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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00636870
		Study Code:	M016455_4124
Generic drug name:	Fexofenadine	**Date:**	22/May/2008

Title of the study:	A randomized, double-blind, repeat-dose, crossover study to evaluate the pharmacokinetics (PK), safety, and tolerability of desloratadine (CLARINEX®) compared to fexofenadine (ALLEGRA®) in healthy adults who have been identified as slow metabolizers for desloratadine
Investigator(s) & Study center(s):	Walter Kraft, MD, Thomas Jefferson University, Philadelphia, PA Robert A. Blum, PharmD, Buffalo Clinical Research Center, LLC, Buffalo, NY
Study period: Date first patient enrolled: 07-Feb-2003 Date last patient completed: 16-Jan-2004	**Phase of development:** Ph. IV clinical study
Objectives:	Primary objective: To evaluate the single-dose and steady state PK of desloratadine (DCL) and fexofenadine (FEX) in desloratadine slow metabolizers Secondary objective: To evaluate the safety and tolerability of DCL compared to FEX following single and multiple oral doses administered to desloratadine slow metabolizers
Study Design:	This study was conducted at two centers and was composed of two parts: Part 1 – Open-label screening: All subjects completed one 24-hour study period in which they received a single 5 mg dose of DCL. Pharmacokinetic data were examined to determine each subject's phenotype for DCL metabolism (ie, slow metabolizer or normal metabolizer). Part 2: Those subjects identified as slow metabolizers in Part 1 were randomized to receive DCL once daily for 7 days and FEX once daily for 7 days in a double-blinded fashion in two study periods separated by a 21-day washout period. Serial blood sampling was performed on Days 1 and 7; trough samples were collected on Days 5 and 6, and 48, 72, 96, 120, and 144 hours after the Day 7 dose.
Number of patients planned:	Part 1: Up to 140 white subjects and 80 black subjects Part 2: 10 to 12 white subjects and 10 to 12 black subjects
Inclusion criteria:	Healthy, adult, non-smoking males and females between 18 and 55 years of age, inclusive, who were within + 35% of their ideal body weight and were either white of European or North American heritage or black of African or Caribbean heritage.

Treatments:	Part 1: Desloratadine (DCL), 5 mg (commercially available CLARINEX), oral, single dose. Part 2: Fexofenadine HCl (FEX), 180 mg (commercially available ALLEGRA), oral, daily for 7 days and DCL, 5 mg (commercially available CLARINEX), oral, daily for 7 days; supplies for Part 2 were from a single batch for each investigational product. Both investigational products were overencapsulated by the sponsor.
Pharmacokinetic data:	The primary PK endpoints were area under the curve (AUC) and maximum plasma concentration (Cmax) for DCL, 3-OH desloratadine (3-OH-DCL), and FEX (for Part 2 only). Secondary PK endpoints included time to maximum plasma concentration (tmax), elimination half-life (t1/2), and accumulation index (AI) as the data permitted.
Pharmacodynamic data:	Not applicable to this study.
Safety data:	Part 1: Spontaneously reported and elicited adverse events. Part 2: Serial 12-lead ECGs, vital signs, clinical laboratory tests, and adverse events (spontaneously reported and elicited).
Statistical procedures:	Part 1–Open label: Phenotype determinations were made by examination of the 3-OH-DCL and DCL AUC ratio. If this ratio of AUC was less than 0.1 (as defined in the prescribing information for CLARINEX), then subjects were declared DCL slow metabolizers (DSMs) and were eligible for Part 2 of the study. Secondarily, if the data permitted, phenotype determinations were made by an estimated elimination half-life, C_{max} and/or t_{max}. Part 2–Randomized double-blind: A logarithmic transformation was performed on AUC and C_{max} prior to analysis. Day 7 exposure (AUC and C_{max}) was compared to Day 1 exposure within treatment group and within racial groups using a two-way analysis of variance (ANOVA) with treatment group, race, and visit as class variables. Secondary PK endpoints were similarly analyzed, except for t_{max}, which was analyzed non-parametrically. Pharmacokinetic Analysis: • Measures of exposure in both Part 1 and Part 2 were determined using non-compartmental methods Safety Analysis: • Adverse events were summarized • Absolute and relative changes from baseline for 12-lead ECG intervals were evaluated with descriptive summary statistics. Analysis of variance (with treatment and race as class effects and baseline value for the interval being analyzed as covariate) was performed. P values for each parameter (eg, RR interval) were provided where appropriate.

Interim analysis:	Plasma concentration-time data for DCL and 3-OH-DCL from Part 1 of the study were analyzed using non-compartmental methods on an ongoing basis to identify DSMs eligible for Part 2 of the study. No other interim analysis, formal or otherwise, was planned or conducted for this study.
Results – Study subjects and conduct:	A total of 212 subjects (121 male, 91 female; 139 white, 73 black) were enrolled in the study. Three subjects did not return for the 24-hour blood sample collection during Part 1. Each of these subjects was ultimately identified as a DNM. Part 1: Of the entire study population (N = 212), 19 subjects (9%) were identified as DSMs that included 17 out of 73 blacks. All subjects received a single dose of 5 mg DCL. Part 2: Of the 19 subjects identified as DSMs in Part 1, 18 were enrolled into Part 2 and one subject (0022077) was lost to follow-up. Of these 18, all DSMs successfully completed Part 2 (i.e., 18 subjects received 7 doses of FEX and 7 doses of DCL in two separate periods). An additional subject (0022052) who was inadvertently randomized into Part 2 was withdrawn due to other reasons (site mistakenly entered 0022052 [DNM] when 0022053 [DSM] should have been enrolled). The Part 2 study population was 88.9% black and 83.3% male.
Results - Pharmacokinetics:	Part 1: The time course of DCL exposure in DSMs was qualitatively different from that in DNMs following a single oral dose of 5 mg DCL, characterized primarily by slower rates of absorption (i.e., later t max) and elimination. The single dose PK for DCL suggested that substantial accumulation of DCL would occur with daily dosing in DSMs. Part 2: Alteration of FEX PK was not apparent in DSMs. The overall disposition of FEX in DSMs was consistent with historical data. The disposition of DCL in DSMs was characterized by a slower rate of absorption (i.e., later tmax) and a slower rate of elimination (i.e., longer t1/2) resulting in pronounced accumulation and a failure to reach steady state after 7 consecutive days of dosing.
Results – Safety:	• Single 5 mg doses of DCL were safe and well tolerated by all subjects participating in Part 1 of the study. FEX 180 mg and DCL 5 mg administered once daily for 7 days (in separate periods) were generally safe and well tolerated by those subjects identified by DSMs who participated in Part 2 of the study. The incidence of treatment-emergent adverse events (TEAEs) was consistent with what is known about both FEX and DCL with no apparent difference between the two investigational products. • DCL induced a significant increase in heart rate in DSMs, reproducing the effect reported in the prescribing information for CLARINEX.
Date of report:	05-May- 2008