Pharmacokinetics of Ciclesonide and Desisobutyryl Ciclesonide After Administration Via Aqueous Nasal Spray or Hydrofluoroalkane Nasal Aerosol Compared With Orally Inhaled Ciclesonide: An Open-Label, Single-Dose, Three-Period Crossover Study in Healthy Volunteers

Ruediger Nave, PhD[1]; Rolf Herzog, MS[1]; Aziz Laurent, MD[2]; and Mark A. Wingertzahn, PhD[3]

[1]Nycomed GmbH, Konstanz, Germany; [2]PPD Development, Austin, Texas; and [3]Nycomed US Inc., Florham Park, New Jersey

ABSTRACT

Background: Ciclesonide, an intranasal corticosteroid, is administered as a prodrug and is converted to the active metabolite, desisobutyryl ciclesonide, in the upper and lower airways. Previous studies have assessed systemic exposure with the ciclesonide hydrofluoroalkane metered dose inhaler (CIC HFA-MDI) and the ciclesonide aqueous nasal spray (CIC-AQ) formulations. However, systemic exposure with ciclesonide HFA nasal aerosol (CIC-HFA) developed for the treatment of allergic rhinitis has not been investigated.

Objective: This study compared the systemic exposure of ciclesonide and desisobutyryl ciclesonide after administration of ciclesonide formulated as an aqueous nasal spray, an HFA nasal aerosol, or as an orally inhaled HFA-MDI.

Methods: Healthy adults (aged 18–60 years) were randomly assigned in an open-label, single-dose, 3-period crossover design to CIC-AQ 300 µg, CIC-HFA 300 µg, or CIC HFA-MDI 320 µg. Serum samples were collected before study drug administration and at 5, 15, and 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 18, 22, and 24 hours after dosing. The primary pharmacokinetic parameters were $AUC_{0-\infty}$ and C_{max} of desisobutyryl ciclesonide. Adverse events were elicited by direct questioning of participants throughout the study.

Results: Thirty volunteers were randomly assigned. Most of the volunteers were male (63% [19/30]) and white (83% [25/30]); the mean age was 36 years and mean weight was 68 kg. Concentrations of desisobutyryl ciclesonide were quantifiable (lower limit of quantitation [LLOQ] = 10 ng/L) in the serum samples of only 5 volunteers (of 30) receiving CIC-AQ, and the highest C_{max} value of desisobutyryl ciclesonide was 26.7 ng/L (mean C_{max}, 15.2 ng/L). The $AUC_{0-\infty}$ of desisobutyryl ciclesonide for CIC-AQ was below the LLOQ of the bioanalytic assay. Mean C_{max} and $AUC_{0-\infty}$ of desisobutyryl ciclesonide were 59.1 ng/L and 397.5 ng · h/L, respectively, for CIC-HFA; and 586.2 ng/L and 2685.0 ng · h/L, respectively, for CIC HFA-MDI. Concentrations of the parent compound, ciclesonide, were below the LLOQ in serum samples after administration of CIC-AQ; they were detectable up to 2 hours after administration of CIC-HFA and up to 4 hours after administration of CIC HFA-MDI. Treatment-emergent adverse events occurred with a low frequency in all 3 treatment groups (30% [9/30] overall) and were mild in intensity as determined by the study investigator.

Conclusions: In this study, compared with that of CIC HFA-MDI, the systemic exposure of desisobutyryl ciclesonide was 10-fold lower after administration of CIC-HFA and at least 40-fold lower after administration of CIC-AQ. All treatments were well tolerated. ClinicalTrials.gov identifier: NCT00458835. (*Clin Ther.* 2009;31:2988–2999) © 2009 Excerpta Medica Inc.

Key words: allergic rhinitis, bioavailability, ciclesonide, hydrofluoroalkane, intranasal corticosteroids, pharmacokinetics.

INTRODUCTION

Allergic rhinitis is a heterogeneous disorder characterized by nasal congestion, sneezing, itching, and rhi-

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norrhea.[1] An estimated 20 to 40 million Americans are affected by the disease. Allergic rhinitis is associated with morbidity, including an increased incidence of asthma, and a reduction in productivity and quality of life, imposing a substantial economic burden on society and the health care system.[2,3]

Current pharmacologic treatments for allergic rhinitis include intranasal corticosteroids, antihistamines, and decongestants. Intranasal corticosteroids are the standard of care for maintenance therapy.[4] Although both inhaled and intranasal corticosteroids are generally considered to be well tolerated, orally inhaled corticosteroids for asthma have been associated with suppression of the hypothalamic-pituitary-adrenal (HPA) axis and are reported to cause growth suppression in children.[5,6] Other potential adverse effects of inhaled corticosteroids include cataract development and an increased risk of fractures[7,8]; however, the effect of low-level corticosteroid exposure (100–400 μg/d) during long-term use (ie, >2 years) is unknown.[5,7,9,10]

The impact of systemic exposure to inhaled and intranasal corticosteroids on HPA axis suppression varies depending on the specific steroid, the formulation, the device, the route of administration, and the prescribed dose.[11,12] Ciclesonide is a corticosteroid with low oral and systemic bioavailability, resulting in low systemic exposure after administration via hydrofluoroalkane metered dose inhaler (HFA-MDI) (<1%).[13–15] Ciclesonide is administered as an inactive parent compound and is activated by intracellular esterases in the upper and lower airways to a pharmacologically active metabolite, desisobutyryl ciclesonide (des-CIC).[16,17] Des-CIC forms reversible intracellular conjugates with fatty acids, whereas free des-CIC is extensively bound (99%) to plasma proteins; this binding significantly limits the systemic amount of free des-CIC.[18] Ciclesonide aqueous nasal spray (CIC-AQ) has been approved for the treatment of seasonal allergic rhinitis in patients aged ≥6 years and for the treatment of perennial allergic rhinitis in patients aged ≥12 years in the United States.[19] An HFA nasal aerosol solution formulation of ciclesonide (CIC-HFA) is being developed for the treatment of allergic rhinitis. The HFA-MDI formulation of ciclesonide (CIC HFA-MDI) is available in the United States for the treatment of asthma in patients aged ≥12 years.[20]

Two recent national surveys, *Allergies in America* and *Pediatric Allergies in America*,[21–23] have reported that perceived sensory attributes and bothersome adverse effects associated with intranasal allergy medications, such as dry feeling, dripping down the throat, drowsiness, and bad taste, may affect patients' satisfaction with therapy and lead to discontinuation of allergy medications.[21,24] HFA nasal aerosols are alcohol based and offer a dryer delivery method in a smaller volume compared with wet, aqueous nasal formulations.

Systemic exposure data on the CIC-AQ and CIC HFA-MDI formulations have been reported.[14,25] However, a search of the literature on MEDLINE for the past 5 years (2004–2009) to investigate systemic exposure with CIC-HFA did not identify any published reports. The objective of this study was to compare the systemic exposure of ciclesonide and des-CIC after administration of ciclesonide as an aqueous nasal spray, an HFA nasal aerosol, or an orally inhaled HFA-MDI.

METHODS

Study Design

This was an open-label, single-dose, 3-period crossover study (**Figure 1**). Each volunteer received 1 dose of study medication followed by a 7- to 14-day washout period before administration of the second and third study medications. Volunteers were randomly assigned to a protocol-specified treatment sequence by means of a computer-generated randomization process. The randomization included 6 treatment sequences according to a Latin-square design. Two Latin squares were used with a total of 6 unique treatment sequences (ABC, BCA, CAB, ACB, BAC, and CBA). The design was balanced with regard to all 3 treatments, such that each treatment was applied to every period the same number of times (twice) and each volunteer received all 3 treatments. Therefore, intrasubject comparisons could be conducted for each of the 3 pairwise comparisons.

This study was approved by IntegReview Ethical Review Board (Austin, Texas) and was conducted in accordance with the principles of the revised Declaration of Helsinki.[26] Written informed consent was obtained from each volunteer before study participation.

Study Volunteers

Adults aged 18 to 60 years who were healthy as assessed during a screening examination and who could demonstrate proper oral inhalation technique

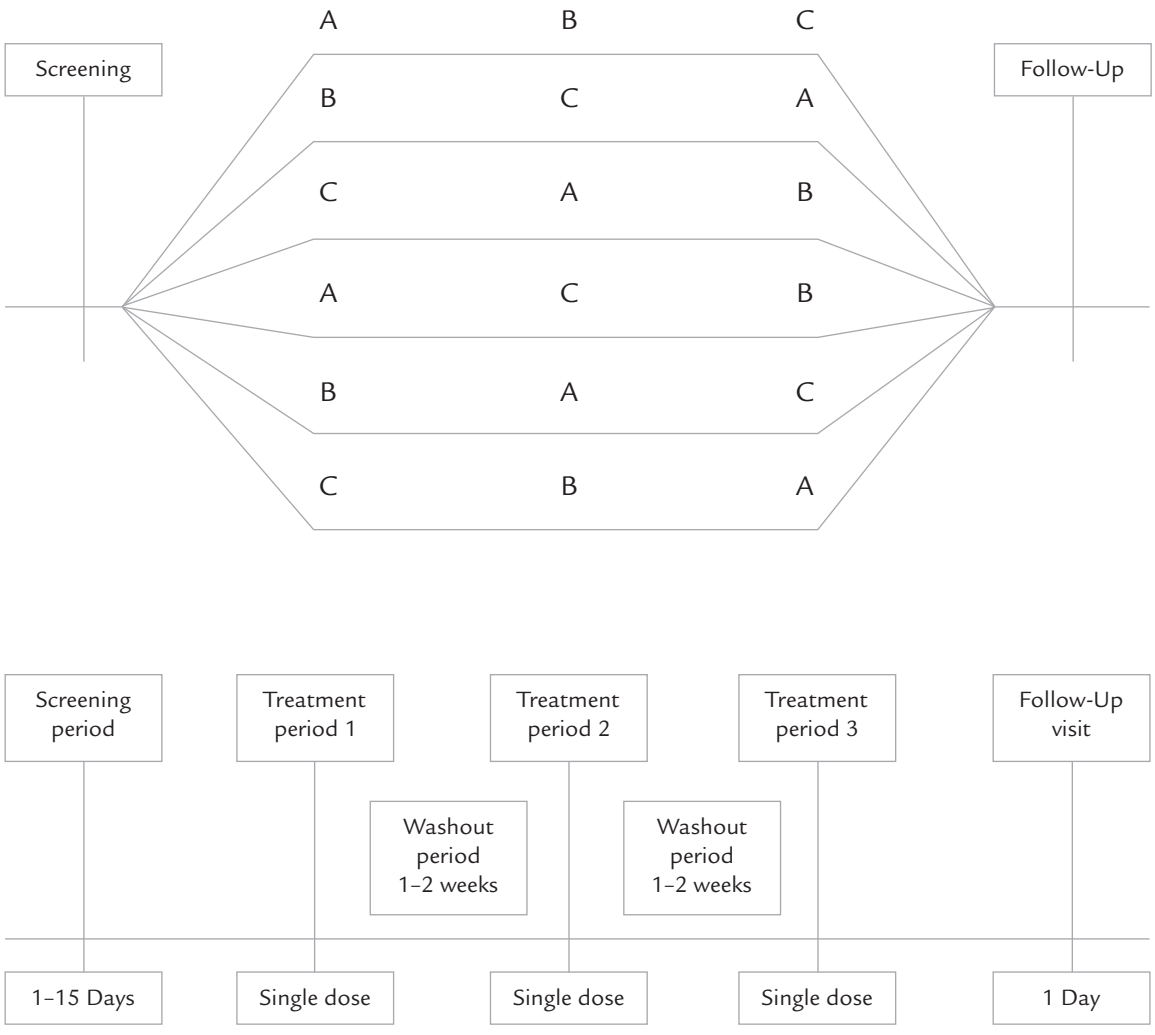

Figure 1. Study design. A = single dose of ciclesonide 300 μg via aqueous nasal spray (3 sprays per nostril, 50 μg per spray); B = single dose of ciclesonide 300 μg via hydrofluoroalkane (HFA) nasal aerosol (2 puffs per nostril, 75 μg per puff); C = single dose of ciclesonide 320 μg via HFA metered dose inhaler (ex actuator, 4 puffs inhaled, 80 μg per puff).

with the HFA-MDI at the screening visit were eligible for the study. The screening examination included medical history, physical examination, vital signs, body mass index (≥18 and ≤28 kg/m^2), weight (>50 kg), ECG, and clinical laboratory tests (blood chemistry, hematology, blood coagulation, serology, urinalysis, urine drug screen, serum pregnancy test, urine pregnancy test, and alcohol breath test). Candidates were excluded if they had a history of nasal pathology, including nasal polyps or other respiratory tract malformations; recent nasal biopsy, nasal trauma, or surgery; atrophic rhinitis or rhinitis medicamentosa within the last 60 days; a respiratory infection or disorder within 30 days before the screening visit; or a respiratory infection that developed during the screening period. Additional exclusion criteria were a history or current evidence of clinically relevant allergies or idiosyncratic reactions to drugs or food; history of allergic reactions to any corticosteroids, including ciclesonide or any excipients of the formulations; participation in any

investigational drug trial within 30 days before the screening visit or during the study; use of any medication within 14 days before trial drug administration or at the screening visit within <10 times the elimination $t_{1/2}$ of the respective drug; or anticipated need for concomitant medications during the entire treatment period.

Treatment

Healthy volunteers were randomly assigned to receive a single dose of CIC-AQ 300 µg (3 sprays per nostril, 50 µg per spray), a single dose of CIC-HFA 300 µg (2 puffs per nostril, 75 µg per puff), or a single dose of CIC HFA-MDI 320 µg (ex actuator, which is the actual amount of dose delivered from the mouthpiece of the MDI; 4 puffs inhaled, 80 µg per puff) on 1 day. All nominal doses were similar, allowing direct pharmacokinetic comparison without dose normalization.

Bioanalytic Method

Concentrations of ciclesonide and its metabolite des-CIC in human serum samples were analyzed by validated HPLC MS/MS using liquid–liquid extraction for sample preparation. Ciclesonide and des-CIC were quantified using the corresponding deuterated isomers (D10-ciclesonide and D10–des-CIC) as internal standards. Mass spectrometry was performed on an MDS Sciex API 4000 (Applied Biosystems/MDS Analytical Technologies, Concord, Ontario, Canada) mass spectrometer in the selective reaction monitoring mode with the Photospray interface (atmospheric pressure photoionization). The lower limit of quantitation (LLOQ) for both ciclesonide and des-CIC was 10 ng/L, and the upper limit of quantitation was 2000 ng/L based on 300 µL of human serum. The standard curves were linear from 10 to 2000 ng/L using weighted linear regression analysis ($1/x^2$, concentration weighting). The bioanalytic assay method was developed internally by the study sponsor (Nycomed GmbH, Konstanz, Germany).

Calibration data, quality-control (QC) data, and chromatograms indicated acceptable performance of the method during sample analysis. The calibration curves for ciclesonide and des-CIC were linear, with coefficients of correlation of ≥0.9979 for ciclesonide and ≥0.9984 for des-CIC. The interday accuracy from the analysis of QC samples (QC levels 30, 60, 1000, and 1600 ng/L) was in the range of 97.0% to 99.0% for ciclesonide, and the interday accuracy for des-CIC was between 99.1% and 102.1%. The interday precision for ciclesonide ranged from 3.7% to 5.8% and that for des-CIC ranged from 2.2% to 5.3%.

Pharmacokinetic Assessments

Serum samples were collected before study drug administration and at 5, 15, and 30 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 18, 22, and 24 hours after dosing. At least 3 mL of blood was taken using serum Monovettes (Sarstedt, Inc., Nümbrecht, Germany) at each sample collection time for the determination of ciclesonide and des-CIC parameters. To avoid contamination, blood sampling was performed with closed Monovette systems. Blood samples were stored immediately after collection for 60 to 90 minutes in ice water (~0°C–4°C) to allow clotting. Samples were centrifuged at 2200*g* (~4°C) for 10 minutes to separate the serum. The serum was transferred into 2 polypropylene tubes (at least 1 mL of serum was collected for the first aliquot) and immediately deep-frozen at –20°C or below for further analysis. The primary pharmacokinetic parameters assessed were $AUC_{0-\infty}$ and C_{max} of des-CIC.[27] To ensure reasonable calculations of individual $AUC_{0-\infty}$ values, the extrapolated areas were required to be <20% of the total $AUC_{0-\infty}$. The secondary pharmacokinetic parameters assessed were AUC_{0-last}, T_{max}, and $t_{1/2}$ for des-CIC and $AUC_{0-\infty}$, AUC_{0-last}, C_{max}, and $t_{1/2}$ for ciclesonide.

Tolerability Assessments

The occurrence of treatment-emergent adverse events was recorded throughout the study by the study investigator. Volunteers were instructed at the beginning of the study to inform the investigator of any and all untoward effects felt during the study. In addition, the volunteers were asked at every clinic visit about any adverse events since the last visit. The investigator was responsible for reporting and documenting all adverse events during the study, including the start and stop date of occurrence, intensity, frequency, course of action, relationship to study medication, and whether the event was serious. The intensity of adverse events was assessed as mild, moderate, or severe.

Statistical Methods

The principal pharmacokinetic comparisons were of CIC-AQ 300 µg and CIC-HFA 300 µg versus CIC HFA-MDI 320 µg as a reference. Because of the low

exposure levels of ciclesonide and des-CIC after administration of CIC-AQ[28] and the lack of information on systemic exposure after CIC-HFA, no information on point estimates and within-subject variances was available. Therefore, sample-size determination was based on the comparison of CIC-AQ and CIC HFA-MDI only, and we assumed that the sample size would be adequate for the comparison of CIC-HFA and CIC HFA-MDI. Using an SD of 0.5, we calculated that 24 total volunteers (12 in each sequence) would provide >95% power to detect a 96% reduction (difference of 3.33 on a log scale) in C_{max} of des-CIC. To account for dropouts and protocol violations, 30 volunteers were to be randomized into the trial.

Both intent-to-treat (ITT) and per-protocol (PP) analyses were used for all pharmacokinetic measures.[29] The PP analysis was the primary means of assessment. The ITT analysis included those volunteers in the full analysis set who had provided at least 1 postdose serum concentration for any treatment. The PP analysis included all volunteers who completed at least 2 treatment periods (had to include at least 1 measurement with CIC HFA-MDI) in the full analysis set without any major protocol violation. Tolerability analyses were performed using the ITT population.

For CIC-AQ, values for the primary variables $AUC_{0-\infty}$ and C_{max} for des-CIC were quantifiable only in a limited number of serum samples. Therefore, the focus of the pharmacokinetic analysis was on descriptive statistics. For CIC-HFA and CIC HFA-MDI, a sufficient number of volunteers in the PP population provided measurable serum des-CIC values; therefore, $AUC_{0-\infty}$ and C_{max} for des-CIC were assessed by ANOVA with period, treatment, and sequence as fixed effects, and patient nested in sequence as a random effect. The 2-sided 90% and 95% CIs were derived for the ratio of means for each respective variable using SAS software (SAS Institute Inc., Cary, North Carolina).

RESULTS

Volunteer Disposition and Baseline Demographic Characteristics

A total of 77 volunteers were screened, and 30 were randomly assigned and included in the ITT population and tolerability analysis (**Figure 2**). Reasons for screening failure included failure to meet 1 or more inclusion criteria (n = 25) or meeting 1 or more exclusion criteria (n = 16). Six volunteers were not randomized because the randomization quota was achieved. One ITT volunteer was a protocol violator and was excluded from the PP population. Most of the study volunteers were male (63% [19/30]) and white (83% [25/30]); the mean age was 36 years and mean weight was 68 kg (**Table I**). Demographic characteristics for the ITT population were similar to those for the PP population.

Pharmacokinetic Assessments

Serum concentrations of ciclesonide were below the LLOQ in samples from volunteers (PP population) after the administration of CIC-AQ. Ciclesonide was quantifiable in most of the serum samples up to 2 hours after the administration of CIC-HFA and up to 4 hours after the administration of CIC HFA-MDI (**Figure 3A**).

Concentrations of des-CIC in the serum were very low after the administration of CIC-AQ (**Figure 3B**). Specifically, concentrations of des-CIC above the LLOQ were quantifiable in only 3% of the serum samples from the volunteers receiving CIC-AQ (16 samples from 5 volunteers) (**Table II**). The highest C_{max} of des-CIC for CIC-AQ was 26.7 ng/L, and the mean C_{max} was 15.2 ng/L. The mean C_{max} of des-CIC was 59.1 ng/L for CIC-HFA and 586.2 ng/L for CIC HFA-MDI. The mean $AUC_{0-\infty}$ of des-CIC for CIC-AQ could not be calculated. The mean $AUC_{0-\infty}$ values of des-CIC for CIC-HFA and CIC HFA-MDI were found to be 397.5 and 2685.0 ng · h/L, respectively.

A sufficient number of paired values were available in the PP population for CIC-HFA (29 volunteers for C_{max} and 18 for $AUC_{0-\infty}$) to allow comparison with CIC HFA-MDI (29 volunteers for C_{max} and 29 for $AUC_{0-\infty}$) (**Table III**). The $AUC_{0-\infty}$ value of des-CIC after administration of CIC-HFA was 14.31% (95% CI, 11.45%–17.87%) lower than that with the CIC HFA-MDI formulation. Similarly, the C_{max} value after administration of CIC-HFA was 9.79% lower (95% CI, 8.20%–11.70%) than that after use of the CIC HFA-MDI.

Pharmacokinetic evaluations of AUC_{0-last}, T_{max}, and $t_{1/2}$ values for des-CIC were also limited to the CIC-HFA and CIC HFA-MDI formulations (**Table IV**). The mean AUC_{0-last} values for CIC-HFA and CIC HFA-MDI were consistent with the $AUC_{0-\infty}$ values. The mean $t_{1/2}$ of des-CIC was apparently longer for CIC HFA-MDI (9.2 hours) compared with CIC-HFA (3.4 hours). All ITT results were similar to the PP population results.

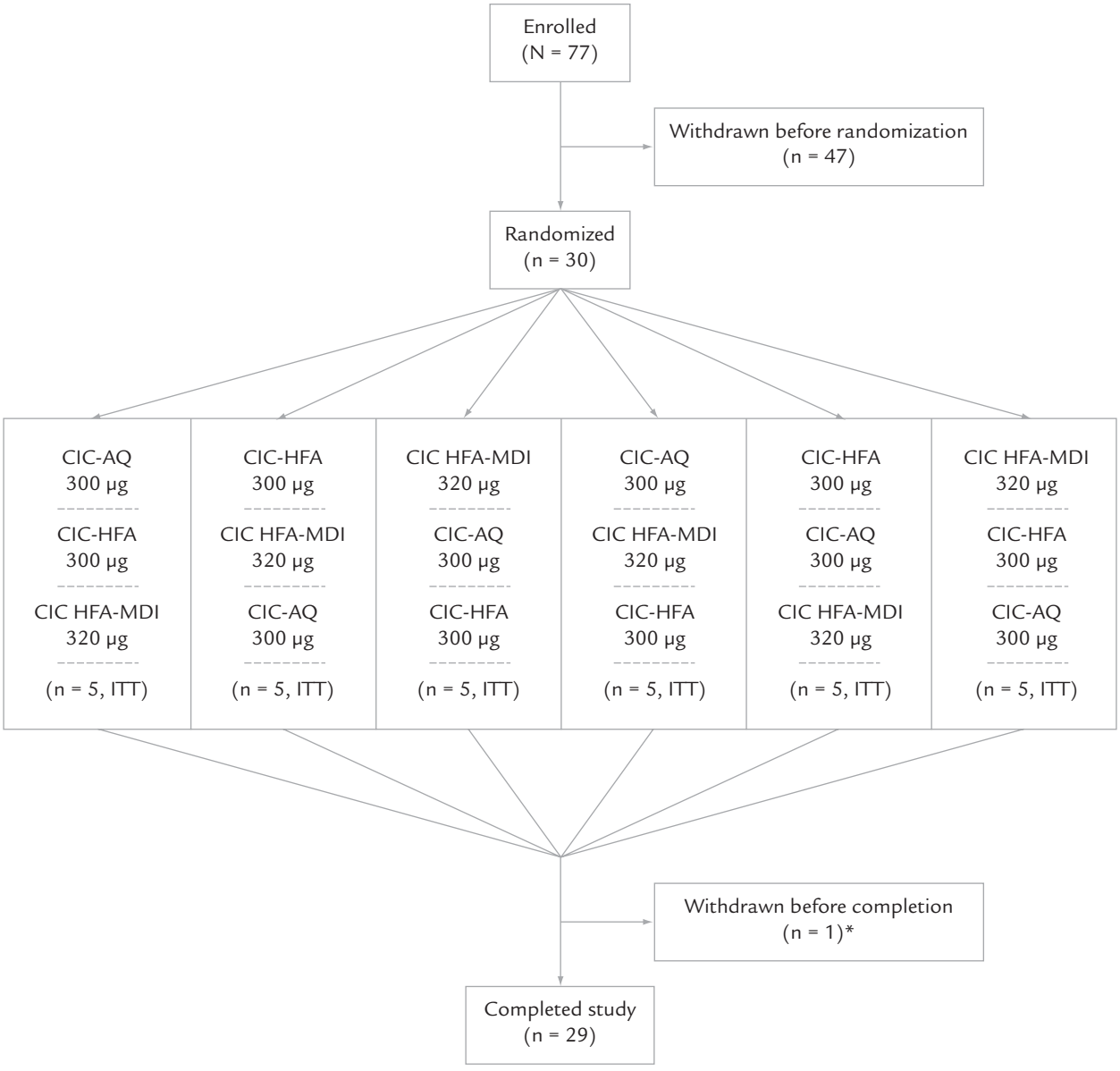

Figure 2. Disposition of the study volunteers. CIC-AQ = ciclesonide aqueous nasal spray; CIC-HFA = ciclesonide hydrofluoroalkane nasal aerosol; CIC HFA-MDI = ciclesonide HFA metered dose inhaler; ITT = intent to treat. *One volunteer withdrew before completion of the third treatment visit.

Tolerability Assessments

The frequency of treatment-emergent adverse events in the ITT population was low. Overall, 9 of 30 volunteers (30.0%) in the ITT population experienced treatment-emergent adverse events, with the most common being headache (13.3% [4/30]) and nasal discomfort (10.0% [3/30]) (**Table V**). Treatment-emergent adverse events in all 3 treatment groups were mild in intensity as determined by the study investigator. Headache, nasal discomfort, and pharyngolaryngeal pain were rated by the study investigator as likely or definitely related to treatment. No serious adverse events were reported. No volunteers withdrew from the study because of an adverse event.

Table I. Demographic characteristics of the volunteers treated with ciclesonide (intent-to-treat population).

Characteristic	Result (N = 30)
Age, mean (range), y	36 (20–58)
Sex, no. (%)	
Male	19 (63)
Female	11 (37)
Weight, mean (range), kg	68 (51–93)
Race, no. (%)	
White	25 (83)
Black	4 (13)
Asian	1 (3)
Ethnicity, no. (%)	
Hispanic	8 (27)
Non-Hispanic	22 (73)

There were no reports of epistaxis with either of the nasally administered CIC-AQ or CIC-HFA treatments.

DISCUSSION

This open-label, crossover pharmacokinetic study directly compared the systemic exposure of des-CIC (the active metabolite of ciclesonide) for the orally inhaled solution of ciclesonide (CIC HFA-MDI) with that of an intranasal aqueous spray (CIC-AQ) and an HFA nasal aerosol delivery system (CIC-HFA). Ciclesonide is a prodrug, and systemic concentrations of ciclesonide are not quantifiable below the LLOQ after intranasal administration of the aqueous formulation of ciclesonide in humans.[28] The principal target compound for the evaluation of systemic bioavailability in this study was des-CIC. The results of this study suggest a low systemic exposure of ciclesonide and des-CIC after administration via each of the 3 delivery systems.

In this study, systemic bioavailability of a single dose of CIC-AQ was minimal and lower than that of CIC HFA-MDI. Despite the robust and sensitive assay used in this study (LLOQ = 10 ng/L), only 5 of 30 volunteers (16 samples) in the CIC-AQ treatment group had serum concentrations of des-CIC above the LLOQ. Serum concentrations of the parent compound ciclesonide or of des-CIC ($AUC_{0-\infty}$) could not be determined in this group. Therefore, no comparisons of $AUC_{0-\infty}$ could be made between CIC-AQ and CIC HFA-MDI.

For both the CIC-HFA and CIC HFA-MDI treatment groups, nearly complete serum concentration profiles of des-CIC were obtained. The $AUC_{0-\infty}$ for des-CIC and ciclesonide could be determined in 18 and 29 volunteers in the CIC-HFA and CIC HFA-MDI treatment groups, respectively. The mean C_{max} value observed for des-CIC was ~40 times greater with use of the CIC HFA-MDI (586.2 ng/L) than with CIC-AQ (15.2 ng/L) and 10 times greater with CIC HFA-MDI than with CIC-HFA (59.1 ng/L).

The low systemic exposure of ciclesonide after administration via CIC-AQ or CIC HFA-MDI observed in this study has been reported previously.[25] In a randomized, crossover study on systemic exposure in 6 healthy individuals, the median C_{max} values of des-CIC were below the LLOQ of 10, 11.5, and 17 ng/L after administration of CIC-AQ 200 µg once daily, 400 µg once daily, or 400 µg twice daily, respectively, for 14 days.[28] In another parallel-group study of the pharmacokinetic disposition of inhaled ciclesonide and des-CIC in 12 healthy individuals and 12 patients with asthma, the systemic exposure (mean C_{max}) of des-CIC on administration of a single dose of ciclesonide via HFA-MDI (1280 µg) was low in healthy individuals (1001 ng/L) as well as in patients with asthma (1002 ng/L) and similar to that observed in the present study (ie, 586.2 ng/L).[25] In another randomized, crossover study of 6 healthy individuals receiving a single oral dose of [^{14}C] ciclesonide (6.9 mg), concentrations of the parent compound ciclesonide were below the LLOQ in serum after oral administration because of almost complete first-pass metabolism,[14] and in another in vitro study of the protein-binding profile of ciclesonide in human plasma, the systemic bioavailability of des-CIC was found to be <1% because of high plasma-protein binding (>99%).[18] In the present study, ciclesonide administered via aqueous nasal spray, HFA nasal aerosol, or HFA-MDI was found to be reasonably well tolerated in all 3 treatment groups, and reported adverse events were mild.

The open-label study design, inclusion of healthy volunteers versus patients with allergic rhinitis, and administration of a single dose of all 3 ciclesonide formulations were some of the limitations of this study and limit the extrapolation of results beyond this small, selected volunteer population.

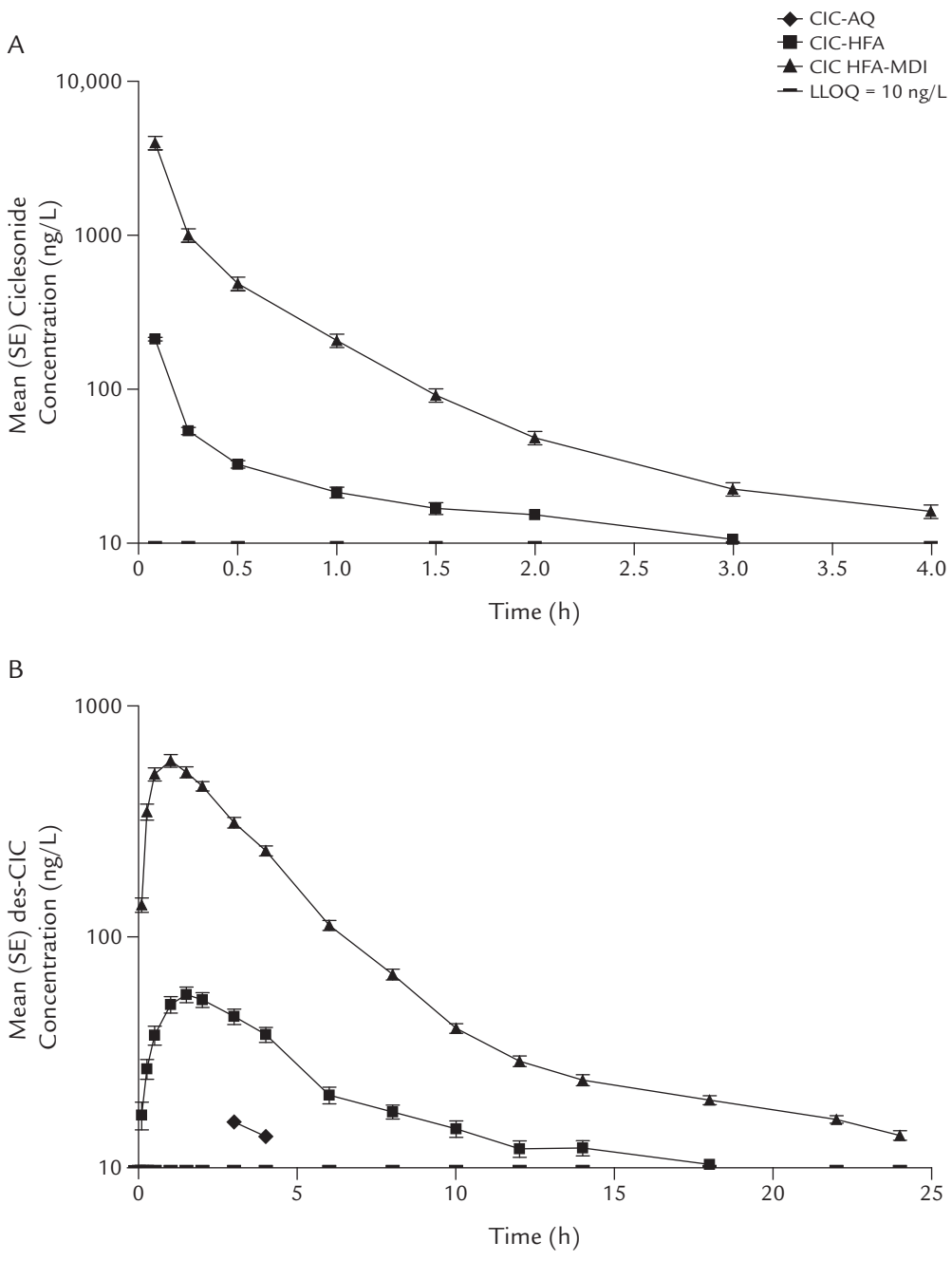

Figure 3. Mean (SE) serum concentrations of (A) ciclesonide and (B) desisobutyryl ciclesonide (des-CIC) over time after a single dose of ciclesonide via aqueous nasal spray (CIC-AQ), hydrofluoroalkane nasal aerosol (CIC-HFA), or HFA metered dose inhaler (CIC HFA-MDI) in healthy volunteers (n > 3; per-protocol population). LLOQ = lower limit of quantitation.

Table II. Serum concentrations of desisobutyryl ciclesonide in healthy volunteers after administration of ciclesonide via aqueous nasal spray (CIC-AQ), hydrofluoroalkane nasal aerosol (CIC-HFA), or HFA metered dose inhaler (CIC HFA-MDI) (per-protocol analysis).

	CIC-AQ 300 µg			CIC-HFA 300 µg		CIC HFA-MDI 320 µg	
Variable	C_{max}, ng/L*	C_{max}, ng/L†	$AUC_{0-\infty}$, ng · h/L	C_{max}, ng/L	$AUC_{0-\infty}$, ng · h/L	C_{max}, ng/L	$AUC_{0-\infty}$, ng · h/L
No. of volunteers	5	29	0	29	18	29	29
Mean (SE)	15.2 (2.9)	2.6 (1.2)	NC	59.1 (4.2)	397.5 (30.2)	586.2 (33.6)	2685.0 (119.6)
Median (range)	12.4 (11.5–26.7)	0 (0–26.7)	NC	59.0 (21.8–111.0)	403.7 (175.8–684.3)	602.0 (332.0–1120.0)	2762.0 (1603.0–4301.0)

NC = could not be calculated.
*Values reported as lower limits of quantitation; values were set to no value.
†Values reported as lower limits of quantitation; values were set to zero.

Table III. Paired value estimates of desisobutyryl ciclesonide in the serum of healthy volunteers after administration of ciclesonide via hydrofluoroalkane nasal aerosol (CIC-HFA) compared with HFA metered dose inhaler (CIC HFA-MDI) (per-protocol analysis).

	No. of Volunteers				Ratio (% of	CI for the Ratio	
Variable	CIC-HFA	CIC HFA-MDI	CIC-HFA	CIC HFA-MDI	HFA-MDI)	90%	95%
C_{max}, ng/L	29	29	55	559	9.79	8.45–11.35	8.20–11.70
$AUC_{0-\infty}$, ng · h/L	18	29	365	2552	14.31	11.92–17.18	11.45–17.87

Table IV. Estimates of secondary pharmacokinetic parameters of desisobutyryl ciclesonide in the serum of healthy volunteers after administration of ciclesonide via hydrofluoroalkane nasal aerosol (CIC-HFA) compared with HFA metered dose inhaler (CIC HFA-MDI) (per-protocol analysis).

Variable	AUC_{0-last}, ng · h/L	T_{max}, h	$t_{1/2}$, h
CIC-HFA			
No. of volunteers	29	29	28
Mean (SE)	281.1 (25.8)	1.6 (0.1)	3.4 (0.3)
Median (range)	291.8 (63.6–577.6)	1.5 (1.0–3.0)	3.0 (1.9–7.3)
CIC HFA-MDI			
No. of volunteers	29	29	29
Mean (SE)	2503.0 (115.7)	0.9 (0.1)	9.2 (0.4)
Median (range)	2509.0 (1490.0–4060.0)	1.0 (0.3–1.5)	9.1 (4.3–14.9)

Table V. Treatment-emergent adverse events (TEAEs) after administration of ciclesonide via aqueous nasal spray (CIC-AQ), hydrofluoroalkane nasal aerosol (CIC-HFA), or HFA metered dose inhaler (CIC HFA-MDI) (intent-to-treat population). Data are number (%) of volunteers.

TEAEs	CIC-AQ 300 µg	CIC-HFA 300 µg	CIC HFA-MDI 320 µg	All Formulations*
≥1 TEAE	4 (13.3)	5 (16.7)	2 (6.7)	9 (30.0)
Headache	1 (3.3)	3 (10.0)	1 (3.3)	4 (13.3)
Nasal discomfort	1 (3.3)	2 (6.7)	0	3 (10.0)
Pharyngolaryngeal pain	1 (3.3)	0	0	1 (3.3)

*A volunteer with multiple occurrences of the same adverse event in >1 treatment period was counted only once in the total.

CONCLUSION

Results from this study suggest that, compared with that of CIC HFA-MDI, the systemic exposure of des-CIC was 10-fold lower after administration of CIC-HFA and at least 40-fold lower after administration of CIC-AQ in these healthy volunteers.

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Address correspondence to: Mark A. Wingertzahn, PhD, Nycomed US Inc., 210 Park Avenue, Florham Park, NJ 07932. E-mail: mark.wingertzahn@nycomed.com