CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-963

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY TEAM LEADER'S MEMO

Subject: NDA 21-963 (Fexofenadine HCl)
Sponsor: Sanofi-Aventis Inc.
OCP Division: DCP-II
OND Division: Pulmonary and Allergy Drug Products
Reviewer: Shinja R. Kim, Ph.D.
Team Leader: Emmanuel Fadiran, Ph.D.
Memo Date: September 6, 2006

This is s clinical pharmacology team leader's memo on NDA 21-963 for Allegra (fexofenadine) suspension by Sanofi-Aventis. The NDA was submitted to the Agency on December 15, 2005 and the original clinical pharmacology review (CPC review dated June 28, 2006) by Dr. Shinja Kim recommended approval subject to a favorable DSI report. The DSI report by Dr. Martin Yau dated July 28, 2006 identified the following two objectionable items:

1. Failure to confirm the accuracy of fexofenadine concentrations in 8 plasma samples as shown in the table below. All of these plasma samples exhibited fexofenadine concentrations above the limit of quantitation (i.e., >150 ng/ml) in the original analysis and were subsequently diluted and re-analyzed. The re-assay and the original data are significantly different (>30%). However, no additional re-analysis was conducted as required by Aventis DMPK/US SOP#08320-003. The re-assay data were used in the bioequivalence determination and a SOP deviation was stated in the study report.

#	Subject #	Study Period	Plasma Sample (hour post-dose)	Original Data (ng/ml)	Re-assay Data (ng/ml)
1	1045	1	4	>150	67.2
2	1052	2	1.5	>150	92.5
3	1052	2	2	>150	68.4
4	1052	2	3	>150	51.5
5	1053	1	1	>150	20.3
6	1053	1	1.5	>150	27.8
7	1053	1	2	>150	33.5
8	1054	2	1	>150	67.8

The accuracy of the fexofenadine concentrations in the eight plasma samples listed in the above table are not reliable and this can significantly affect the accuracy of the relevant Cmax and AUC values in Subjects 1045, 1052, 1053 and 1054. DSI recommends that these 8 plasma samples be re-assayed again in duplicate, provided these samples are available and stored in proper conditions (i.e., -20°C) at the site and their integrity is covered by storage stability data. However, if the re-assay of these

plasma samples are not feasible, the Review Division should consider discarding the Cmax and AUC values from Subjects 1045 (Period 1), 1052 (Period 2), 1053 (Period 1) and 1054 (Period 2) from bioequivalence determination.

At the inspection close-out meeting, the site acknowledged the above 483 observation and stated they would submit a written response to the Agency soon.

2. Failure to conduct study to demonstrate the lack of matrix effect in the fexofenadine LC/MS/MS assay.

   During the inspection, the site agreed that they will provide the data or conduct study to demonstrate the lack of matrix effect in the fexofenadine assay.

The DSI recommended that 483 Item 1 should be resolved before approval of the application.

The Sponsor excluded the 4 subjects affected by 483 Item 1 from the bioequivalence determination and was able to demonstrate bioequivalence to the tablet formulation. The supplement submitted to the NDA was reviewed by Dr. Shinja Kim (CPB review dated August 17, 2006) who found the response to 483 Item 1 acceptable but recommended that the Sponsor should respond to 483 Item 2 as agreed with the DSI.

A clinical pharmacology briefing (CPB) was held on this NDA on August 25, 2006 at which the clinical pharmacology reviewer (Dr. Shinja Kim) was not able to clearly delineate the impact of the DSI report on the approval of the NDA. Following the CPB I sent an e-mail to Dr. Martin Yau and then followed this with a telephone conversation. During my telephone conversation with Dr. Yau I got the following clarifications regarding the 483 Item 1: There were 63 samples that were re-assayed and only 8 samples failed the Aventis SOP and were supposed to be re-assayed but they were not and the Sponsor did not give any good reason for their failure to follow the SOP.
2. The dilution factor of 3 was already taken into consideration in the calculation of the re-assay data in the table shown in the DSI report.
3. The SOP of not greater than 30% difference between re-assay and original data was made by Aventis and not a standard set by DSI.

On the 483 Item 2, I discussed with Dr. Yau that since a solid phase extraction procedure followed by LC-MS/MS was used I did not see how there was going to be any matrix effect on the assay. Dr. Yau mentioned to me that what the report was trying to address was that the Sponsor used plasma from only one source for the assay validation and that they normally recommend using plasma from various sources. He agreed with me that this issue does not have to be resolved before approval.

The Sponsor has therefore satisfactorily addressed the 483 Item 1 and this NDA is therefore recommended for approval.

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/s/

Emmanuel Fadiran
9/7/2006 09:33:30 AM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

Subject:	Addendum to the original NDA 21-963 (Fexofenadine HCl)
Sponsor:	Sanofi Aventis Inc.
OCP Division:	DCP-II
OND Division:	Pulmonary and Allergy Drug Products
Reviewer:	Shinja R. Kim, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph.D.

The Sponsor submitted an NDA for Allegra (fexofenadine HCl) suspension on December 15, 2005 and this was reviewed by this reviewer (Office of Clinical Pharmacology review dated 06/28/06). Form 483 was issued after the OCP review was finalized. The conclusions in the original review are contingent on the assumption that the outcome of the inspection will be favorable. Therefore, this review is an addendum to the original review.

Following the inspection of the analytical portion for Study M016455I/1004 at [redacted] Form 483 was issued by the Division of Scientific Investigation (DSI). The objectionable items and the recommendation by DSI of the findings are as follows:

1. Failure to confirm the accuracy of fexofenadine concentrations in 8 plasma samples as shown in the table below. All of these plasma samples exhibited fexofenadine concentrations above the limit of quanitation (i.e., >150 ng/ml) in the original analysis and were subsequently diluted and re-analyzed. The re-assay and the original data are significantly different (>30%). However, no additional re-analysis was conducted as required by Aventis DMPK/US SOP#08320-003. The re-assay data were used in the bioequivalence determination and a SOP deviation was stated in the study report.

#	Subject #	Study Period	Plasma Sample (hr post-dose)	Original Data (ng/ml)	Re-assay Data (ng/ml)
1	1045	1	4	>150	67.2
2	1052	2	1.5	>150	92.5
3	1052	2	2	>150	68.4
4	1052	2	3	>150	51.5
5	1053	1	1	>150	20.3
6	1053	1	1.5	>150	27.8
7	1053	1	2	>150	33.5
8	1054	2	1	>150	67.8

Recommendation: The 8 plasma samples be re-assayed again, provided these samples are available, however if the re-assay of these plasma samples are not feasible, the Review Division should consider discarding the Cmax and AUC values from these subjects for bioequivalence determination.

2. Failure to conduct study to demonstrate the lack of matrix effect in the fexofenodine LC/MS/MS assay.

Recommendation: The site agreed that they will provide the data or conduct study to demonstrate the lack of matrix effect in the fexofenodine assay. Upon receipt of the written response, DSI will evaluate and determine if the 483 observations are adequately resolved.

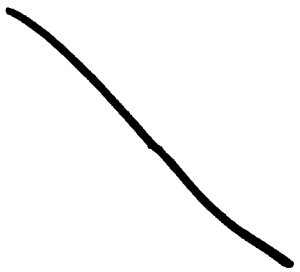
Revised bioequivalence analysis

Background:

Study M016455I/1004 was a two-way crossover, randomized, open-label bioequivalence study comparing the fexofenadine HCl suspension to the marketed fexofenadine HCl (Allegra®) tablet in healthy adult subjects. A total of 54 subjects were enrolled in the study; 53 of them received all doses of study medication and completed the study according to the protocol and these 53 subjects were included in the assessment of bioequivalence. The conclusions of the study were: A 30 mg dose of the fexofenadine HCl 6 mg/mL suspension was bioequivalent to the marketed 30 mg tablet in healthy adult subjects under fasted conditions.

During the bioanalysis of samples, there was one deviation from Standard Operating Procedure (SOP) that affected a total of eight plasma samples from four subjects (Subjects 1045, 1052, 1053, 1054). This deviation was reported in the Bioanalytical Report QKAN-2004-1139-BIO issued on 25 May 2005 and these four subjects were included in the original bioequivalence assessment. Aventis DMPK/US SOP # 08320-003, "Selection and Reporting of Samples for Reanalysis" states that if the original value is >upper limit of quantitation (ULQ) but the reassay value is <70% of the ULQ then the reassay result may not represent the true value and an additional reassay will be performed. If the additional reassay cannot be done, the result will be reported as "N.R." The sponsor stated that these eight samples were not reassayed a second time for conformation because the single reassay samples were found to be consistent with adjacent PK sample values for each subject, these values were used in the previous PK assessments. Note that these 8 samples were obtained after administration of Allegra 30 mg tablet (i.e., Treatment A, reference). Affected data from 4 subjects (and others) are shown in the table below.

Treatment[a]	Subject number	Period	Scheduled time (h) 0	0.5	1	1.5	2	3	4	6	8	12	24	30	36	47
A																



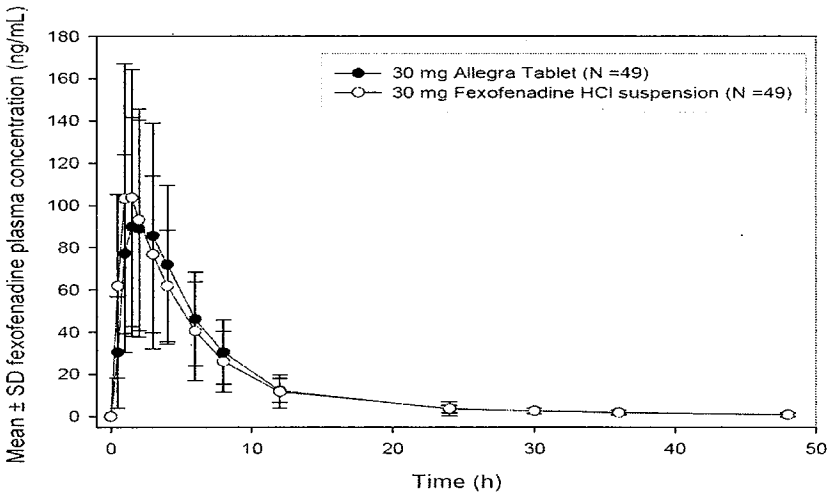
Results: Bioequivalence assessment was conducted by excluding Subjects 1045, 1052, 1053 and 1054 from the PK population. Fexofenadine PK parameters and the between-treatment comparisons are summarized in Table 1. Figure 1 presents the mean concentration-time profiles.

Table 1: Summary statistics and ANOVA results for fexofenadine PK parameters

					Treatment Comparisons [b]	
Parameter (unit)	**Treatment [a]**	**N**	**Arithmetic Mean (CV%)**	**Geometric LS Mean**	**Ratio [c] (%)**	**90% CI**
AUC(0-∞) (ng·h/mL)	Tablet	49	732 (44.5)	665	97.5	87.7 - 109
	Suspension	49	714 (47.5)	649		
Cmax (ng/mL)	Tablet	49	109 (55.0)	95.5	109	96.1 - 122
	Suspension	49	118 (56.2)	104		
AUC(0-last) (ng·h/mL)	Tablet	49	707 (45.6)	638	97.7	87.5 - 109
	Suspension	49	691 (48.8)	624		
Tmax [d] (h)	Tablet	49	1.5 (0.5 - 4.0)	-	-	-
	Suspension	49	1.0 (0.5 - 4.0)			
t1/2 (h)	Tablet	49	11.0 (31.2)	-	-	-
	Suspension	49	10.9 (27.9)			
CLpo (L/h)	Tablet	49	46.3 (47.4)	-	-	-
	Suspension	49	47.1 (41.1)			

Notes: CV% = coefficient of variation; LS = least-squares; CI = confidence interval.
[a] Tablet: single dose of 30 mg fexofenadine HCl as marketed tablet (reference).
Suspension: single dose of 30 mg fexofenadine HCl as 5 mL of 6 mg/mL suspension (test).
[b] 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.
[c] Ratio = geometric LS mean test /geometric LS mean reference (Suspension/Tablet).
[d] Tmax reported as median (range) values.

Figure 1: Mean ± SD fexofenadine concentration-time plot



Following a single dose, the geometric least-squares means of $AUC_{(0-\infty)}$, $AUC_{(0-last)}$, and Cmax, were similar for the suspension formulation (test) and the marketed tablet (reference), with associated 90% confidence intervals for the test/reference ratio of geometric least-squares means of 87.7 to 109%, 87.5 to 109%, and 96.1 to 122%, respectively.

The median fexofenadine Tmax was 1.0 h for the test suspension formulation and 1.5 h for the reference tablet formulation. Mean $t_{1/2}$ was approximately 11 h for both treatments. CLpo was approximately 47 L/h for the test formulation and 46 L/h for the reference formulation.

Summary and Conclusion: The results of bioequivalence assessment in the revised pharmacokinetic population (N =49) show that the 90% confidence intervals for the ratio of geometric least-square means of fexofenadine test to reference formulations of $AUC_{(0-\infty)}$, $AUC_{(0-last)}$, and Cmax, are narrow, falling entirely within the 80 to 125% bioequivalence range. In conclusion, a 30 mg dose of the fexofenadine HCl 6 mg/mL suspension was bioequivalent to the marketed 30 mg tablet fexofenadine HCl in healthy adult subjects under fasted conditions when the four subjects were excluded. This conclusion is consistent with the previous results when the four subjects were included in the bioequivalence assessment.

Reviewer's comment: Analysis for bioequivalence was performed after removing the data from these 4 subjects instead of just excluding the 8 samples (from these 4 subjects), which is acceptable.

Recommendation: The re-assessment of bioequivalence in NDA 21-963 is acceptable from an OCP standpoint provided that the second objectionable item in the Form 483 is adequately resolved.

Shinja R. Kim, Ph.D., DCP II

Emmanuel Fadiran, Ph.D., Team Leader

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/s/

Shinja Kim
8/17/2006 12:58:57 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
8/17/2006 01:24:38 PM
BIOPHARMACEUTICS
I concur.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-963**	**Brand Name**	**Allegra®**
OCPB Division (I, II, III)	**DPE-II**	**Generic Name**	**Fexofenadine HCl**
Medical Division	**HFD-570**	**Drug Class**	**Anti-Histamine**
OCPB Reviewer	**Shinja Kim**	**Indication(s)**	**Allergic rhinitis**
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	**6 mg/mL suspension**
		Dosing Regimen	BID for SAR in children 2-11 yrs old and CIU in children 6 months - 11 yrs old
Date of Submission	**12/15/05**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**8/15/06**	**Sponsor**	[redacted]
PDUFA Due Date	**10/15/06**	**Priority Classification**	**S**
Division Due Date	**9/15/06**		

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			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
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:	x	1		
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	2		
replicate design; single / multi dose:				
Food-drug interaction studies:	x	1		
Dissolution:	x	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		3 PK studies and 1 pop-PK analysis

Filability and QBR comments

	"X" if yes	Comments
Application filable?	x	**Fileable per CPB standpoint. However, the problems identified in the FDA-483 must be satisfactorily resolved by the CMC and medical review teams.**
Comments sent to firm?		
QBR questions (key issues to be considered)	• Is the formulation used in the bio-studies identical to the to-be-marketed formulation? • Is the tested formulation bioequivalent to the reference product? • Are food effect profiles comparable between the proposed and referenced product? • Has the applicant developed adequate dissolution method and specification to assure in vivo performance and quality of the product? • What bioanalytical methods are used to assess concentrations of active moiety?	

Note: Request for DSI consultation for the BE study (M016455I/1004) by the project manager: Analysis of the plasma samples undertaken by [redacted]

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/s/

Shinja Kim
2/8/2006 12:24:29 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
2/10/2006 02:24:26 PM
BIOPHARMACEUTICS
I concur.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-963:	Submission Date: 15-December 2005
Brand Name:	Allegra® Oral Suspension
Generic Name:	Fexofenadine hydrochloride
Reviewer:	Shinja Kim, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph. D.
OCPB Division:	DCP 2
ORM Division:	DPADP
Sponsor:	[redacted]
Submission Type:	Original (S000)
Formulation; Strength(s):	Oral Suspension, 6 mg/mL
Indication:	Twice daily treatment of seasonal allergic rhinitis (SAR) in children 2 to 11 years of age and uncomplicated skin manifestations of chronic idiopathic urticaria (CIU) in children 6 months to 11 years of age

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendation: The Office of Clinical Pharmacology has reviewed the information provided in NDA 21-963. OCP found this application acceptable provided that the sponsor agrees with the Agency's labeling recommendations as well as favorable DSI findings. Please convey labeling recommendations (page 12) to the sponsor.

1.2 Phase 4 Commitment: None

1.3 Summary of clinical Pharmacology and Biopharmaceutics Findings

To support the NDA, the sponsor conducted three clinical pharmacology studies. The results are summarized below.

Study M016455I/1004: This was an open label, randomized, single dose, two-way crossover study designed to establish the bioequivalence of 30 mg fexofenadine when administered as a to-be-marketed suspension relative to the marketed 30 mg fexofenadine tablet (Allegra®) under fasting conditions in healthy male and female subjects, 18-45 years of age. The study showed that the proposed formulation was bioequivalent to Allegra® as 90% confidence intervals around ratios of AUC and C_{max} were within the acceptance bioequivalence (BE) range of 80-125% (Table 1).

Table 1. Statistical comparisons for fexofenadine suspension and Allegra Tablet given as a single 30-mg dose under fasting conditions (Study M016455I/1004)

Parameter (unit)	Treatment[a]	N	Arithmetic mean (CV%)[b]	N	Geometric LS Mean[c]	Treatment comparisons[d]	
						Ratio[e] (%)	90% CI
$AUC_{(0-\infty)}$ (ng•h/mL)	Tablet Suspension	53 53	744 (42.5) 703 (47.6)	53	680 638	93.8	84.3 – 104
C_{max} (ng/mL)	Tablet Suspension	53 53	110 (52.8) 117 (55.8)	53	97.2 103	106	93.5 – 119
$AUC_{(0-last)}$ (ng•h/mL)	Tablet Suspension	53 53	719 (43.5) 680 (48.9)	53	653 614	94.0	84.1 – 105

LS = least-squares, CI = confidence interval.

[a]Allegra® 30 mg Tablet (reference), Fexofenadine HCl as 5 mL of a 6 mg/mL suspension (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 $AUC_{(0-\infty)}$, $AUC_{(0-last)}$, and Cmax.

[e]Ratio = geometric LS mean test/geometric LS mean reference (Suspension/Tablet).

Study M016455I/1003: This was an open label, randomized, single dose, two-way crossover study designed to compare the bioavailability of 30 mg fexofenadine when administered as a to-be-marketed suspension under fed and fasted conditions. The results showed that the 30 mg fexofenadine HCl suspension administered with food was not bioequivalent to the 30 mg fexofenadine HCl suspension administered without food: co-administration of the suspension formulation with a high-fat breakfast resulted in a 30% decrease in AUC, a 47% decrease in Cmax, and a 1.5 hour increase in Tmax (Table 2).

Table 2. Statistical comparisons for fexofenadine suspension given as a single 30-mg dose under fasted and fed conditions (Study M016455I/1003)

Parameter (unit)	Treatment[a]	N	Arithmetic mean (CV%)[b]	N[c]	Geometric LS Mean[c]	Treatment comparisons[d]	
						Ratio[e] (%)	90% CI
$AUC_{(0-\infty)}$ (ng•h/mL)	Fasted Fed	47 48	667 (30) 457 (23)	47 47	638 445	69.7	64.0 – 76.0
C_{max} (ng/mL)	Fasted Fed	50 50	106 (40) 53.7 (27)	50 50	98.2 51.9	52.9	47.9 – 58.3
$AUC_{(0\text{-last})}$ (ng•h/mL)	Fasted Fed	50 50	615 (35) 414 (25)	50 50	576 401	69.6	63.7 – 76.0
t_{max}[f] (h)	Fasted Fed	50 50	1.0 (0.5 – 4.0) 2.5 (1.0 – 6.0)	–	–	–	–

Annotations are the same as Table 1, except suspension formulation was used under fasted and fed conditions

Study M016455I/1005: This was an open label, randomized, single dose, multi-center study designed to compare the bioavailability of 30 mg fexofenadine when administered as a to-be-marketed suspension under fasted conditions in pediatric subjects 2 to 5 years of age with allergic rhinitis.

Table 3. Summary statistics for fexofenadine pharmacokinetic parameters (Study M016455I/1005)

	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0\text{-}24)}$ (ng•h/mL)
N	50	50	50
Mean	224	1.0[a]	898
Range	110 – 437	1.0 – 4.0	459 – 1966
CV%	39.3	53.3	34.3

[a] t_{max} (time to maximum plasma concentration) reported as median value

Information from NDA 20-872: The mean (±STD) PK parameter estimates for different age groups (obtained from population PK analysis) are shown in the table below (review dated 4/24/03):

Summary of fexofenadine PK parameter estimates from the final model

		15 mg		30 mg		60 mg	
	n	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)
6 months - <2 yrs							
Weight ≤10.5 kg	*	1080±332	185±51	2140±546	361±122	-	-
Weight >10.5 kg	**	761±247	136±44	1460±708	253±150	-	-
2 - 5 yrs	21	-	-	930±234	154±39	-	-
7 – 12 yrs	***	-	-	1060±220	153±56	2110±561	303±115
Adults	269	-	-	-	-	1290±424	165±56

*based on 5 and 8 subjects for 15 and 30 mg dose, respectively;
**based on 14 and 15 subjects for 15 and 30 mg dose, respectively;
***based on 14 and 13 subjects for 30 and 60 mg dose, respectively;

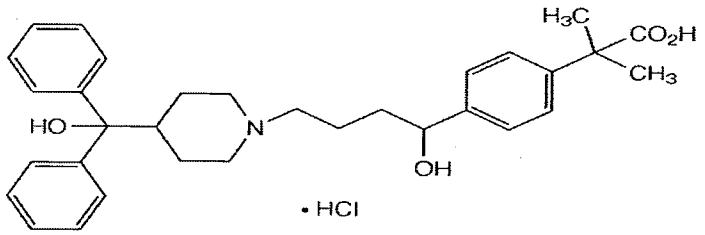
AUC from Study M016455I/1005 (898 ng•h/mL) for children age 2-5 years is similar to that obtained from the population PK study submitted NDA to 20-872 (930 ng•h/mL) shown in the table above. Although the Cmax from Study M016455I/1005 (224 ng/mL) is higher than that obtained from the same age group (154 ng/mL) using population PK analysis, the value is still within the Cmax obtained from all other age groups. Overall, it may be concluded that this study supports the selection of a 30 mg dose of fexofenadine HCl suspension for children 2 to 5 years of age.

2. QUESTION BASED REVIEW

2.1 General Attribute [redacted]

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The chemical name for fexofenadine hydrochloride is (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-(alpha), (alpha)-dimethyl benzeneacetic acid hydrochloride, and has the following chemical structure:



Fexofenadine hydrochloride is a white to off-white crystalline powder. It is freely soluble in methanol and ethanol, slightly soluble in chloroform and water, and insoluble in hexane. Fexofenadine hydrochloride is a racemate and exists as a zwitterion in aqueous media at physiological pH.

ALLEGRA [redacted] Suspension, a white uniform suspension, contains 6 mg fexofenadine hydrochloride per mL and the following excipients: polypropylene glycol, edetate disodium, propylparaben, butylparaben, xanthan gum, poloxamer 407, titanium dioxide, sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, artificial raspberry cream flavor, sucrose, xylitol and purified water.

2.1.2. What are the proposed dosage(s), route(s) of administration, and indications for ALLEGRA [redacted] Suspension?

The recommended dose of ALLEGRA [redacted] Suspension is as follows:

Seasonal Allergic Rhinitis (SAR) in Children 2 to 11 Years: A dose of 30 mg (5 mL) twice daily. Thirty mg once daily is recommended as the starting dose in pediatric patients with decreased renal function.

Chronic Idiopathic Urticaria (CIU) in Children 6 Months to 11 years: Thirty mg (5 mL) twice daily for patients [redacted] For pediatric patients with decreased renal function, the recommended starting doses are 30 mg (5 mL) once daily for patients [redacted]

2.2. *General Clinical Pharmacology*

2.2.1. What are the known clinical pharmacology characteristics of fexofenadine HCl?

Mechanism of action: Fexofenadine is an antihistamine with selective peripheral H_1-receptor antagonist activity. In laboratory animals, no anticholinergic, α_1-adrenergic or β-adrenergic-receptor blocking effects were observed. No sedative or other central nervous system effects were observed.

Phamacokinetics: The Tmax occurred at 2.6 hours post-dose of two 60 mg fexofenadine capsules administered to healthy male volunteers with the mean elimination half-life of 14.4 hours. The tablet formulations are bioequivalent to the capsule when administered at equal doses. Fexofenadine pharmacokinetics is linear for oral doses up to a total daily dose of 240 mg (120 mg twice daily). Approximately 5% of the total oral dose was metabolized. Based on increases in bioavailability and half-life, the recommended starting dose in patients with decreased renal function is half of the normal dose. No dose adjustment is need in patients with hepatic impairment.

2.2.2. What are the rationales of this submission?

The sponsor previously conducted Study M016455T/1123 (and two Phase III studies) in response to the Division's Written Request for pediatric studies, and submitted in an NDA labeling supplement (NDA 20-872). Study M016455T/1123 was a phase 1 study to characterize the pharmacokinetics of fexofenadine HCl in children ≥6 months to <2 years of age after a single oral dose of 15 mg or 30 mg. At the time of the application, the sponsor did not have a marketable pediatric formulation, thus an allergic rhinitis or chronic idiopathic urticaria indication for fexofenadine in children ≥6 months to <6 years of age could not be supported. The Division concluded that the sponsor's pharmacokinetic studies provided an appropriate dose of fexofenadine for children from ≥6 months to <6 years of age, and that extrapolation of efficacy could be considered if the sponsor had a marketable pediatric formulation. Consequently, the sponsor has developed the fexofenadine suspension formulation, and conducted 3 clinical pharmacology studies including a pediatric study (Study M016455I/1005).

2.2.3. Was bioequivalence established when the proposed suspension formulation of fexofenadine HCl was compared to maketed fexofenadine HCl tablet (Allegra®)?

Yes. The pivotal bioequivalence study M016455I/1004 was conducted as an open-label, randomized, single-dose, 2-treatment, 2-period, complete crossover design in 54 healthy adult male and female subjects. The 2 treatments were:

- Treatment A: Marketed tablet as reference - a single oral dose of fexofenadine HCl 30 mg administered under fasted conditions.
- Treatment B: Suspension as test - a single oral dose of fexofenadine HCl 30 mg (5 mL of a 6 mg/mL fexofenadine HCl suspension) administered under fasted conditions.

Treatments A and B were administered with 240 mL of water. There was a washout period of at least 6 days between each dose. The mean (±SD) plasma concentration-time profiles for the marketed formulation (reference) and the suspension formulation (test) are presented in Figure 1, and fexofenadine pharmacokinetic parameters and the between-treatment comparisons are summarized in Table 1.

Figure 1. Mean (±SD) plasma fexofenadine concentration-time plot for a 30 mg dose of the fexofenadine HCl 6 mg/mL oral suspension (test) compared to the Allegra® 30 mg tablet (reference).

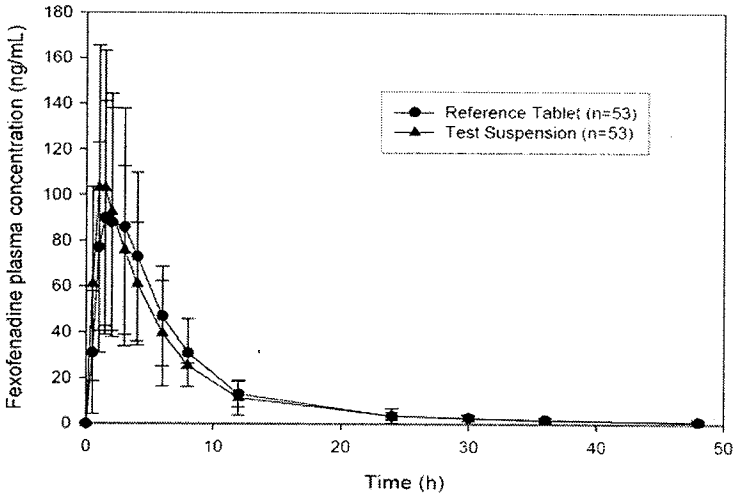


Table 1. Summary Statistics and ANOVA Results for Fexofenadine PK Parameters

Parameter (unit)	Treatment[a]	N	Arithmetic mean (CV%)[b]	N	Geometric LS Mean[c]	Treatment comparisons[d]	
						Ratio[e] (%)	90% CI
$AUC_{(0-\infty)}$ (ng•h/mL)	Tablet	53	744 (42.5)	53	680	93.8	84.3 – 104
	Suspension	53	703 (47.6)		638		
C_{max} (ng/mL)	Tablet	53	110 (52.8)	53	97.2	106	93.5 – 119
	Suspension	53	117 (55.8)		103		
$AUC_{(0\text{-last})}$ (ng•h/mL)	Tablet	53	719 (43.5)	53	653	94.0	84.1 – 105
	Suspension	53	680 (48.9)		614		
t_{max}[f] (h)	Tablet	53	1.5 (0.5 – 4.0)	–	–	–	–
	Suspension	53	1.0 (0.5 – 4.0)				
$t_{1/2}$ (h)	Tablet	53	11.0 (30.0)	–	–	–	–
	Suspension	53	11.0 (28.4)				
CL_{po} (h)	Tablet	53	45.2 (47.5)	–	–	–	–
	Suspension	53	47.8 (40.6)				

LS = least-squares, CI = confidence interval.
[a] Tablet: single dose of 30 mg fexofenadine HCl as marketed tablet administered under fasted conditions.
Suspension: single dose of 30 mg fexofenadine HCl as 5 mL of a 6 mg/mL suspension administered under fasted conditions.
[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 $AUC_{(0-\infty)}$, $AUC_{(0\text{-last})}$, and C_{max}.
[e] Ratio = geometric LS mean test/geometric LS mean reference (Suspension/Tablet).
[f] t_{max} (time to maximum plasma concentration) reported as median (range) values.

The 90% confidence intervals for geometric means ratios for AUC_t, $AUC_{(0-\infty)}$, and C_{max} met the criteria of BE by falling within the 80-125% range for fexofenadine. It can be concluded that the proposed formulation of the fexofenadine suspension 30 mg is bioequivalent to the Allegra® 30 mg Tablet in healthy adult subjects under fasted conditions.

2.2.4. Was the bioavailability similar when the proposed formulation of fexofenadine HCl was conducted under fed and fasted conditions?

No. The pivotal food-effect study M016455I/1003 was conducted as an open-label, randomized, single-dose, 2-treatment, 2-period, complete crossover design in a single center in 54 healthy adult male and female subjects. The 2 treatments were:

- Treatment A: Single oral dose of fexofenadine HCl 30 mg (5 mL of a 6 mg/mL fexofenadine HCl suspension) administered under fasted conditions.
- Treatment B: Single oral dose of fexofenadine HCl 30 mg (5 mL of a 6 mg/mL fexofenadine HCl suspension) administered under fed conditions (i.e., following a high-fat breakfast).

Treatments A and B were administered with an additional 235 mL water for a total administered volume of 240 mL. There was a washout period of at least 6 days between treatment periods.

The mean (±SD) plasma concentration-time profiles for the oral suspension administered under fasted and fed conditions are presented in Figure 2. Fexofenadine pharmacokinetic parameters and the between-treatment comparisons are summarized in Table 2.

Figure 2. Mean (±SD) plasma fexofenadine concentration-time plot for a 30 mg dose of the fexofenadine HCl 6 mg/mL oral suspension under fasted and fed conditions.

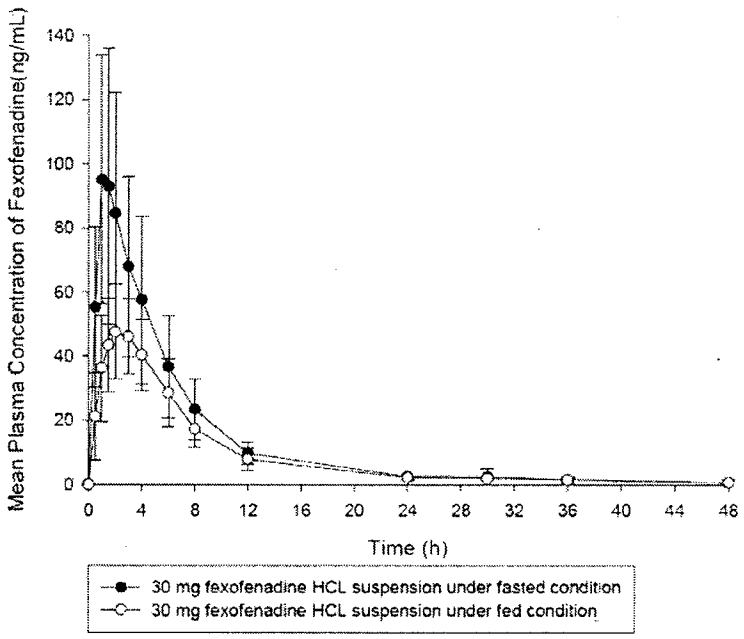


Table 2. Summary Statistics and ANOVA Results for Fexofenadine PK Parameters (Study M016455I/1003)

Parameter (unit)	Treatment[a]	N	Arithmetic mean (CV%)[b]	N[c]	Geometric LS Mean[c]	Treatment comparisons[d]	
						Ratio[e] (%)	90% CI
$AUC_{(0-\infty)}$ (ng•h/mL)	Fasted Fed	47 48	667 (30) 457 (23)	47 47	638 445	69.7	64.0 – 76.0
C_{max} (ng/mL)	Fasted Fed	50 50	106 (40) 53.7 (27)	50 50	98.2 51.9	52.9	47.9 – 58.3
$AUC_{(0\text{-last})}$ (ng•h/mL)	Fasted Fed	50 50	615 (35) 414 (25)	50 50	576 401	69.6	63.7 – 76.0
t_{max}[f] (h)	Fasted Fed	50 50	1.0 (0.5 – 4.0) 2.5 (1.0 – 6.0)	–	–	–	–
$t_{1/2}$ (h)	Fasted Fed	47 48	12.2 (41) 13.7 (53)	–	–	–	–
CL_{po} (h)	Fasted Fed	47 48	45.8 (30.7) 64.2 (21.9)	–	–	–	–

LS = least-squares; CI = confidence interval.
[a] Fasted (Treatment A): single dose of 30 mg fexofenadine HCl as 5 mL of 6 mg/mL suspension under fasted conditions (reference).
Fed (Treatment B): single dose of 30 mg fexofenadine HCl as 5 mL of 6 mg/mL suspension under fed conditions (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 $AUC_{(0-\infty)}$, $AUC_{(0\text{-last})}$, and C_{max}.
[e] Ratio = geometric LS mean test/geometric LS mean reference (Fed/Fasted).
[f] t_{max} (time to maximum plasma concentration) reported as median (range) values.

Co-administration of the suspension formulation with a high-fat breakfast resulted in a 30% decrease in $AUC_{0-\infty}$, a 47% decrease in Cmax, and a 1.5 hour increase in the median time to maximum plasma concentration (tmax) value. In summary, the 30 mg fexofenadine HCl suspension administered with food was not bioequivalent to the 30 mg fexofenadine HCl suspension administered without food.

2.2.5. What are the PK parameters in children 2 to 5 years of age following 30 mg fexofenadine suspension? Do the study results support the current dosing recommendation for this population?

The pharmacokinetic study M016455I/1005 was conducted as an open-label, single-dose, multicenter study in pediatric subjects 2 to 5 years of age with allergic rhinitis. The subjects received a single dose of 30 mg fexofenadine HCl oral suspension (6 mg/mL).

The mean (±SD) plasma concentration-time profile for the fexofenadine HCl oral suspension in pediatric subjects 2 to 5 years of age is presented in Figure 3. Fexofenadine pharmacokinetic parameters are summarized in Table 3. The terminal elimination phase had less than 3 concentration time points and therefore, λz (the terminal elimination rate constant), $t_{1/2}$, $AUC_{(0-\infty)}$, and CLpo were not estimated for any subject.

Figure 3. Mean (±SD) plasma fexofenadine concentration-time plot for the fexofenadine HCl oral suspension administered to pediatric subjects 2 to 5 years of age with allergic rhinitis

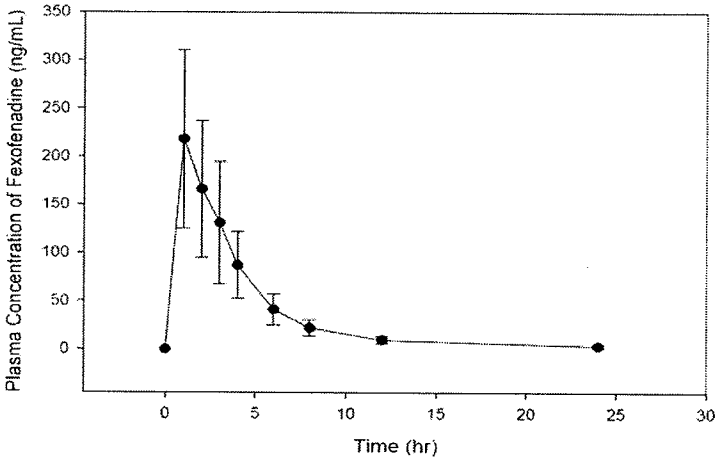


Table 3. Summary Statistics for Fexofenadine PK Parameters (Study M016455I/1005)

	C_{max} (ng/mL)	t_{max} (h)	$AUC_{(0-24)}$ (ng•h/mL)
N	50	50	50
Mean	224	1.0[a]	898
Range	110 – 437	1.0 – 4.0	459 – 1966
CV%	39.3	53.3	34.3

[a] t_{max} (time to maximum plasma concentration) reported as median value

Information from NDA 20-827: The mean (±STD) PK parameter estimates for different age groups (obtained from population PK analysis) are shown in the table below:

Summary of fexofenadine PK parameter estimates from the final model

		15 mg		30 mg		60 mg	
	n	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)
6 months - <2 yrs							
Weight ≤10.5 kg	*	1080±332	185±51	2140±546	361±122	-	-
Weight >10.5 kg	**	761±247	136±44	1460±708	253±150	-	-
2 - 5 yrs	21	-	-	**930±234**	**154±39**	-	-
7 – 12 yrs	***	-	-	1060±220	153±56	2110±561	303±115
Adults	269	-	-	-	-	1290±424	165±56

*based on 5 and 8 subjects for 15 and 30 mg dose, respectively;
**based on 14 and 15 subjects for 15 and 30 mg dose, respectively;
***based on 14 and 13 subjects for 30 and 60 mg dose, respectively;

AUC from Study M016455I/1005 (898 ng•h/mL) for children age 2-5 years is similar to that obtained from the population PK study submitted to NDA 20-872 (930 ng•h/mL) shown in the table above. Although the Cmax from Study M016455I/1005 (224 ng/mL) is higher than that obtained from the same age group (154 ng/mL) using population PK analysis, the value is still within the Cmax obtained from all other age groups. Overall, it may be concluded that this study supports the selection of a 30 mg dose of fexofenadine HCl suspension for children 2 to 5 years of age.

2.3. Biopharmaceutics

2.3.1. Is the formulation used in the PK studies identical to the to-be-marketed formulation?

Yes. Four [redacted] pilot-scale batches, representing [redacted] commercial batch size, were manufactured for use in pivotal clinical and registration stability studies. Fexofenadine HCL suspension is an immediate release oral suspension intended for twice-a-day dosing. Each 5-mL (one teaspoon) dose contains 30 mg of fexofenadine HCl. The product is packaged in [redacted] and [redacted] mL) amber polyethylene terephthalate (PET) plastic bottles [redacted] The quantitative composition of the fexofenadine HCl suspension is provided in Table 4.

Table 4. Quantitative Composition of Fexofenadine HCl Suspension

Components	Function	mg per 5-mL Dose
Fexofenadine HCl	Drug Substance	30.00
[redacted]		
Edetate Disodium, USP[1]	[redacted]	
Propylparaben, NF		
Butylparaben, NF	[redacted]	
Xanthan Gum, NF		
Poloxamer 407, NF		
Titanium Dioxide, USP	[redacted]	
Sodium Phosphate Monobasic Monohydrate, USP		
Sodium Phosphate Dibasic Heptahydrate, USP	[redacted]	
Artificial Raspberry Cream Flavor	[redacted]	
Sucrose, NF		
Xylitol, NF	[redacted]	
Water, Purified USP		
	[redacted]	

[1] Also referred to as disodium edetate, disodium EDTA, or EDTA disodium
[2] Edetate disodium demonstrates a marked synergistic effect when used in conjunction with parabens, increasing their antimicrobial activity.

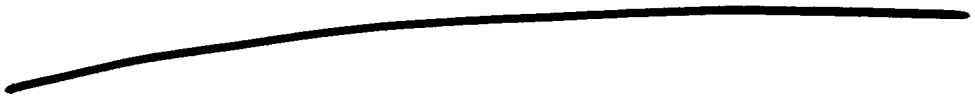
2.5. Analytical section

2.5.1. What bio-analytical methods are used to assess concentrations?

High performance liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) was used for the quantitative determination of fexofenadine concentrations in human plasma. Two bioanalytical methods were used,

Method PJAY005A (*Report K-94-0822-D*) was used to quantitate fexofenadine concentration in human plasma samples collected in M016455I/1003 and M016455I/1004. The assay has a lower limit of quantitation of 1 ng/mL using 0.5 mL of plasma. Sample preparation involved

Method FexPed-P1A (Report QKAN-2005-0574-BIO *Bioanalytical Methods report*) was used to quantitate fexofenadine concentration in human plasma samples collected in M016455I/1005. The assay was developed to utilize a smaller volume for drug detection so that lower total blood volumes could be drawn from pediatric subjects. This assay has a lower limit of quantitation of 1 ng/mL using 50 µL of plasma. Sample preparation involved



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4.2. INDIVIDUAL STUDIES

4.2. INDIVIDUAL STUDIES

Protocol M016455I/1004

Study Type: Bioequivalence study, single-dose.

Title: Two-way Crossover, Randomized, Open-label Pivotal Bioequivalence Study Comparing the Fexofenadine Hydrochloride Suspension to the Marketed Allegra. Tablet in Healthy Adult Subjects

Investigator: Dennis N. Morrison, DO, Springfield, Missouri, United States

Objectives:

- The primary objective was to establish the bioequivalence of fexofenadine when administered as a to-be-marketed suspension (30 mg fexofenadine hydrochloride dose) relative to the marketed 30 mg fexofenadine hydrochloride tablet under fasted conditions.
- The secondary objective was to assess the safety and tolerability of the suspension 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.

Number of subjects planned: 54 subjects were to be enrolled in the study to obtain at least 50 randomized subjects. Dropout subjects were not to be replaced.

Inclusion criteria: Non-smoking, healthy male or female subjects between 18 and 45 years of age who were within 15% of desirable body weight for height and frame size were eligible for inclusion in the study.

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

- Treatment A (reference) - a single oral dose of 30 mg fexofenadine HCl (Allegra®) tablet.
- Treatment B (test) - a single oral dose of 30 mg fexofenadine hydrochloride (5 mL of a 6 mg/mL fexofenadine hydrochloride suspension).

Treatments A and B were administered under fasted conditions with 240 mL water. Each dose was ingested from the dose container and followed immediately by the ingestion of three consecutive distilled water rinses along with additional water so that the total volume, including dose, was 240 mL. All subjects received each treatment once.

Bioanalytics: Plasma samples were analyzed by liquid chromatography/tandem mass spectrometry to determine fexofenadine concentrations. The accuracy and precision statistics of the plasma methods across study sample analyses are summarized in Table 1.

Table 1. Summary of Method Performance Across Sample Analyses (Batch-to-Batch Statistics)

Analyte	Samples	Accuracy [a]	Precision [b]
Fexofenadine (M016455)	QC samples [c]	96.3 to 102%	4.5 to 8.9%
	Calibration standards	98.0 to 101%	6.7 to 9.1%

Note: QC = quality control.

[a] Accuracy, expressed as % recovery, relative to theory.

[b] Precision, expressed as % coefficient of variation.

[c] QC sample concentrations ranged from 2.50 to 125 ng/mL.

Pharmacokinetic data: Blood samples were collected prior to dosing (predose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 30, 36, and 47 hours following study drug administration. PK parameters included Cmax, Tmax, $AUC_{0\text{-last}}$, $AUC_{0\text{-}8}$, and $t_{1/2}$ and were determined from fexofenadine plasma concentrations by noncompartmental analysis.

Safety data: Adverse events, 12-lead electrocardiograms, clinical laboratory evaluations, physical exams, and vital signs were collected to monitor safety.

Statistical procedures: Descriptive statistics were summarized by treatment for the plasma concentration data at each planned sampling time point and for the derived PK parameters. Bioequivalence was assessed using the standard two one-sided tests on the treatment difference of least squares (LS) mean estimates of the log-transformed values of the primary pharmacokinetic parameters, $AUC_{(0\text{-}\infty)}$ and Cmax, obtained from an analysis of variance (ANOVA) model. The terms in the ANOVA model were treatment sequence, subjects nested within sequence, period, and treatment effects. Subjects within sequence was considered as a random effect and other terms were considered as fixed effects. From these analysis, treatment least-squares (LS) means, treatment differences, and 90% confidence intervals (CI) for treatment differences were obtained for Cmax, $AUC_{(0\text{-last})}$, and $AUC_{(0\text{-}\infty)}$ on the log-scale. The results were transformed back to the original scale by exponentiation to obtain geometric LS means, point estimates of the geometric test (Treatment B)/reference (Treatment A) LS mean ratios and 90% CI for these ratios. The 90% CI of the ratio of the geometric means of log-transformed $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\infty)}$, and Cmax were used to assess bioequivalence between the test and reference using the equivalence interval of 80% and 125%. Bioequivalence was declared if the 90% CI for the ratio fell within 80% and 125% for $AUC_{(0\text{-}\infty)}$ and Cmax.

Results

Study subjects and conduct: A total of 54 subjects were enrolled in the study; 53 of them received all doses of study medication and completed the study according to the protocol. One subject received Treatment B during Period 1, but was lost to follow-up prior to receiving Treatment A. The healthy, nonsmoking adult subjects enrolled in this study had a mean age of 25.1 ±7.4 years. Thirty-six (67%) subjects were male and 18 (33%) subjects were female. Subject height average 174.5 ±10.1 cm and weight average 74.3 ±13.0 kg. Forty-nine (91%) subjects were White, 2 (4%) subjects were Black, and 3 (6%) were other races.

Pharmacokinetics: Fexofenadine PK parameters and the mean concentration-time profile are shown in Table 2 and Figure 1, respectively.

Figure 1. Mean fexofenadine concentration-time profile

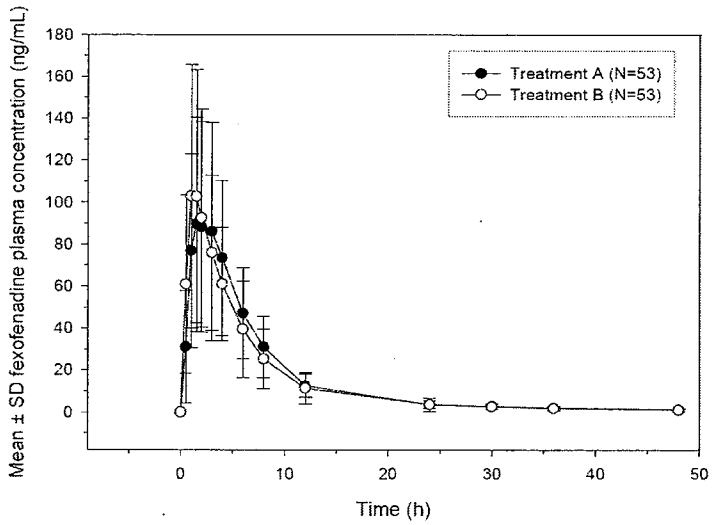

Table 2. Summary Statistics and ANOVA Results for Fexofenadine PK Parameters

					Treatment Comparisons [b]	
Parameter (unit)	**Treatment [a]**	**N**	**Arithmetic Mean (CV%)**	**Geometric LS Mean**	**Ratio [c] (%)**	**90% CI**
AUC(0-∞) (ng·h/mL)	A	53	744 (42.5)	680	93.8	84.3 - 104
	B	53	703 (47.6)	638		
Cmax (ng/mL)	A	53	110 (52.8)	97.2	106	93.5 - 119
	B	53	117 (55.8)	103		
AUC(0-last) (ng·h/mL)	A	53	719 (43.5)	653	94.0	84.1 - 105
	B	53	680 (48.9)	614		
Tmax [d] (h)	A	53	1.5 (0.5 - 4.0)	-	-	-
	B	53	1.0 (0.5 - 4.0)			
t1/2 (h)	A	53	11.0 (30.0)	-	-	-
	B	53	11.0 (28.4)			
CLpo (L/h)	A	53	45.2 (47.5)	-	-	-
	B	53	47.8 (40.6)			

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 5 mL of 6 mg/mL suspension (test).

[b] 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.

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

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

Summary:

- Statistical analysis of $AUC_{(0-\infty)}$, $AUC_{(0\text{-last})}$, and Cmax revealed 90% CIs for the ratio of geometric least-square means of fexofenadine test to reference formulations of 84.3 to 104.4%, 84.1 to 105.0%, and 93.5 to 119.3%, respectively.
- The resultant intra-subject coefficients of variation for the parameters $AUC_{(0-\infty)}$, $AUC_{(0\text{-last})}$, and Cmax revealed variability of approximately 34%, 35%, and 39%, respectively.
- There was no significant sequence or period effects.
- The median fexofenadine Tmax was 1.0 hours for the test formulation and 1.5 hours for the reference formulation.
- Mean $t_{1/2}$ was approximately 11 h for both treatments.
- CLpo was approximately 48 L/h for the test formulation and 45 L/h for the reference formulation.
- The study medications administered in this study were well tolerated (per Sponsor).

Conclusion:

- A 30 mg dose of the fexofenadine hydrochloride 6 mg/mL suspension was bioequivalent to the marketed 30 mg tablet in healthy adult subjects under fasted conditions.

Protocol M016455I/1003

Study Type: Single-dose, Food effect study.

Title: Two-way Crossover, Randomized, Open-label Pivotal Study Comparing the Bioavailability of Fexofenadine Hydrochloride Suspension in Fed and Fasted Healthy Adult Subjects.

Investigator: Dennis N. Morrison, DO, Springfield, Missouri, United States

Objectives:

- The primary objective was to compare the bioavailability of fexofenadine when administered as a to-be-marketed suspension (30 mg fexofenadine hydrochloride dose) under fed and fasted conditions.
- The secondary objective was to assess the safety and tolerability of the suspension administered under fed and 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 treatment periods.

Number of subjects planned: Fifty-four (54) subjects were to be enrolled in the study to obtain at least 50 evaluable subjects. Dropout subjects were not replaced.

Inclusion criteria: Nonsmoking, healthy male or female subjects between 18 and 45 years of age who were within 15% of desirable body weight for height and frame size were eligible for inclusion in the study.

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

- *Treatment A*: Single oral dose of 30 mg fexofenadine HCl (5 mL of a 6 mg/mL fexofenadine hydrochloride suspension) administered under fasted conditions.
- *Treatment B*: Single oral dose of 30 mg fexofenadine HCl (5 mL of a 6 mg/mL fexofenadine hydrochloride suspension) administered under fed conditions.

Treatments A and B were administered with an additional 235 mL water for a total administered volume of 240 mL. Treatment A was administered following an overnight fasting period. Treatment B was administered following a high-fat breakfast. A ll subjects were to receive each treatment once. Subjects were assigned a subject number prior to the first dose of study medication in Treatment Period 1.

Bioanalytics: Plasma samples were analyzed by liquid chromatography/tandem mass spectrometry to determine fexofenadine concentrations. The accuracy and precision statistics of the plasma methods across study sample analyses are summarized in Table 1.

Table 1. Summary of Method Performance Across Sample Analyses (Batch-to-Batch Statistics)

Analyte	Samples	Accuracy [a]	Precision [b]
Fexofenadine (M016455)	QC samples [c]	94.0 to 100%	7.3 to 15.1%
	Calibration standards	99.2 to 101%	4.3 to 6.7%

Note: QC = quality control.
[a] Accuracy, expressed as % recovery, relative to theory.
[b] Precision, expressed as % coefficient of variation.
[c] QC sample concentrations ranged from 2.50 to 125 ng/mL.

Pharmacokinetic data: Blood samples 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. PK parameters were determined from fexofenadine plasma concentrations by noncompartmental analysis and included: Cmax, Tmax, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}8)}$, $t_{1/2}$, λz, and CLpo.

Safety data: Adverse events, 12-lead electrocardiograms, clinical laboratory evaluations, physical examinations, and vital signs were collected to monitor safety.

Statistical procedures: Descriptive statistics were summarized by treatment for the plasma concentration data at each planned sampling time point and for the derived pharmacokinetic parameters. Bioequivalence was assessed using the standard two one-sided tests procedure on the treatment difference of least-squares (LS) mean estimates of the log-transformed values of the primary pharmacokinetic parameters, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\infty)}$, and Cmax, obtained from an analysis of variance (ANOVA) model. The terms in the ANOVA model were treatment sequence, subjects nested within sequence, period, and treatment effects. Subjects within sequence were considered as a random effect and other terms in the model were considered as fixed effects. From these analyses, treatment LS means, LS treatment differences, and 90% confidence intervals (CI) for treatment differences on the log transformed data were obtained for Cmax, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\infty)}$,. The results were transformed back to the original scale by exponentiation to obtain geometric LS means, point estimates of the geometric test (Treatment B)/reference (Treatment A) LS mean ratios, and 90% CI for these ratios. The 90% CI of the ratio of the geometric means of log-transformed $AUC_{(0\text{-}\infty)}$ and Cmax were used to assess the bioequivalence between the test and reference using the equivalence interval of 80% to 125%. Bioequivalence was declared if the 90% CI for the ratio fell within 80% and 125% for $AUC_{(0\text{-}\infty)}$ and Cmax. Descriptive statistics were summarized for Tmax and $t_{1/2}$.

Results

Study subjects and conduct: A total of 54 subjects were enrolled in the study; 50 subjects received all doses of study medication with 49 of these subjects completing the study according to the protocol. Five subjects discontinued the study prematurely; 4 subjects withdrew consent and 1 subject discontinued due to adverse events. Subjects who enrolled in this study had a mean age of 23.4 ±5.3 years. 34 subjects (63%) were male and 20 (37%) were female. Subject height averaged 174.5 ±9.1 cm and weight averaged 77.6 ±12.7 kg. Forty-eight (89%) subjects where White, 5 (9%) subjects were Black, and the race for 1 (2%) subject was reported as Other.

Pharmacokinetics: Fexofenadine PK parameters and the mean concentration-time profile are shown in Table 2 and Figure 1, respectively.

Figure 1. Mean fexofenadine concentration-time profile

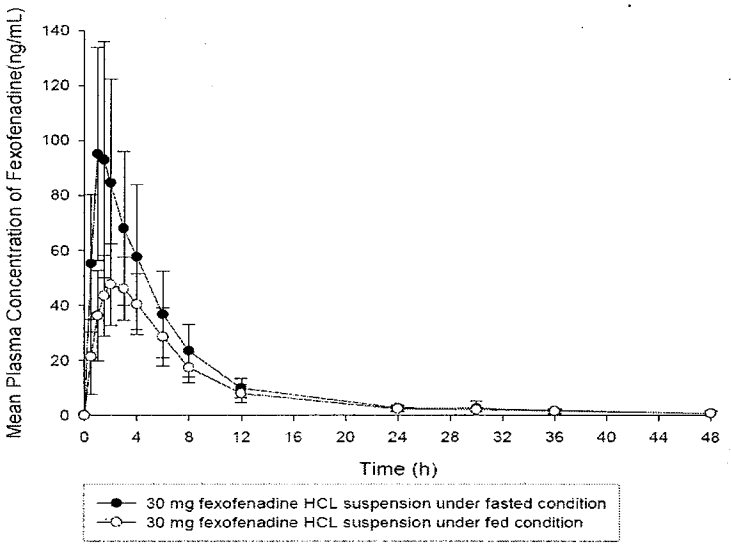

Table 2. Summary Statistics and ANOVA Results for Fexofenadine PK Parameters

						Treatment Comparisons [d]	
Parameter (unit)	**Treatment [a]**	**N [b]**	**Arithmetic Mean (CV%) [b]**	**N [c]**	**Geometric LS Mean [c]**	**Ratio [e] (%)**	**90% CI**
AUC(0-∞)	Fasted	47	667 (30)	47	638	69.7	64.0 – 76.0
(ng·h/mL)	Fed	48	457 (23)	47	445		
Cmax	Fasted	50	106 (40)	50	98.2	52.9	47.9 – 58.3
(ng/mL)	Fed	50	53.7 (27)	50	51.9		
AUC(0-last)	Fasted	50	615 (35)	50	576	69.6	63.7 – 76.0
(ng·h/mL)	Fed	50	414 (25)	50	401		
Tmax [f]	Fasted	50	1.0 (0.5 - 4.0)		-	-	-
(h)	Fed	50	2.5 (1.0 - 6.0)				
t1/2	Fasted	47	12.2 (41)		-	-	-
(h)	Fed	48	13.7 (53)				
CLpo	Fasted	47	45.8 (30.7)		-	-	-
(L/h)	Fed	48	64.2 (21.9)				

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

[a] Fasted (Treatment A): single dose of 30 mg fexofenadine HCl as 5 mL of 6 mg/mL suspension under fasted conditions (reference).
Fed (Treatment B): single dose of 30 mg fexofenadine HCl as 5 mL of 6 mg/mL suspension under fed conditions (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 (Fed/Fasted).

[f] Tmax reported as median (range) values

Summary:

- Statistical analysis of $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\infty)}$, and Cmax revealed 90% CIs for the ratio of geometric least-square means for fexofenadine Treatment B (fed) to Treatment A (fasted) of 64.0 to 76.0%, 63.7 to 76.0%, and 47.9 to 58.3%, respectively.
- The resultant inter-subject coefficients of variation for the parameters $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\infty)}$, and Cmax revealed variability of approximately 30%, 35%, and 40%, respectively, for Treatment A (fasted), and of approximately 23%, 25%, and 27%, respectively, for Treatment B (fed).
- There was no significant sequence or period effects. The median fexofenadine Tmax was 1.0 hours for Treatment A and 2.5 hours for Treatment B.
- Mean $t_{1/2}$ was approximately 12.2 and 13.9 hours for Treatments A and B, respectively.
- Mean CLpo was approximately 45.8 and 64.2 L/h for Treatments A and B, respectively.
- The study medications administered in this study were well tolerated (per Sponsor).

Conclusions:

- The 30 mg fexofenadine HCl suspension administered with food is not bioequivalent to the 30 mg fexofenadine HCl suspension administered without food.
- Administration of food decreases both the extent of absorption (AUC) and Cmax of the fexofenzdine HCl 6 mg/mL suspension.

Protocol M016455I/1005

Study Type: Single-dose PK in pediatric patients.

Title: A multicenter study to assess the safety and pharmacokinetics of open-label 30 mg single dose fexofenadine hydrochloride oral suspension (6 mg/mL) in pediatric subjects 2 to 5 years of age

Investigator(s): Multi-center study.

Objectives:

- The primary objective of this study was to characterize the PK behavior of a single dose of 30 mg fexofenadine HCl administered as an oral suspension (fexofenadine HCl 6mg/mL) in pediatric subjects with allergic rhinitis (AR) who were 2 to 5 years of age.
- The secondary objective of this study was to evaluate the safety and tolerability of a single dose of 30 mg fexofenadine HCl administered as an oral suspension (fexofenadine HCl 6 mg/mL) in pediatric subjects with AR who were 2 to 5 years of age.

Design: This was a multi-center, open-label, single-dose PK study conducted at 6 study sites in the US. Subjects were received single-dose 30-mg fexofenadine HCl oral suspension (6 mg/mL).

Number of subjects: Forty-eight (48) subjects were planned for enrollment into this study.
Inclusion criteria: Pediatric subjects 2 to 5 years (2 to ≤5 years) of age whose physician has determined them to be a candidate for antihistamine therapy or who have tolerated a therapeutic course of antihistamine therapy for the treatment of allergic rhinitis without adverse effects.

Bioanalytics: Plasma samples were analyzed by liquid chromatography/tandem mass spectrometry to determine fexofenadine concentrations. The accuracy and precision statistics of the plasma methods across study sample analyses are summarized in Table 1.

Table 1. Summary of Method Performance Across Sample Analyses (Batch-to-Batch Statistics)

Analyte	Samples	Accuracy[a]	Precision[b]
Fexofenadine	QC Samples[c]	95.1–111.2%	3.2–9.4%
	Calibration Standards	97.6–102.8%	4.7–10.4%

[a] Accuracy expressed as % recovery, relative to theoretical concentration

[b] Precision expressed as % coefficient of variation

[c] QC sample concentrations ranged from 2.50 to 125.0 ng/mL

Pharmacokinetic data: Blood samples were collected prior to dosing (predose) and at 1, 2, 3, 4, 6, 8, 12, and 24 hours following study drug administration. PK parameters included Cmax, tmax, $AUC_{(0\text{-last})}$, and were determined from fexofenadine plasma concentrations by noncompartmental analysis.

Safety data: Pphysical examinations, adverse events reported and observed, electrocardiogram (ECG) parameters, and vital signs (body temperature, heart and respiratory rates, and blood pressure) and clinical laboratory data.

Statistical procedures: Descriptive statistics were summarized for the plasma concentration data at each planned sampling time point and for the derived pharmacokinetic parameters.

RESULTS

Study subjects: A total of 50 subjects were enrolled and received study medication. All 50 completed the study according to protocol. The mean age of the subjects was 3.5 ± 1.1 years, 26 (52%) were male and 24 (48%) were female. Subject height averaged 103 ± 8.4 cm and weight averaged 17.6 ± 3.6 kg. Twenty-nine (58%) were white, 9 (18%) were black, 6 (12%) were multiracial, and 6 (12%) were other races.

Pharmacokinetics: Fexofenadine PK parameters and the mean concentration-time profile are shown in Table 2 and Figure 1, respectively.

Figure 1. Mean fexofenadine concentration-time profile

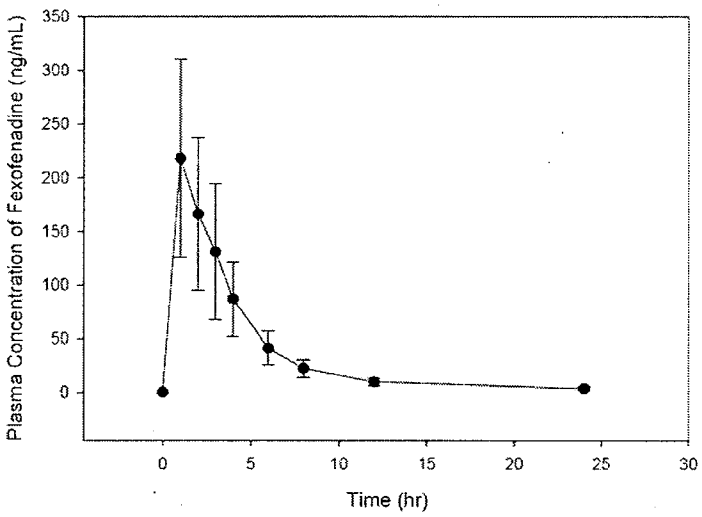

Table 2. Mean plasma fexofenadine PK parameters after administration of single 30 mg dose of fexofenadine HCl suspension to children aged 2 to 5 years

	C_{max} (ng/mL)	t_{max} (h)	AUC (0-last) (ng•h/mL)
n	50	50	50
Mean	224	1.0[a]	898
Range	110 – 437	1.0 – 4.0	459 - 1966
CV%	39.3	53.3	34.3

[a] t_{max} reported as median value

Summary:

- The mean Cmax and $AUC_{(0\text{-last})}$ values after administration of 30 mg dose of the fexofenadine HCl suspension to children 2 to 5 years of age are 224 ng/mL and 898 ng•h/mL respectively.
- The median tmax value was 1 h. Sponsor reported the terminal elimination phase had less than three concentration time points and therefore, λz, $t_{1/2}$, $AUC_{(0\text{-}\infty)}$, and CLpo were not estimated for any subject.

Information from NDA20-827: The mean (±STD) PK parameter estimates for different age groups (obtained from the population PK analysis) are shown in the table below:

Summary of fexofenadine PK parameter estimates from the final model

		15 mg		30 mg		60 mg	
	n	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)	AUC (ng•h/mL)	C_{max} (ng/mL)
6 months - <2 yrs							
Weight ≤10.5 kg	*	1080±332	185±51	2140±546	361±122	-	-
Weight >10.5 kg	**	761±247	136±44	1460±708	253±150	-	-
2 - 5 yrs	21	-	-	**930±234**	**154±39**	-	-
7 – 12 yrs	***	-	-	1060±220	153±56	2110±561	303±115
Adults	269	-	-	-	-	1290±424	165±56

*based on 5 and 8 subjects for 15 and 30 mg dose, respectively;
**based on 14 and 15 subjects for 15 and 30 mg dose, respectively;
***based on 14 and 13 subjects for 30 and 60 mg dose, respectively;

AUC from Study M016455I/1005 (898 ng•h/mL) for children age 2-5 years is similar to that obtained from the population PK study submitted to NDA 20-872 (930 ng•h/mL) shown in the table above. Although the Cmax from Study M016455I/1005 (224 ng/mL) is higher than that obtained from the same age group (154 ng/mL) using population PK analysis, the value is still within the Cmax obtained from all other age groups.

Overall, it may be concluded that this study supports the selection of a 30 mg dose of fexofenadine HCl suspension for children 2 to 5 years of age.

5. Filing

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	**21-963**	**Brand Name**	**Allegra®**
OCPB Division (I, II, III)	**DCP 2**	**Generic Name**	**Fexofenadine HCl**
Medical Division	**DPADP**	**Drug Class**	**Anti-Histamine**
OCPB Reviewer	**Shinja Kim**	**Indication(s)**	**Allergic rhinitis**
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	**6 mg/mL suspension**
		Dosing Regimen	BID for SAR in children 2-11 yrs old and CIU in children 6 months - 11 yrs old
Date of Submission	**12/15/05**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**8/15/06**	**Sponsor**	[redacted]
PDUFA Due Date	**10/15/06**	**Priority Classification**	**S**
Division Due Date	**9/15/06**		

3 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			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
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:	x	1		
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design: single / multi dose:	x	2		
replicate design: single / multi dose:				
Food-drug interaction studies:	x	1		
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3	3	3 PK studies

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable?	x	**Fileable per CPB standpoint. However, the problems identified in the FDA-483 must be satisfactorily resolved by the CMC and medical review teams.**
Comments sent to firm?		
QBR questions (key issues to be considered)	• Is the formulation used in the bio-studies identical to the to-be-marketed formulation? • Is the tested formulation bioequivalent to the reference product? • Are food effect profiles comparable between the proposed and referenced product? • What bioanalytical methods are used to assess concentrations of active moiety?	

Note: Request for DSI consultation for the BE study (M016455I/1004) by the project manager: Analysis of the plasma samples undertaken by [redacted]

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

/s/

Shinja Kim
6/28/2006 12:25:56 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
6/28/2006 12:33:45 PM
BIOPHARMACEUTICS
I concur