile compared with drug delivered by conventional inhalational nasal spray (Flonase®), even when doses were comparable. Importantly, systemic exposure to FP as measured by plasma drug concentrations was shown to remain within levels previously determined to be well-tolerated. However, consistent with expectations of the delivery of the drug to a larger and more porous surface area with an EDS compared with a conventional nasal spray, the systemic exposure to fluticasone with Xhance®, although low on an absolute basis, was higher than with Flonase®. Specifically, systemic exposure with Xhance® (186 μg) was comparable to approximately double that with the dose of Flonase® (400 μg), and with a higher C_{max}. A similar FP profile shape was observed with the higher Xhance® dose, albeit with a less-than-proportional increase in systemic exposure in comparison to fold-dose. The reason for this nonlinearity is unclear but was also observed with EDS delivery of sumatriptan[39] and could possibly be an effect of the delivery of a higher dose relative to the absorptive capacity at the site of action. The relationship between the results with Xhance® and conventional nasal spray delivery was similar when similar drug masses were directly compared (Xhance® 372 μg compared with Flonase® 400 μg). The significantly higher relative bioavailability of FP with the use of Xhance® compared with Flonase® substantiates prior evidence that the use of an EDS results in a significantly larger fraction of the dose reaching the superior and posterior regions of the nasal cavity, where there is respiratory epithelium featuring columnar cells that absorb drugs and a greater surface area for drug absorption, and where topically acting treatment is targeted in the treatment of CRS.[40]

The present study also provides evidence that systemic exposure (both C_{max} and AUC) is substantially lower with the highest tested dose of Xhance® (372 μg administered intranasally by exhaler) than with Flovent® HFA 440 μg (orally inhaled) in patients with asthma. The upper limits of the 90.00% CIs of the GMRs of both C_{max} and $AUC_{0-\infty}$ were <80.00% with Xhance® and Flovent® HFA. Therefore, it can be concluded that FP bioavailability and systemic exposure with Xhance® 372 μg are less than with Flovent® HFA 440 μg, which is important because of the preexisting body of evidence concerning the systemic effects—in particular, HPA suppression—of exposure to FP with Flovent® HFA.

The potential systemic effects of orally inhaled FP HFA on the HPA axis were previously studied in both healthy volunteers and in patients with asthma. The effects of FP 440 or 880 μg BID given by inhalational aerosol were compared with those with placebo in oral corticosteroid–dependent patients with asthma (range of mean dose of prednisone at baseline, 13–14 mg/d) in a 16-week study.[17] Due to oral corticosteroid use, the majority of patients had abnormal plasma cortisol responses to short cosyntropin stimulation at baseline (69% of those later randomized to placebo and 78% of those later

assigned to FP HFA). At study end, 73% of patients on placebo, 54% of those on FP HFA 440 μg BID, and 68% of those on FP HFA 880 μg BID had abnormal poststimulation cortisol levels.[17] In the present study, the concentration–time profile of plasma FP with Xhance® 372 μg showed considerably lower C_{max} and $AUC_{0-\infty}$ values than with Flovent® HFA 440 μg.

CONCLUSIONS

The systemic exposure profile of Xhance® is unique to the delivery system and FP formulation contained within, with an FP exposure profile substantially different from those of both the Flonase® and Flovent® HFA, even at comparable doses. Although FP exposure was greater with single doses of the highest currently approved dose of Xhance®, 372 μg, than with 400 μg of Flonase® (FP delivered by conventional inhaled nasal spray), exposure was considerably lower than with the use of 440 μg of Flovent® HFA (FP by oral inhalation), creating reference to a body of prior data on the tolerability of FP to support the systemic tolerability profile of Xhance®. Therefore, based on extensive prior evidence of the systemic tolerability of FP with the use of Flovent® HFA, and based on this evidence that systemic exposure to FP is substantially lower with Xhance® than with Flovent® HFA at comparable doses, it can be concluded that Xhance® will have a similar or better profile of systemic effects such as HPA-axis suppression and other AEs.

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J.C. Messina, J.L. Carothers, and R.A. Mahmoud are employees of, and own stock options in, OptiNose Inc. R.A. Mahmoud is listed as an inventor on nasal delivery device patents. E. Offman is an employee of Certara, which provided paid consulting services to OptiNose Inc. All of the authors signed confidentiality agreements with the sponsor, had full access to the data, and vouch for the accuracy of the findings. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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