

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201373Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW (Addendum)

NDA Number: 201-373
Brand Name: ALLEGRA® Oral Suspension
Generic Name: Fexofenadine hydrochloride
Sponsor: Sanofi-Aventis
Submission Type: *Partial switch* from prescription-to-nonprescription
Dosage Form: 30 mg/5 mL
Indication: Relief of symptoms associated with allergic rhinitis in adults and children ≥ 2 years of age and itching due to hives in adults and children ≥ 6 years of age.
Submissions Date: March 26, 2010
OCP Division: Clinical Pharmacology 2
OND Division: Pulmonary, Allergy, and Rheumatology Products
Reviewer: Arun Agrawal, Ph.D.
Team Leader (Acting): Yun Xu, Ph.D.

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1. EXECUTIVE SUMMARY

NDA 020-786 review was put in DARRTS on 22 Nov 2010 (by Arun Agrawal, Ph.D.). After this review, sponsor submitted 8 additional clinical pharmacology related study reports in Dec 2010 for safety updates, which were not submitted previously. Review of these study reports revealed no additional information that will have any impact on our recommendations and/or the label. The reviews for individual studies are listed below.

2. INDIVIDUAL STUDY REPORTS REVIEW

Study No.:	M016455Q/BDR11250
Study Title:	A double-blind, randomized, 5-day repeated-dose, dose ascending, crossover bioavailability, safety and tolerability study of fexofenadine and pseudoephedrine fixed-dose combination tablet in comparison with the marketed Allegra tablet in Japanese healthy male subject
Phase:	1
Principal Investigator:	Setsuo Hasegawa, MD, PhD
Study Population:	Japanese healthy male subjects aged 20 to 45 years
Study Site:	Sekino Hospital, Ikebukuro, Toshima-ku, Tokyo, Japan
Study Period:	22-Mar-2010 to 25-Jun-2010

OBJECTIVE(S)

Primary objective: To evaluate the relative bioavailability of fexofenadine between fexofenadine/ pseudoephedrine fixed-dose combination (FEX/PSE-FDC) tablet and the reference marketed Allegra film-coated (FEX-FC) tablet in Japanese healthy male subjects.

Secondary objective: To assess the pharmacokinetic parameters of fexofenadine and pseudoephedrine after repeated oral ascending doses of FEX/PSE-FDC tablet in Japanese healthy male subjects. To assess safety and tolerability of repeated twice-daily (BID) oral doses of FEX/PSE-FDC tablet in Japanese healthy male subjects.

STUDY DESIGN

A Phase 1, single-center, double-blind, randomized, 5-day repeated-dose, dose ascending two-cohort, two-sequence for two-treatment, two-period crossover study with a minimum 10-day washout period between two consecutive administrations within one cohort.

STUDY TREATMENT

Dose: Two fexofenadine HCl 30 mg/pseudoephedrine HCl 60 mg-FDC (FEX30/PSE60-FDC) tablets BID, one fexofenadine HCl 60 mg/pseudoephedrine HCl 60 mg-FDC (FEX60/PSE60-FDC) tablet BID, Fixed Dose Combination (FDC) tablet -placebo BID.

Administration: Oral, in fasted conditions, with 180 mL water. Twice-daily (BID) administrations on morning and evening for 5 days, except on Day 5 with a last dosing on morning (Total 9 doses).

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Blood samples for the determination of plasma fexofenadine and pseudoephedrine concentrations were collected during each period from Day 1 to Day 8. Plasma concentrations of fexofenadine and pseudoephedrine were determined using validated liquid chromatography methods with tandem mass spectrometric detection with lower limits of quantification of 0.5 ng/mL and 3 ng/mL, respectively.

RESULTS

Estimates of treatment ratio with 90% confidence interval from pooled Day 5 fexofenadine data with two cohorts

Parameter	Comparison	Estimate	90% CI
C _{max}	FEX60/PSE60 vs. FEX60	0.96	(0.88 to 1.05)
	FEX60/PSE120 vs. FEX60	1.12	(0.95 to 1.32)
AUC ₀₋₁₂	FEX60/PSE60 vs. FEX60	0.96	(0.89 to 1.03)
	FEX60/PSE120 vs. FEX60	1.10	(0.97 to 1.24)

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The 90% CIs for Day 5 fexofenadine C_{max} and AUC₀₋₁₂ for FEX60/PSE60 vs. FEX60 were 0.88 to 1.05 and 0.89 to 1.03, respectively, and those for FEX60/PSE120 vs. FEX60 were 0.95 to 1.32 and 0.97 to 1.24, respectively. These values were within the bioequivalence criteria except for C_{max} for FEX60/PSE120.

Pseudoephedrine plasma concentrations appeared to reach a steady state within 1 day between 60 mg and 120 mg when administered twice daily as FEX/PSE-FDC. Estimates of accumulation ratios for pseudoephedrine C_{max} and AUC₀₋₁₂ calculated based on the pooled data following the administration of FEX60/PSE60 and FEX60/PSE120 were 1.51 and 1.59, respectively. C_{max} and AUC₀₋₁₂ values of pseudoephedrine increased in a dose proportional manner following single and repeated twice-daily administration of 60 mg and 120 mg of FEX/PSE in Japanese healthy male subjects. There was no statistical effect of pseudoephedrine dose on t_{1/2} values, and the estimate of t_{1/2} values for pseudoephedrine following the pooled FEX60/PSE60 and FEX60/PSE120 data were 6.42 hours.

CONCLUSION(S)

With respect to fexofenadine, 1 tablet of fexofenadine 60 mg/pseudoephedrine 60 mg fixed dose combination (FEX60/PSE60) was bioequivalent to 1 tablet of marketed Allegra film-coated tablet in Japanese healthy male subjects following twice-daily repeated administration of each formulation.

Fexofenadine bioavailability from 2 tablets of fexofenadine 30 mg/pseudoephedrine 60 mg fixed dose combination (FEX60/PSE120) was comparable to 1 tablet of marketed Allegra film-coated tablet in Japanese healthy male subjects following twice-daily repeated administration of each formulation for 5 days. Following the first dose, the bioavailability of fexofenadine was somewhat higher when given in combination with this higher dose of pseudoephedrine, but this appeared to represent more rapid attainment of steady state fexofenadine exposure.

Pseudoephedrine exposure increased in a dose proportional manner between 60 mg and 120 mg when administered twice-daily as the FEX/PSE-FDC. Pseudoephedrine steady state was reached within 1 day following twice-daily repeated doses, with the accumulation ratios for C_{max} and AUC₀₋₁₂ being 1.51 and 1.59, respectively.

Fexofenadine and pseudoephedrine fixed-dose combination tablet was safe and well-tolerated in Japanese healthy male subjects following repeated oral doses up to fexofenadine HCl 60 mg / pseudoephedrine HCl 120 mg BID over 5 days.

Study No.:	M016455S/1001
Study Title:	A Pivotal /Steady-State Bioequivalence Study of 180 mg Fexofenadine HCl – 240 mg Pseudoephedrine HCl Combination Tablets in Fasting Healthy Subjects
Phase:	1
Principal Investigator:	Dennis N. Morrison, DO
Study Population:	Healthy subjects
Study Site:	Springfield, Missouri, United States
Study Period:	19-Nov-2002 to 13-Jan-2003

OBJECTIVE(S)

The study objective was to establish the single dose and steady-state bioequivalence of fexofenadine and pseudoephedrine in a new combination formulation (fexofenadine HCl 180 mg - pseudoephedrine HCl 240 mg extended-release tablet) manufactured at commercial scale, relative to the marketed fexofenadine HCl 180 mg immediate-release and the pseudoephedrine HCl 240 mg extended-release (Sudafed® 24 Hour) tablets taken concurrently.

STUDY DESIGN

The study was an open-label, randomized, two-treatment, two-period, crossover design. All subjects were randomized with an allocation ratio of 1:1 to either of the 2 treatments groups (Treatment A, test or Treatment B, reference) in Period 1. After at least an 8-day drug free washout period, the subjects entered Period 2 and received the alternate treatment.

STUDY TREATMENT

Each subject received the following treatments according to the randomization schedule.

Treatment A (test): Combination experimental tablet formulation containing fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg, administered as a single dose on Day 1 and once daily on Day 4 through Day 9.

Treatment B (reference): Concurrent administration of fexofenadine HCl 180 mg (ALLEGRA®) tablet and pseudoephedrine HCl 240 mg (Sudafed® 24 Hour) extended release tablet administered as a single dose on Day 1 and once daily on Day 4 through Day 9.

ANALYSIS OF PHARMACOKINETIC PARAMETERS

In order to determine plasma concentrations of fexofenadine and pseudoephedrine, venous blood samples were collected prior to dosing and serially postdose on Day 1 for 72 hours and on Day 9 for 24 hours in each treatment period. Predose samples were collected daily from Day 4 through Day 9. Fexofenadine and pseudoephedrine pharmacokinetic parameters were calculated using noncompartmental analysis. In the description of pharmacokinetic parameters, the “1” and “7” refer to parameters calculated following administration of a single dose (Day 1, dose 1) and multiple doses (Day 9, dose 7), respectively.

RESULTS

The 90% confidence intervals for the ratio of geometric LS means (to-be-marketed test formulation) to geometric LS means (reference) for single and multiple dose pharmacokinetic parameters calculated for fexofenadine and pseudoephedrine were contained entirely within the bioequivalent range of 80% to 125%. In addition, the 90% confidence intervals for fexofenadine and pseudoephedrine $C_{min,7}$ were contained entirely within the 80% to 125% bioequivalence range. The mean (CV %) estimates for half-life for fexofenadine and pseudoephedrine following a single dose were similar; fexofenadine half-life was 14.6 (39%) and 14.9 (38%) hours for the test and reference treatments, respectively, and pseudoephedrine half-life was 7.1 (21%) and 6.8 (21%) hours for the test and reference treatments, respectively. The summary statistics for the primary pharmacokinetic comparisons are presented below:

Summary ANOVA Statistics Results of Fexofenadine and Pseudoephedrine Pharmacokinetic Parameters after a Single Dose (Dose 1, Day 1) and at Steady-State (Dose 7, Day 9)

Parameter (units)	Geometric LS Mean		Treatment Comparisons	
	Test [a] Trt A	Reference [a] Trt B	Mean Ratio [b] (%)	90% CI
Fexofenadine				
AUC(0-∞) _{,1} (ng·h/mL)	4052.5	3956.3	102.4	(94.5 – 111.1)
C _{max,1} (ng/mL)	569.4	561.6	101.4	(89.6 – 114.8)
AUC(0-24) _{,7} (ng·h/mL)	3831.0	3725.5	102.8	(94.5 – 112.0)
C _{max,7} (ng/ml)	631.3	584.6	108.0	(96.7 – 120.7)
C _{min,7} (ng/mL)	15.2	16.4	92.6	(84.3 – 101.7)
Pseudoephedrine				
AUC(0-∞) _{,1} (ng·h/mL)	7988.1	8536.9	93.6	(89.8 – 97.5)
C _{max,1} (ng/mL)	393.7	370.0	106.4	(102.1 – 110.9)
AUC(0-24) _{,7} (ng·h/mL)	8490.0	8930.4	95.1	(90.2 – 100.2)
C _{max,7} (ng/ml)	488.0	472.1	103.4	(97.9 – 109.1)
C _{min,7} (ng/mL)	157.3	162.8	96.6	(86.3 – 108.2)

[a] Test (Trt A) = fexofenadine HCl 180 mg - pseudoephedrine HCl 240 mg extended-release tablet.
Reference (Trt B) = marketed fexofenadine HCl 180 mg and pseudoephedrine HCl 240 mg tablets.
[b] Ratio = Geometric LS mean test/ geometric LS mean reference (A/B).

CONCLUSION(S)

- The fexofenadine HCl 180 mg - pseudoephedrine HCl 240 mg extended-release tablet is bioequivalent to the marketed individual components, ALLEGRA® 180 mg and Sudafed® 24 Hour, under single dose and steady-state conditions.
- Plasma concentrations at the end of the dosing interval at steady-state were equivalent between the test and reference treatments for both fexofenadine and pseudoephedrine.
- The study medications administered during the study were well tolerated.

Study No.:	M016455S/1002
Study Title:	An open label, randomized study to assess the effect of food on the pharmacokinetics of 180 mg fexofenadine-240 mg pseudoephedrine combination tablets in healthy subjects
Phase:	1
Principal Investigator:	Dennis N. Morrison, DO
Study Population:	Healthy subjects
Study Site:	Springfield, Missouri, United States
Study Period:	06-May-2003 to 14-Jun-2003

OBJECTIVE(S)

Primary objective: The primary objective was to evaluate the effect of a high-fat breakfast on the rate and extent of absorption of fexofenadine and pseudoephedrine following a single oral dose of fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg extended-release tablet.

Secondary objective: The secondary objective was to evaluate the effect of the time of meal on the rate and extent of fexofenadine absorption following a single oral dose of fexofenadine HCl 180 mg pseudoephedrine HCl 240 mg extended-release tablet.

STUDY DESIGN

The study was conducted in an open-label, single-dose, randomized, 3-period, 3-treatment, complete crossover design. There was a drug-free washout period of at least 6 days between each treatment period. This study assessed the relative bioavailability of the fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg extended-release tablet given after high-fat breakfasts in relation to the same tablet administered under fasting conditions. The relative bioavailability of the fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg extended-release tablet administered at various times after breakfast in relation to the same tablet administered under fasting conditions was assessed. The breakfast was given at either 30 minutes (standard conditions) or 1.5 hours before administration of the scheduled dose. The meal was consumed within 25 minutes. Blood samples were collected at predetermined time points up to 48 hours postdose in each treatment period for the determination of fexofenadine and pseudoephedrine in plasma.

STUDY TREATMENT

Each subject received the following treatments according to the randomization schedule.

Treatment A: A single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered under fasting conditions.

Treatment B: A single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered 30 minutes after start of a high-fat breakfast.

Treatment C: A single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered 1.5 hours after start of a high-fat breakfast.

The high-fat breakfast consisted of 2 eggs fried in butter, 2 strips of bacon, 2 pieces of buttered toast, 4 oz hash browns, and 8 oz whole milk (approximately 55 g fat; 33 g protein; 58 g carbohydrate).

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Serial venous blood samples were collected prior to dosing and serially up to 48 hours following dosing. The blood samples were analyzed by liquid chromatography/tandem mass spectrometry to determine fexofenadine and pseudoephedrine concentrations. Noncompartmental pharmacokinetic parameters were calculated for fexofenadine and pseudoephedrine plasma concentrations. Pseudoephedrine plasma concentrations were not quantitated for Treatment C (dose given 1.5 h after the high-fat breakfast).

RESULTS

The bioavailability of fexofenadine following administration of the combination tablet with a high-fat breakfast (Treatment B) was significantly lower than after administration under fasted conditions (Treatment A). The point estimates for the fed to fasted ratios were 58.4% and 45.8% for AUC(0-∞) and C_{max}, respectively. Likewise, fexofenadine point estimates for AUC(0-∞) and C_{max} ratios of Treatment C (given 1.5 h following the start of the high-fat breakfast) were 55.4% and 42.7%, respectively. The time the breakfast was given before the dose did not appear to affect the severity of the observed food interaction. Both fed treatments had approximately the same magnitude of decreased drug absorption. For pseudoephedrine, no significant food interaction was observed when the fasted treatment was compared to the fed treatment with the high-fat breakfast given 30 minutes before the dose.

Fexofenadine median t_{max} for Treatments A, B, and C were 2.0, 2.5, and 3.0 h, respectively. Median t_{max} for pseudoephedrine were 8.0 and 12.0 h for Treatments A and B, respectively. Mean (CV %) fexofenadine half-life estimates following the single dose in each treatment were 14.9 (29%), 18.8 (36%), and 18.6 (50%) h for Treatments A, B, and C, respectively. Pseudoephedrine t_{1/2} was 7.0 (22%) and 7.8 (21%) h for Treatments A and B, respectively.

The summary statistics for the primary pharmacokinetic comparisons are presented below.

Summary of the ANOVA and Statistics Results for Fexofenadine and Pseudoephedrine Pharmacokinetic Parameters

Parameter (units)	Geometric LS Mean			Treatment Comparisons	
	Reference Trt A [a]	Test Trt B [a]	Test Trt C [a]	Mean Ratio [b](%)	90% CI
Fexofenadine					
AUC(0-∞) (ng-h/mL)	3930.4	2296.9	2178.2	B/A = 58.4 C/A = 55.4	(51.0 – 66.9) (48.3 – 63.6)
AUC(0-last) (ng-h/mL)	3812.0	2131.9	1995.8	B/A = 55.9 C/A = 52.4	(48.9 – 63.4) (45.8 – 59.9)
C _{max} (ng/mL)	625.7	286.8	267.0	B/A = 45.8 C/A = 42.7	(37.9 – 55.4) (35.3 – 51.6)
t _{max} [c] (h)	2.0 (1.0 - 6.0)	2.5 (2.0 - 4.0)	3.0 (1.0 - 6.0)	-	-
Pseudoephedrine					
AUC(0-∞) (ng-h/mL)	7683.1	6972.0	[d]	B/A = 90.7	(87.8 – 93.8)
AUC(0-last) (ng-h/mL)	7521.0	6768.2	[d]	B/A = 90.0	(87.1 – 93.0)
C _{max} (ng/mL)	384.6	351.0	[d]	B/A = 91.2	(86.2 – 96.6)
t _{max} [c] (h)	8.0 (6.0-12.0)	12.0 (8.0-12.0)	[d]	-	-

[a] Trt A: single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered under fasting conditions.
 Trt B: single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered 30 min after start of a high-fat breakfast.
 Trt C: single fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg tablet administered 1.5 h after start of a high-fat breakfast.
 [b] Ratio = Geometric LS mean test/ geometric LS mean reference.
 [c] t_{max} presented as median and range
 [d] No data, pseudoephedrine for Trt C was not quantitated.

CONCLUSION(S)

- Administration of the fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg extended release tablet with a high-fat meal decreased fexofenadine absorption by approximately 50%. A similar magnitude of reduction was observed when the dose was administered 1 hour after the completion of a high-fat meal.
- Administration of the fexofenadine HCl 180 mg-pseudoephedrine HCl 240 mg extended release tablet with a high-fat meal had no impact on pseudoephedrine absorption.
- The study medications administered during the study were well tolerated.

Study No.:	M016455/BEQ11466
Study Title:	Three-way crossover, randomized, open-label pivotal bioequivalence study comparing the fexofenadine hydrochloride orally disintegrating tablet (ODT) formulation (60 mg) administered without or with water to the marketed Allegra® tablet (60 mg) in Japanese healthy subjects
Phase:	1
Principal Investigator:	Setsuo Hasegawa
Study Population:	Japanese healthy subjects
Study Site:	2 centers (Sekino Clinical Pharmacology Clinic, 3-28-3 Ikebukuro, Toshima-ku, Tokyo, 171-0014 JAPAN and Sekino Hospital, 3-28-3 Ikebukuro, Toshima-ku, Tokyo, 171-0014 JAPAN)
Study Period:	28-Apr-2010 to 27-Jul-2010

OBJECTIVE(S)

Primary objective: To establish the bioequivalence of fexofenadine when administered as an ODT formulation with or without water (60 mg) manufactured at industrial scale relative to the marketed Allegra tablet (60 mg) administered under fasting conditions.

Secondary objective: To assess the safety and tolerability of fexofenadine when administered without or with water as an ODT formulation (60 mg fexofenadine HCl) administered under fasting conditions.

STUDY DESIGN

Open-label, randomized, single-dose, three-way complete cross-over design

STUDY TREATMENT

Investigational product:

Dose: Fexofenadine HCl 60 mg ODT, single dose

Administration: Oral administration under fasting condition with and without water

Reference therapy:

Dose: Allegra 60 mg tablet, single dose

Administration: Oral administration under fasting condition

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Blood samples were to be collected prior to dosing (0 hour) and at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72 hours following study drug administration in each treatment period. Plasma concentrations of fexofenadine were analyzed by a validated LC-MS/MS. The lower limit of quantification (LLOQ) was 0.5 ng/mL.

RESULTS

The 60 mg ODT formulation, manufactured at industrial scale and administered either with or without water, was bioequivalent to the 60 mg Allegra marketed tablet when the

60 mg ODT was administered in fasted conditions, as the 90% CIs for the Test/Reference ratios of geometric means for C_{max} and AUC₀₋₇₂ were within the bioequivalence reference interval of 0.80 to 1.25.

Pharmacokinetic results:

Mean ± SD (Geometric Mean) [CV%] of fexofenadine pharmacokinetic parameters			
Parameter	Treatment A	Treatment B	Treatment C
N	117	118	116
C _{max} (ng/mL)	278 ± 124 (253) [44.8]	243 ± 90.3 (227) [37.1]	280 ± 95.8 (264) [34.2]
AUC ₀₋₇₂ (ng·h/mL)	1790 ± 631 (1700) [35.2]	1650 ± 504 (1570) [30.6]	1820 ± 567 (1740) [31.1]
AUC _{last} (ng·h/mL)	1780 ± 631 (1690) [35.4]	1640 ± 505 (1570) [30.8]	1810 ± 568 (1730) [31.3]
AUC (ng·h/mL)	1820 ± 641 (1730) [35.2] ^b	1670 ± 504 (1600) [30.1] ^c	1850 ± 577 (1770) [31.1]
t _{max} ^a (h)	2.00 (0.33 - 4.00)	2.00 (0.75 - 6.00)	1.50 (0.75 - 4.00)
t _{1/2z} (h)	16.6 ± 21.1 (12.6) [126.7]	19.0 ± 47.6 (12.4) [250.3]	16.6 ± 19.0 (12.8) [114.8]
t _{lag} ^a (h)	0.17 (0.00 - 0.33)	0.00 (0.00 - 0.17)	0.00 (0.00 - 0.17)
λ _z (1/h)	0.0640 ± 0.0309 (0.0548) [48.3]	0.0650 ± 0.0305 (0.0558) [46.9]	0.0634 ± 0.0304 (0.0543) [48.0]
MRT (h)	10.4 ± 6.28 (9.41) [60.5] ^b	9.86 ± 3.94 (9.37) [40.0] ^c	10.5 ± 9.33 (9.17) [89.1]

Tabulated values are Mean ± SD (Geometric Mean) [CV%]; N = number of subjects;

^a Median (Min - Max); ^b n=116; ^c n=115

A = 60mg Allegra marketed tablet; B = 60 mg ODT without water; C = 60 mg ODT with water

Source = PKS Study : BEQ11466; Scenario: P-D-A-EV-OD-E02, Version 2

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Estimates of treatment ratios with 90% confidence interval for fexofenadine

Parameter	Comparison	Estimate	90% CI
C _{max}	B/A	0.90	(0.84 to 0.97)
	C/A	1.05	(0.97 to 1.13)
AUC ₀₋₇₂	B/A	0.93	(0.89 to 0.98)
	C/A	1.03	(0.97 to 1.08)

A: Allegra marketed tablet, B: ODT without water, C: ODT with water

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CONCLUSION(S)

The 60 mg ODT formulation of fexofenadine, administered with and without water, was bioequivalent to the 60 mg Allegra marketed tablet administered in fasted condition in Japanese subjects. The treatments of the 60 mg ODT both with and without water were well tolerated in Japanese subjects, just as the treatment of the Allegra® marketed tablet was.

Study No.:	M016455/BDR10707
Study Title:	Two-way crossover, randomized, open-label study to investigate oral mucosa absorption of fexofenadine hydrochloride orally disintegrating tablet (ODT) formulation (60 mg) in Japanese healthy subjects
Phase:	1
Principal Investigator:	Setsuo Hasegawa
Study Population:	Japanese healthy subjects
Study Site:	Sekino Hospital, 3-28-3 Ikebukuro, Toshima-ku, Tokyo, 171-0014 JAPAN
Study Period:	18-Apr-2008 to 23-May-2008

OBJECTIVE(S)

Primary objective: To investigate the absorption of fexofenadine from oral cavity when an ODT formulation (60 mg fexofenadine hydrochloride [HCl]) is kept in the mouth for two minutes.

Secondary objective: To assess the safety and tolerability of fexofenadine when administered without water as an ODT formulation (60 mg fexofenadine HCl) administered under fasting conditions.

STUDY DESIGN

Open-label, randomized, single-dose, two-way complete cross-over study

STUDY TREATMENT

Dose: Fexofenadine HCl 60 mg, single dose

Administration: Oral administration with swallowing (Treatment A; swallowed) or without swallowing (Treatment B; expelled).

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Blood samples (2 mL each) were to be collected prior to dosing (0 hour) and at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours following study drug administration in each treatment period. Plasma concentrations of fexofenadine were assayed by LC-MS/MS method. The lower limit of quantification (LLOQ) of LC-MS/MS method was 0.5 ng/mL. The pharmacokinetic parameters (C_{max} , AUC_{last} , AUC, t_{max} , $t_{1/2z}$, t_{lag} , and MRT) were determined by non-compartmental method. Saliva samples were to be collected when the ODT was administered to subjects in Treatment B. Fexofenadine concentrations in saliva were determined by HPLC method. The LLOQ of HPLC method was 30 µg/mL.

RESULTS

Lack of oral mucosal absorption for ODT was concluded because ratio of AUC_{last} (Treatment B/Treatment A) was 0.0896% (<5%).

Pharmacokinetic results: Pharmacokinetic parameters of fexofenadine for Treatment A (swallowed) and Treatment B (expelled) are as follows;

Fexofenadine pharmacokinetic parameters

PK Parameter	Swallowed (n=12)	Expelled (n=12)
C _{max} (ng/mL)	210 ± 77.5 (37) [198]	0.393 ± 0.569 (145) [NC]
t _{max} (h)	1.75 (1.00 , 4.00)	3.00 ^a (1.50 , 4.00)
t _{1/2z} (h)	12.7 ± 6.16 (48) [11.3]	2.85 ^b (NC) [2.85]
AUC _{last} (ng.h/mL)	1380 ± 364 (26) [1340]	1.27 ± 2.26 (178) [NC]
AUC (ng.h/mL)	1400 ± 375 (27) [1360]	NC
t _{lag} (h)	0.00 (0.00 , 0.17)	1.00 ^a (0.50 , 2.50)
MRT (h)	9.49 ± 2.69 (28) [9.15]	NC

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} and t_{lag} where values are Median (Min, Max)

a: n=5, b: n=1, NC: Not possible to calculate.

In treatment B (an ODT expelled), all 12 subjects had some unavailable PK parameters, described as follows:

- AUC_{last} and C_{max}: In seven out of 12 subjects, all plasma concentrations were below lower the limit of quantitation (<LLOQ). Therefore, the AUC_{last} and the C_{max} were calculated as zero.
- t_{max} and t_{lag}: calculated for five subjects whose plasma concentrations were observed.
- t_{1/2z}: calculated for one subject but not for four remaining subjects, because most of the plasma concentrations were <LLOQ.
- AUC and MRT: not calculated for all subjects because λ_z were not calculated, or percentage of AUC extrapolation ((AUC-AUC_{last})/AUC × 100) was more than 30% of AUC.

Estimates of Treatment ratio in AUClast (%)

Parameter	Statistics	Treatment ratio (%)
		B / A
AUClast	N	12
	Mean	0.0896
	SD	0.1554
	Median	0.000
	Min	0.000
	Max	0.399

A: ODT 60 mg swallowed, B: ODT 60 mg expelled
PGM=M016455/BDR10707/CSR/BS/PGM_RPT/PK_BDR10707.sas OUT=OUTPUT/pk_TR_k_t_i.rtf (28AUG2008 - 9:21)

CONCLUSION(S)

Lack of oral mucosal absorption for ODT was concluded, because the AUClast ratio of Treatment B (expelled) to Treatment A (swallowed) was 0.0896%, which was lower than the predefined criteria of absorption from the oral mucosa (5%).

The treatments of the ODT (60 mg) were well tolerated and safe in healthy Japanese subjects.

Study No.:	M016455/BEQ10111
Study Title:	Three-way crossover, randomized, open-label pivotal bioequivalence study comparing the fexofenadine hydrochloride orally disintegrating tablet (ODT) formulation (60 mg) administered without or with water to the marketed Allegra® tablet (60 mg) in Japanese healthy subjects
Phase:	1
Principal Investigator:	Setsuo Hasegawa
Study Population:	Japanese healthy subjects
Study Site:	Sekino Hospital, 3-28-3 Ikebukuro, Toshima-ku, Tokyo, 171-0014 JAPAN
Study Period:	01-Feb-2008 to 08-May-2008

OBJECTIVE(S)

Primary objective: To establish the bioequivalence of fexofenadine when administered without or with water as an ODT formulation (60 mg fexofenadine hydrochloride [HCl]) manufactured at pilot scale relative to the marketed 60 mg fexofenadine HCl tablet administered under fasting conditions.

Secondary objective: To assess the safety and tolerability of fexofenadine when administered without or with water as an ODT formulation (60 mg fexofenadine HCl) administered under fasting conditions.

STUDY DESIGN

Three-way crossover, randomized, open-label pivotal bioequivalence study

STUDY TREATMENT

Investigational product:

Dose: Fexofenadine HCl 60 mg ODT, single dose

Administration: Oral administration under fasting condition with and without water

Reference therapy:

Dose: Allegra 60 mg tablet, single dose

Administration: Oral administration under fasting condition

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Blood samples (2 mL each) were to be collected prior to dosing (0 hour) and at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36, 48, 72 hours following study drug administration in each treatment period. Plasma concentrations of fexofenadine were analyzed by LC-MS/MS. The lower limit of quantification (LLOQ) was 0.5 ng/mL. The pharmacokinetic parameters (C_{max}, AUC_{last}, AUC, t_{max}, t_{1/2z}, t_{lag} and MRT) were determined by non-compartmental method.

RESULTS

The 60 mg ODT formulation was bioequivalent to the marketed 60 mg Allegra tablet when the 60 mg ODT was administered to Japanese subjects in conditions both with and without water, as the 90% CIs for the ratios (Treatments B/A and C/A) of C_{max} and AUC_{last} were within the 0.80 to 1.25, bioequivalence reference interval.

Pharmacokinetic results: Pharmacokinetic parameters of fexofenadine after administrations of the marketed Allegra tablet (60 mg), the ODT (60 mg) without water, and the ODT (60 mg) with water are as follows:

Fexofenadine pharmacokinetic parameters

PK Parameter	Marketed tablet n=115	ODT without water n=117	ODT with water n=117
C _{max} (ng/mL)	225 ± 92.4 (41) [208]	200 ± 80.6 (40) [186]	227 ± 83.7 (37) [214]
t _{max} (h)	2.00 (0.75 , 6.00)	2.50 (0.75 , 6.00)	2.00 (0.50 , 6.00)
T _{1/2α} (h)	13.9 ± 7.21 (52) [12.5]	13.9 ± 6.17 (44) [12.8]	13.8 ± 8.10 (59) [12.4]
AUC _{last} (ng.h/mL)	1490 ± 500 (33) [1420]	1360 ± 494 (36) [1290]	1540 ± 477 (31) [1480]
AUC (ng.h/mL)	1520 ± 502 (33) [1440]	1390 ± 496 (36) [1320]	1570 ± 478 (30) [1500]
t _{lag} (h)	0.17 (0.00 , 0.33)	0.00 (0.00 , 0.75)	0.00 (0.00 , 0.00)
MRT (h)	9.62 ± 3.47 (36) [9.18]	10.0 ± 2.88 (29) [9.64]	9.39 ± 3.85 (41) [8.93]

Tabulated values are Mean ± SD (CV%) [Geometric Mean] except for t_{max} and t_{lag} where values are Median (Min, Max)

Treatment ratio estimates and 90% CIs

Parameter	Comparison	Estimate	90% CI
C _{max} (ng/mL)	B / A	0.89	(0.84 to 0.95)
	C / A	1.02	(0.96 to 1.08)
AUC _{last} (ng.h/mL)	B / A	0.91	(0.87 to 0.95)
	C / A	1.04	(0.99 to 1.08)

A: Allegra marketed tablet, B: ODT without water, C: ODT with water
PGM=M016455/BEQ10111/CSR/BS/PGM_RPT/PK_BEQ10111.sas OUT=OUTPUT/pk_BA_k_t_2_irf(25SEP2008 - 8:57)

CONCLUSION(S)

The 60 mg ODT formulation was bioequivalent to the marketed 60 mg Allegra tablet when the ODT was administered to Japanese subjects in conditions both with and without water, as the 90% CIs for treatment ratios of C_{max} and AUC_{last} were within the 0.80 to 1.25, bioequivalence reference interval.

The treatments of the 60 mg ODT both with and without water were well tolerated in Japanese subjects, just as the treatment of the marketed Allegra tablet was.

Study No.:	M016455H/1007
Study Title:	Two-way Crossover, Randomized, Open-label Pivotal Bioequivalence Study Comparing the Fexofenadine Hydrochloride Orally Disintegrating Tablet (ODT) Formulation (30 mg) to the Marketed Allegra [®] Tablet (30 mg) in Healthy Adult Subjects
Phase:	1
Principal Investigator:	Dennis N. Morrison, DO
Study Population:	Healthy subjects
Study Site:	Springfield, Missouri, United States
Study Period:	31-Aug-2004 to 04-Oct-2004

OBJECTIVE(S)

Primary objective: The primary objective was to establish the bioequivalence of fexofenadine when administered as an orally disintegrating tablet formulation (30 mg fexofenadine hydrochloride) manufactured at commercial scale relative to the marketed 30 mg fexofenadine hydrochloride tablet under fasted conditions.

Secondary objective: The secondary objective was to assess the safety and tolerability of the orally disintegrating tablet formulation administered under fasted conditions.

STUDY DESIGN

The study was conducted as an open-label, randomized, single-dose, 2-way, complete crossover design. There was a washout period of at least 6 days between each dose.

STUDY TREATMENT

Each subject received Treatment A (reference) and Treatment B (test) according to the randomization schedule.

Treatment A: Marketed tablet as reference - a single oral dose of 30 mg fexofenadine hydrochloride administered under fasted conditions.

Treatment B: Orally disintegrating tablet as test - a single oral dose of 30 mg fexofenadine hydrochloride tablet administered under fasted conditions.

Treatments A and B were administered under fasted conditions with 240 mL water. Subjects receiving the orally disintegrating tablet (Treatment B) were asked to place a single tablet on their tongue and briefly close their mouth. After the tablet disintegrated and the contents were swallowed (up to 1-2 minutes after tablets were placed in the mouth), subjects were asked to rinse their mouth with 20 mL of water and swallow so that all the tablet granules were ingested. The subjects were to ingest the remainder of the 240-mL aliquot of water. All subjects received each treatment once. Subjects were assigned a subject number prior to the first dose of study medication in Treatment Period 1.

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Blood samples (5 mL each) were collected prior to dosing (predose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours following study drug administration. Plasma samples were analyzed by liquid chromatography/tandem mass spectrometry to determine fexofenadine concentrations. Pharmacokinetic parameters were determined from fexofenadine plasma concentrations by noncompartmental analysis.

RESULTS

Statistical analysis of AUC(0-∞), AUC(0-last), and Cmax revealed 90% confidence intervals for the ratio of geometric least-square means of fexofenadine test to reference formulations of 92.3 to 106%, 92.3 to 107.1%, and 85.3 to 101.9% respectively. There were no significant sequence or period effects. Intra-subject variabilities within the pharmacokinetic population for the aforementioned parameters were <30%. The median fexofenadine Tmax and mean t1/2 and CLpo were similar for both treatments with values of 2 h, approximately 12 h, and 48 L/h, respectively, for both treatments.

Results - Pharmacokinetics and pharmacodynamics

Parameter (unit)	Treatment [a]	Arithmetic Mean (CV%) [b]	Geometric LS Mean [c]	Treatment Comparisons [d]	
				Ratio [e] (%)	90% CI
AUC(0-∞) (ng-h/mL)	A	637 (29.2)	612	98.9	92.3 - 106
	B	635 (31.2)	606		
Cmax (ng/mL)	A	93.8 (33.3)	88.9	93.2	85.3 - 102
	B	88.0 (35.5)	82.9		
AUC(0-last) (ng-h/mL)	A	607 (30.7)	582	99.4	92.3 - 107
	B	608 (32.9)	579		
Tmax [f] (h)	A	2.0 (1.0-4.0)	-	-	-
	B	2.0 (0.5-6.0)	-		
t1/2 (h)	A	11.6 (27.8)	-	-	-
	B	11.8 (31.8)	-		
CLpo (L/h)	A	47.4 (27.4)	-	-	-
	B	48.3 (32.2)	-		

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval.

[a] Treatment A: single dose of 30 mg fexofenadine HCl as marketed tablet (reference).

Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet (test).

[b] Arithmetic mean calculated from all subjects with evaluable data; N = 52 for all Treatment B parameters and AUC(0-last), Cmax, and Tmax for Treatment A; N = 51 for Treatment A AUC(0-∞), t1/2, and CLpo.

[c] Geometric mean calculated from balanced pair data; N = 52 for AUC(0-last) and Cmax; N = 51 for AUC(0-∞).

[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.

[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A).

[f] Tmax reported as median (range) values.

CONCLUSION(S)

- The fexofenadine HCl 30 mg ODT formulation was bioequivalent to the market 30 mg tablet in healthy adult subjects under fasted conditions.
- The study medications administered in this study were well tolerated.

Study No.:	M016455H/1008
Study Title:	Two-way Crossover, Randomized, Open-label Study Comparing the Bioavailability of the Fexofenadine Hydrochloride Orally Disintegrating Tablet (ODT) Formulation (30 mg) Given With and Without Water to Healthy Adult Subjects
Phase:	1
Principal Investigator:	Dennis N. Morrison, DO
Study Population:	Healthy subjects
Study Site:	Springfield, Missouri, United States
Study Period:	29-Nov-2004 to 26-Jan-2005

OBJECTIVE(S)

Primary objective: The primary objective was to compare the bioavailability of fexofenadine hydrochloride orally disintegrating tablet formulation (30 mg) manufactured at commercial scale when administered with and without water under fasted conditions.

Secondary objective: The secondary objective was to assess the safety and tolerability of the orally disintegrating tablet formulation administered under fasted conditions.

STUDY DESIGN

The study was conducted as an open-label, randomized, single-dose, 2-period, 2-treatment, complete crossover design. There was a washout period of at least 6 days between treatment periods.

STUDY TREATMENT

Each subject received Treatment A (reference) and Treatment B (test) according to the randomization schedule.

Treatment A: Orally disintegrating tablet as a single oral dose of 30 mg fexofenadine hydrochloride tablet administered under fasted conditions with 240 mL of water

Treatment B: Orally disintegrating tablet as a single oral dose of 30 mg fexofenadine hydrochloride tablet administered under fasted conditions without water

Subjects were asked to place a single tablet on their tongue and briefly close their mouth until the tablet disintegrated and the contents were swallowed (up to 1 to 2 minutes after tablets were placed in the mouth). The subjects assigned to receive Treatment A ingested 240 mL water following tablet disintegration. All subjects received each treatment once. Subjects were assigned a subject number prior to the first dose of study medication in Treatment Period 1.

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Blood samples (6 mL each) were collected prior to dosing (predose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 48 hours following study drug administration in each

treatment period. Plasma samples were analyzed by liquid chromatography/tandem mass spectrometry to determine fexofenadine concentrations. Pharmacokinetic parameters were determined from fexofenadine plasma concentrations by noncompartmental analysis.

RESULTS

Following a single dose, the percentage ratios of the geometric least-squares means of fexofenadine AUC(0-∞), AUC(0-last), and Cmax values for the ODT formulation administered without water (test) compared with the ODT formulation administered with water (reference) were 112%, 113%, and 113%, respectively. The associated 90% confidence intervals for the test/reference ratio of geometric least-square means were 102 to 122%, 103 to 125%, and 100 to 127%, respectively.

Parameter (unit)	Treatment [a]	N	Arithmetic Mean (CV%) [b]	N	Geometric LS Mean [c]	Treatment Comparisons [d]	
						Ratio [e] (%)	90% CI
AUC(0-∞) (ng·h/mL)	A	52	628 (34.3)	51	601	112	102 - 122
	B	53	699 (40.5)	51	671		
Cmax (ng/mL)	A	53	86.3 (50.9)	52	78.5	113	100 - 127
	B	53	96.5 (46.7)	52	88.5		
AUC(0-last) (ng·h/mL)	A	53	589 (38.4)	52	552	113	103 - 125
	B	53	668 (42.7)	52	625		
Tmax [f] (h)	A	53	2.0 (1.0-8.0)	-	-	-	-
	B	53	2.0 (1.0-8.0)	-	-	-	-
t1/2 (h)	A	52	12.8 (52.9)	-	-	-	-
	B	53	12.0 (54.6)	-	-	-	-
CLpo (L/h)	A	52	49.5 (31.8)	-	-	-	-
	B	53	46.8 (42.8)	-	-	-	-

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval.

[a] Treatment A: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet with 240 mL water (reference).

Treatment B: single dose of 30 mg fexofenadine HCl as orally disintegrating tablet without water (test).

[b] Arithmetic mean calculated from all subjects with evaluable data.

[c] Geometric mean calculated from balanced pair data.

[d] ANOVA with terms for sequence, period, and treatment as fixed effects and subject nested within sequence as random effect performed on the natural log-transformed AUC(0-∞), AUC(0-last), and Cmax.

[e] Ratio = geometric LS mean test/geometric LS mean reference (B/A).

[f] Tmax reported as median (range) values.

CONCLUSION(S)

The 30 mg fexofenadine orally disintegrating tablet administered without water was bioequivalent to the tablet administered with water with respect to extent of absorption [AUC(0-∞)]. However, the upper limit of Cmax was slightly outside of the bioequivalence bounds (90% CI: 100 to 127).

The study medications administered in this study were well tolerated.

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/s/

ARUN K AGRAWAL
01/07/2011

YUN XU
01/07/2011

CLINICAL PHARMACOLOGY REVIEW

NDA Number: 201-373
Brand Name: ALLEGRA[®] Oral Suspension
Generic Name: Fexofenadine hydrochloride
Sponsor: Sanofi-Aventis
Submission Type: *Partial switch* from prescription-to-nonprescription
Dosage Form: 30 mg/5 mL
Indication: Relief of symptoms associated with allergic rhinitis in adults and children ≥ 2 years of age and itching due to hives in adults and children ≥ 6 years of age.
Submissions Date: March 26, 2010
OCP Division: Clinical Pharmacology 2
OND Division: Pulmonary, Allergy, and Rheumatology Products
Reviewer: Arun Agrawal, Ph.D.
Team Leader (Acting): Yun Xu, Ph.D.

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1. EXECUTIVE SUMMARY

This submission provides for the partial change of status from prescription-to-nonprescription use of fexofenadine hydrochloride oral suspension, 6 mg/mL. *Fexofenadine suspension for pediatric patients younger than 6 years of age with chronic idiopathic urticaria (CIU) will not be switched from prescription-to-nonprescription status.* The Sponsor will maintain NDA 21-963 for the prescription use of fexofenadine suspension for CIU in pediatric patients 6 months to less than 6 years of age.

The proposed nonprescription use for the mono-products of fexofenadine is for the temporary relief of symptoms due to hay fever or other upper respiratory allergies (runny nose, sneezing, itchy, watery eye, itching of nose or throat), as well as for the reduction of hives and the relief of itching due to hives (urticaria). For the oral suspension formulation provided in this NDA, the use for allergic rhinitis is for adults and children ≥ 2 years of age and itching due to hives in adults and children ≥ 6 years of age.

The Sponsor has also submitted 23 study reports, which were not submitted previously, mainly for the purpose of safety updates. Thirteen of those study reports are related to clinical pharmacology evaluations. Review of those 13 clinical pharmacology related study reports revealed no additional information that will have any impact on our recommendations and/or the label. The following recommendations in the prescription label should also be carried over to the nonprescription label:

- Ask your doctor before use if you have kidney disease.
- Ask your doctor before use if you are 65 years old or older.
- Do not take at the same time as aluminum and magnesium containing antacids.
- Do not take with fruit juice, take with water.

1.1 Recommendation

From the Clinical Pharmacology perspective, the application is acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the agency regarding the language in the package insert.

1.2 Clinical Pharmacology related information in the current label

Fexofenadine HCl (henceforth referred to as fexofenadine) is a selective H1-receptor antagonist, that has been approved under the trade name Allegra as a mono-product (capsule [60 mg], tablet [30, 60, and 180 mg], oral suspension [6 mg/mL], and an orally disintegrating tablet [ODT], [30 mg]) and under the trade names Allegra -D 12 Hour and Allegra -D 24 Hour in fixed-dose combinations with pseudoephedrine (fexofenadine 60 mg/pseudoephedrine 120 mg and fexofenadine 180 mg/pseudoephedrine 240 mg, respectively). Fexofenadine was first approved in the USA in 1996 for seasonal allergic rhinitis (SAR) or hay fever, and CIU or hives as a 60 mg capsule formulation (NDA 20-625), a dosage formulation that is currently no longer marketed in the USA. In subsequent submissions, a tablet formulation of 3 different dose strengths (30 mg, 60 mg, and 180 mg) was approved in 2000 and 2005 for SAR and chronic idiopathic urticaria (CIU) or hives (NDA 20-872). The fexofenadine suspension was approved October 2006

for the treatment of SAR and CIU in pediatric patients 2 to less than 12 years of age, inclusive (ie ≥ 2 to <12 years of age) at a dose of 30 mg twice daily [BID] and for the treatment of CIU in pediatric patients 6 months to less than 2 years of age, inclusive (ie, ≥ 6 months to <2 years of age), at a dose of 15 mg BID.

This submission provides for the partial change of status from prescription-to-nonprescription use of fexofenadine suspension, 6 mg/mL. Fexofenadine suspension for pediatric patients younger than 6 years of age with CIU will not be switched from prescription-to-nonprescription status. The Sponsor will maintain NDA 21-963 for the prescription use of fexofenadine suspension for CIU in pediatric patients 6 months to less than 6 years of age.

The proposed nonprescription use for the mono-products of fexofenadine is for the temporary relief of symptoms due to hay fever or other upper respiratory allergies (runny nose, sneezing, itchy, watery eyes, itching of nose or throat), as well as for the reduction of hives and the relief of itching due to hives (urticaria). For the oral suspension formulation provided in this NDA, the use for allergic rhinitis is for adults and children ≥ 2 years of age and itching due to hives in adults and children ≥ 6 years of age. The Sponsor is requesting the same nonprescription uses for the fexofenadine suspension as for the fexofenadine oral tablets; however, the proposed drug facts labeling directions are modified for the population, accordingly.

No new human pharmacokinetics and bioavailability, and clinical pharmacology studies for the intended use were conducted in support of the switch application because of the extensive data, including post-marketing safety data already available on prescription Allegra. Per Agency's request for safety updates, the sponsor submitted 13 previously conducted clinical pharmacology related study reports. However, no additional information from these reports will have any impact on our recommendations and/or the label.

In the prescription label of the product, it is noted that Allegra should not be taken with fruit juice and/or antacids. In addition, dose reduction is recommended for patients with decreased renal function. It is also mentioned in the label that because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. These recommendations in the prescription label should also be carried over to the nonprescription label.

The clinical pharmacology related information in the prescription label is summarized below.

1.2.1 Effect of food

A dose of 5 mL of Allegra oral suspension containing 30 mg of fexofenadine hydrochloride is bioequivalent to a 30 mg dose of Allegra tablets. Following oral administration of a 30 mg dose of Allegra oral suspension to healthy adult subjects, the mean C_{max} was 118 ng/mL and occurred at approximately 1 hour. The administration of

30 mg Allegra oral suspension with a high fat meal decreased the AUC and the mean C_{max} by approximately 30 and 47%, respectively in healthy adult subjects.

1.2.2 Drug interactions

1.2.2.1 Antacids

In healthy adult subjects, administration of 120 mg of fexofenadine (2 x 60 mg capsule) within 15 minutes of an aluminum and magnesium containing antacid (Maalox[®]) decreased fexofenadine AUC by 41% and C_{max} by 43%.

In healthy adult subjects, administration of 180 mg of fexofenadine within 15 minutes of an aluminum and magnesium containing antacid (Maalox[®]) decreased fexofenadine mean AUC by 56% and C_{max} by 58%. Maalox[®] decreased the bioavailability of fexofenadine by 56%.

Pharmacokinetic parameters

Antihistamine	Pharmacokinetic Variable	Geometric Mean		Ratio (90% CI)	p-value ^a
		With Maalox [®]	Without Maalox [®]		
Fexofenadine HCl	AUC ₍₀₋₁₂₎	1209.63	2903.09	2.40 (1.81, 3.18)	<0.001
	AUC ₍₀₋₁₈₎	1331.28	3157.36	2.37 (1.80, 3.12)	<0.001
	AUC _(0-∞)	1472.68	3370.99	2.29 (1.76, 2.98)	<0.001
	C _{max}	230.91	554.82	2.40 (1.71, 3.37)	<0.001

In drug interactions section of the prescription label highlights, it is mentioned that “Do not take at the same time as aluminum and magnesium containing antacids”.

1.2.2.2 Erythromycin and Ketoconazole

Fexofenadine has been shown to exhibit minimal (~5%) metabolism. However, co-administration of fexofenadine with either ketoconazole or erythromycin led to increased plasma concentrations of fexofenadine in healthy adult subjects. Fexofenadine had no effect on the pharmacokinetics of either erythromycin or ketoconazole. In 2 separate studies in healthy adult subjects, fexofenadine 120 mg twice daily (240 mg total daily dose) was co-administered with either erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to healthy adult subjects (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine alone or in combination with either erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

Effects on Steady-State Fexofenadine Pharmacokinetics After 7 Days of Co-Administration with Fexofenadine Hydrochloride 120 mg Every 12 Hours (two times the recommended twice daily dose) in Healthy Volunteers (n=24)		
Concomitant Drug	C _{max SS} (Peak plasma concentration)	AUC _{SS(0-12h)} (Extent of systemic exposure)
Erythromycin (500 mg every 8 hrs)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials. The mechanism of these interactions has been evaluated in *in vitro*, *in situ*, and *in vivo* animal models. These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to transport-related effects, such as p-glycoprotein. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

Reviewer's comments:

Although an increase in plasma fexofenadine exposure was observed when co-administered with ketoconazole or erythromycin, the changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials. Therefore, the prescription label does not recommend dose adjustment or use with caution.

1.2.2.3 Fruit Juices

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. The size of wheal and flare were significantly larger when fexofenadine was administered with either grapefruit or orange juices compared to water. Based on the literature reports, the same effects may be extrapolated to other fruit juices such as apple juice. The clinical significance of these observations is unknown. In addition, based on the population pharmacokinetics analysis of the combined data from grapefruit and orange juices studies with the data from a bioequivalence study, the bioavailability of fexofenadine was reduced by 36%. Therefore, to maximize the effects of fexofenadine, it is recommended that Allegra® should be taken with water. *In drug interactions section of the prescription label highlights, it is mentioned that "Take with water, not fruit juice".*

1.2.3 Use in specific populations

1.2.3.1 Geriatric Use

In older subjects (≥ 65 years old), peak plasma levels of fexofenadine were 99% greater than those observed in younger subjects (<65 years old). Mean fexofenadine elimination half lives were similar to those observed in younger subjects. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

1.2.3.2 Renal Impairment

In subjects with mild to moderate (creatinine clearance 41-80 mL/min) and severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma concentrations of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in healthy subjects. Peak plasma concentrations in subjects on dialysis (creatinine clearance ≤ 10 mL/min) were 82% greater and half-life was 31% longer than observed in healthy subjects. Based on

increases in bioavailability and half-life, a dose of 60 mg once daily is recommended as the starting dose in adult patients with decreased renal function. For pediatric patients with decreased renal function, the recommended starting dose of fexofenadine is 30 mg once daily for patients 2 to 11 years of age and 15 mg once daily for patients 6 months to less than 2 years of age.

1.2.3.3 Hepatic Impairment

The pharmacokinetics of fexofenadine in subjects with hepatic impairment did not differ substantially from that observed in healthy subjects.

1.2.3.4 Effect of Gender

Across several trials, no clinically significant gender-related differences were observed in the pharmacokinetics of fexofenadine.

1.2.4 QT Interdisciplinary Review Team Consult

A consult was sent by the Medical Officer to the QT Interdisciplinary Review Team on March 25, 2010 regarding evaluation of ECG data and cardiac adverse event data for fexofenadine, as part of prescription to nonprescription switch of fexofenadine (Allegra) tablets, oral disintegrating tablets, and oral suspension (NDA 201-613, 021-909 and 201-373). As of today (November 22, 2010) the team is waiting for the final recommendations from the QT Interdisciplinary Review Team.

2. DETAILED LABELING RECOMMENDATIONS

The following recommendations in the prescription label should also be carried over to the nonprescription label:

- Ask your doctor before use if you have kidney disease.
- Ask your doctor before use if you are 65 years old or older.
- Do not take at the same time as aluminum and magnesium containing antacids.
- Do not take with fruit juice, take with water.

3. INDIVIDUAL STUDY REPORTS

Study Number:	M016455/J001
Study Title:	Phase I single dose administration study in Japan
Phase:	1
Investigator:	M. Kawashima
Study Population:	Healthy adult male subjects
Study Site:	Tokyo women's Medical College
Study Period:	06-Sep-1995 to 19-Sep-1995

OBJECTIVE(S)

To evaluate the safety and pharmacokinetics of single dose administration of fexofenadine HCl

STUDY DESIGN

Placebo controlled, single blind, parallel intergroup comparison, single dose administration

STUDY TREATMENTS

40 Healthy adult male subjects participated in this study.

MDL 16,455A (fexofenadine HCl) 20 mg and 60 mg capsules, and placebo.

Single oral dose administration of 20, 60, 120, and 240 mg of MDL 16,455A (fexofenadine HCl) and placebo to fasting subjects; doses were successively increased based on safety assessments. Each treatment group included 8 subjects treated with the respective dose of fexofenadine HCl and 2 subjects treated with placebo.

RESULTS - PHARMACOKINETICS

Plasma and urinary concentrations of fexofenadine, and urinary concentration of MDL 4,829 (only in fexofenadine HCl 120 mg group) were determined.

Pharmacokinetic studies of MDL 16,455 (fexofenadine) detected plasma drug concentrations soon after oral dosing, with a t_{max} of 1.9 to 2.2 hours. There were dose-dependent increases in the C_{max} and AUC(0-∞) values. The elimination phase t_{1/2} of 7.7 to 13.8 hours was not related to dose level.

CONCLUSION(S)

Fexofenadine HCL was well tolerated at single oral doses of 20 to 240 mg. The coding of adverse event data in MedDRA did not change the safety profile of fexofenadine HCL.

Study Number:	M016455/J002
Study Title:	Phase I repeat dose administration study in Japan
Phase:	1
Investigator:	M. Kawashima
Study Population:	Healthy male subjects
Study Site:	Tokyo Women's Medical College
Study Period:	08-Dec-1995 to 06-Feb-1996

OBJECTIVE(S)

To evaluate the safety and pharmacokinetics of repeated dose administration of fexofenadine HCl

STUDY DESIGN

Placebo controlled, double-blind, parallel intergroup comparison, repeated dose administration

STUDY TREATMENT

24 Healthy adult male subjects participated in this study. Each subject received a single 60 or 120 mg dose of MDL 16,455A (fexofenadine HCl) or single dose of placebo after fasting. Two days after receiving the initial doses, each subject then received repeated BID oral doses of study medication or placebo for 7 days. Placebo was administered to all subjects the day before the abovementioned initial single doses. Each treatment group included 8 subjects treated with the respective dose of fexofenadine HCl and 4 subjects treated with placebo.

PHARMACOKINETIC BLOOD SAMPLING

Plasma and urinary concentrations of fexofenadine were measured.

RESULTS PHARMACOKINETICS

Plasma MDL 16,455 (fexofenadine) reached near steady-state concentration from trough levels by the second day after dosing. Administration of repeated doses had no significant influence on the pharmacokinetic parameters of MDL 16,455 (fexofenadine).

CONCLUSION(S)

Twice daily administration of 60 and 120 mg fexofenadine HCL for 7 days was generally well tolerated. The coding of adverse event data in MedDRA did not change the safety profile of fexofenadine HCL.

Study No.:	M016455/1122
Study Title:	A Study of the safety and pharmacokinetics of once-daily repeated oral administration of fexofenadine hydrochloride (180 mg) for 7 days in healthy adult males
Phase:	1
Principal Investigator:	Shigeto Kanada, MD
Study Population:	Healthy Volunteers
Study Site:	Osaka Clinical Pharmacology Research Clinic
Study Period:	14-Oct-2000 to 30-Nov-2000

OBJECTIVE(S)

Primary Objective - To investigate the safety of once-daily repeated oral administration of fexofenadine hydrochloride (180 mg) for 7 days in healthy adult males.

Secondary Objective - To investigate the pharmacokinetics of once-daily repeated oral administration of fexofenadine hydrochloride (180 mg) for 7 days in healthy adult males.

STUDY DESIGN

Randomized, placebo-controlled, double-blind, single and repeated dose study. Twelve healthy adult males were given a single dose of placebo on Day 1, followed by either a single oral dose of placebo or fexofenadine hydrochloride (180 mg) on Day 2, and then once-daily repeated oral doses of either placebo or fexofenadine hydrochloride (180 mg) for 7 days from Day 4 to Day 10.

STUDY TREATMENT

Dosage and administration:

Three 60 mg tablets (180 mg) orally once-daily, with 200 mL of water, after at least 10 hours of fasting.

Drug form: Film-coated tablets each containing 60 mg of fexofenadine hydrochloride

Lot number: FX00T15

Control drug: Placebo

Dosage and administration:

Three placebo tablets orally once-daily, with 200 mL of water, after at least 10 hours of fasting.

Drug form: Film-coated tablets containing lactose that are identical in appearance to the study drug tablets

ANALYSIS OF PHARMACOKINETIC PARAMETERS

The t_{max} , C_{max} , AUC, $t_{1/2}$ and systemic clearance for the single and repeated doses were calculated based on the actual measured values and the effects of repeated dosing were studied.

RESULTS

Plasma pharmacokinetics:

From the changes in the values immediately before administration in the repeated dose part of the study, it is believed that a steady-state was reached on the second day of administration since no elevation of the plasma concentration of fexofenadine was observed subsequent to Day 2.

The pharmacokinetic parameters for single and repeated doses of 180 mg fexofenadine are shown in the table below. Compared to the single dose, 90% confidence intervals for the t_{\max} and $t_{1/2}$ were judged to be within the equivalent range, while the AUC and C_{\max} in the repeated-dose period were 37% and 28% higher, respectively, than those in the single-dose period.

Table 1 – Pharmacokinetic parameters for single and repeated doses of 180 mg fexofenadine HCl

Pharmacokinetic parameter	Single dose period (A)	Repeated dose period (B)	Ratio** (%) B/A	90% Confidence interval
AUC (ng·hr/mL)*	3348 (31.2)	4164 (24.6)	137	[100, 175]
C_{\max} (ng/mL)	584 (32.8)	718 (25.5)	128	[105, 152]
t_{\max} (hr)	2.3 (39.4)	2.3 (51.8)	100	[78, 122]
$t_{1/2}$ (hr)	5.6 (23.0)	5.9 (11.5)	108	[97, 119]

Average (CV%), n=8

* Single dose period: $AUC_{0-\infty}$, Repeated dose period: AUC_{0-24}

** Calculated from logarithmic conversion value

Urine pharmacokinetics:

The cumulative excretion amount of fexofenadine in 48 hours after administration was 11552 ± 3811 μ g in the single dose period and 15789 ± 4949 μ g in the repeated dose period. The urinary excretion rates in relation to the dose were $6.42 \pm 2.12\%$ for the single dose period and $8.77 \pm 2.75\%$ for the repeated dose period.

CONCLUSION(S)

- Fexofenadine was rapidly detected in the plasma after administration and the changes in the plasma concentrations of fexofenadine were almost the same following a single dose and repeated doses.
- The plasma concentration of fexofenadine did not increase after Day 2 of repeated administration so it is thought the plasma concentration had reached a steady state. No accumulation due to repeated administration was observed.

Based on the above results, it is concluded that once-daily repeated oral administration of 180 mg of fexofenadine hydrochloride for 7 days in healthy adult males does not have any effects on the pharmacokinetics of the drug and that the drug is well tolerated. Therefore, we do not foresee any problem with moving on to clinical trials using patients.

Study No.:	M016455J/1104 (PJPR0104)
Study Title:	Pivotal bioequivalence study of 60 mg fexofenadine hydrochloride: peach oblong vs. white round tablets
Phase:	1
Principal Investigator:	Dennis Morrison, DO
Study Population:	Healthy Volunteers
Study Site:	Bio-Kinetic Clinical Applications 1816 W. Mount Vernon Springfield, MO 65802
Study Period:	23-Oct-1998 to 02-Nov-1998

OBJECTIVE(S)

To establish the bioequivalence of the 60 mg fexofenadine HCl white round tablet formulation relative to the 60 mg to-be-marketed peach oblong tablet formulation.

STUDY DESIGN

The study was conducted as an open-label, randomized, single-dose, complete crossover design using two treatments and two periods. There was a drug-free washout period of 6 days between each period.

STUDY TREATMENT

A single fexofenadine HCl (60 mg) dose was administered on day 1 of each period of the study with 240 mL of water. All drug administrations and study procedures were conducted in the clinical facility.

PHARMACOKINETIC BLOOD SAMPLING

During each treatment period, serial venous blood (plasma) samples for the determination of fexofenadine were collected prior to dosing and at 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 30, 36, and 48 hours following administration.

ANALYTICAL METHODS

Table 2 – Bioanalytical method used in protocol M016455J/1104/1305 sample analysis

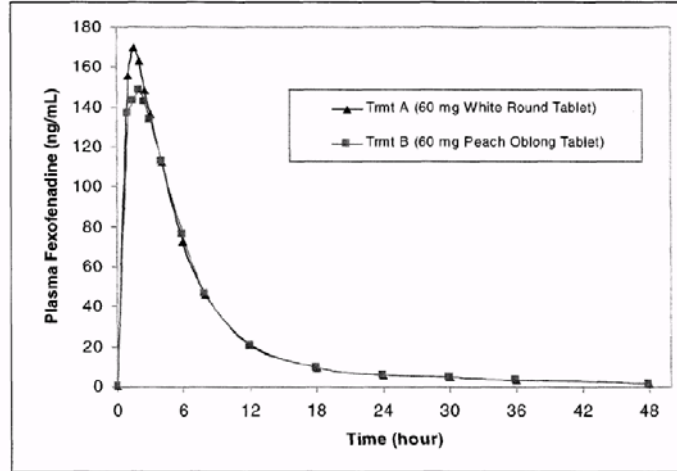
Laboratory	Matrix	Bioanalytical Method No.	Analyte(s) Measured	Assay Range
(b) (4)	Plasma	V1011P1	Fexofenadine (MDL 16,455)	1.0 - 100 ng/mL

Plasma Method Validation Report – MDL 16.455 (Report Number K-95-0517-D)

RESULTS

The mean fexofenadine plasma concentrations versus time for each treatment are illustrated in the following figure.

Figure 1 – Mean plasma fexofenadine concentration versus time profiles



Mean fexofenadine pharmacokinetic parameters for each treatment and pairwise treatment comparisons are presented in the following table.

Table 3 – Treatment comparisons for key plasma fexofenadine pharmacokinetic parameters

Parameter	Treatment	N	Mean	%CV	Adjusted Mean	Pairwise Comparisons ^a			
						Pair	Ratio (%)	90% CI on Ratio	P-value
AUC _(0-z) (hr•ng/mL)	A	50	1167.13	36.95	1095.97	-	-	-	-
	B	50	1136.58	35.97	1069.02	B/A	97.54	(89.5, 106.3)	0.628
AUC _(0-∞) (hr•ng/mL)	A	50	1201.19	35.85	1132.38	-	-	-	-
	B	50	1170.43	34.96	1104.42	B/A	97.53	(89.7, 106.0)	0.617
C _{max} (ng/mL)	A	50	196.14	50.20	175.33	-	-	-	-
	B	50	183.84	57.01	165.50	B/A	94.40	(83.3, 106.9)	0.442
t _{max} (hr)	A	50	1.80	49.88	1.61	-	-	-	-
	B	50	2.10	55.06	1.85	B/A	114.55	(98.5, 133.3)	0.139

A: Fexofenadine HCl (1 x 60 mg) white round tablet (Lot # RK9607) given as a single dose

B: Fexofenadine HCl (1 x 60 mg) peach oblong tablet (Lot # RD9619) given as a single dose

^a: Log transformed results of the ANOVA were transformed to the original scale by exponentiation to obtain the adjusted mean, ratio and 90% confidence interval (CI)

The time to maximum concentration t_{max} was not significantly different for white round and peach oblong tablets.

The ratios of the mean fexofenadine AUC_(0-z) and C_{max} values for the peach oblong tablet compared to the reference white round tablet were 97.54% and 94.40%, respectively. In addition, the 90% confidence intervals (CI) for those ratios were both within the 80% to 125% limit, indicating that the peach oblong tablet formulation was bioequivalent to the reference white round tablet.

CONCLUSION(S)

Fexofenadine HCl was well tolerated at the 60 mg dose.

The peach oblong tablet, given as a single dose of 1 x 60 mg, was bioequivalent to the reference white round tablet given as a single dose of 1 x 60 mg.

The recoding of adverse event data did not change the safety profile of fexofenadine HCl.

Study Protocol No.: M016455Q/1124

Study Title:	Bioequivalence study of fexofenadine hydrochloride (MDL 16,455A) 60 mg tablets and 180 mg tablets
Phase:	1
Principal Investigator:	Dr. Kyoko Matsukuma
Study Population:	Healthy Volunteers
Study Site:	Kyushu Clinical Pharmacology Research Clinic, Souseikai Medical Corp.
Study Period:	27-Jul-2001 to 29-Sep-2001

OBJECTIVE(S)

To verify the bioequivalence of 60 mg and 180 mg fexofenadine hydrochloride tablets.

STUDY DESIGN

Non-blind, two way cross over study of two preparations by the Latin square method (with a washout period at least 1 week)

STUDY TREATMENT

One tablet of the study preparation is given as single oral administration under fasting condition (for at least 10 hours) with 150 mL of water.

ANALYSIS OF PHARMACOKINETIC PARAMETERS

The bioequivalence of the study preparation (180 mg tablets) and standard preparation (60 mg tablets) is verified with the primary valuables, the C_{max} and AUC₀₋₄₈ of fexofenadine (MDL 16,455) concentration in plasma.

Urinary pharmacokinetics of the study drug is investigated.

RESULTS**Plasma pharmacokinetics**

As for the study drug, T_{max} was 2.0 hours post-dosing, C_{max} was 540 ng/mL and t_{1/2} was 12.2 hours. The AUC₀₋₄₈ up to 48 hours post-dosing was 3,622 ng•hr/mL (mean values in all cases). Plasma fexofenadine concentrations showed similar profiles between the study preparation and the standard preparation.

As for the C_{max} of plasma fexofenadine concentration, the point estimate of mean ratios of the standard preparation to study preparation was 94.7 %, and the lower and the upper confidence interval limit of 90% confidence coefficient for mean ratios were 82.0 % and 109.3 % respectively. As for the AUC₀₋₄₈ of plasma fexofenadine concentration analyzed by the same method, the point estimate of the mean ratio was 98.9 %, and the lower and the upper confidence interval limit of 90% confidence coefficient for mean ratios were 88.5 % and 110.6 %, respectively.

Urinary pharmacokinetics

Cumulative urinary excretion volume up to 24 and 48 hours after administration of the study preparation (mean values ± SD, from now on) was 16.629 ± 6.122 mg and 17.407 ± 6.244 mg, respectively. Moreover, cumulative urinary excretion rates for doses up to 24 and 48 hours after administration were 9.24 ± 3.40 % and 9.67 ± 3.47 %, respectively.

CONCLUSION(S)

- Tmax, Cmax and $t_{1/2}$ were 2.0 hours, 540 ng/mL and 12.2 hours in the study preparation, respectively.
- The cumulative excretion volume and the cumulative urinary excretion rate up to 48 hours after the study drug administration were 17.407 mg, and 9.67 %, respectively.
- As for plasma fexofenadine concentration, the 90% confidence intervals for mean ratios of Cmax and AUC₀₋₄₈ of the standard preparation to the study preparation were Cmax: [82.0, 109.3] and AUC₀₋₄₈: [88.5, 110.6] respectively, which were within the acceptable range for bioequivalence (confidence interval for ratio was 80% - 125%) Consequently, the 180 mg tablets of the study preparation and the 60 mg tablets of the standard preparation were, therefore, assessed to be bioequivalent.
- No adverse events and abnormal fluctuations in laboratory tests were observed in this study, and there were no abnormal fluctuations and findings in other safety parameters (subjective/objective signs and symptoms, blood pressure, pulse rate, body temperature, laboratory tests, standard 12-lead ECG). Consequently, there were no problems on safety of the both preparations.

Study Protocol No.:	M016455Q/1125
Study Title:	Bioequivalence study of fexofenadine hydrochloride (MDL 16,455A) 60 mg tablets and 120 mg tablets
Phase:	1
Principal Investigator:	Dr. Kyoko Matsukuma
Study Population:	Healthy Volunteers
Study Site:	Kyushu Clinical Pharmacology Research Clinic, Souseikai Medical Corp.
Study Period:	29-Aug-2001 to 15-Oct-2001

OBJECTIVE(S)

To verify the bioequivalence of 60 mg and 120 mg fexofenadine hydrochloride tablets.

STUDY DESIGN

Non-blind, two way cross over study of two preparations by the Latin square method (with a washout period of at least 1 week)

STUDY TREATMENT

One 120 mg tablet of the study preparation is given as single oral administration under fasting condition (for at least 10 hours) with 150 mL of water.

Two 60 mg tablets of the standard preparation are given as single oral administration under fasting condition (for at least 10 hours) with 150 mL of water.

ANALYSIS OF PHARMACOKINETIC PARAMETERS

The bioequivalence of the study preparation (120 mg tablets) and standard preparation (60 mg tablets) is verified with the primary valuables, the C_{max} and AUC₀₋₄₈ of fexofenadine (MDL 16,455) concentration in plasma.

Urinary pharmacokinetics of the study drug is investigated.

RESULTS

Plasma pharmacokinetics

As for the study drug, T_{max} was 1.9 hours post-dosing, C_{max} was 439 ng/mL and t_{1/2} was 10.8 hours. The AUC₀₋₄₈ up to 48 hours post-dosing was 2,775 ng•hr/mL (mean values in all cases). Plasma fexofenadine concentrations showed similar profiles between the study preparation and the standard preparation.

As for the C_{max} of plasma fexofenadine concentration, the point estimate of mean ratios between the study preparation and standard preparation was 96.7%, and the lower and the upper confidence interval limit of 90% confidence coefficient for mean ratios were 84.1% and 111.1% respectively. As for the AUC₀₋₄₈ of plasma fexofenadine concentration analyzed by the same method, the point estimate of the mean ratio was 100.6%, and the lower and the upper confidence interval limit of 90% confidence coefficient for mean ratios were 91.7% and 110.2%, respectively.

Urinary pharmacokinetics

Cumulative urinary excretion volume up to 24 and 48 hours after administration of the study preparation (mean values ± SD, from now on) was 13.236 ± 4.397 mg and 13.860 ± 4.441 mg, respectively. Moreover, cumulative urinary excretion rates for doses up to 24 and 48 hours after administration were 11.03 ± 3.66% and 11.55 ± 3.70%, respectively.

CONCLUSION(S)

- T_{max} , C_{max} and $t_{1/2}$ were 1.9 hours, 439 ng/mL and 10.8 hours in the study preparation, respectively.
- The cumulative excretion volume and the cumulative urinary excretion rate up to 48 hours after the study drug administration were 13.860 mg, and 11.55%, respectively.
- As for plasma fexofenadine concentration, the 90% confidence intervals for mean ratios of C_{max} and AUC₀₋₄₈ between the study preparation and the standard preparation of the ratio of mean values for the study preparation to those for the standard preparation in C_{max} and AUC₀₋₄₈ of plasma fexofenadine concentration were C_{max} : [84.1, 111.1] and AUC₀₋₄₈: [91.7, 110.2] respectively, which were being within the acceptable range for bioequivalence (confidence interval of for ratio was 80% - 125%), and Consequently, the 120 mg tablets of the study preparation and the 60 mg tablets of the standard preparation were therefore assessed to be bioequivalent.
- In the present study, 1 adverse event (fever) was observed seen in 1 subject (subject No. 202). As this event case was observed 2 hours after the administration post-dosing (near T_{max}), the causal relationship with the study drug was assessed by the investigator as "cannot be ruled out." No abnormal fluctuations or findings for safety were found seen in any of the other subjects for in any of the safety parameters (subjective/objective signs and symptoms, blood pressure, pulse rate, body temperature, laboratory tests, standard 12-lead ECG), and there were no problems on with the safety of either of the preparations.

Study No.:	M016455/4124
Study Title:	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
Phase:	4
Principal Investigator:	Walter Kraft, MD; Robert A. Blum, PharmD
Study Population:	Healthy Volunteers
Study Site:	Two Study centers - US
Study Period:	07-Feb-2003 to 16-Jan-2004

OBJECTIVE(S)

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.

STUDY TREATMENT

Part 1: Up to 140 white subjects and 80 black subjects

Part 2: 10 to 12 white subjects and 10 to 12 black subjects

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 over encapsulated by the sponsor

ANALYSIS OF PHARMACOKINETIC PARAMETERS

The primary PK endpoints were area under the curve (AUC) and maximum plasma concentration (C_{max}) for DCL, 3-OH desloratadine (3-OH-DCL), and FEX (for Part 2 only). Secondary PK endpoints included time to maximum plasma concentration (t_{max}), elimination half-life (t_{1/2}), and accumulation index (AI) as the data permitted.

RESULTS

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 (ie, 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 (ie, later t_{max}) and a slower rate of elimination (ie, longer t_{1/2}) resulting in pronounced accumulation and a failure to reach steady state after 7 consecutive days of dosing.

CONCLUSION(S)

The prevalence of the DSM phenotype in the general and black populations was consistent with the limited information presently available. There was an apparent predominance of this phenotype in males, the relevance or significance is unknown.

Substantial accumulation of DCL occurred with recommended daily dosing, while there was no significant accumulation or apparent alteration of FEX disposition in DSMs.

Both DCL and FEX were well tolerated in otherwise healthy DSMs over 7 days of dosing.

Study No.:	M016455/1105
Study Title:	Drug-drug interactions of fexofenadine HCl and erythromycin in healthy volunteers
Phase:	1
Principal Investigator:	Akinori Urae
Study Population:	Healthy Volunteers
Study Site:	Kyushu Clinical Pharmacology Research Clinic
Study Period:	06-Jul-1998 to 05-Oct-1998

OBJECTIVE(S)

Primary objectives:

The primary objective was to investigate the effect of fexofenadine HCl on QTc with a steady state plasma drug concentration during co-administration with erythromycin. Analyses were performed to test the hypothesis that the change of the diurnal mean QTc (the mean value over 2 days) after erythromycin (EM) + MDL16,455A (fexofenadine HCl) treatment was ≤ 12 msec and that the change of the diurnal mean QTc (the mean value over 2 days) after EM + MDL16,455A treatment was equivalent to that after treatment with EM alone.

Secondary objectives:

Secondary endpoints examined were the effects of MDL16,455A co-administered with EM on the following with a steady-state plasma drug concentration:

- the pharmacokinetic parameters of MDL16,455A,
- the pharmacokinetic parameters of EM,
- ECG parameters other than QTc, and
- safety parameters (symptoms, blood pressure, pulse rate, temperature, and laboratory tests).

STUDY DESIGN

Double-blind, multiple-dose, randomized, 3-treatment 3-stage, cross-over study using the orthogonal Latin square method. There was a 14-day wash-out between the last dose in the previous stage and the first dose (day 2) of MDL16,455A in the next stage.

STUDY TREATMENT

Study drug 1

Drug code : MDL16,455A
Generic name (INN) : fexofenadine hydrochloride
Formulation : Film-coated tablets containing 60 mg of fexofenadine hydrochloride.
Lot No. : RK9607

Study drug 2 (Placebo for study drug 1)

Formulation : Film-coated tablets containing (b) (4) which are indistinguishable from study drug 1.
Lot No. : RK9610

Study drug 3

Generic name : erythromycin
Formulation : Film-coated tablets containing 100 mg of erythromycin.
Lot No. : PC8011

Study drug 4 (placebo for study drug 3)

Formulation : Film-coated tablets containing (b) (4) which are indistinguishable from study drug 3.
Product No. : CP8012

Dosage

MDL16,455A alone : 120 mg twice daily for 7 days (only once in the morning on day 7).
Erythromycin (EM) alone : 300 mg four times daily for 7 days (only once in the morning on day 7).
Combined treatment : fexofenadine HCl at 120 mg twice daily for 7 days + erythromycin at 300 mg four times daily for 7 days (both drugs only once in the morning on day 7).

Prior to these treatments, placebo was administered for 2 days.

ANALYSIS OF PHARMACOKINETIC PARAMETERS

The plasma and urinary concentrations of fexofenadine HCl and the plasma concentration of erythromycin were determined. Using these data, pharmacokinetic parameters were calculated, including the C_{max}, AUC(0-12), T_{max}, t_{1/2}, total clearance relative to AUC(0-12) (CL_{tot}), cumulative urinary excretion (A_e), percent dose urinary excretion, and renal clearance (CL_{ren}) of fexofenadine HCl. The parameters obtained after multiple oral doses of fexofenadine HCl plus erythromycin were compared with those obtained after multiple oral dose of fexofenadine HCl or erythromycin alone.

RESULTS

The steady-state pharmacokinetic parameters of fexofenadine HCl, including AUC(0-12), C_{max}, and urinary excretion, were significantly higher during MDL16,455A + EM treatment than after multiple oral doses of MDL16,455A alone. In contrast, the plasma concentration of EM was not modified by combined administration with MDL16,455A.

Table 1 – Steady-state pharmacokinetic parameters of fexofenadine HCl during treatment with fexofenadine alone or fexofenadine + erythromycin treatment

Parameter	MDL16,455A alone [Mean (CV)]	MDL16,455A +EM [Mean (CV)]	Point estimate (90% confidence interval) (MDL16,455A + EM/MDL16,455A alone)
AUC _{ss(0-12)} (ng•h/mL)	2754 (23.4)	5763 (28.0)	2.060 (1.852, 2.292)
Cl _{po,ss(0-12)} (L/h)	45.97 (24.2)	22.83 (36.2)	0.497 (0.432, 0.561)
C _{max,ss} (ng/ml)	488 (26.8)	980 (24.8)	2.022 (1.807, 2.264)
T _{max,ss} (h)	2.2 (58.9)	3.2 (31.1)	1.0* (0.4, 1.6)
t _{1/2,ss} (h)	10.0 (25.7)	9.63 (27.0)	-0.36* (-1.73, 1.00)
CL _{r,ss (0-12)} (mL/min)	67.20 (20.8)	75.97 (20.7)	1.130 (1.089, 1.177)
A _{e,ss (0-12)} (mg)	8.95 (18.7)	21.07 (21.3)	2.333 (2.094, 2.599)

n=18, *: The point estimates for T_{max} and t_{1/2} represent estimates of differences

Table 2 – Steady-state pharmacokinetic parameters of erythromycin during treatment with erythromycin alone or erythromycin + fexofenadine

Parameter	MDL16,455A alone [Mean (CV)]	MDL16,455A +EM [Mean (CV)]	Point estimate (90% confidence interval) (MDL16,455A + EM/MDL16,455A alone)
AUC _{ss(0-6)} (ng•h/mL)	11017 (42.2)	10088 (52.4)	0.916 (0.763, 1.069)
Cl _{po,ss(0-6)} (L/h)	32.15 (41.0)	42.42 (69.4)	1.179 (0.972, 1.430)
C _{max,ss} (ng/ml)	2899 (38.0)	2455 (43.1)	0.810 (0.675, 0.971)
T _{max,ss} (h)	3.2 (16.2)	3.5 (35.7)	0.3* (-0.2, 0.8)
t _{1/2,ss} (h)	4.10 (38.2)	4.56 (30.4)	0.46* (-0.4, 1.32)

n=18, *: The point estimates for T_{max} and t_{1/2} represent estimates of differences

CONCLUSION(S)

Fexofenadine HCl and erythromycin were administered to healthy adult male subjects to assess their interactions. The AUC_{ss(0-12)}, C_{max}, and urinary excretion of fexofenadine HCl were significantly higher during combined treatment with erythromycin than during treatment with fexofenadine HCl alone. In contrast, the plasma concentration of erythromycin was not altered by combined treatment with fexofenadine HCl. The QTc was not prolonged during fexofenadine HCl treatment, and when fexofenadine HCl was administered in combination with erythromycin there was no effect on the QTc.

Good tolerability was demonstrated during combined treatment with fexofenadine HCl and erythromycin, and there was no influence on the 12-lead ECG findings.

The coding of adverse event data in MedDRA did not change the safety profile of fexofenadine HCl.

Study No.:	M016455I/1120
Study Title:	Pharmacokinetics and pharmacodynamics of oral fexofenadine hydrochloride tablets administered to healthy adult male subjects
Phase:	1
Principal Investigator:	Lars Nyman, MD
Study Population:	Healthy Volunteers
Study Site:	Quintiles AB, Islandsгатan 2, S-753 18 Uppsala, Sweden
Study Period:	13-Nov-2000 to 08-Dec-2000

OBJECTIVE(S)

Primary objective:

To characterize the pharmacokinetics of oral fexofenadine hydrochloride (HCl) tablets in healthy adult male subjects.

Secondary objective:

To characterize the inhibitory effects of oral fexofenadine hydrochloride tablets on skin wheal and flare induced by histamine in healthy adult male subjects.

STUDY DESIGN

This study was a single center, double blind, single dose, randomized, four period, complete crossover design in healthy adult male subjects with blood sampling up to 48 hours.

At each period, subjects arrived at the clinic the morning of the dose and were released after the 24-hour blood collection and wheal and flare tests. Subjects returned to the clinic for the 30-, 36- and 48-hour procedures on Days 2 and 3. Subjects returned for a post-study assessment made within 3 days of completing the last pharmacokinetic sample at the last study period.

STUDY TREATMENT

Each subject received the following treatments:

Treatment A: Single dose oral administration of 30 mg fexofenadine hydrochloride

Treatment B: Single dose oral administration of 60 mg fexofenadine hydrochloride

Treatment C: Single dose oral administration of 120 mg fexofenadine hydrochloride

Treatment D: Single dose oral administration of placebo

All subjects received the same treatments in a random sequence. Subjects were assigned a subject number at the time they received the first dose of study medication. Each dose was separated by a washout period of at least 7 days.

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Serial pharmacokinetic blood samples were collected in all subjects prior to (0 hours) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36 and 48 hours after administration of each dose. Plasma samples were analyzed for fexofenadine hydrochloride using a validated liquid chromatography-mass spectrometry method.

RESULTS

A proportionate increase in C_{max} and $AUC(0-\infty)$ was observed with increasing fexofenadine HCl dose. The following figure illustrates the fexofenadine plasma concentration-time profiles by treatment.

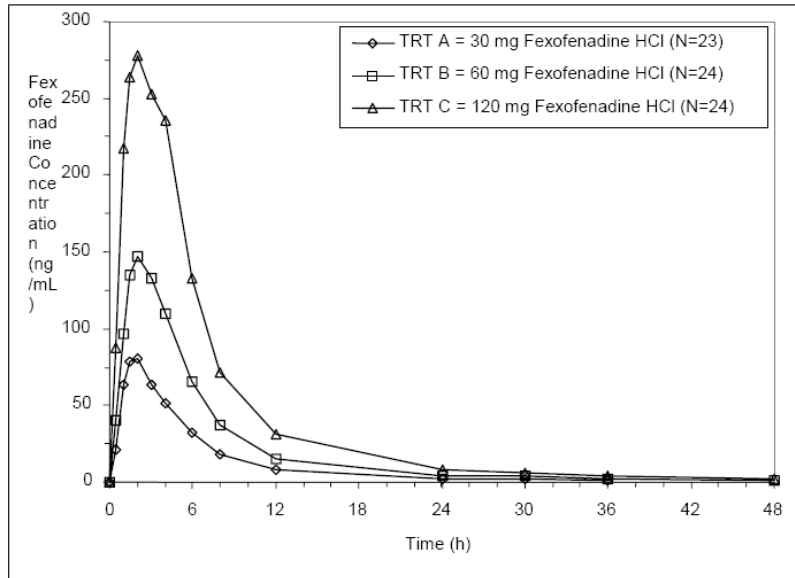


Table 1 – Key mean fexofenadine pharmacokinetic parameters

		<i>Fexofenadine HCl</i>		
		<i>30 mg</i>	<i>60 mg</i>	<i>120 mg</i>
		<i>N=23</i>	<i>N=23</i>	<i>N=24</i>
C_{max} (ng/mL)	Mean (CV%)	90.3 (65)	166.8 (56)	320.0 (69)
t_{max} (h)	Mean (CV%)	1.7 (43)	2.0 (37)	2.2 (46)
$AUC(0 - \infty)$ (ng-h/mL)	Mean (CV%)	551.5 (44)*	1052.4 (45)	2055.4 (59)
Cl_{po} (L/h)	Mean (CV%)	60.1 (43)*	62.3 (40)	71.5 (47)
$t_{1/2}$ (h)	Mean (CV%)	16.1 (77)*	14.0 (43)	17.3 (69)

*Unevaluable in one subject. CV%, percentage coefficient of variation

Source: Table 1120/1pk0001f.lst in original Clinical Study Report R2000CLN0597

CONCLUSION(S)

- Administration of single oral doses of 30, 60, and 120 mg fexofenadine HCl to healthy male volunteers resulted in dose proportional increases in C_{max} and $AUC(0-\infty)$.
- All fexofenadine HCl doses caused clear inhibition of histamine induced wheal and flare areas, whereas placebo did not. The 30 mg fexofenadine HCl dose appears less effective in inhibiting the histamine induced wheal and flare areas than the two higher doses.
- All doses of fexofenadine HCl were safe and well tolerated.
- The recoding of adverse event data did not change the safety profile of fexofenadine HCl.

Study No.:	M016455/4123
Study Title:	A double-blind, controlled, parallel-group, randomized, monocentric, comparative study of suppression of wheal and flare induced by increasing doses of histamine after oral administration of fexofenadine 180 mg versus loratadine 10 mg versus desloratadine 5 mg versus placebo during 7 days in healthy volunteer subjects: relation with plasma and tissue concentrations.
Phase:	4
Principal Investigator:	Professor Christian Brandt
Study Population:	Healthy Volunteers
Study Site:	Clinical Investigation Centre, France
Study Period:	22-Apr-2002 to 13-Sep-2002

OBJECTIVE(S)

Principal objective

To compare the shift in histamine dose-response curves at different time points after 7 days of treatment with fexofenadine hydrochloride (HCl), loratadine, or desloratadine versus placebo by the wheal and flare area measurements.

Secondary objectives

To relate these shifts to consistency and relative efficacy of the antihistamines.

To study the correlation between wheal and flare data versus plasma and tissue concentrations.

STUDY DESIGN

This was a randomized, placebo-controlled, double-blind, multiple-dose, single-center, parallel-group study in healthy subjects. Subjects were randomized to receive one of the following four investigational products to be taken orally on a daily basis for 7 days: fexofenadine HCl 180 mg, loratadine 10 mg, desloratadine 5 mg, or placebo. All tablets were overencapsulated in an opaque gelatin capsule to maintain the double-blind procedure. On the last day of dosing (Day 7), pharmacokinetic/pharmacodynamic sampling was performed at steady state (24 hours after the Day 6 dosing) and at 1, 2, 4, and 8 hours after dosing. A tissue biopsy was obtained 2 hours postdose. A follow-up safety evaluation was performed within 48 hours to 1 week after dosing.

STUDY TREATMENT

Subjects were randomized to receive one of the following four investigational products to be taken orally on a daily basis for 7 days:

Fexofenadine HCl, 180-mg tablet

Loratadine, 10-mg tablet

Desloratadine, 5-mg tablet

Placebo tablet

All tablets were overencapsulated in an opaque gelatin capsule to maintain the double-blind procedure.

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Plasma concentrations of fexofenadine HCl, loratadine, and desloratadine were determined. Blood samples were collected at the same time points as described for the prick tests (see section for pharmacodynamic data).

Tissue concentrations of fexofenadine HCl, loratadine, and desloratadine were determined. A tissue biopsy was obtained 2 hours postdose to evaluate the tissue concentration of antihistamines.

RESULTS

The maximum concentration for fexofenadine HCl (553 ng/mL), loratadine (3.7 ng/mL), and desloratadine (4.5 ng/mL) occurred at the 2-hour time point. At 2 hours after administration of the investigational product, no significant correlation was demonstrated between plasma and tissue concentrations for fexofenadine HCl (Pearson correlation coefficient = 0.40), or desloratadine (Pearson correlation coefficient = 0.31). Results from the Pearson analysis to evaluate potential relationships between plasma and tissue concentrations showed a correlation between the 2-hour plasma concentrations and skin biopsy concentrations for loratadine (Pearson correlation coefficient = 0.8669)

CONCLUSION(S)

In this population of healthy volunteers ages 18 to 44 years who received either fexofenadine HCl 180 mg, loratadine 10 mg, desloratadine 5 mg, or placebo on a daily basis for 7 days, the side effect profiles of the active treatments were similar to each other and more favorable than that of placebo.

No dose-related effect on histamine-induced wheal and flare inhibition was evident with fexofenadine 180 mg, since maximal or near-maximal wheal and flare inhibition was observed at all histamine doses. However, loratadine 10 mg and desloratadine 5 mg generally showed a dose-related decrease in median percent inhibition with increasing histamine dose.

Fexofenadine showed superior wheal and flare inhibition compared to loratadine, desloratadine, or placebo, particularly at the higher histamine doses (10 mg and 100 mg/mL).

For all antihistamine treatments (fexofenadine, loratadine, or desloratadine), there was a lag time between achievement of plasma concentrations and manifestation of antihistaminic effect. Plasma and skin biopsy concentrations were correlated with one another for loratadine but not for fexofenadine and desloratadine.

Study No.:	M016455/J003
Study Title:	Histamine intradermal challenge testing in Japan
Phase:	1
Principal Investigator:	M Kawashima
Study Population:	Healthy Volunteers
Study Site:	Department of Dermatology, Tokyo Women's Medical College
Study Period:	05-Apr-1996 to 13-May-1996

OBJECTIVE(S)

To evaluate the inhibitory effects of single doses of MDL 16,455A (fexofenadine HCl) on histamine-induced skin wheal and flare responses, and to evaluate the pharmacokinetic profile of fexofenadine HCl.

STUDY DESIGN

Placebo controlled, double-blind, 5-drug, 5-stage crossover, single dose administration study.

STUDY TREATMENT

MDL 16,455A (fexofenadine HCl) 20 mg and 60 mg capsules and placebo
Single oral doses of placebo and MDL 16,455A (fexofenadine HCl) 20, 60, 120, and 180 mg to fasting subjects, with drug-free intervals of at least 7 days

ANALYSIS OF PHARMACOKINETIC PARAMETERS

Plasma concentrations of MDL 16,455 (fexofenadine)

RESULTS

Pharmacokinetic studies of MDL 16,455 (fexofenadine) showed dose-dependent increases in the AUC and Cmax values. The Tmax was 2.1 to 3.2 hours.

CONCLUSION(S)

The areas under the percent change curves for the histamine-induced skin wheal and flare responses decreased in a dose-dependent manner, but the differences between doses of 60 mg and greater were relatively small. These findings indicate that 60 mg or higher of MDL 16,455A (fexofenadine HCl) would be a suitable clinical dose. Single oral doses of 20 to 180 mg of MDL 16,455A (fexofenadine HCl) were generally well tolerated.

Study No.:	M016455/J006 (JTAM-CL-006)
Study Title:	Double-blind, randomized study of the pharmacokinetics of MDL 16,455 and suppression of the histamine-induced skin reaction following single oral doses of MDL 16,455A and terfenadine in healthy adult male volunteers
Phase:	1
Principal Investigator:	Makoto Kawashima
Study Population:	Healthy Volunteers
Study Site:	Dept of Dermatology, Tokyo Women's Medical College
Study Period:	12-May-1997 to 11-Jul-1997

OBJECTIVE(S)

Primary objective:

The primary objective of the study was to evaluate the pharmacokinetics and pharmacodynamics of MDL16,455 (fexofenadine) in healthy adult male subjects given single oral doses of 60 mg and 120 mg of the drug with 60 mg of terfenadine being used for comparison. The primary endpoints were the C_{max} and AUC of MDL16,455 (fexofenadine) as well as the suppression of histamine-induced skin reactions (maximum reduction of the area of histamine-induced wheals and erythema and the AUC for each effect). The bioavailability and the antihistamine effect of MDL16,455A (fexofenadine HCl) were also compared with those of terfenadine.

Secondary objectives:

A secondary endpoint of the study was the safety of MDL16,455A (fexofenadine HCl) when administered at single oral doses of 60 and 120 mg to healthy adult men versus the safety of a single 60 mg oral dose of terfenadine. Safety was assessed from the changes of symptoms and signs, vital signs (blood pressure, pulse rate, and body temperature), the standard 12-lead electrocardiogram, and laboratory data.

STUDY DESIGN

This was a randomized, balanced, double-blind, three-way cross-over, single dose study which compared two dose levels of MDL16,455A (fexofenadine HCl) with terfenadine. There was a 7-day washout period between two successive study sessions.

STUDY TREATMENT

Test drug

Investigational drug code : MDL16,455A
Dosage : MDL16,455A was given orally together with 150 ml of water at 30 min after a meal.
Generic name (INN) : Fexofenadine hydrochloride
Formulation : Film-coated tablets containing 60 mg of MDL16,455A.

Control drug

Product name : Triludan®
Dosage : Triludan was given orally together with 150 ml of water after a meal.
Generic name (INN) : Terfenadine
Formulation : Film-coated tablets containing 60 mg of terfenadine.

Placebo 1

Film-coated tablets containing (b) (4) which were indistinguishable from the test drug in appearance and odor.

Placebo 2

Film-coated tablets containing (b) (4) which were indistinguishable from the control drug in appearance and odor.

ANALYSIS OF PHARMACOKINETIC PARAMETERS

The pharmacokinetics of MDL16,455 (fexofenadine) following single doses of the drug and terfenadine were assessed based on major pharmacokinetic parameters (e.g., C_{max}, AUC, and A_e) calculated from the plasma and urinary concentration data.

RESULTS

Following a single oral dose of 120 mg of MDL16,455A (fexofenadine HCl), the C_{max}, AUC₀₋₁₂, AUC_{0-t}, and A_e of MDL16,455 were similar to the values obtained after a single oral dose of 60 mg of terfenadine, with the MDL16,455A/terfenadine ratios for the respective parameters being 1.036, 1.006, 1.031, and 0.954. The same pharmacokinetic parameters calculated after a single oral dose of 60 mg of MDL16,455A (fexofenadine HCl) were about half those obtained after 60 mg of terfenadine, with the corresponding ratios being 0.524, 0.515, 0.523, and 0.468. The maximum percent change (MAXINH) in the areas of the wheal and erythema responses to histamine and the AUCs for these changes (AUECs) after a single 120-mg oral dose of MDL16,455A (fexofenadine HCl) were similar to those observed after 60 mg of terfenadine. A 60-mg single oral dose of MDL16,455A (fexofenadine HCl) exerted a slightly smaller antihistaminic effect, as assessed in terms of the two erythema parameters.

CONCLUSION(S)

In healthy adult male subjects, a single postprandial dose of MDL16,455A (fexofenadine HCl) achieved about half the bioavailability of a single postprandial dose of terfenadine and caused slightly less suppression of histamine-induced skin reactions.

The coding of adverse event data in MedDRA did not change the safety profile of fexofenadine HCl.

Study No.:	M016455I/1119
Study Title:	Pharmacokinetics and pharmacodynamics of oral fexofenadine hydrochloride tablets administered to children from 6 through 11 years of age
Phase:	1
Principal Investigator:	Christophe Pedroletti, MD
Study Population:	6 through 11 year-old subjects with allergic rhinitis
Study Site:	Astrid Lindgrens Barnsjukhus, S-171 75 Stockholm, Sweden
Study Period:	25-Sep-2000 to 20-Dec-2000

OBJECTIVE(S)

Primary objective:

To characterize the pharmacokinetics of oral fexofenadine hydrochloride (HCl) tablets in 6 through 11 year-old pediatric subjects with allergic rhinitis.

Secondary objective:

To characterize the inhibitory effects of oral fexofenadine hydrochloride tablets, on skin wheal and flare induced by histamine, in 6 through 11 year-old pediatric subjects with allergic rhinitis.

STUDY DESIGN

This study was a single center, double blind, single dose, randomized, two period, incomplete block crossover design in pediatric subjects (6 through 11 years of age) with allergic rhinitis.

At each period, subjects arrived at the clinic in the morning of Day 1, and were released overnight after the 8-hour blood collection and wheal and flare test. The subjects returned in the morning of

Day 2 for the 24, 30, and 34-hour procedures. Subjects returned for a post-study assessment within 3 days of completion of the second study period.

Time data for plasma concentration and wheal and flare, were limited at the request of the ethics committees, to reduce the length and frequency of sampling required in the pediatric subjects.

STUDY TREATMENT

Treatment A: Single dose oral administration of 15 mg fexofenadine hydrochloride

Treatment B: Single dose oral administration of 30 mg fexofenadine hydrochloride

Treatment C: Single dose oral administration of 60 mg fexofenadine hydrochloride

Treatment D: Single dose oral administration of placebo

All subjects received two of the four treatments in a random sequence. Subjects were assigned a subject number at the time they received the first dose of study medication. Each dose was separated by a washout period of at least 7 days.

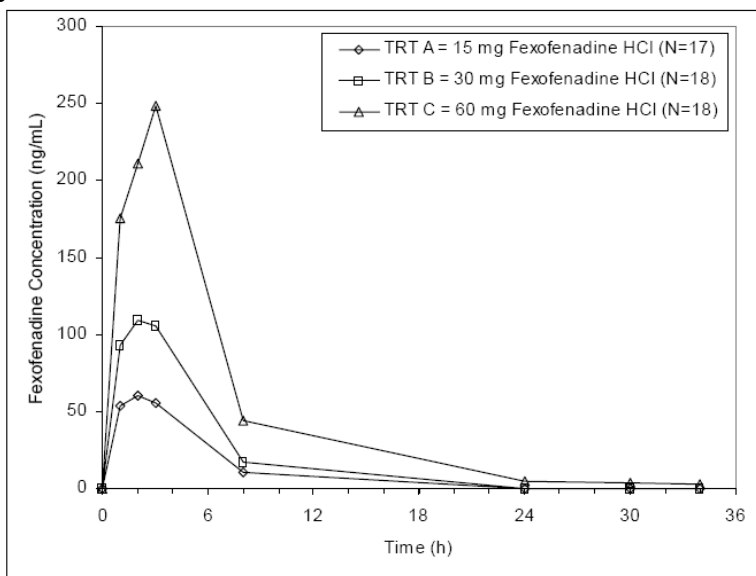
ANALYSIS OF PHARMACOKINETIC PARAMETERS

Serial pharmacokinetic blood samples were collected in all subjects prior to (0 hours) and at 1, 2, 3, 8, 24, 30 and 34 hours after administration of each dose. Plasma samples were

analyzed for fexofenadine hydrochloride using a validated liquid chromatography-mass spectrometry method.

RESULTS

A proportionate increase in C_{max} and $AUC(0-8)$ was observed with increasing fexofenadine HCl dose. These observations are consistent with a previous population analysis of fexofenadine pharmacokinetic data collected in pediatric seasonal allergic rhinitis subjects. The following figure illustrates the mean fexofenadine concentration-time profiles by treatment.



Apparent terminal half-life and overall exposure (as expressed by $AUC(0-\infty)$) could not be evaluated in all treatment groups due to the limited sampling requested by the president of the ethics committee. To allow comparison across fexofenadine doses, overall exposure over the 0 to 8 hour collection interval ($AUC(0-8)$) was calculated. The subsequent table summarizes the key mean fexofenadine pharmacokinetic parameters.

Table 1 – Key mean fexofenadine pharmacokinetic parameters

		<i>Fexofenadine HCl</i>		
		<i>15 mg</i> <i>N = 17</i>	<i>30 mg</i> <i>N = 18</i>	<i>60 mg</i> <i>N = 18</i>
C_{max} (ng/mL)	Mean (CV%)	71 (55.0)	128 (49.4)	288 (46.5)
t_{max} (h)	Mean (CV%)	1.8 (44.4)	1.8 (38.6)	2.1 (39.3)
$AUC(0-8)$ (ng-h/mL)	Mean (CV%)	308 (54.7)	560 (50.9)	1241 (42.2)
$AUC(0-\infty)$ (ng-h/mL)	Mean (CV%)	ND	ND	1670 (35.3)*
CL_{po} (L/h)	Mean (CV%)	ND	ND	39 (42.9)*
$t_{1/2}$ (h)	Mean (CV%)	ND	ND	15 (37.3)*

CV%: percentage coefficient of variation, ND: Could not be determined due to insufficient terminal concentration-time data.

* Unevaluable in one subject

CONCLUSION(S)

Administration of single oral doses of 15 mg, 30 mg and 60 mg fexofenadine HCl to pediatric patients (6-11 years of age) resulted in dose proportional increases in C_{max} and AUC(0-8).

All fexofenadine HCl doses caused inhibition of histamine induced wheal and flare areas, whereas placebo did not. However, large variability in the baseline and treatment responses limited quantitative inferences of the pharmacodynamic effect. Overall, it appears that 15 mg may not be as effective as the two higher doses.

All 3 doses of fexofenadine HCl were safe and well tolerated.

The recoding of adverse event data did not change the safety profile of fexofenadine HCl.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARUN K AGRAWAL
11/22/2010

YUN XU
11/22/2010

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	201-373	Brand Name	Allegra oral suspension
OCP Division (I, II, III, IV, V)	II	Generic Name	Fexofenadine HCl
Medical Division	DNCE	Drug Class	Antihistamine
OCP Reviewer	Arun Agrawal, Ph.D.	Indication(s)	SAR & CIU
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form	30 mg/5 mL
Pharmacometrics Reviewer		Dosing Regimen	30 mg BID, 2-11 years old; (b) (4)
Date of Submission	March 25, 2010	Route of Administration	Oral
Estimated Due Date of OCP Review		Sponsor	Sanofi Aventis
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	January 25, 2011		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x	13		Only synopsis of new studies provided
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x			
multiple dose:	x			
Patients-				
single dose:	x			
multiple dose:	x			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x			
In-vivo effects of primary drug:	x			
In-vitro:				
Subpopulation studies -				
ethnicity:				

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gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	13			Only synopsis of new studies provided

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			Reference to previous NDAs
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			Reference to previous NDAs
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			Reference to previous NDAs
5	Has a rationale for dose selection been submitted?	x			Reference to previous NDAs
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			Reference to previous NDAs
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			Reference to previous NDAs

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8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			Reference to previous NDAs
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			x	
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			Reference to previous NDAs
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

 Yes

Comments to the sponsor in the 74-day letter

Submit full study report for studies M016455/J001, M016455/J002, M016455/1122, M016455J/1104, M016455Q/1124, M016455Q/1125, M016455/4124, M016455/1105, M016455I/1120, M016455/4123, M016455/J003, M016455/J006, and M016455I/1119.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Arun Agrawal, Ph.D.

Reviewing Clinical Pharmacologist

Date

Yun Xu, Ph.D.

Acting Team Leader

Date

BACKGROUND

Fexofenadine hydrochloride is an antihistamine with selective peripheral H1-receptor antagonist activity. The suspension formulation was approved on October 2006 for the treatment of SAR and CIU in pediatric patients 2 to less than 12 years of age, inclusive (≥ 2 to < 12 years of age) at a dose of 30 mg twice daily (BID) and for the treatment of CIU in pediatric patients 6 months to less than 2 years of age, inclusive (≥ 6 months to < 2 years of age), at a dose of 15 mg BID.

This submission is for the **partial change** of status of ALLEGRA® oral suspension (fexofenadine HCl, 6 mg/mL) from prescription-to-nonprescription use. Fexofenadine HCL suspension for pediatric patients younger than 6 years of age CIU will not be switched from prescription-to-nonprescription status. The Sponsor will maintain NDA 21-963 for the prescription use of fexofenadine suspension for CIU in pediatric patients 6 months to less than 6 years of age. The indication of the proposed product is for the temporary relief of symptoms due to hay fever or other upper respiratory allergies (runny nose, sneezing, itchy, watery eye, itching of nose or throat), as well as for the reduction of hives and the relief of itching due to hives (urticaria).

The applicant has also submitted synopsis of the following 13 new studies, related to Clinical Pharmacology, that were not previously submitted to an IND/NDA. In Clinical Pharmacology Summary of Module 2, the applicant indicates there is no new clinical pharmacology information in this submission. However, in Module 5 of the submission, the applicant has submitted synopsis of the following 13 studies, related to Clinical Pharmacology, that were not previously submitted to an IND/NDA. The applicant submitted these studies for global integrated safety database updates. A preliminary review of the summary of these studies appears that the overall Clinical Pharmacology recommendations for this prescription-to-nonprescription (Rx-to-OTC) switch and labeling will not be affected by these additional submissions, however, we would like to request the full reports of those studies for thorough review.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Table 1 - Additional studies contributing to the Global Integrated Safety Database, not previously submitted in a regulatory submission in the United States

Study	Study Title
[M016455/J001] in NDA 20-872 section 5.3.5.3	Phase I single dose administration study in Japan
[M016455/J002] in NDA 20-872 section 5.3.5.3	Phase I repeated dose administration study in Japan
[M016455/1122] in NDA 20-872 section 5.3.5.3	A study of the safety and pharmacokinetics of once-daily repeated oral administration of fexofenadine hydrochloride (180 mg) for 7 days in healthy adult males
[M016455/J/1104] in NDA 20-872 section 5.3.5.3	Pivotal bioequivalence study of 60 mg fexofenadine hydrochloride: peach oblong vs. white round tablets
[M016455Q/1124] in NDA 20-872 section 5.3.5.3	Bioequivalence study of fexofenadine hydrochloride (MDL 16,455A) 60 mg tablets and 180 mg tablets
[M016455Q/1125] in NDA 20-872 section 5.3.5.3	Bioequivalence study of fexofenadine hydrochloride (MDL 16,455A) 60 mg tablets and 120 mg tablets
[M016455/4124] in NDA 20-872 section 5.3.5.3	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
[M016455/1105] in NDA 20-872 section 5.3.5.3	Drug-drug interactions of fexofenadine HCl and erythromycin in healthy volunteers
[M016455I/1120] in NDA 20-872 section 5.3.5.3	Pharmacokinetics and pharmacodynamics of oral fexofenadine hydrochloride tablets administered to healthy adult male subjects
[M016455/4123] in NDA 20-872 section 5.3.5.3	A double-blind, controlled, parallel-group, randomized, monocentric, comparative study of suppression of wheal and flare induced by increasing doses of histamine after oral administration of fexofenadine 180 mg versus loratadine 10 mg versus desloratadine 5 mg versus placebo during 7 days in healthy volunteer subjects: relation with plasma and tissue concentrations.
[M016455/J003] in NDA 20-872 section 5.3.5.3	Histamine intradermal challenge testing in Japan
[M016455/J006] in NDA 20-872 section 5.3.5.3	Double-blind, randomized study of the pharmacokinetics of MDL 16,455 and suppression of the histamine-induced skin reaction following single oral doses of MDL 16,455A and terfenadine in healthy adult male volunteers
[M016455I/1119] in NDA 20-872 section 5.3.5.3	Pharmacokinetics and pharmacodynamics of oral fexofenadine hydrochloride tablets administered to children from 6 through 11 years of age

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201373	ORIG-1	SANOFI AVENTIS US LLC	FEXOFENADINE HCL

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/s/

ARUN K AGRAWAL
05/26/2010

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