

The Pharmacokinetics of Fluticasone Furoate Given Intranasally in Healthy Subjects Using an Ultra-Sensitive Analytical Assay

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ABSTRACT

Purpose It has been previously shown that the complete pharmacokinetic profile, in particular the elimination phase, of intranasal fluticasone furoate has not been fully characterized due to the inability to quantify concentrations at low enough levels. This study was designed to evaluate the pharmacokinetic profile of intranasal FF using a validated, ultra-sensitive analytical method in healthy subjects.

Methods This was an open-label, single-dose, two-period, one-treatment, crossover study. A dose of 880 µg fluticasone furoate was administered intra nasally. Blood samples for pharmacokinetic analysis were collected at 23 time points up to 36 h and analyzed for FF plasma levels using a lower limit of quantitation (LLOQ) of 0.1 pg/mL. Medical and adverse events (AE) were monitored throughout the study.

Results Eighteen subjects were enrolled in and 17 completed the study. The results showed that all 17 subjects had measurable fluticasone furoate plasma concentrations at all time points with a clearly defined elimination phase, thus allowing estimation of AUC_{inf} and $t_{1/2}$. Median T_{max} was 1.33 h (range = 0.75–6.00), mean C_{max} was 13.05 ± 7.59 pg/mL, mean AUC_t was 148.48 ± 77.76 pg/mL * h, mean AUC_{inf} was 279.07 ± 187.81 pg/mL * h, and mean $t_{1/2}$ was 31.67 ± 29.23 h. In total 4 subjects (22.2%) experienced 4 AEs.

Conclusion Using a lower LLOQ than what has been previously reported, a complete characterization of intranasal fluticasone furoate pharmacokinetics, including a clearly defined terminal elimination phase, was achieved. This method will allow for further investigations into the pharmacokinetics of fluticasone furoate.

Introduction

Fluticasone furoate is an enhanced-affinity intranasal corticosteroids (INCS) approved for the treatment of allergic rhinitis (AR) in adults and children 2 years of age and older [1]. It exhibits its anti-inflammatory effect as an entire molecule and is therefore not a prodrug or a salt [2]. The exact mechanism of action of fluticasone furoate in treating AR is not full known, and may affect the early and late phase inflammatory response [3]. It is suggested that being a corticosteroid, it exhibits its anti-inflammatory effect on multiple inflammatory cells (such as, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (such as, histamine, eicosanoids, leukotrienes, and cytokines) [1, 3]. Other

theories suggest that fluticasone furoate can suppress inflammatory gene activation through multiple mechanisms, such as inhibition of pro-inflammatory transcription factors like the NFκB [2, 4]. Symptom relief can be achieved approximately 8 h after starting treatment and can last for up to 24 h [3].

Intranasal corticosteroids are considered the mainstay therapy of AR, are highly effective in treating AR-associated symptoms of nasopharyngeal itching, sneezing, rhinorrhea, and nasal congestion, help improving ocular symptoms, and are recommended to be used on a continuous basis for optimum efficacy [5–7].

To date, there is no evidence that one INCS is more clinically effective than another despite differences in potency [5, 8]; however,

different INCS are characterized by different pharmacological and pharmacokinetic properties [8]. It is reported that fluticasone furoate has the highest relative glucocorticoid receptor affinity and lipophilicity, an extensive hepatic first-pass metabolism, and with one of the lowest systemic exposures and potential risks among INCS used for AR [3, 8].

The systemic bioavailability of fluticasone furoate is very low [9, 10], with reported average oral bioavailability of 1.26% [9] and absolute bioavailability of 0.5% [10]. Following multiple doses of 800 µg IN fluticasone furoate every 8 h for 10 days, mean AUC_t was reported to be 74.92 pg/mL * h (95% CI = 43.64–128.63 pg/mL * h), mean C_{max} was 20.53 pg/mL (95% CI = 16.04–26.27 pg/mL), and median was T_{max} 0.75 h (range = 0.08–8.00 h). The half-life ($t_{1/2}$) and AUC_{inf} were not derived due to lack of quantifiable concentrations at the terminal phase [10].

Fluticasone furoate was shown to be highly bound (>99%) to plasma proteins in vitro studies, and to undergo extensive first-pass metabolism by the cytochrome P450 isozyme CYP3A4 to form the 17β-carboxylic acid metabolite via hydrolysis. Following oral and intravenous (IV) administration, fluticasone furoate was shown to be more than 90% eliminated in the feces, with minimal (1–2.6%) urinary excretion. Following a single 250 µg IV dose of fluticasone furoate showed a $t_{1/2}$ of 15.12 h (95% CI = 11.82–19.35 h), volume of distribution of 608.4 L (95% CI = 375.4–985.8 L), and clearance of 57.45 L/h (95% CI = 45.51–72.52 L/h) [1, 2]. One study reported a mean AUC_{inf} of 4259.39 pg/mL * h (95% CI = 3869.68–4688.34 pg/mL * h), $t_{1/2}$ of 10.584 h (95% CI = 7.713–14.525 h), mean AUC_t of 3787.47 pg/mL * h (95% CI = 3478.52–4123.86 pg/mL * h), mean C_{max} 6652.10 pg/mL (95% CI = 5803.01–7625.43 pg/mL), volume of distribution at steady state of 361.7 L (95% CI = 264.8–494.0 L), clearance of 58.70 L/h (95% CI = 53.33–64.60 L/h), and median T_{max} of 0.29 h (range = 0.08–0.33 h), following a single 250 µg IV dose of fluticasone furoate [10].

Previous studies have shown that fluticasone furoate plasma levels measured using a lower limit of quantitation (LLOQ) of 10 pg/mL were mostly undetectable (below the limit of quantitation [BLQ]), except when IV or supra-therapeutic IN doses were used, and that the elimination phase could not be characterized following IN administration due to unquantifiable concentrations during the terminal phase [9–11]. This study was designed to evaluate the pharmacokinetic profile of fluticasone furoate using a validated analytical method with a lower LLOQ, after a single dose in healthy subjects.

Methods

Study design

This was an open-label, single-dose, one-treatment, crossover study conducted at Pharma Medica Research Inc., Saint Charles, Missouri, USA. The crossover design was chosen to determine the intra-subject coefficient of variation of fluticasone furoate (results not shown). The results of the study are presented summarizes the pharmacokinetics of fluticasone furoate. Due to the exploratory nature of this study, a planned sample size of 18 subjects was deemed appropriate.

Previous reports have shown that at lower doses, there were a very low number of samples with quantifiable fluticasone furoate concentrations [11]. A dose of 880 µg was chosen for this study as it was deemed to be a reliable and safe dose to estimate fluticasone furoate bioavailability and pharmacokinetic profile [1, 2, 10, 11].

One formulation of fluticasone furoate nasal spray (from GSK Consumer Healthcare, USA) containing 27.5 µg per spray was used in both periods. Each subject received one total dose of 880 µg fluticasone furoate as 2 sprays in alternating nostrils until 16 sprays had been delivered in each nostril within approximately 2 min. Subjects were given approximately 5–8 seconds to sniff or deeply inhale through their nose after every two sprays, when alternating between each nostril. The time of the first spray was considered the time of drug administration. The 2 periods were separated by a washout of 7 days between drug administrations.

Subjects remained at the clinic for approximately 10 h before and 24 h after drug administration and fasted for approximately 10 h before and 4 h after drug administration. Water was restricted from 1 h before until 1 h after drug administration. From screening to end-of-study (EOS), the planned duration of the study was up to 37 days.

Study participants

Non-smoking male and female subjects were eligible for this study if they were 18 years of age or older, had a body mass index (BMI) of 18.0–33.0 kg/m², inclusive, were healthy with no clinically significant findings from medical history, 12-lead electrocardiogram (ECG), laboratory evaluation, physical examination, and vital signs measurements, and were willing to use acceptable effective methods of contraception.

Subjects were excluded from participation if they mainly: had a known history or presence of clinically significant diseases (including conditions compromising nasal absorption such as chronic postnasal drip, epistaxis, nasal ulcer, sores, surgery, or trauma, chronic sinusitis, or significantly abnormal nasal passage), infection, or any hypersensitivity to fluticasone or related drug substances; were pregnant or lactating females; had recently participated in other clinical trial and/or donated or lost whole blood within the safe acceptable timeframe; had known history or suspected presence of tuberculosis; showed any positive serology test, urine screen test, or breath alcohol test results; used inhibitors or inducers of hepatic drug metabolism or drugs that alter gastrointestinal pH/movement within 30 days prior to drug administration. Subjects received financial compensation for their participation.

Study endpoints

The primary endpoint of this study was to characterize the pharmacokinetics of fluticasone furoate using our validated analytical method with a low LLOQ following the administration of a single intra-nasal dose in healthy subjects. The secondary objective was to assess safety and tolerability of fluticasone furoate.

Sample collection for pharmacokinetic evaluation

In each period, a blood sample for pharmacokinetic analysis was collected by direct venipuncture in a 10-mL tube containing K₂EDTA as the anticoagulant, before drug administration and at 5, 10, 15, 20, 30, and 45 min, and at 1 h, 1 h 20 min, 1 h 40 min,

2h, 2h 20 min, 2h 40 min, and 3, 4, 5, 6, 8, 10, 12, 16, 24, and 36 h after drug administration.

Whole blood samples were centrifuged at approximately 4 °C for approximately 10 min at 3000 rpm within 60 min of collection. The separated plasma was divided into 2 approximately equal aliquots (using the second aliquot as backup) in labeled polypropylene tubes. The plasma aliquots were stored at -80 ± 15 °C within 60 min of whole blood collection, pending assay, and shipped on dry ice to the bioanalytical laboratory of Pharma Medica Research Inc., Ontario, Canada.

Bioanalytical method and procedures

At the bioanalytical facility, the plasma samples were analyzed for fluticasone furoate, using fluticasone furoate- d_5 as the internal standard. The standard calibration range was 0.100–100 pg/mL using a plasma sample volume of 0.800 mL. The concentration of the internal standard was 300 pg/mL. Plasma samples, treated with K_2EDTA as the anticoagulant, were processed by liquid-liquid extraction with Methyl-tert-Butyl-Ether (MtBE):Hexane (60:40), the organic phase was dried and the reconstituted sample was transferred for analysis. Samples were analyzed by LC-MS/MS (Shimadzu Prominence UFLC & SCIEX API 6500) and reverse phase chromatography under gradient conditions with mobile phases composed of 0.01 % Ammonium Hydroxide in Water and Methanol (100 %). Chromatographic separation was achieved using serial analytical columns (C18, 50 × 3 mm, 2.6 μm and Biphenyl, 50 × 3 mm, 2.6 μm). Fluticasone furoate was analyzed using positive ion scan mode and a parent-daughter mass to charge ion transition of 539–293 and 544–293 for the internal standard. The retention time for fluticasone furoate was approximately 3.3 min.

Correlation was obtained between peak area ratios and the corresponding calibration standard concentrations over the entire calibration range. A linear equation ($y = ax + b$) with $1/x^2$ weighting

► **Table 1** Accuracy and Precision of the Validated Analytical Method.

	Precision (%)	Accuracy (%)
LLOQ intra-day	≤ 14.4	84.7–111.0
LLOQ inter-day	14.4	101.0
QC L, M, H intra-day	≤ 6.4	94.3–112.0
QC L, M, H inter-day	≤ 7.2	101.0–102.3
QC quality control, H high (80 pg/mL), L low (0.3 pg/mL), LLOQ lower limit of quantitation (0.1 pg/mL), M medium (50 pg/mL).		

► **Table 2** Stability of Fluticasone Furoate in Human Samples.

Condition	Stability
In whole blood	3.00 h at room temperature
	3.00 h in ice-water bath
In plasma	Four cycles at -80 ± 15 °C
	19.00 h at room temperature
	20.00 h in ice-water bath
Processed samples	145.25 h at approximately 5 °C
	45.00 h at approximately 5 °C
	2.50 h at room temperature
	2.50 h at room temperature

was used. The coefficients of determination of the single-point calibration curves were ≥ 0.999 . The recoveries of fluticasone furoate and the internal standard were 93.7–94.1 % and 92.1–95.2 %, respectively. The accuracy and precision of the method are presented in ► **Table 1** and the stability of fluticasone furoate in human samples is presented in ► **Table 2**.

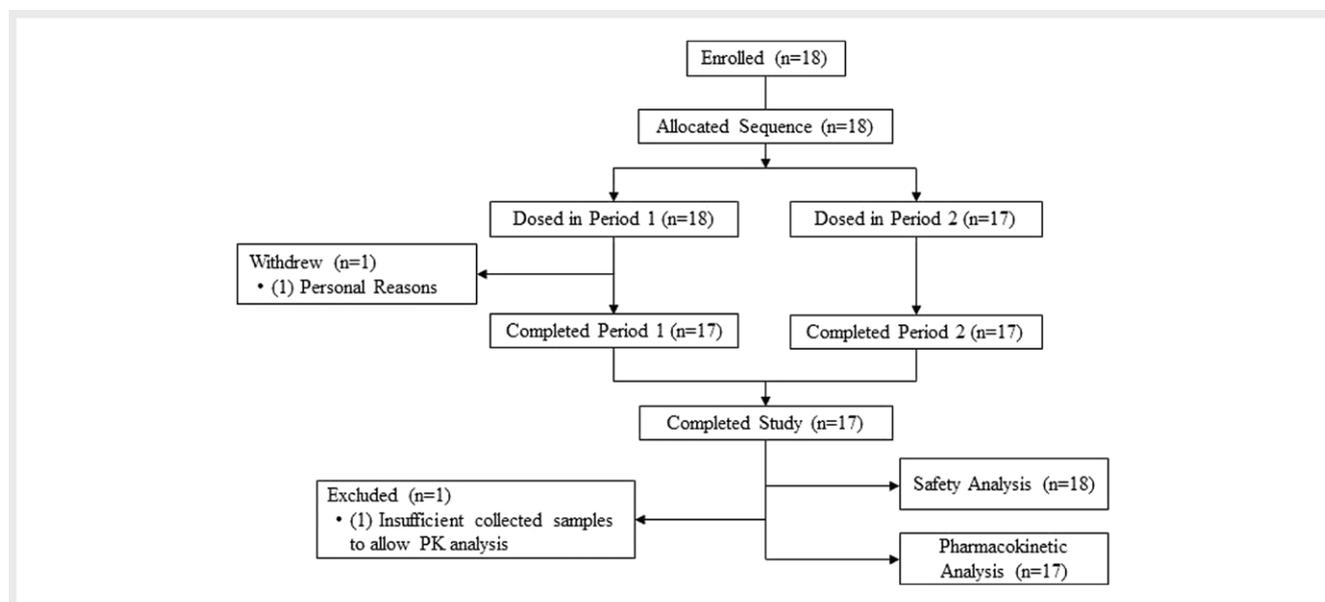
Safety evaluation

Physical examination, vital signs (blood pressure, heart rate, respiratory rate, and temperature) measurements, and clinical laboratory tests (biochemistry, hematology, and urinalysis) were performed at screening and EOS. Serology blood tests (human immunodeficiency virus, hepatitis C antibody, and hepatitis B surface antigen), 12-lead ECG recording, serum human chorionic gonadotropin (hCG) test for female participants, urine drug screen, urine cotinine test, and tuberculosis questionnaire evaluation were also obtained at screening. In addition, in each period, urine drug screen, urine cotinine test, urine hCG test for female participants, and breath alcohol tests were performed at check-in, blood pressure and heart rate were measured prior to drug administration and at 1, 3, and 6 h post-dose, and temperature was measured daily during confinement. All clinical laboratory tests were performed by Quest Diagnostics Lenexa, Kansas, USA.

The use of herbal products, nutritional supplements, vitamins, grapefruit and grapefruit-containing products, alcohol and alcohol-containing products, caffeine- and xanthine-containing products, and inhalers-, nasal sprays-, or steam inhalation-based practices were restricted during the study. Concomitant medications were not allowed during the study unless requested or approved by the investigator. Nondrug therapies that did deviate from protocol procedures were allowed. Medical and adverse events (AE) were monitored from screening to EOS.

Pharmacokinetic and statistical analysis

The pharmacokinetic parameters were estimated for fluticasone furoate using a non-compartmental approach in Phoenix WinNonLin version 6.4 (Certara USA, Inc., Princeton, NJ). The actual post-dose sample collection times were used in the pharmacokinetic analysis. The peak concentration (C_{max}) and the time to reach C_{max} (T_{max}) were determined from individual plasma concentration-time profiles for FF. The area under the plasma concentration-time curve (AUC_t) was calculated using the linear up-log down trapezoidal method from 0 to 36 h. The area under the plasma concentration-time curve from zero to time infinity (AUC_{inf}) was calculated as $AUC_t + C_t/k_{el}$, where C_t is the last measurable concentration and k_{el} is the terminal rate constant. The terminal half-life ($t_{1/2}$) was calculated as $0.693/k_{el}$. All obtained samples were assayed; however, subjects with sufficient data to allow pharmacokinetic characterization were included in the pharmacokinetics and statistical analyses. Descriptive statistics for the pharmacokinetic parameters of fluticasone furoate were calculated. Safety and tolerability of FF were assessed using descriptive statistics for all subjects who participated in the study and were primarily based on the occurrence and severity of AE.



► **Fig. 1** Subjects disposition.

► **Table 3** Summary of Demographic Characteristics.

Demographics	Study Population N = 18
Gender, n (%)	
Female	11 (61.1)
Male	7 (38.9)
Age, years, mean ± SD (range)	40.5 ± 12.4 (22–59)
BMI, kg/m ² , mean ± SD (range)	26.5 ± 3.6 (19.6–31.4)
Weight, kg, mean ± SD (range)	76.9 ± 12.3 (155.8–183.6)
Height, cm, mean ± SD (range)	170.2 ± 7.9 (56.1–101.9)
Race, n (%)	
White	8 (44.4)
Black or African American	10 (55.6)
Ethnicity, n (%)	
Hispanic or Latino	0 (0.0)
Not Hispanic or Latino	18 (100.0)
Arithmetic means are reported in this table. BMI body mass index, SD standard deviation.	

Results

Subjects' disposition and demographics

Eighteen healthy subjects were enrolled in and 17 subjects completed the study (► **Fig. 1**). Overall, 11 female and 7 male subjects participated in the study. The subjects had a mean age of 40.5 years and BMI of 26.5 kg/m². Eight (44.4%) subjects were white and 10 (55.6%) were black or African American (► **Table 3**).

Pharmacokinetic analysis

A total of 23 samples were collected from each of the 18 subjects. One subject withdrew from the study approximately 10 min after dosing due to personal reasons (difficult phlebotomy), and was thus excluded from the pharmacokinetic and statistical analyses. All the

remaining samples collected from the 17 subjects had measurable fluticasone furoate plasma concentrations, including concentrations during the elimination phase. As such, all the 17 subjects showed concentration-time profiles with a clearly defined terminal elimination phase and so the AUC_{inf} and t_{1/2} could be confidently estimated.

Bioanalytical analysis

The concentrations of all the samples analyzed were within the validated range. A calibration standard and quality control samples of at least 6% of the total study samples at three different concentrations were extracted and analyzed within each batch. All seven extracted batches during the entire study conduct passed the acceptance criteria. The inter-day precision (%CV) was ≤ 5.6% and accuracy was 91.8% to 101.6%. A total of 782 samples were analyzed in this study (391 samples in period 1), of which 79 samples were randomly selected around the C_{max} and the elimination phase of each profile for incurred sample reanalysis (ISR). The results of the ISR showed 96.4% confirmation of the original values within ± 20%.

Statistical results

Following a single 880 µg dose of IN fluticasone furoate, median T_{max} was 1.33 h (range = 0.75–6.00 h), mean C_{max} was 13.05 ± 7.59 pg/mL, mean AUC_t was 148.48 ± 77.76 pg/mL * h, mean AUC_{inf} was 279.07 ± 187.81 pg/mL * h, and mean t_{1/2} was 31.67 ± 29.23 h (► **Table 4**, ► **Fig. 2**). The intra-subject variability was estimated to be 22% for AUC_t and 24% for C_{max}.

Safety and tolerability

The administration of 880 µg of IN FF under fasted conditions was well tolerated by the healthy subjects who participated in the study. Four subjects (22.2%) experienced 4 AEs in total: 3 subjects (16.7%) experienced 3 AEs (one venipuncture site reaction and 2 headache events) in period 1 and one subject (5.6%) experienced 1 AE

► **Table 4** Pharmacokinetic Parameters Based on Plasma Fluticasone Furoate Following Administration of Single Intranasal Dose of 880 µg to Healthy Subjects.

PK Parameter	N	Mean ± SD
AUC _{inf} , pg/mL * h	17	279.07 ± 187.81
AUC _t , pg/mL * h	17	148.48 ± 77.76
C _{max} , pg/mL	17	13.05 ± 7.59
t _{1/2} , h	17	31.67 ± 29.23
		Median (Range)
T _{max} , h	17	1.33 (0.75–6.00)

Arithmetic means are reported in this table. AUC_{inf} area under the concentration versus time curve from time zero to infinity, AUC_t area under the concentration versus time curve, from time zero to the time of the last measurable concentration (t), C_{max} maximum measured concentration over the sampling period, PK pharmacokinetic, SD standard deviation, t_{1/2} apparent elimination half-life, T_{max} time of the maximum measured concentration over the sampling period.

(venipuncture site reaction) in period 2. In total, the 2 headache AEs reported by 2 subjects (11.1%) in period 1 were considered to be possibly related to FF. All AEs were mild in severity and resolved.

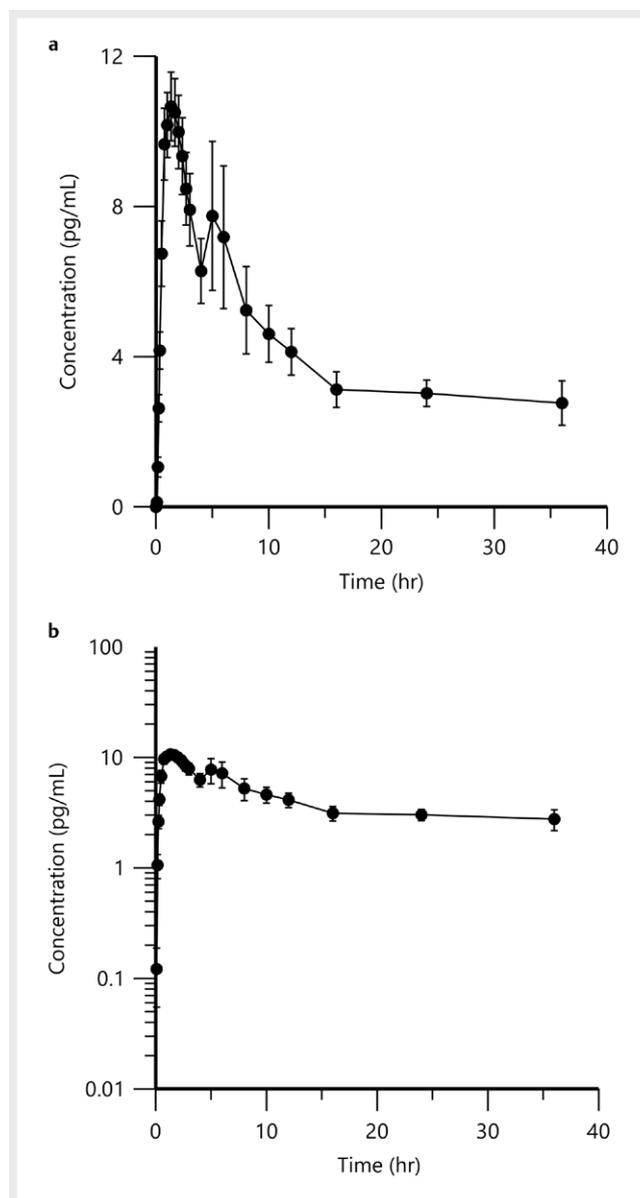
There were no AE-related withdrawals or serious AEs reported in this study. There were no clinically meaningful trends in laboratory safety measurements, vital signs, physical examinations, or ECGs reported during this study. All measurements were either within normal range or were deemed by the investigator to be not clinically significant for all subjects.

Discussion

With an increase in the development of newer drugs and dosage forms, a full understanding of their pharmacokinetics is essential in characterizing their disposition. The development of newer analytical methods that can quantify concentrations at lower thresholds (i. e. having a low LLOQ) plays an important role. The lack of a sensitive enough LLOQ poses a barrier in being able to confidently evaluate the complete pharmacokinetic behaviour of these drugs.

Fluticasone furoate is one of the newest INCS, is available as prescription or over-the-counter medicine, and may be more preferred by patients compared to other INCS [12]. It is one of the first-line treatments recommended in AR treatment [13–15]. Previous pharmacokinetic characterization of IN fluticasone furoate was based on an LLOQ of 10 pg/mL [1, 9–11, 16], rendering plasma levels at the terminal elimination phase undetectable resulting in a limited amount of pharmacokinetic information that can be obtained.

A dose escalation study involving the administration of IN fluticasone furoate over a dose range of 55–440 µg once daily for 2 weeks, showed that from 1476 plasma samples collected from 502 patients, 12 years of age or older with seasonal AR, only 5.3% of total samples from 11.8% of patients had detectable fluticasone furoate levels when an LLOQ of 10 pg/mL was used. In addition, with higher doses, more samples had quantifiable concentrations, but did not exceed 15.4% of the samples collected at the 440 µg dose nor three times the LLOQ [11]. Furthermore, following the administration of a multiple-dose IN fluticasone furoate regimen of 2640 µg daily for 3 days followed by 880 µg on the day of PK sam-



► **Fig. 2** Mean plasma fluticasone furoate concentration-Time profiles in linear (a) and log-linear scale (b) following administration of a single intranasal dose to healthy subjects. Error bars represent the standard deviation about the mean.

pling to 16 healthy subjects, 50.00% of subjects had BLQ plasma concentrations at 8 h post-dose, 6.25% had BLQ plasma concentrations at all time points, and 6.25% had only 1 measurable plasma concentration [10].

This study implemented a validated analytical method able to measure fluticasone furoate plasma concentrations using an LLOQ of 0.1 pg/mL following administration of a single 880 µg dose of IN fluticasone furoate. As a result, all the samples (100.00%) collected from all the subjects who completed the study had detectable and quantifiable plasma levels of FF at all collection time points, including the terminal linear phase, and as such allowed for a better characterization of the pharmacokinetic profile of fluticasone furoate than before. The results showed that sampling for a longer time would likely have led to more measurable concentrations, thus

allowing for a more complete evaluation of the terminal pharmacokinetic parameters.

The results showed a higher mean AUC_t (148.48 pg/mL * h) and median T_{max} (1.33 h), and lower C_{max} (13.05 pg/mL) compared to previously reported values for IN fluticasone furoate (74.92 pg/mL * h, 0.75 h, and 20.53 pg/mL, respectively) [10]. The T_{max} range (0.75 to 6.00 h) fell within previously reported values for IN fluticasone furoate (0.08 to 8.00 h) [10]. Differences in these parameters values can be explained by the number of measurable concentrations used to calculate them owing to the LLOQ used in the analytical method. When an LLOQ of 10 pg/mL was used, C_{max} and T_{max} were derived from 15 subjects with at least 2 measurable plasma concentrations, including 1 subject with only 1 measurable plasma concentration, and AUC_t was derived from 14 subjects with at least 2 measurable plasma concentrations, including several subjects with undetectable plasma concentrations at 8 h post-dose [10]. In this study, however, C_{max} , T_{max} , and AUC_t were calculated based on data from 17 subjects who had all their plasma concentrations quantifiable at all pharmacokinetic sampling time points, using a 100 times lower lower limit of quantitation.

This study provides a breakthrough in the bioanalysis and pharmacokinetics of fluticasone furoate given intra-nasally. It allowed for a more accurate characterization of the concentration-time profile of fluticasone furoate following a single intra-nasal dose in healthy subjects, such that the terminal elimination phase was clearly defined allowing for a more confident estimation of AUC_{inf} and $t_{1/2}$. In addition, the new method eliminates the need to expose healthy subjects to multiple doses and allows calculation of the pharmacokinetic parameters following a single dose even as low as 110 mcg, which corresponds to the standard dose that is given clinically.

Conclusion

Using a lower limit of quantitation of 0.1 pg/mL, the complete characterization of fluticasone furoate pharmacokinetics, including a clearly defined terminal elimination phase, was achieved following a single dose given intranasally. The improved bioanalytical method enabled further insight into the pharmacokinetics of fluticasone furoate that was not possible with other analytical methods that used a higher lower limit of quantitation. With this new proven sensitivity, it will allow for more optimal study designs investigating intra-nasal or inhaled formulations of fluticasone furoate as the expected concentrations following both routes of administration are expected to be low. This improved bioanalytical method will allow for further investigations into the pharmacokinetics of fluticasone furoate.

Authors Contributions

MB contributed to the study concept and the bioanalytical method development and validation. ZT contributed to the study design, pharmacokinetic and statistical data analyses, study results interpretation, and writing of the initial drafts of the article. MB and ZT have reviewed and approved the final manuscript for submission, and MB holds the final responsibility of the article submission.

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Compliance with Ethical Standards

This study was approved by Salus Institutional Review Board (IRB), Texas, USA. All study procedures involving human participants were conducted in conformance with the 1964 Declaration of Helsinki and its later amendments, the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations, IRB ethical standards, the United States standards and requirements and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. All subjects provided written informed consent before trial initiation.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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