Data Analysis:
Pharmacokinetic parameters for the individual protocols were computed using model independent methods. Computed pharmacokinetic parameters obtained from normal volunteers and pediatric patients were combined into a single database for analysis. To maintain consistency with previous population analyses, data for AUCinf and Cmax were normalized to an 80 mg dose.
Pharmacokinetic studies have previously determined that fexofenadine demonstrates linear pharmacokinetics over the dose range (up to 120 mg) being normalized for this analysis. If a volunteer received more than one fexofenadine hydrochloride treatment during a study, pharmacokinetic parameters were computed for each exposure separately. All included exposures were for capsule formulations. If a volunteer participated in more than one study all data for the volunteer were processed as being multiple exposures from a single volunteer.

The combined pharmacokinetic parameter database was analyzed by NONMEM to determine estimates for population pharmacokinetic parameters and their variability.

Three separate population parameter models were examined in this analysis. These included:
1. Simple model: assume and estimate a common mean for normal subjects and pediatric patients.
2. Expanded model: allow different means for adult volunteers and pediatric patients.
3. Covariate model: assume and estimate a common mean, for normal subjects and pediatric patients, that is a function of demographic or study related covariates (eg, weight, age, height, dose).

Results:

The population pharmacokinetic parameter models and the descriptive statistics, mean (standard deviation), for the individual subjects/patients parameter estimates are summarized in the following table.

Table. Summary of NONMEM Population Parameter Estimates

Parameter	*Population* Model	*Parameter Estimate for Adult Subjects Mean(±SD)*	*Parameter Estimate for Pediatric Patients*
AUC inf (ng hr/ml) *	AUC = 8260 / weight $^{0.354}$	1774(±433)	2773(±687)
CL po (L/h)	CLpo = 25.4 · BSA**	50.7 (± 16.0)	30.3 (± 8.3)
C max (ng/ml)	C max = 484 / BSA**	250(±52)	460 (± 118)
* Data for AUC(inf) and Cmax have been dose normalized to the 80 mg dose. ** Body Surface Area (BSA, m^2) = weight $^{0.51456}$ * height $^{0.42246}$ · 0.0235 (Gehan and George formula)			

Conclusions/ Comments:

- Equivalent doses of fexofenadine hydrochloride administered to children will result in higher exposure compared to that observed in adults.

- There is no difference in fexofenadine oral clearance (CLpo), between pediatric and adult volunteers, when clearance is normalized for Body Surface Area (BSA). The apparent oral clearance of fexofenadine, in pediatric and adult volunteers, is approximately CLpo = 25.4 · BSA

- Total fexofenadine exposure, as measured by AUC, and maximum fexofenadine exposure, as measured by Cmax, are similar between adult and pediatric volunteers when adjusted for weight and body surface areas, respectively.

- The exposure after administration of 30 mg in children is comparable with that after 60 mg dose in adult.

APPENDIX I-10. Protocol M016455BI3081, Report K-98-0093-D

Title: Population pharmacokinetics of fexofenadine in patients with seasonal allergic rhinitis

Protocol Number: M016455B/3081

Project Report Number: K-98-0093-D

Objectives:
To characterize the population pharmacokinetics of fexofenadine in adult patients with seasonal allergic rhinitis (SAR) for fexofenadine.

To determine the impact of covariates on pharmacokinetic parameter estimates for fexofenadine.

Formulation:
Data included in this analysis were from a Phase III study where fexofenadine 120 mg or 180 mg tablets were administered once per day in combination with other medications. A summary of the manufacturing history of fexofenadine formulations used in this study is given in *Table*

Table . Fexofenadine Formulations

Protocol	*Treatment*	*Formula Number*	*Lot number*	*Dosage Form*	*Strength*	*Batch Size*
PJPR0081	Fexofenadine HCl 120 mg	PJXTXL 6-004	RE9728	Tablet	120 mg	tab
PJPR0081	Fexofenadine HCl 180 mg	PJXTX7-005	RE9734	Tablet	180 mg	tab

Study Design and Sampling:
This study utilized a double-blind, randomized, placebo-controlled, parallel, multicenter study design with single-blind placebo lead in. The study included four visits. A 1 -week single-blind placebo lead in period preceeded a 2-week double-blind treatment period.
On their first visit, patients were screened for entry into the study. At this point subjects were given placebo tablets to assess for placebo effects. Patients were asked to take their medication at 8,AM ± 1 h daily. On visit 2 (week 2) subjects were randomly assigned either placebo, fexofenadine 120 mg tablets, or fexofenadine 180 mg tablets. On visit 3 (week 3) and 4 (week 4) a blood sample was collected and the time of the last dose recorded.

Number of Subjects:
A total of 1088 fexofenadine plasma concentrations were collected from 563 subjects. Of these 1971 plasma concentrations from 548 individuals were included in this analysis Some subjects were discarded from the analysis for the following reasons: plasma concentrations were equal to zero, patient was assigned to placebo, possible incorrectly recorded dosing event, or possible missing dosing event. A summary of the demographics for the 548 subjects with plasma concentration data is shown in the following table.

Table . Subject Demographics

	Age (yr) Mean(±SD	Height (cm) Mean(±SD)	Weight (kg) Mean(±SD)	Body Surface Area (m2) Mean (±SD)	Gende r#Males #Females	RACE
Full Data Set(N=563)	32.5 (±12.3)	167.8 (±9.9)	72.3 (±18.1)	1.841(±0.261)	199 Males 364 Females	39 African-Americans 10 Asians 14 Multiracial
Data Set Used in NONMEM Analysis(N=548)	32.5 (±12.2)	167.8 (±9.9)	72.5 (±18.2)	1.842(±O.262)	196 Males 352 Females	489 Caucasians 37Aftican-Americans 10 Asians 12 Multiracial

Assay:

Data Analysis:
Observed fexofenadine plasma concentration data obtained in this study were analyzed by nonlinear mixed-effects modeling (NONMEM program, Version 4.0, Level 2.0) to develop appropriate population pharmacokinetic models. The final step of the process was to incorporate demographics into the population pharmacokinetic model.

Based upon the results of the base population pharmacokinetic model, exploratory data analysis techniques were used to relate the individual predicted pharmacokinetic parameters to subject demographics. The potential covariates examined for use in the population pharmacokinetic model were age, weight, height, body surface area (BSA), gender, race, dose, and presence or absence of concomitant medications. Body surface area was computed using the equation developed by Gehan and George,

$$BSA = 0.0235 * \text{Height (in cm)}^{0.42246} * \text{Weight (in kg)}^{0.51456}$$

Continuous variables were examined using stepwise multiple linear regression. Rank normalized transformation of the pharmacokinetic parameters was done to transform the residuals to homoscedasticity. Categorical variables, eg, dose, sex, etc, were examined using the Kruskal-Wallis analysis of variance.

Covariates showing evidence of influence were evaluated sequentially using NONMEM by comparing the full model with covariate included to the reduced model without covariate. Evaluation criteria used when comparing NONMEM models included a significant reduction in the objective function value based on the Likelihood Ratio Test or Akaike Information Criterion (AIC), the goodness-of-fit parameters [including a less systematic distribution of weighted residual plots against covariates and a decrease in 1) standard error, 2) the elements in the correlation matrix of the parameter estimates, 3) intersubject variability of the pharmacokinetic parameters, and/or 4) residual error], the random distribution in the weighted residual against the predicted effect or other covariates to be tested, and a coefficient of variation (CV%) of the parameters estimated of less than 50%.

Results:
A total of 971 fexofenadine plasma concentrations collected from 548 subjects were included for analysis. The median number of samples per subject was two. The preliminary models included both IV and oral dose administration for both the one-compartment and two-compartment model. Based upon the NONMEM objective function value and precision of the parameter estimates the two-compartment oral model was established as the BASE MODEL.

Two covariates, sex and height, were evaluated sequentially in NONMEM by comparing the full model with covariate included to the reduced model with covariate deleted. None of the covariate models improved the goodness of fit of the base model nor did they improve the predictability of the model. Although some models resulted in a significant decrease in the NONMEM objective function, they also had significantly greater residual error and significantly larger standard error estimates on the peripheral compartment volume compared to the base model. A summary of the population pharmacokinetic model (which is based upon the covariate free model) parameters is presented in the following Table..

Table. Summary of Fexofenadine NONMEM Population Parameter Estimates

Parameter	*Estimate*	*95% Confidence Interval*
Apparent Clearance (L/h)	55.2	(49.4,61.0)
Apparent Volume of Distribution (L)	364	(356,373)
Inter-compartmental Clearance (L/h)	16.6	(10.0,23.2)
Peripheral Compartment Model (L)	3380	(1692,5068)
Absorption Rate Constant (per h)	1.67	(0.70,2.64)
Inter-Subject Variance	0.382 (CV=68%)	
Residual Variance	0.723 (CV= 103%)	
Note: 95% confidence intervals calculated using the asymptotic approximation, Estimate±1.96 * SE (Estimate)		

Sponsor's Conclusions:

- The population pharmacokinetic model best describing the data was a two-compartment oral model with proportional residual error structure.
- Base model population parameter estimates agreed with previous pharmacokinetic studies.
- Clearance values in prior studies with healthy male volunteers ranged from 18.2 to 128 L/h across the same fexofenadine doses.
- Using Bayesian posterior density estimation under the base model, the population was estimated to have an average clearance of 64.3 ± 12.3 L/h (mean ± std dev, N=548) with a range of 11.1 to 85.0 L/h.
- Inclusion of covariates into the population pharmacokinetic model did not improve the goodness of fit of the base model nor did they improve the predictability of the model.
- In this study, the pharmacokinetics of fexofenadine in patients with seasonal allergic rhinitis appear to be unaffected by patient demographics.

APPENDIX I-11. Protocol PJPR003910067

Title: Population pharmacokinetics of fexofenadine in patients with chronic idiopathic urticaria enrolled in clinical protocols PJPR0039 and PJPR0067

Protocol Number: PJPR0039 & PJPR0067

Project Report Number: K-98-0120-D

Objectives:
This study was conducted to determine the efficacy and safety of fexofenadine hydrochloride at 20 mg, 60 mg BID, 120 mg BID, and 240 mg BID compared to placebo in the treatment of chronic idiopathic urticaria (CIU). In addition, and as a secondary objective, this study was conducted to assess the pharmacokinetics of fexofenadine using population analysis. The purpose of this analysis is to characterize the population pharmacokinetics of fexofenadine HCl in adult patients with chronic idiopathic urticaria (CIU).

Formulation:

Fexofenadine HCl was supplied as 20, 60, 120, and 180 mg tablets. All medications were supplied by Hoechst Marion Roussel, Inc., and were tested and released according to appropriate standards.

Treatment	*Lot number*	*Dosage Form*	*Strength*	*Batch Size tablet*
Fexofenadine	RH 9617	Tablet	20 mg	
	RD9619	Tablet	60mg	
	RG9527	Tablet	120mg	
	RG9529	Tablet	180 mg	

Study Design and Sampling:

Protocols PJPR0039 and PJPR0067 were identical in design.
Both studies utilized a multicenter, double-blind, randomized, placebo-controlled, parallel study design with a 24-hour single-blind placebo lead-in. Patients were randomly assigned to one of five treatment groups (placebo BID, fexofenadine HCl 20 mg BID, fexofenadine HCl 60 mg BID, fexofenadine HCl 120 mg BID, or fexofenadine HCl 240 mg BID). The treatment period was 4 weeks long and consisted of three or four visits. Patients who presented at visit 1 with a diagnosis of CIU and satisfied inclusion and exclusion criteria were randomized to double-blind study medication and instructed to take their first dose of study medication at 7:00 PM (±1 hour) the evening of visit 1. Subsequent doses of study medication were taken each day at 7:00 AM (± 1hour) and 7:00 PM (± 1 hour). The first two doses were single-blind placebo; subsequent doses were double-blind study medication. Patients returned at visit 2 following 15 (± 2) days of treatment and visit 3 (final visit) following 30 (± 4) days of treatment.

For patients who satisfied inclusion and exclusion criteria at visit I with the exception of symptom assessment criteria and/or criteria for the use of prescribed medication prior to visit 1, patients were given another opportunity to qualify for entry into the study by returning at visit IA between 24 hours and 14 days following visit 1.

A total of two blood samples were taken during the study for the analysis of fexofenadine levels; one at visit 2 and one at the final visit (or early termination visit) or in the event of a serious adverse event.

Number of Patients:
A total of 1200 fexofenadine plasma concentrations collected from 660 patients were included in this analysis.

Assay:

Data Analysis:
Observed fexofenadine plasma concentration-time data obtained in this study were analyzed by nonlinear mixed-effects modeling (NONMEM program, Version 4.0, Level 2.0) to develop an appropriate population pharmacokinetic model. The preliminary pharmacokinetic models included one-, two-, and three-compartment models with first-order absorption and elimination for the determination of the base model. Error was modeled exponentially for the pharmacokinetic parameters and for fexofenadine concentration.

Following the identification of the base model, individual estimates of clearance were generated by POSTHOC estimation in NONMEM. These clearance values were subsequently tested by stepwise forward regression analysis with backward elimination (SAS, PROC REG, in: P<0.15, stay: 0.05) to identify significant covariates for incorporation into the model. Potential covariates were incorporated into the clearance estimate for the base model in a stepwise fashion to arrive at the full regression model for clearance. Once the final model had been established for clearance, the process was repeated for all other pharmacokinetic parameters where interindividual variabilities could be estimated.

The potential covariates examined in the population pharmacokinetic model were age, weight, height, gender, race, dose, country, and concomitant medications.

Results:
Based upon NONMEM objective function values (OF), the two-compartment oral model was established as the BASE MODEL. Population model improvements were observed when apparent oral clearance (CLpo) was adjusted for age and height according to Equation 1 below.

Equation 1. $CLpo = (0.198 * Height) + (0.510 * Age)$

No covariates were established for volume of distribution (V2), as interindividual variability (q) for this parameter could not be established for the model.

Table . Summary of Fexofenadine NONMEM Population Parameter Estimates

Population estimates				95 % CI	
parameters		estimate	STD Error	Lower	Upper
θ_{Height}	L/h/cm	0.198	0.0606	0.0816	0.314
θ_{Age}	L/h/year	0.510	0.243	0.0434	0.977
V2	L	169	34.2	103	235
Q	L/h	85.6	20.2	4608	124
V3	L	3390	701	2044	4736
ka	1/h	0.666	0.0797	0.513	0.819
ω^2	Random effect variance	0.218	0.0377	0.146	0.290
σ^2	Random effect variance	0.380	0.0504	0.283	0.477

According to this model, the coefficient of variation on the population estimate of fexofenadine oral clearance was 49.4%. The coefficient of variation for the estimate of plasma fexofenadine concentration was 68%.

The estimated values of clearance across the height range (130 to 199 cm) and age range (12 to 68 years) for this population according to Equation I would be 32 L/h (at the minima) to 74 L/h (at the maxima).

Sponsor's Conclusions:
Based upon population pharmacokinetic modeling results, the pharmacokinetics of fexofenadine in patients with chronic idiopathic urticaria (CIU) may be affected by patient demographics.
The population pharmacokinetic model best describing the data is a two-compartment oral model with oral clearance increasing with both patient age and height.
Application of this model outside this data set may not be warranted, however. There was an unusually high residual variability in the base model (CVbase=72%) which was not substantially reduced by the addition of the covariates (CVfinal=68%). Neither the base nor final population models reliably predicted the highest fexofenadine concentrations (>1000 ng/mL). Finally, the suggestion that clearance would increase with age is a curious one for fexofenadine, since it opposes the conclusion reached in a focused study of the pharmacokinetics of fexofenadine in the elderly .
Despite these limitations, however, model predicted clearance values for the CIU patient population were within the range normally observed for fexofenadine. In a study of healthy male volunteers, clearance values ranged from 18.2 to 128 L/h across the same fexofenadine doses. In this study, individual POSTHOC estimates of clearance ranged form 12.6 to 90.7 L/h. Using the population model across the height and age range for this study, clearance ranged from 32 to 74 L/h.

APPENDIX I-12. Protocol 016455PR0019, Report W-96-0023-D

TITLE
Population Pharmacokinetic Analysis of Data from Clinical Protocol 016455PR0019.

PROTOCOL NUMBER
016455PR0019

CLINICAL PROJECT REPORT NUMBER
W-96-0016-C

INVESTIGATOR AND LOCATION
Multicentre

OBJECTIVES
The objective of this analysis was to characterize the population pharmacokinetics of fexofenadine in patients having a history and diagnosis and chronic idiopathic urticaria and to determine the impact of population demographic variables on the pharmacokinetic parameters.

FORMULATION

Strength	Lot #	Dosage form	Batch size
60 mg	RH9411	Capsule	
Placebo	RH9410	Capsule	

STUDY DESIGN
The study was conducted as a multicenter, randomized, double-blind, parallel study with a treatment period of 6 weeks, and five treatment groups. Patients of 18 years and over, and with a history and diagnosis of chronic idiopathic urticaria, were screened.
Patients attended 4 - 5 visits: screening, entry (these two were allowed to be combined), and at 2, 4 and 6 weeks; (visits 3, 4 and 5). During visit 3, 4 and 5, a single blood sample was collected for the determination of fexofenadine plasma levels. For the purposes of population pharmacokinetic analysis, sampling times were not fixed.

STUDY POPULATION
A total of 254 patients were screened at 52 investigative sites, and 224 were exposed to double-blind medication. The data set used in the pharmacokinetic analysis was comprised of 258 observations from 106 patients.

ASSAY

DATA ANALYSIS
Plasma fexofenadine concentration-time data were analyzed by nonlinear mixed effect modeling computer program (NONMEM, version IV, level 2.0). Multiple stepwise, regression analysis (PROC REG with STEPWISE option in SAS) was used to identify covariates that have significant influence ($p < 0.05$) on population pharmacokinetic parameters.

A two-compartment oral (2CPO) pharmacokinetic model was used to describe the data obtained in these clinical trials. The parameters estimated by the nonlinear mixed effect

modelling (NONMEM) program were oral clearance (CLpo) and volume of distribution (V2), intercompartmental clearance (Q), peripheral volume (V3), and absorption rate constant (Ka), A proportional error model was used to calculate intersubject variability. Both proportional and constant error models were used to calculate intrasubject error. To reduce the number of NONMEM runs, the pharmacokinetic parameters for the individual patients and modeling prediction errors (weighted residuals) were analyzed by multiple regression analysis (PROC REG with STEPWISE option in SAS) to identify covariates that could potentially be influencing the pharmacokinetics. Additional pharmacokinetic models were then analyzed using NONMEM to evaluate the effect of potential covariates on pharmacokinetic parameters.

RESULTS

Estimation of the final pharmacokinetic model indicated that a gender effect was present in apparent oral clearance. No other patient demographic variables appeared to significantly influence the pharmacokinetics of fexofenadine. The 56 % greater apparent oral clearance values predicted for males (87.4 L/h vs. 56.2 L/h for females) are supported by results obtained in other fexofenadine studies. For patients with seasonal allergic rhinitis (SAR) the predicted apparent oral clearance for males was 14 % greater than for females (61.2 L/h compared to 53.5 L/h for female patients). In studies with normal volunteers male subjects had a 26% greater apparent oral clearance values than for female subjects.

SPONSOR'S CONCLUSIONS

The oral clearance of male urticaria patients was 56% higher than female urticaria patients, and was consistent with the differences in apparent oral clearance previously observed in normal volunteers (26%) and patients (14%) with seasonal allergic rhinitis (SAR).

Estimated population apparent oral clearance values for urticaria patients (87.4 and 56.2 L/h for male and female patients, respectively) were consistent with apparent oral clearance values observed in normal volunteers (57.8 L/h for male subjects) and patients with seasonal allergic rhinitis (61.2 and 53.5 l/h for male and female SAR patients, respectively).

No additional patient demographic factors examined (age, race, dose, concomitant medications, weight) were found to influence the pharmacokinetic model.

APPENDIX I-13. Protocol PJPROO6610077, Report K-98-0119-D

Title
Population Pharmacokinetics of Fexofenadine in Pediatric Seasonal Allergic Rhinitis Patients Enrolled in Clinical Protocols PJPR0066 and PJPR0077

Protocol Numbers PJPR0066, PJPR0077

Project Report Number K-98-0119-D

Objectives
The primary objective of PJPR0066 and PJPR0077 was to determine the efficacy and safety of fexofenadine HCl at 15 mg BID, 30 mg BID and 60 mg BID compared to placebo in pediatric patients 6 to 11 years of age in the treatment of seasonal allergic rhinitis (SAR).
These studies were conducted to characterize the population pharmacokinetics of fexofenadine in pediatric SAR patients.

Formulation
Fexofenadine HCl was supplied in 15 mg, 30 mg and 60 mg tablets. Matching placebo tablets were utilized in these studies. All medications were supplied by Hoechst Marion Roussel, Inc., and were tested and released according to appropriate standards.

Table Formulation Information

Treatments	Lot Number	Dosage Form/ Strength	Batch Size*(Tablets)*
15 mg BID	RD9726	15 mg Tablet	
30 mg BID	RD9728	30 mg Tablet	
60 mg BID	RD9723	60 mg Tablet	
All batches were manufactured at greater than % of full scale			

Study design and sampling
Data included in this analysis are from PJPR0066 and PJPR0077, two identical Phase III safety and efficacy trials where three dose strengths of fexofenadine HCl (15, 30 and 60 mg tablets BID) were administered to pediatric seasonal allergic rhinitis patients for two weeks.

These trials were identical in study design and utilized a double-blind, randomized, multi-center, placebo-controlled, parallel group design to study the safety and efficacy of fexofenadine in male and female pediatric seasonal allergic rhinitis patients following a one week placebo lead-in.

Subjects enrolled in these trials were administered either 0 mg (placebo), 15 mg, 30 mg or 60 mg fexofenadine HCl BID for 2 weeks. During the final clinic visit (visit 4, or Early Discontinuation Visit) blood samples were collected 1 to 3 hours after dosing for the determination of plasma fexofenadine concentration. At designated study sites at visit 3 (interim visit) a blood sample was also collected 6 to 11 hours after dosing for determination of plasma fexofenadine concentration.

Number of Subjects
A total of 730 fexofenadine plasma concentrations collected from 523 subjects were included in this analysis. A summary of the demographics for the 523 subjects with plasma concentration data is presented in *the following table.*

Table . Subject Demographics for Modeled Subjects

Age (y) Mean(±SD)	*Height (cm) Mean(±SD)*	*Weight (kg) (Mean(±SD)*	*Body Surface* Area (m2) Mean (±SD)	*Gender*	*Race*
9.1(±1.6) n = 593	138.0(±11.5) n = 588	35.5(±11.0) n = 588	1.175(±0.215) n = 588	343 Males 250 Females	523 White46 Black7 Asian/Oriental 17 Multiracial

This contains demographic data for subjects included in analysis that have plasma concentration observations. Subjects with no plasma concentration observations do not contribute information to the modeling process.

Assay

Data Analysis

Observed fexofenadine plasma concentration-time data obtained in this study were analyzed by nonlinear mixed-effects modeling (NONMEM program, Version 4.0, Level 2.0) to develop appropriate population pharmacokinetic models. The preliminary pharmacokinetic models included both intravenous bolus and oral dose administration, and both one-compartment and two-compartment pharmacokinetic models. The oral pharmacokinetic models assume first order drug absorption. All pharmacokinetic models assume first order elimination.

A multivariate linear regression was used to relate the individual predicted pharmacokinetic parameters and prediction errors from the preliminary population pharmacokinetic model to subject demographics. A natural log transformation of the pharmacokinetic parameters was done to stabilize the variance of the predicted pharmacokinetic parameters. The transformed pharmacokinetic parameters were examined using the stepwise multivariate linear regression.

The potential covariates examined for use in the population pharmacokinetic model were age, weight, height, body surface area (BSA), gender, dose, and race. Body surface area was computed from a formula, $BSA(m^2) = (weight^{0.51456}) \times (height^{0.42246}) \times 0.0235$. The predicted pharmacokinetic parameters and the prediction errors (NONMEM weighted residuals) obtained for each individual from the preliminary NONMEM base model were compared with the potential covariates. The potential covariates exhibiting a significant relationship ($p < 0.05$) with the predicted pharmacokinetic parameters, or prediction errors, were then evaluated in NONMEM

models to determine if their inclusion satisfied the primary and secondary covariate selection criteria.

The final step of the process was to incorporate demographic covariates into the population pharmacokinetic model. Covariates showing evidence of influence were evaluated sequentially using NONMEM by comparing the full model (with covariate included) with the model from which the covariate being evaluated was deleted. Various evaluation criteria were used when comparing NONMEM models. These included a significant reduction in the objective function value based on the Likelihood Ratio Test or Akaike Information Criterion (AIC), goodness-of-fit parameters (including a less systematic distribution of weighted residual plots against covariates and a decrease in standard error, elements in the correlation matrix of the parameter estimates, intersubject variability of the pharmacokinetic parameters, and residual error), the random distribution in the weighted residual against the predicted effect or other covariates to be tested, and a coefficient of variation (CV%) of the parameters estimated of less than 50%.

Results
Based upon NONMEM OFV (objective function value), the two compartment oral model was established as the BASE model. Population model improvements were observed when apparent oral clearance (CLpo) was adjusted for height.

Table . Summary of Fexofenadine NONMEM Population Parameter Estimates

Parameter	Population model
CL po/F (L/h)	CL po = 0.306 x height: For typical 135 cm pediatric SAR patients CLpo=41.4 L/h
V2/F (L)	79.3
Q (L/h)	10.3
V3 (L)	27.0
Ka (1/h)	0.356

Sponsor's conclusions
Based upon population pharmacokinetic modeling results, the pharmacokinetics of fexofenadine in pediatric seasonal allergic rhinitis patients appear to be affected by subject demographics. The population pharmacokinetic model best describing the data is a two-compartment oral model with apparent oral clearance (CLpo,/F) based upon height. Body weight and age were not significant covariates, within the range studied.

For fexofenadine the population estimated apparent oral clearance is 0.306 L/h/cm. For an average subject with a height of 135 cm the apparent oral clearance is predicted to be 41.3 L/h. The population estimated apparent volume of distribution is L.

There was a sizable residual (prediction) variability in the base model (CV% = 73.2%) which was not substantially reduced by the addition of covariates (CV% = 69.6%). The modeled intersubject variability across subjects for apparent oral clearance is 37.1 %.

Reviewer's comment:
There are no identifiable gender, race or dose differences in the pharmacokinetics of fexofenadine indicating no differences in the in vivo performance of the three dosage strengths.

Please refer to the additional pharmacometric node's review on the population pharmacokinetics (Attachment VII)

APPENDIX I-14. Protocol PJPR002710031, Report K-98-0117-D

Title: Population Pharmacokinetics of Fexofenadine in Normal Healthy Subjects Enrolled in 6- and 12-Month Safety and Tolerance Trials

Protocol Number: PJPR0027, PJPR0031

Project Report Number: K-98-0117-D

Objectives:
The primary objective of PJPR0031 was to compare the safety and tolerance of 60 mg fexofenadine HCl capsules BID and placebo BID in normal healthy subjects over a period of 6 months.
The primary objective of PJPR0027 was to compare the safety and tolerance of 240 mg fexofenadine HCl capsules QD and placebo QD in normal healthy subjects over a period of 12 months.

The purpose of this analysis is to characterize the population pharmacokinetics of fexofenadine HCl in normal healthy subjects.

Formulation:
Fexofenadine HCl was supplied in 60 mg capsules. All medications were supplied by Hoechst Marion Roussel, Inc., and were tested and released according to appropriate standards. Study medication for these two protocols were from the same manufacturing lot.

Treatment	Lot #	Dosage form/strength	Batch size
240 mg QD (60 mg X4)	RH 9417	60 mg capsule	
60 mg BID	RH 9417	60 mg capsule	

Study Design and Sampling:

Protocol PJPR0027
This trial utilized a double-blind, randomized, multi-center, placebo-controlled, parallel group design to study the safety and tolerance of fexofenadine in normal healthy male and female subjects.
Subjects enrolled in this trial were administered 240 mg fexofenadine QD for 12 months. Blood samples for the determination of fexofenadine plasma concentration were collected monthly.

Protocol PJPR0031
This trial utilized a double-blind, randomized, multi-center, placebo-controlled, parallel group design to study the safety and tolerance of fexofenadine in normal healthy male and female subjects. Subjects enrolled in this trial were administered 60 mg fexofenadine BID for 6 months. Blood samples for the determination of fexofenadine plasma concentration were collected monthly.

Number of Subjects
A total of 3,110 fexofenadine plasma concentrations collected from 423 subjects were included in this analysis. A summary of the demographics for the 423 subjects with plasma concentration data is presented in the following table.

Table . Subject Demographics for Modeled Subjects

Age (y) Mean(±SD)	*Height (cm) Mean(±SD)*	*Weight (kg) (Mean(±SD)*	*Body Surface* Area (m2) Mean (±SD)	*Gender*	*Race*
34.0(±12.3) N=423	*170.2(±9.6) N=422*	*73.9(±16.6) N=422*	*1.875(±0.241) N=422*	*245 Males 178 Females*	*398 White 12 Black 8 Asian/Oriental 5 Multiracial*

Assay:

Data Analysis:
Observed fexofenadine plasma concentration-time data obtained in this study were analyzed by nonlinear mixed-effects modeling (NONMEM program, Version 4.0, Level 2.0) to develop appropriate population pharmacokinetic models. The preliminary pharmacokinetic models included both intravenous bolus and oral dose administration, and both one-compartment and two-compartment pharmacokinetic models. The oral pharmacokinetic models assume first order drug absorption. All pharmacokinetic models assume first order elimination.

A multivariate linear regression was used to relate the individual predicted pharmacokinetic parameters and prediction errors to subject demographics. A natural log transformation of the pharmacokinetic parameters was done to stabilize the variance of the predicted pharmacokinetic parameters. Rank normalized transformation of the pharmacokinetic parameters was also done to transform the residuals to homoscedacticity. The original, log transformed and rank normalized transformed pharmacokinetic parameters were examined using the stepwise multivariate linear regression.

The potential covariates examined for use in the population pharmacokinetic model were age, weight, height, body surface area (BSA), gender, dose, and race. Body surface area was computed from a formula , BSA(m^2) = (weight $^{0.51456}$) x (height $^{0.42246}$) x 0.0235. The predicted pharmacokinetic parameters and the prediction errors (NONMEM weighted residuals) obtained for each individual from the preliminary NONMEM base model were compared with the potential covariates. The potential covariates exhibiting a significant relationship ($P< 0.005$) with the predicted pharmacokinetic parameters, or prediction errors, were then evaluated in NONMEM models to determine if their inclusion satisfied the primary and secondary covariate selection criteria.

The final step of the process was to incorporate demographic covariates into the population pharmacokinetic model. Covariates showing evidence of influence were evaluated sequentially using NONMEM by comparing the full model (with covariate included) with the model from which the covariate being evaluated was deleted. Various evaluation criteria were used when comparing NONMEM models. These included a significant reduction in the objective function value based on the Likelihood Ratio Test or Akaike Information Criterion (AIC), goodness-of-fit parameters (including a less systematic distribution of weighted residual plots against covariates and a decrease in standard error, the elements in the correlation matrix of the parameter estimates, intersubject variability of the pharmacokinetic parameters, and residual error), random distribution in the weighted residual against the predicted effect or other covariates to be tested, and a coefficient of variation (CV%) of the parameters estimated of less than 50%.

Results:
Based upon NONMEM OFV, the two-compartment oral model was established as the BASE MODEL. Population model improvements were observed when apparent oral clearance (CLpo) was adjusted for dose and body surface area (BSA). A summary of the population pharmacokinetic model parameters is presented in the following table.

Summary of Fexofenadine NONMEM Population Parameter Estimates

Parameter	Population model
CL po/F (L/h)	CL po = 23.9 X BSA: For typical 1.875 BSA, 44.8 L/h (for 60 mg BID) and 26.7 L/h (for 240 mg QD), respectively.
V2/F (L)	380
Q (L/h)	149
V3 (L)	4210
Ka (1/h)	0.844

Sponsor's conclusions:
Based upon population pharmacokinetic modeling results, the pharmacokinetics of fexofenadine in normal healthy subjects appear to be affected by subject demographics. The population pharmacokinetic model best describing the data is a two-compartment oral model with apparent oral clearance (CLpo) based upon body surface area. A difference in apparent oral clearance is noted between the two studies, 60 mg BID versus 240 mg QD dosing regimens.

For fexofenadine the population estimated apparent oral clearance (CLpo,/F) is 23.9 L/h/m^2 and 14.2 L/h/m^2 following 60 mg BID and 240 mg QD dosing regimens, respectively. For an average subject with a weight of 74 kg, a height of 170 cm, and a body surface area (BSA) of 1.875 m^2 the apparent oral clearance (CLpo) for the 60 mg BID and 240 QD dosing regimens would be predicted to be 44.8 L/h, and 26.7 L/h, respectively. The population estimated apparent volume of distribution is L.

There are no identifiable gender or race differences in the pharmacokinetic of fexofenadine.

There was a sizable residual (prediction) variability in the base model (CV% = 71.2%) which was not substantially reduced by the addition of covariates (CV% = 64.2%). The modeled variability

across subjects for apparent oral clearance (CLpo) is 46.7%, and the modeled variability across subjects for apparent volume of distribution (V) is 135.2%.

APPENDIX I-15. Protocol 0164,5,5PROO22, Report W-96-0022-D

Title: Effect of gastric pH on the pharmacokinetics of MDL 16,455 following a single oral dose of MDL 16,455A in healthy male volunteers

Protocol Number: PJPR0022

Project Report Number: W-96-0022-D

Investigator and Location:

Objectives:
The primary objective of the study was to evaluate the effect of using both local and peripheral mechanisms of increasing gastric pH on the pharmacokinetics of MDL 16,455 following a single oral dose of MDL 16,455A in healthy male volunteers.

The secondary objectives of the study as stated in the protocol were:

- to evaluate any correlation between observed changes in MDL 16,455 pharmacokinetics and increased gastric pH, and to assess these observed changes with respect to the different mechanisms for increased pH; and
- to monitor safety, through the observation of any adverse events and any clinically significant changes in laboratory values.

Formulations:

Treatment	Lot #	Dosage form/strength	Batch size
A,B,C, MDL 16,455A	RH9411	Capsule 60 mg	

A. Single 111.88 mg dose of MDL 16,455 (given as 120 mg of the hydrochloride salt, MDL 16,455A prepared as two capsules each containing 60 mg).

B. Single 20 mg dose of omeprazole approximately 10 hours prior to a single 40 mg dose administration of omeprazole (2x20 mg), followed 1 hour later by a single 111.88 mg dose of MDL 16,455 as for treatment A.

C. Single 20 ml dose of MAALOX® suspension followed 15 minutes later by a single 111.88 mg dose of MDL 16,455 as for treatment A.

All MDL 16,455 doses were given under fasted conditions. The 20 mg omeprazole capsules and MAALOX suspension were supplied by the investigator.

Study Design and Sampling:
The study was conducted as an open-label, randomized, three-period, complete crossover design in which healthy male volunteers received a single dose of 111.88 mg of MDL 16,455 (2 x 60 mg capsules) alone or in combination with omeprazole or Maalox. All MDL 16,455A doses were administered after fasting for 10 hours.

There was a washout period of 6 days between each treatment. Serial blood samples were collected for 30 hours following MDL 16,455A administration, and were analyzed for MDL 16,455 concentration.

The extent of change of gastric pH was measured using a pH calibrated radiotelemetric capsule during the period from 2 hours prior to dosing to 5 hours following dosing of MDL 16,455A.

Number of Subjects:
A total of 24 healthy male subjects, aged 19 to 44 years, were enrolled in the study. Of the 24 subjects entering the study, 20 completed all three treatments, 22 completed two treatments and 24 completed one treatment. One subject was withdrawn from the study after visit 3 due to an adverse event, and three subjects withdrew consent to participate in the study. The total number of subjects exposed to each treatment was: Treatment A, n=21; Treatment B, n=23; Treatment C, n=22.

Assay:

Data analysis:
All subjects dosed with MDL 16,455A were included in the safety analysis. All subjects dosed with Treatment A and at least one of Treatments B and C were included in the pharmacokinetic analyses. Pharmacokinetic parameters were calculated from serial plasma MDL 16,455 concentration-time data using model independent techniques. The following pharmacokinetic parameters were calculated for each subject-treatment: Cmax, (the maximum plasma concentration); Tmax (the time to maximum concentration); AUC(0-4), AUC(0-30), AUCinf (area under the plasma concentration time curve to 4 hours, 30 hours, and extrapolated to infinite time).

Treatment comparisons were evaluated with an analysis of the natural log transformed data. A three-way analysis of variance with terms for subject, treatment and period was performed for AUC(0-30), Cmax and Tmax from which 90% confidence intervals for the ratio of treatment means were obtained.

Results:
Treatment comparisons for key pharmacokinetic parameters calculated from plasma fexofenadine concentrations from the study 016455PR0022

Parameter	*Trmt*	*Mean*	%CV	*pair*	Ratio (%)	90 % CI
AUC inf	A	1967	50.4			
ng·h/ml	B	1894	47.5	B/A	101	86 – 119
	C	1101	34.4	C/A	59	51 – 70
Cmax	A	331	52.2			
(ng/mL)	B	329	65.7	B/A	98	80 – 119
	C	177.8	35.4	C/A	57	47 – 69
Tmax	A	2.84	56.1			
(h)	B	2.81	56.3	B/A	102	78 – 135
	C	2.33	63.8	C/A	81	62 - 107

A. Single 111.88 mg dose of MDL 16,455 (given as 120 mg of the hydrochloride salt, MDL 16,455A prepared as two capsules each containinfg 60 mg)

B. Single 20 mg dose of omeprazole approximately 1 0 hours prior to a single 40 mg dose of omeprazole ((2X20 mg), followed 1 hour later by a single 111.88 mg dose of MDL 16.455 as for treatment A.

C. Single 20 ml dose of MAALOX suspension followed 15 minutes later by a single 111.88 mg dose of MDL 16,455 for treatment A.

Median gastric pH measures taken during the absorption phase of MDL 16,455A indicate that the Maalox elevated pH above 5.5 at the time of dosing of MDL 16,455A with the gastric pH recovering to less than 3.5 within 45 minutes. Median gastric pH measures for omeprazole showed elevation above pH 5.5 from between 50 and 180 minutes after the MDL 16,455A dose and slowly recovering to below pH 3.5 approximately 3 hours postdose.

Conclusions/ Comments:

- The administration of MDL 16,455A in the presence of MAALOX decreases bioavailability [as described by mean AUC(0-30)] by approximately 41 %. A corresponding decrease in rate of absorption of approximately 43% was observed.

- There was no significant change in either AUC(0-30) or max observed when MDL 16,455A was given in the presence of omeprazole. This may be because, fexofenadine was administered 1 hour after omeprazole administration (not a true concomitant administration.)

- Dosage adjustment may not be warranted based on the Maalox coadministration. However, it is recommended that a precautionary statement with respect to the decreased AUC that may result upon concomitant administration of Maalox with Allegra may need to be included in the labeling. It is recommended that antacids and Allegra should not be administered at the same time.

APPENDIX II. QUANTITATIVE COMPOSITION OF THE INVESTIGATIONAL TABLET

243_tbl

Table 2–6. Quantitative composition of the investigational fexofenadine HCl tablet batches

Tablet Lots	*15 mg*	*20 mg*	*30 mg*	*40 mg*	*60 mg*	*90 mg*	*120 mg*	*180 mg*	*180 mg*	*180 mg*	*180 mg*	*180 mg*
	RD9726	*RH9617*	*RD9728*	*RC9624*	*RD9723* *RD9619*	*RF9633*	*RJ9729* *RE9728* *RG9527*	*RG9529* *RG9610* *RG9611* *RG9612* *RG9636* *RG9638* *RG9734*	*RA9537*	*RA9538*	*RA9539*	*RG9533*
Components of Core Tablet	Weight (mg, tab)											
Fexofenadine HCl	15.00	20.00	30.00	40.00	60.00	90.00	120.00	180.00	180.0	180.00	180.00	180.00
Lactose												
Microcrystalline Cellulose												
Pregelatinized Starch												
Calcium Carbonate												
Gelatin												
Sodium Starch Glycolate												
Croscarmellose Sodium												
Magnesium Stearate												
Water (Purified) *												
Core Tablet Weight (mg)												
Components of Film Coating												
Colloidal Silicon Dioxide (M-7)												
Hydroxyprophl Methycellulose E-15												
Hydroxypropyl Methycellulose E-5												
Povidone												
Titanium Dioxide												
Polethylene Glycol 400												
Pink Iron Oxide Blend												
Yellow Iron Oxide Blend												
Water (Purified) *												
Total Tablet Weight (mg)												

* Removed during processing

Table 2–7. Quantitative composition of the investigational fexofenadine HCl capsule batches

Capsule Lots	*RE9501*	*RB9603*	*RF9414 RH9411 98053501 RH9417 RA9536 RK9532*
Components	Weight (mg/capsule)		
Fexofenadine HCl	30.00	40.00	60.00
Lactose			
Microcrystalline Cellulose			
Starch			
Gelatin			
Croscarmellose Sodium			
Magnesium Stearate			
Water (Purified) *			
Capsule Shell, Size			
Total Capsule Weight (mg)			

* Removed during processing

6.C Drug formulation development summary table

6.3_R

Table 6–3. Drug formulation development summary

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Protocol No. Report No.	*Lot No.*	*Dosage Form and Strength*	*Batch Size Date of Manufacture*	*Formulation or Significant Manufacturing Change (if any) and Reason for Change*	*Effect of Change*
Formulation support studies					
Protocol PJPR0033, Report K-96-1037-D, S6–V1.29–P2	RA9538	180 mg lactose-gelatin tablets.	tablets 02/95	Small-scale, white, scored, capsule-shaped, film-coated tablets in a modification of the current immediate-release capsule formulation.	Bioavailable compared to reference.
	RA9539	180 mg lactose-free tablets similar to the outer layer of SELDANE-D.	tablets 02/95	Small-scale, white, oval-shaped, film-coated tablets in a lactose-free formulation similar to the outer layer SELDANE-D.	Bioavailable compared to reference.
	RA9537	180 mg lactose-free tablets with AC-DI-SOL.	tablets 02/95	Small-scale, white, scored, capsule-shaped, film-coated tablet.	Bioavailable compared to reference.
	RF9414	60 mg marketed capsules.	capsules* 07/94	Full-scale, white, gelatin capsule, size 0 containing white to off-white powder.[1]	Reference
Protocol PJPR0045, Report K-96-0021-D, S6–V1.31–P1	RG9529	180 mg lactose-free tablets with AC-DI-SOL (lactose-free tablet).	tablets† 07/95	Pivotal-size lot, peach, capsule-shaped, film-coated tablets similar to RA9537. Only difference is this is peach colored and is representative of full-scale.	Bioequivalent to reference.
	RG9533	180 mg lactose-gelatin tablets.	tablets† 08/95	Pivotal-size lot, peach, capsule-shaped, film-coated tablets similar to RA9538. Only difference is this is peach colored and is representative of full-scale.	Bioequivalent to reference.
	RH9411	60 mg marketed capsules.	capsules 08/94	Full-scale, white gelatin capsule size 0, containing white to off-white powder.	Reference

NA Not applicable

* The critical step of the process, i.e., granulation, was manufactured at kg, using full-scale equipment.

† The critical step in the manufacturing process, i.e., granulation, was made at greater than % full scale, sufficient to yield greater than tablets

Table 6–3. Drug formulation development summary

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Protocol No. Report No.	*Lot No.*	*Dosage Form and Strength*	*Batch Size Date of Manufacture*	*Formulation or Significant Manufacturing Change (if any) and Reason for Change*	*Effect of Change*
Protocol PJPR0062, Report K-96-0891-D, S6–V1.32–P1	RG9529	180 mg lactose-free tablet.	tablets† 7/95	Same as lot used in *PJPR0045.*	NA (food effect study)
Protocol PJPR0094, Report K-98-0063-D, S6–V1.33–P1	RD9723	60 mg lactose-free tablets.	tablets 6/97	Pivotal size lot, peach, modified oval-shape, film-coated tablets; granulation is identical to RG9529.	Bioequivalent to reference
	98053501	60 mg marketed ALLEGRA capsules.	capsules 10/96	Full-scale, white gelatin capsule size 0, containing white to off-white powder.	Reference
Protocol PJPR0098, Report K-98-0065-D (Part 1), S6–V1.35–P1	RJ9729	120 mg lactose-free tablets.	tablets 10/97	Pivotal size lot, peach, modified oval-shape, film-coated tablets; granulation is identical to RG9529.	NA (food effect and pharmacokinetic study)

NA Not applicable

* The critical step of the process, i.e., granulation, was manufactured at kg, using full-scale equipment.

† The critical step in the manufacturing process, i.e., granulation, was made at greater than 10% full scale, sufficient to yield greater than) tablets

Table 6–3. Drug formulation development summary

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Protocol No. Report No.	*Lot No.*	*Dosage Form and Strength*	*Batch Size Date of Manufacture*	*Formulation or Significant Manufacturing Change (if any) and Reason for Change*	*Effect of Change*
Protocol PJPR0071, Report K-97-0145-D, S6–V1.36–P1,	RG9610	180 mg lactose-free tablets.	tablets 07/96	Small-scale, peach, capsule-shaped, film-coated tablets similar to RG9529. Only difference is anhydrous fexofenadine HCl with a surface area of 4.39 m^2/g was used.	Bioavailable compared to RG9611.
	RG9529	180 mg lactose-free tablets.	tablets† 07/95	Same lot was used in *PJPR0045.*	Bioavailable compared to RG9611.
	RG9636	180 mg lactose-free tablets.	tablets 07/96	Small-scale, peach, capsule-shaped, film-coated tablets similar to RG9529. Only difference is anhydrous fexofenadine HCl with a surface area of 3.02 m^2/g was used.	Bioavailable compared to RG9611 and RG9636.
	RG9612	180 mg lactose-free tablets.	tablets 07/96	Small-scale, peach, capsule-shaped, film-coated tablets similar to RG9529. Only difference is anhydrous fexofenadine HCl with a surface area of 1.79 m^2/g was used.	Bioavailable compared to RG9611.
	RG9611	180 mg lactose-free tablets.	tablets 07/96	Small-scale, peach, capsule-shaped, film-coated tablets similar to RG9529. Only difference is anhydrous raw material is unmilled and has surface area of 1.03 m^2/g.	Reference

NA Not applicable

• The critical step of the process, i.e., granulation, was manufactured at kg, using full-scale equipment.

† The critical step in the manufacturing process, i.e., granulation, was made at greater than % full scale, sufficient to yield greater than tablets

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Table 6–3. Drug formulation development summary

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Protocol No. Report No.	*Lot No.*	*Dosage Form and Strength*	*Batch Size Date of Manufacture*	*Formulation or Significant Manufacturing Change (if any) and Reason for Change*	*Effect of Change*
Protocol PJPR0071, Report K-97-0145-D, S6–V1.36–P1	RG9638	180 mg lactose-free tablets.	tablets 07/96	Small-scale, peach, capsule-shaped, film-coated tablets similar to RG9529. Only difference is anhydrous fexofenadine HCl with a surface area of 3.02 m^2/g was converted to the hydrated form during granulation.	Bioavailable compared to RG9636.
Formulations used in pharmacokinetic & pharmacodynamic studies					
Protocol PJPR0068, Report K-97-0066-D, S6–V1.38–P1	RF9633	90 mg lactose-free tablets.	tablets* 06/96	Pivotal-size lot, peach, capsule-shaped, film-coated tablets. Granulation is identical to RG9529.	NA (pharmacokinetic study)
Protocol PJPR0068, Report K-97-0066-D, S6–V1.38–P1	RC9624	40 mg lactose-free tablets.	tablets* 5/96	Full-scale, peach, capsule-shaped, film-coated tablets similar to RG9529. Granulation is identical to RG9529.	NA (pharmacokinetic study)
Protocol PJPR0037, Report K-96-0929-D, S6–V1.41–P1	RE9501	30 mg immediate-release capsules.	capsules 5/95	Small-scale, size 2 hard-gelatin capsule. This has the same active: excipient ratio as marketed 60 mg capsule.	NA (pharmacokinetic study)
Protocol PJPR0098, Report K-98-0071-D (Part II) S6–V1.40–P1	RJ9729	120 mg lactose-free tablets.	tablets 10/97	Pivotal-size lot, peach, capsule-shaped, film-coated tablets similar to RG9529. Granulation is identical to RG9529.	NA (pharmacokinetic study)

NA Not applicable

* The critical step of the process, i.e., granulation, was manufactured at kg, using full-scale equipment.

† The critical step in the manufacturing process, i.e., granulation, was made at greater than % full scale, sufficient to yield greater than tablets

Table 6–3. Drug formulation development summary

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Protocol No. Report No.	*Lot No.*	*Dosage Form and Strength*	*Batch Size Date of Manufacture*	*Formulation or Significant Manufacturing Change (if any) and Reason for Change*	*Effect of Change*
Formulations used in clinical safety and efficacy studies					
Protocol M016455B/3081, Report K-98-0093-D, S6–V1.44–P1	RE9728 RE9734	Lactose-free tablets. 120 mg 180 mg	tablets† 6/97 tablets† 7/97	Pivotal-size lot, peach, capsule-shaped, film-coated tablets similar to RG9529. Only difference is tablets are compressed to a weight proportional to strength.	NA (pivotal safety and efficacy study in SAR)
Protocol PJPR0039/0067, Report K-98-0120-D, S6–V1.45–P1	RH9617 RD9619 RG9527 RG9529	Lactose-free tablets. 20 mg 60 mg 120 mg 180 mg	tablets† 8/96 tablets 5/96 tablets 7/95 tablets† 7/95	Pivotal-size lot, peach, capsule-shaped, film-coated tablets similar to RG9529. Only difference is tablets are compressed to a weight proportional to strength.	NA (pivotal safety and efficacy studies in CIU)
Protocol 016455PR0019, Report W-96-0023-D, S6–V1.46–P1	RH9411	60 mg marketed capsules.	capsules 8/94	Full-scale, white gelatin capsule size 0, containing white to off-white powder.	NA (supportive safety and efficacy study in CIU)
Protocol PJPR0066/0077, Report K-98-0119-D, S6–V1.48–P1	RD9726	Lactose-containing tablets. 15 mg	tablets 6/97	Pivotal-size lot, modified, capsule-shaped, film-coated tablets.	NA (pivotal safety and efficacy study in pediatric SAR)
Protocol PJPR0066/0077, Report K-98-0119-D, S6–V1.48–P1	RD9728 RD9723	Lactose-free tablets. 30 mg 60 mg	tablets 6/97 tablets 6/97	Pivotal-size lot, peach, capsule-shaped, film-coated tablets similar to RG9529. Only difference is tablets are compressed to a weight proportional to strength.	NA (pivotal safety and efficacy study in pediatric SAR)
Protocol PJPR0027, Report K-98-0117-D, *S6–V1.51–P1*	RH9417	60 mg marketed capsules.	capsules 11/94	Full-scale, white gelatin capsule size 0, containing white to off-white powder.	NA (6-month safety study)

NA Not applicable

• The critical step of the process, i.e., granulation, was manufactured at kg, using full-scale equipment.

† The critical step in the manufacturing process, i.e., granulation, was made at greater than % full scale, sufficient to yield greater than tablets

Table 6–3. Drug formulation development summary

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Protocol No. Report No.	*Lot No.*	*Dosage Form and Strength*	*Batch Size Date of Manufacture*	*Formulation or Significant Manufacturing Change (if any) and Reason for Change*	*Effect of Change*
Protocol PJPR0031, Report K-98-0117-D, *S6–V1.51–P1*	RH9417	60 mg marketed capsules.	capsules 11/94	Full-scale, white gelatin capsule size 0, containing white to off-white powder.	NA (12-month safety study)
Formulations used in drug interaction studies					
Protocol 016455PR0022, Report W-96-0022-D, S6–V1.54–P1	RH9411	60 mg marketed capsule	capsules 9/94	Full-scale, white gelatin capsule size 0, containing white to off-white powder.	NA (drug interaction study)

NA Not applicable

• The critical step of the process, i.e., granulation, was manufactured at kg, using full-scale equipment.

† The critical step in the manufacturing process, i.e., granulation, was made at greater than % full scale, sufficient to yield greater than tablets

APPENDIX III. ANALYTICAL METHOD USED FOR EACH STUDY

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pages of trade secret and/or confidential commercial information

APPENDIX IV. DISSOLUTION PERFORMANCE FOR FORMULATIONS USED IN EACH STUDY

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Table 6–5. Drug product dissolution performance summary

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Lot No.	*Date of Test*	*Dosage Form and Strength*	*Protocol No. Report No.*	*Dissolution Apparatus Rotation Speed (Method No.)*	*Media/ Temperature*	*Collection Time*	*Units Tested/Mean/Range/%CV*				
							N	*Mean*	*High*	*Low*	*%CV*
RA9538	02/21/95	180 mg lactose-gelatin tablet	*Protocol PJPR0033, Report K-96-1037-D, S6–V1.29–P2*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1581)	1800 mL 10 mM Phosphate buffer/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	27.6 67.8 81.5 86.9 90.1			20.3 3.3 1.7 2.1 2.4
RA9539	02/21/95	180 mg tablet similar to outer layer of SELDANE-D	*Protocol PJPR0033, Report K-96-1037-D, S6–V1.29–P2*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1582)	1800 mL 50 mM Phosphate buffer/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	72.4 82.7 94.4 97.7 98.6			49.8 3.0 0.6 0.8 0.9
RA9537	02/21/95	180 mg lactose-free tablet with AC-DI-SOL (Lactose- free tablet)	*Protocol PJPR0033, Report K-96-1037-D, S6–V1.29–P2*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1581)	1800 mL 10 mM Phosphate buffer/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	53.8 74.8 85.2 92.3 91.7			3.7 1.3 1.6 2.1 1.8
RF9414	07/25/94	60 mg marketed capsule	*Protocol PJPR0033, Report K-96-1037-D, S6–V1.29–P2*	USP type 2 paddle apparatus set to 50 rpm (Method No. 1338)	900 mL Deionized water/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	58.9 78.5 85.3 88.2 90.5			5.0 3.3 2.8 2.5 2.3

* The high value was verified upon re-injection. The probable cause is that at the 5-minute sampling, point the tablets are still in the process of breaking up and some pieces were possibly drawn up into the sampling syringe and dissolved as they were forced through the filter.

Table 6–5. Drug product dissolution performance summary

Page 2 of 5

Lot No.	Date of Test	Dosage Form and Strength	Protocol No. Report No.	Dissolution Apparatus Rotation Speed (Method No.)	Media/ Temperature	Collection Time	Units Tested/Mean/Range/%CV				
							N	Mean	High	Low	%CV
RG9529	08/16/95	180 mg lactose-free tablet	*Protocol PJPR0045, Report K-96-0021-D, S6–V1.31–P1 Protocol PJPR0062, Report K-96-0891-D, S6–V1.32–P1 Protocol PJPR0071, Report K-97-0145-D S6–V1.36–P1 Protocol PJPR0039/0067, Report K-98-0120-D, S6–V1.45–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	59.4 84.0 92.1 94.6 95.4			8.5 2.3 1.7 1.1 1.5
RG9533	08/17/95	180 mg lactose-gelatin tablet	*Protocol PJPR0045, Report K-96-0021-D, S6–V1.31–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	52.4 90.1 95.1 98.0 98.7			8.9 1.8 1.7 1.5 1.4
RH9411	09/15/94	60 mg marketed capsule	*Protocol PJPR0045, Report K-96-0021-D, S6–V1.31–P1 Protocol 016455PR0019, Report W-96-0023-D, S6–V1.46–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1338)	900 mL Deionized water/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	55.7 79.2 85.3 88.7 90.3			7.6 4.4 4.4 4.3 4.3
RF9633	07/01/96	90 mg lactose-free tablet	*Protocol PJPR0068, Report K-97-0066-D, S6–V1.38–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	83.2 97.5 101.0 101.9 102.2			2.6 1.4 1.4 1.1 1.2
RC9624	06/13/96	40 mg lactose-free tablet	*Protocol PJPR0068, Report K-97-0066-D, S6–V1.38–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	900 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	18 18 18 18	83.7 94.6 97.8 98.9			3.8 1.7 1.4 1.2

Table 6–5. Drug product dissolution performance summary

Page 3 of 5

Lot No.	Date of Test	Dosage Form and Strength	Protocol No. Report No.	Dissolution Apparatus Rotation Speed (Method No.)	Media/ Temperature	Collection Time	Units Tested/Mean/Range/%CV				
							N	Mean	High	Low	%CV
RG9610	08/20/96	180 mg lactose-free tablet	*Protocol PJPR0071, Report K-97-0145-D, S6–V1.36–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	70.3 87.7 92.6 94.1			5.5 3.2 3.0 2.4
RG9636	08/15/96	180 mg lactose-free tablet	*Protocol PJPR0071, Report K-97-0145-D, S6–V1.36–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	62.2 83.3 88.9 90.9			7.6 4.8 3.2 2.6
RG9612	08/15/96	180 mg lactose-free tablet	*Protocol PJPR0071, Report K-97-0145-D, S6–V1.36–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	69.0 87.5 92.9 94.3			4.0 2.4 1.8 1.6
RG9611	08/20/96	180 mg lactose-free tablet	*Protocol PJPR0071, Report K-97-0145-D, S6–V1.36–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	65.7 82.4 88.7 90.8			6.3 4.5 3.3 2.8
RG9638	08/16/96	180 mg lactose-free tablet	*Protocol PJPR0071, Report K-97-0145-D, S6–V1.36–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	55.6 79.6 88.5 91.6			7.9 4.4 3.3 2.7
RD9723	06/09/97	60 mg lactose-free tablet	*Protocol PJPR0094, Report K-98-0063-D, S6–V1.33–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	900 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	62.5 91.2 97.1 98.8			8.3 1.1 0.8 0.9
98053501	2/25/98	60 mg marketed Allegra capsules	*Protocol PJPR0094, Report K-98-0063-D, S6–V1.33–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	900 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	55.4 81.5 88.2 91.5 93.4			6.1 3.5 4.1 4.1 4.0

Table 6–5. Drug product dissolution performance summary

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Lot No.	Date of Test	Dosage Form and Strength	Protocol No. Report No.	Dissolution Apparatus Rotation Speed (Method No.)	Media/ Temperature	Collection Time	Units Tested/Mean/Range/%CV				
							N	Mean	High	Low	%CV
RJ9729	10/8/97	120 mg lactose-free tablet	*Protocol PJPR0098, Report K-98-0065-D, S6–V1.35–P1 (part 1) Protocol PJPR0098, Report K-98-0071-D, S6–V1.40–P1 (part 2)*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	69.3 83.3 89.9 92.8			12.4 9.7 7.5 6.1
RH9417	11/10/94	60 mg marketed capsule	*Protocol PJPR0027/0031, Report K-98-0117-D, S6–V1.51–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1338)	900 mL Deionized water/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	58.5 82.1 88.5 90.8 93.0			9.1 5.3 4.3 3.8 4.0
RG9527	8/24/95	120 mg lactose-free tablet	*Protocol PJPR0039/0067, Report K-98-0120-D, S6–V1.45–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min 60 min	18 18 18 18 18	72.9 89.4 94.4 96.8 97.4			4.6 2.0 1.5 1.4 1.4
RD9619	6/12/96	60 mg lactose-free tablet	*Protocol PJPR0039/0067, Report K-98-0120-D, S6–V1.45–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	900 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	18 18 18 18	84.2 95.3 98.1 99.6			2.5 2.5 2.3 2.5
RH9617	9/13/96	20 mg lactose-free tablet	*Protocol PJPR0039/0067, Report K-98-0120-D, S6–V1.45–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	900 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	85.4 94.5 96.9 97.7			2.4 2.7 2.3 2.2
RD9726	6/9/97	15 mg peach, round, film-coated tablet	*Protocol PJPR0066/0077, Report K-98-0119-D, S6–V1.48–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1540)	900 mL Deionized water/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	33.5 90.6 99.9 100.9 100.8			9.1 3.0 0.9 1.1 1.4
RD9728	6/9/97	30 mg lactose-free tablet	*Protocol PJPR0066/0077, Report K-98-0119-D, S6–V1.48–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	900 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	16.6 70.9 90.1 96.2			10.2 3.1 1.7 1.4

Table 6–5. Drug product dissolution performance summary

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Lot No.	Date of Test	Dosage Form and Strength	Protocol No. Report No.	Dissolution Apparatus Rotation Speed (Method No.)	Media/ Temperature	Collection Time	Units Tested/Mean/Range/%CV				
							N	Mean	High	Low	%CV
RD9723	6/9/97	60 mg lactose-free tablet	*Protocol PJPR0066/0077, Report K-98-0119-D, S6–V1.48–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	900 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	62.5 91.2 97.1 98.8			8.3 1.1 0.8 0.9
RE9728	7/8/97	120 mg lactose-free tablet	*Protocol M016455B/3081, Report K-98-0093-D, S6–V1.44–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	74.7 87.6 93.1 94.9			2.9 3.3 3.5 3.3
RE9734	7/8/97	180 mg lactose-free tablet	*Protocol M016455B/3081, Report K-98-0093-D, S6–V1.44–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1673)	1800 mL 1 mM HCl/ 37°C	5 min 15 min 30 min 45 min	12 12 12 12	66.3 81.7 88.1 90.9			5.0 4.1 4.2 4.1
RE9501	5/22/95	30 mg capsule	*Protocol PJPR0037, Report K-96-0929-D, S6–V1.41–P1*	USP type 2 paddle apparatus set to 50 rpm (Method No. P1338)	900 mL Deionized water/ 37°C	5 min 15 min 30 min 45 min 60 min	12 12 12 12 12	50.8 78.6 87.3 91.5 93.4			8.7 5.0 3.4 3.1 2.9

APPENDIX V. PROPOSED LABELING

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commercial

information

APPENDIX VI. BIOPHARMACEUTICS STUDY SUMMARY TABLE

Table 6–1. Biopharmaceutics study summary
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IND No. Protocol No. Report No.	*Route*	*Study Design*	*Dosage Form(s)*	*Dose*	*Plant Lot No. Date of Manufacture*	*Number of Subjects Exposed*	*Applicant Conclusion(s)*
Bioavailability/bioequivalence							
IND 16455PR0033 *Protocol PJPR0033, Report K-96-1037-D, S6–V1.29–P2*	Oral	Single-dose bioavailability, formulation screen. Part 1 was designed to evaluate bioavailability of prototype sustained-release formulations; Part 2 was designed to evaluate bioavailability of prototype immediate-release tablets. Part 2 was an open-label, single-dose, randomized, 4-period, complete crossover design. (Only Part 2 results will be summarized here)	180 mg tablet in a modification of the current immediate-release capsule formulation (lactose-gelatin tablet). 180 mg tablet in a lactose-free formulation similar to outer layer of SELDANE-D®. 180 mg tablet in a formulation similar to the lactose-free formulation above, but utilizing AC-DI-SOL as disintegrant. 60 mg marketed capsules.	180 mg 180 mg 180 mg 180 mg	US RA9538 2/95 US RA9539 2/95 US RA9537 2/95 US RF9414 7/94	20 healthy adult males	All immediate-release formulations provided acceptable bioavailability relative to the IR capsules. The lactose-free formulation utilizing AC-DI-SOL® as disintegrant was selected as the primary formulation for further development based upon its bioavailability and ease of manufacture. The lactose-gelatin formulation was designated as the back-up.
IND 16455PR0045 *Protocol PJPR0045, Report K-96-0021-D, S6–V1.31–P1*	Oral	Single-dose, pivotal bioequivalence study conducted using an open-label, randomized, repeat-treatment (3 treatments), 6-period crossover design.	180 mg tablet in a lactose-free formulation with AC-DI-SOL as disintegrant (lactose-free tablet). 180 mg lactose-gelatin tablet. 60 mg marketed capsules.	180 mg 180 mg 180 mg	US RG9529 7/95 US RG9533 8/95 US RH9411 8/94	27 healthy adult males	Both tablet formulations were bioequivalent to the marketed capsule. The lactose-free tablet formulation with AC-DI-SOL was selected for marketing based upon bioequivalence and ease of manufacture.

Table 6–1. Biopharmaceutics study summary
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IND No. Protocol No. Report No.	*Route*	*Study Design*	*Dosage Form(s)*	*Dose*	*Plant Lot No. Date of Manufacture*	*Number of Subjects Exposed*	*Applicant Conclusion(s)*
IND 16455PR0062 *Protocol PJPR0062, Report K-96-0891-D, S6–V1.32–P1,*	Oral	Single-dose, food effect study in an open-label, randomized 2-period complete crossover design.	180 mg lactose-free tablet under fasted and fed conditions.	180 mg	US RG9529 7/95	22 healthy adult males	Food decreased adjusted mean C_{max} by 20% and AUC(0-∞) by 21%.
IND M016455F/1094 *Protocol PJPR0094, Report K-98-0063-D, S6–V1.33–P1*	Oral	Single-dose pivotal bioequivalence study conducted using an open-label, randomized, 2-period, complete crossover design.	60 mg lactose-free tablet. 60 mg marketed capsules.	60 mg 60 mg	US RD9723 6/97 US 98053501 10/96	50 healthy adult males	The 60 mg lactose-free tablet was bioequivalent to the 60 mg marketed capsule.
IND M016455F/1098 *Protocol PJPR0098, Report K-98-0065-D (Part I) S6–V1.35–P1*	Oral	Single-dose, food effect study in an open-label, randomized, 2-period, complete crossover design.	120 mg lactose-free tablet under fasted and fed conditions.	120 mg	US RJ9729 10/97	22 healthy adult males	Food decreased adjusted mean C_{max} by 14% and AUC(0-∞) by 15%.
IND 16455PR0071 *Protocol PJPR0071, Report K-97-0145-D, S6–V1.36–P1*	Oral	Open-label, randomized, single-dose, 4-period, 6-treatment, incomplete crossover design.	180 mg tablet in a lactose-free tablet a. Anhydrous, surface area (SA) 4.39 m^2/g. b. Anhydrous, SA 3.02 m^2/g. c. Anhydrous, SA 1.79 m^2/g. d. Anhydrous, SA 1.03 m^2/g. e. Hydrate, SA 3.02 m^2/g. f. Anhydrous, SA 2.73 m^2/g.	180 mg	US RG9610 7/96 US RG9636 7/96 US RG9612 7/96 US RG9611 7/96 US RG9638 7/96 US RG9529 7/95	30 healthy adult males	Fexofenadine HCl tablets made with raw material of different surface areas show similar bioavailability. Anhydrous fexofenadine exhibits similar bioavailability to the hydrated form.

Table 6–1. Biopharmaceutics study summary
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IND No. *Protocol No.* *Report No.*	*Route*	*Study Design*	*Dosage Form(s)*	*Dose*	*Plant* *Lot No.* *Date of Manufacture*	*Number of Subjects Exposed*	*Applicant Conclusion(s)*
Pharmacokinetics/pharmacodynamics							
IND 16455PR0068 *Protocol PJPR0068,* *Report K-97-0066-D,* *S6–V1.38–P1*	Oral	Single- and multiple-dose pharmacokinetic study. Open-label, randomized, 3-period, single- and multiple-dose complete crossover design.	90 mg lactose-free tablet. 40 mg lactose-free tablet.	180 mg single dose then 180 mg q.d. for 6 days 90 mg b.i.d. for 6 days 40 mg b.i.d. for 6 days	US RF9633 6/96 US RF9633 6/96 US RC9624 5/96	24 healthy adult males	At equal total daily doses, fexofenadine exhibits similar pharmacokinetics whether administered as a once-daily or twice-daily regimen. Single-dose pharmacokinetics at the 180 mg q.d. regimen underpredicts steady-state exposure by approximately 21%. The pharmacokinetics of the 40 mg b.i.d. regimen were adequately characterized.
IND M016455F/1098 *Protocol PJPR0098,* *Report K-98-0071-D (Part II),* *S6–V1.40–P1*	Oral	Single- and multiple-dose pharmacokinetic study. Open-label, single period, randomized, single- and multiple- dose design.	120 mg lactose-free tablet.	120 mg single dose, then 120 mg q.d. for 6 days	US RJ9729 10/97	22 healthy adult males	Differences between 120 mg q.d steady-state and single dose C_{max} and AUC are less than 8%.

Table 6–1. Biopharmaceutics study summary
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IND No. Protocol No. Report No.	*Route*	*Study Design*	*Dosage Form(s)*	*Dose*	*Plant Lot No. Date of Manufacture*	*Number of Subjects Exposed*	*Applicant Conclusion(s)*
IND *Protocol PJPR0037, Report K-96-0929-D, S6–V1.41–P1* *Report on comparison to adults subjects: Report K-96-0978-D, S6–V1.43–P1*	Oral	Single-dose pharmacokinetic/ pharmacodynamic study. Double-blind, randomized, 2-period, complete crossover design.	30 mg capsules, with identical active:excipient ratio as marketed 60 mg capsules.	30 mg 60 mg	US RE9501 5/95	15 male and female 7- to 12-year-old patients with allergic rhinitis.	Dose-proportional increase in AUC (0-∞) were observed in pediatric patients. Inhibition of histamine-induced wheal and flare was observed in pediatric patients following both 30 mg and 60 mg doses. Equivalent doses of fexofenadine HCl administered to children will result in about 56% higher AUC (0-∞) compared to that observed in adults.

Table 6–1. Biopharmaceutics study summary
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IND No. Protocol No. Report No.	*Route*	*Study Design*	*Dosage Form(s)*	*Dose*	*Plant Lot No. Date of Manufacture*	*Number of Subjects Exposed*	*Applicant Conclusion(s)*
Population pharmacokinetics							
IND *Protocol M016455B/3081, Report K-98-0093-D, S6–V1.44–P1* *Clinical Report: K-98-0040-C S8–V1.64–P20*	Oral	Double-blind, randomized, placebo-controlled, parallel safety and efficacy study in Seasonal Allergic Rhinitis patients.	120 mg and 180 mg lactose-free tablets.	120 mg q.d. 180 mg q.d.	US RE9728 6/97 US RE9734 6/97	571 male and female SAR patients.	None of the demographic factors affected fexofenadine pharmacokinetics. Oral clearance was similar to healthy subjects
IND 16455PR0039/ 16455PR0067 *Protocol PJPR0039/0067, Report K-98-0120-D, S6–V1.45–P1* *Clinical reports: K-97-0479-C S8–V1.170–P2 K-97-0484-C S8–V1.189–P1*	Oral	Double-blind, randomized, placebo-controlled, parallel safety and efficacy study in chronic idiopathic urticaria (CIU) patients.	20, 60, 120 and 180 mg lactose-free tablets.	20 mg b.i.d. 60 mg b.i.d. 120 mg b.i.d. 240 mg b.i.d.	US RH9617 8/96 US RD9619 5/96 US RG9527 7/95 US RG9529 7/95	360 male and female CIU patients in *PJPR0039.* 367 male and female CIU patients in *PJPR0067.*	Oral clearance in CIU patients was similar to that in healthy subjects.
16455PR0019 *Protocol 016455PR0019, Report W-96-0023-D, S6–V1.46–P1* *Clinical report: W-96-0016-C S8–V1.207–P1* *Study conducted in Europe; not filed to US IND.*	Oral	Double-blind, randomized, placebo-controlled, parallel safety and efficacy study in CIU patients.	60 mg marketed capsule.	60 mg q.d. 120 mg q.d. 180 mg q.d. 240 mg q.d.	US RH9411 8/94	171 male and female CIU patients.	Oral clearance in males was 56% higher than females. No additional demographic factors were found to influence the pharmacokinetic model.

Table 6–1. Biopharmaceutics study summary
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IND No. Protocol No. Report No.	*Route*	*Study Design*	*Dosage Form(s)*	*Dose*	*Plant Lot No. Date of Manufacture*	*Number of Subjects Exposed*	*Applicant Conclusion(s)*
IND 16455PR0066/ 16455PR0077 *Protocol PJPR0066/0077, Report K-98-0119-D, S6–V1.48–P1 Clinical Report: K-98-0147-C S8–V1.225–P2*	Oral	Double-blind, randomized, placebo-controlled, parallel safety and efficacy study in pediatric patients with Seasonal Allergic Rhinitis.	15 mg lactose-containing tablets; 30 mg and 60 mg lactose-free tablets.	15 mg b.i.d. 30 mg b.i.d. 60 mg b.i.d.	US RD9726 6/97 US RD9728 6/97 US RD9723 6/97	646 male and female pediatric SAR patients.	Oral clearance was 23% to 34% lower than in older SAR patients.
IND 16455PR0027/ *PJPR0027* *16455PR0031/ PJPR0031 Protocol PJPR0027/0031, Report K-98-0117-D, S6–V1.51–P1 Clinical Reports PJPR0027: K-96-0878-C S8–V1.259–P2 NDA 20-625, PJPR0031 K-96-0306-C, S9.1-V1-P1*	Oral	Double-blind, randomized, placebo-controlled, parallel safety study.	60 mg marketed capsules.	240 mg q.d. for 1 year (*PJPR0027*) 60 mg b.i.d. for 6 months (*PJPR0031*)	US RH9417 11/94 US RH9417 11/94	240 male and female subjects in *PJPR0027*. 208 male and female subjects in *PJPR0031*.	Oral clearance at 60 mg b.i.d. was similar in CIU patients and SAR patients. Oral clearance at 240 mg q.d. was comparable to values seen at higher doses.

Table 6–1. Biopharmaceutics study summary
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IND No. *Protocol No.* *Report No.*	*Route*	*Study Design*	*Dosage Form(s)*	*Dose*	*Plant* *Lot No.* *Date of Manufacture*	*Number of Subjects Exposed*	*Applicant Conclusion(s)*
Drug Interaction							
16455PR0022 *Protocol 016455PR0022,* *Report W-96-0022-D,* *S6–V1.54–P1* *Conducted in the UK, not filed to US IND.*	Oral	Open-label, randomized, 3-period, complete crossover design. Fexofenadine HCl was administered either alone, 1 hour after omeprazole, or 15 minutes after MAALOX®.	60 mg marketed capsule. 20 mg omeprazole capsule. 20 mL of Maalox suspension.	120 mg single dose 20 mg 10 h prior, and 40 mg 1 h prior to fexofenadine 20 mL 15 minutes prior to fexofenadine	US RH9411 8/94 N/A N/A	24 healthy adult male subjects	Omeprazole does not affect fexofenadine pharmacokinetics. Fexofenadine administration within 15 minutes of MAALOX decreases fexofenadine AUC by 41% and C_{max} by 43%.

N/A Omeprazole capsules and MAALOX were purchased as commercial packs from a pharmacy.

6.B In vivo summary data table

6.2.R1

Table 6–2. In vivo summary data

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Protocol No. Report No.	*Administration Schedule*	*Population Age/Sex Mean±SD*	*Oral Dosage Forms*	*Dose mg*	*C_{max} ng/mL*	*T_{max} hr*	*AUC ng x hr/mL*	*T1/2 hr*	*CLpo L/hr*	*Comments*
Bioavailability/bioequivalence										
Protocol PJPR0033, Report K-96-1037-D, S6–V1.29–P2 (Part 2) (Note: Part 1 evaluated prototype sustained-release dosage forms and will not be discussed further.)	Single-dose, fasted	Normal, healthy adult males 25±7 years	**Lot No. RA9538** 180 mg lactose-gelatin tablet.	180 mg	397.58	2.61	2849.84	N.R.	N.R.	Relative bioavailability of all immediate-release formulations compared to immediate-release capsules was greater than 93% based on adjusted mean. Lot No. RA9537 was chosen for further development based upon ease of manufacture. Lot No. RA9538 was chosen as back-up, based upon manufacturing considerations.
			Lot No. RA9539 180 mg tablet in a lactose-free formulation similar to outer layer of SELDANE-D.	180 mg	484.57	1.92	3090.96	N.R.	N.R.	
			Lot No. RA9537 180 mg tablet in a formulation similar to the lactose-free formulation above, but utilizing AC-DI-SOL as disintegrant. (lactose-free tablet).	180 mg	485.40	1.84	3267.31	N.R.	N.R.	
			Lot No. RF9414 60 mg marketed capsules.	180 mg	416.66	2.34	3129.61	N.R.	N.R	

N.R. Not Reported

Table 6–2. In vivo summary data

Protocol No. Report No.	*Administration Schedule*	*Population Age/Sex Mean±SD*	*Oral Dosage Forms*	*Dose mg*	*C_{max} ng/mL*	*T_{max} hr*	*AUC ng x hr/mL*	*T1/2 hr*	*CLpo L/hr*	*Comments*
Protocol PJPR0045, Report K-96-0021-D, S6–V1.31–P1	Single-dose, fasted	Normal, healthy adult males 27±5 years	**Lot No. RG9529** 180 mg lactose-free tablets similar to Lot No. RA9537 used in *PJPR0033.*	180 mg	494.24	2.0	3330.08	11.60	56.54	Both tablet formulations were bioequivalent to the reference. The lactose-free tablet was selected for marketing based upon bioequivalence and manufacturing considerations.
			Lot No. RG9533 180 mg lactose-gelatin tablets similar to Lot No. RA9538 used in *PJPR0033.*	180 mg	453.64	2.5	3192.02	11.21	57.77	
			Lot No. RH9411 60 mg marketed capsules.	180 mg	476.32	2.6	3396.65	10.93	54.37	
Protocol PJPR0062, Report K-96-0891-D, S6–V1.32–P1	Single-dose, fed and fasted	Normal, healthy, adult males 27.5±7.3 years	**Lot No. RG9529** 180 mg lactose-free tablets.	180 mg under fasted conditions	559.91	2.2	3462.92	13.16	60.55	Administration with a high-fat breakfast decreased AUC by 21%, and C_{max} by 20%.
			Lot No. RG9529 180 mg lactose-free tablets.	180 mg under fed conditions	399.92	2.6	2582.15	14.85	69.03	
Protocol PJPR0094, Report K-98-0063-D, S6–V1.33–P1	Single-dose, fasted	Normal, healthy adult males 22.8±5.4 years	**Lot No. RD9723** 60 mg lactose-free tablets.	60 mg	141.80	1.7	973.77	14.74	64.94	The 60 mg lactose-free tablet is bioequivalent to the marketed 60 mg capsule.
			Lot No. 98053501 60 mg marketed capsules.	60 mg	131.25	2.5	958.98	14.21	64.54	

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Table 6–2. In vivo summary data

Protocol No. Report No.	*Administration Schedule*	*Population Age/Sex Mean±SD*	*Oral Dosage Forms*	*Dose mg*	C_{max} *ng/mL*	T_{max} *hr*	*AUC ng x hr/mL*	*T1/2 hr*	*CLpo L/hr*	*Comments*
Protocol PJPR0098, Report K-98-0065-D, S6–V1.35–P1 (Part I)	Single-dose, fed and fasted	Normal, healthy, adult males 60 mg 20.5±2.2 years	Lot No. RJ9729 120 mg lactose-free tablets.	120 mg under fasted conditions	289.31	2.5	2013.66	12.79	64.50	Administration with a high-fat breakfast decreases AUC by 15%, and Cmax by 14%.
				120 mg under fed conditions	235.81	2.6	1642.16	16.30	72.44	
Protocol PJPR0071, Report K-97-0145-D, S6–V1.36–P1	Single-dose, fasted	Normal, healthy adult males 31±7 years	Lot No. RG9610 180 mg lactose-free tablets similar to Lot No. RG9529, except anhydrous fexofenadine HCl with a surface area of 4.39 m^2/g was used.	180 mg	571.35	2.1	3805.81	14.14	53.26	Fexofenadine HCl tablets made with raw material of different surface areas show similar bioavailability. Anhydrous fexofenadine exhibits similar bioavailability to the hydrate.
			Lot No. RG9636 180 mg lactose-free tablets similar to Lot No. RG9529, except anhydrous fexofenadine HCl with a surface area of 3.02 m^2/g was used.	180 mg	495.63	1.8	3145.27	13.47	63.40	
			Lot No. RG9612 180 mg lactose-free tablets similar to Lot No. RG9529, except anhydrous fexofenadine HCl with a surface area of 1.79 m^2/g was used.	180 mg	627.21	1.7	3919.55	12.97	45.67	

Table 6–2. In vivo summary data

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Protocol No. Report No.	*Administration Schedule*	*Population Age/Sex Mean±SD*	*Oral Dosage Forms*	*Dose mg*	*C_{max} ng/mL*	*T_{max} hr*	*AUC ng x hr/mL*	*T1/2 hr*	*CLpo L/hr*	*Comments*
Protocol PJPR0071, Report K-97-0145-D, S6–V1.36–P1 (Cont'd)			**Lot No. RG9611** 180 mg lactose-free tablets similar to Lot No. RG9529, except unmilled anhydrous fexofenadine HCl with a surface area of 1.03 m^2/g was used.	180 mg	614.48	2.0	3924.05	13.72	50.64	
			Lot No. RG9638 180 mg lactose-free tablets similar to Lot No. RG9529, except anhydrous fexofenadine HCl with a surface area of 3.02 m^2/g was converted to the hydrated form during granulation.	180 mg	484.12	2.3	3422.83	15.12	55.82	
			Lot No. RG9529 180 mg lactose-free tablets. Fexofenadine HCl with a surface area of 2.73 m^2/g was used.	180 mg	553.96	2.1	3791.14	13.67	52.36	

Table 6–2. In vivo summary data

Protocol No. Report No.	*Administration Schedule*	*Population Age/Sex Mean±SD*	*Oral Dosage Forms*	*Dose mg*	*C_{max} ng/mL*	*T_{max} hr*	*AUC ng x hr/mL*	*T1/2 hr*	*CLpo L/hr*	*Comments*
Pharmacokinetics/pharmacodynamics										
Protocol PJPR0068, Report K-97-0066-D, S6–V1.38–P1	Single- and multiple- dose, fasted	Normal, healthy adult males 25.6±5.2 years	**Lot No. RF9633** 90 mg lactose-free tablets similar to Lot No. RG9529 used in *PJPR0045.*	180 mg single dose	568.44	2.0	3313.04	12.52	59.09	At equal daily doses, fexofenadine exhibits similar pharmacokinetics whether administered in a once-daily or a twice-daily regimen. Single-dose pharmacokinetics at the 180 mg q.d. regimen underpredicts steady-state exposure by 21%. This is similar to what has been observed with 20 mg, 60 mg, and 120 mg b.i.d. regimens. The pharmacokinetics of the 40 mg b.i.d. regimen were adequately characterized.
			Lot No. RF9633 90 mg lactose-free tablets similar to Lot No. RG9529 used in *PJPR0045.*	180 mg q.d. for 6 days	681.43	2.3	3874.33	11.68	47.90	
			Lot No. RF9633 90 mg lactose-free tablets similar to Lot No. RG9529 used in *PJPR0045.*	90 mg b.i.d. for 6 days	396.17	2.2	3515.50	11.28	52.87	
			Lot No. RC9624 40 mg lactose-free tablets similar to Lot No. RG9529 used in *PJPR0045.*	40 mg b.i.d. for 6 days	161.60	1.8	1436.73	11.06	55.71	

Table 6–2. In vivo summary data

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Protocol No. Report No.	*Administration Schedule*	*Population Age/Sex Mean±SD*	*Oral Dosage Forms*	*Dose mg*	*C_{max} ng/mL*	*T_{max} hr*	*AUC ng x hr/mL*	*T1/2 hr*	*CLpo L/hr*	*Comments*
Protocol PJPR0098, Report K-98-0071-D (Part II) S6–V1.40–P1	Single- and multiple- dose, fasted	Normal, healthy adult males 27.7±7.8 years	**Lot No. RJ9729** 120 mg lactose-free tablets	120 mg single dose 120 mg q.d. for 6 days	323.89 348.91	2.0 1.9	1978.83 2033.52	16.63 15.27	64.02 63.02	Differences between 120 mg q.d. steady-state and single dose C_{max} and AUC are less than 8%.
Protocol PJPR0037, Report K-96-0929-D, S6–V1.41–P1	Single-dose, fasted	Male and female pediatric patients 9.0±1.6 years	**Lot No. RE9501** 30 mg immediate release capsules (identical to marketed capsules except smaller fill weight).	30 mg single dose 60 mg single dose	183.52 280.12	2.2 2.5	1090.67 1899.87	8.78 9.05	29.05 31.57	Dose-proportional increase in AUC and C_{max} were observed. Inhibition of histamine-induced wheal and flare areas was observed for both 30 mg and 60 mg doses.
			Population pharmacokinetics							
Protocol M016455B/3081, Report K-98-0093-D, S6–V1.44–P1	Q24h for 2 weeks	Male and female SAR patients 32.5±12.3 years	Lactose-free tablets **Lot No. RE9728** 120 mg **Lot No. RE9734** 180 mg	120 mg 180 mg	N/A	N/A	N/A	N/A	64.3	None of the demographic factors affected fexofenadine pharmacokinetics. Oral clearance in SAR patients was similar to that in healthy subjects.
Protocol PJPR0039/0067, Report K-98-0120-D, S6–V1.45–P1	Q12h for 6 weeks	Male and female CIU patients 39±12 years	Lactose-free tablets **Lot No. RH9617** 20 mg **Lot No. RD9619** 60 mg **Lot No. RG9527** 120 mg **Lot No. RG9529** 180 mg	20 mg 60 mg 120 mg 240 mg	N/A	N/A	N/A	N/A	55.3	Oral clearance in CIU patients was similar to that in healthy subjects.

N/A Not Applicable

Table 6–2. In vivo summary data

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Protocol No. Report No.	*Administration Schedule*	*Population Age/Sex Mean±SD*	*Oral Dosage Forms*	*Dose mg*	*C_{max} ng/mL*	*T_{max} hr*	*AUC ng x hr/mL*	*T1/2 hr*	*CLpo L/hr*	*Comments*
Protocol 016455PR0019, Report W-96-0023-D, S6–V1.46–P1	Q24h for 6 weeks	Male and female CIU patients 43.9±14.7 years	**Lot No. RH9411** 60 mg marketed capsules.	60 mg 120 mg 180 mg 240 mg	N/A	N/A	N/A	N/A	87.4 L/h for males and 56.2 L/h for females	Oral clearance in males was greater than in females, similar to that observed in b.i.d. SAR trials.
Protocol PJPR0066/0077, Report K-98-0119-D, S6–V1.48–P1	Q12h for 2 weeks	Male and female pediatric SAR patients 9.1±1.6years	Lactose-containing tablets **Lot No. RD9726** 15 mg Lactose-free tablets **Lot No. RD9728** 30 mg **Lot No. RD9723** 60 mg	15 mg 30 mg 60 mg	N/A	N/A	N/A	N/A	42.6	Oral clearance in pediatric SAR patients was 23% to 34% lower than in older SAR patients.
Protocol PJPR0027, Report K-98-0117-D, *S6–V1.51–P1,*	240 mg Q24h for 12 months	Male and female healthy subjects 34.6±12.9years	**Lot No. RH9417** 60 mg marketed capsules.	240 mg q.d.	N/A	N/A	N/A	N/A	29.3	Oral clearance at 240 mg q.d. was comparable to values seen at higher doses.
Protocol PJPR0031, Report K-98-0117-D, *S6–V1.51–P1*	60 mg Q24h for 6 months	Male and female healthy subjects 33.3±11.7years	**Lot No. RH9417** 60 mg marketed capsules.	60 mg b.i.d.	N/A	N/A	N/A	N/A	45.4	Oral clearance at 60 mg b.i.d. was similar to that observed in CIU patients.

N/A Not Applicable

6.2.28

Table 6–2. In vivo summary data

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Protocol No. Report No.	*Administration Schedule*	*Population Age/Sex Mean±SD*	*Oral Dosage Forms*	*Dose mg*	*C_{max} ng/mL*	*T_{max} hr*	*AUC ng x hr/mL*	*T1/2 hr*	*CLpo L/hr*	*Comments*
Drug Interaction										
Protocol 016455PR0022, Report W-96-0022-D, S6–V1.54–P1	120 mg fexofenadine HCl single-dose alone.	Normal, healthy adult males. 27.8±7.0 years	**Lot No. RH9411** 60 mg marketed capsules.	120 mg	331.1	2.8	1967.3	N.R.	N.R.	Administration with omeprazole does not affect fexofenadine pharmacokinetics while administration immediately after MAALOX decreases AUC by 41% and C_{max} by 43%.
	20 mg omeprazole, followed 9 hours later by 40 mg omeprazole, then 120 mg fexofenadine HCl 1 hr later.		**Lot No. RH9411** 60 mg marketed capsules. Omeprazole purchased commercially.	120 mg	329.0	2.8	1894.0	N.R.	N.R.	
	120 mg fexofenadine HCl 15 minutes after administration of 20 mL MAALOX.		**Lot No. RH9411** 60 mg marketed capsules. MAALOX purchased commercially.	120 mg	177.8	2.3	1101.8	N.R.	N.R.	

N.R. Not Reported

APPENDIX VII. THE PHARMACOMETRIC NODE'S REVIEW ON POPULATION PHARMACOKINETICS

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II (HFD-870)

Memorandum

To:	Young-Moon Choi Ramana Uppoor Mei-Ling Chen
From:	Michael J. Fossler Pharmacometrics Scientist
Consult received:	6/15/99
Date:	7/9/99
Re:	Pharmacometrics Consult Request for NDA 20-872 (Fexofenadine HCl)

As discussed previously, due to the short review time of this consult, a formal review could not be completed in time in order to meet the goal date. However, Pharmacometrics has performed some preliminary analyses which will be compared to the sponsor's results.

Data from two studies were used in this analysis, the objective of which was to determine if there were differences in the pharmacokinetics of fexofenadine between adult and pediatric SAR patients. The two studies used were K-98-0093-D, a phase 3 study in 563 adult SAR patients given fexofenadine 120 or 180 mg once daily, or placebo, and K-98-0119-D, a phase 3 study in (n=593) pediatric patients aged 6-11 years old given 15, 30, or 60 mg BID fexofenadine. Both studies utilized a sparse plasma sampling design.

The reviewer used NONMEM version 5 to analyze the data. A one compartment model was used (in contrast to the two compartment model the firm used) since reliable estimates for some of these parameters could not be obtained. A base model (without covariates) was first fitted to the data. S-PLUS version 4.5 was then used to plot covariates against the residual parameter plots in order to determine if any of the covariates explained any variability. The following covariates were examined: age, weight, height, body surface area, and PED, which was a dichotomous variable that took one of two values: 0 if age=5-11 or 1=12 and over.

Results

Figure 1 shows the individual observed vs. predicted plasma concentrations plotted against the unit (y=x) line. The close proximity of the points to the unit line indicates a reasonable fit was obtained. The weight residual vs. mean prediction is shown in Figure 2.. There is some bias at lower concentrations which may indicate a problem with the error model used (combined additive/proportional); however, a variety of other residual error models were tried and the problem persisted.

Figure 1: Observed vs. Predicted plot

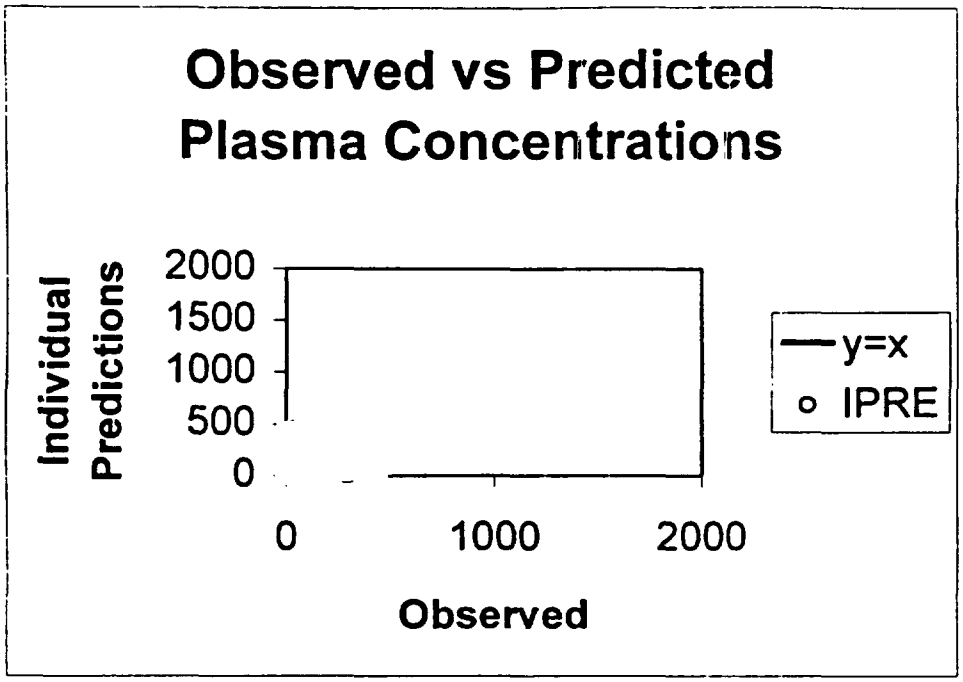


Figure 2: WRES vs. PRED

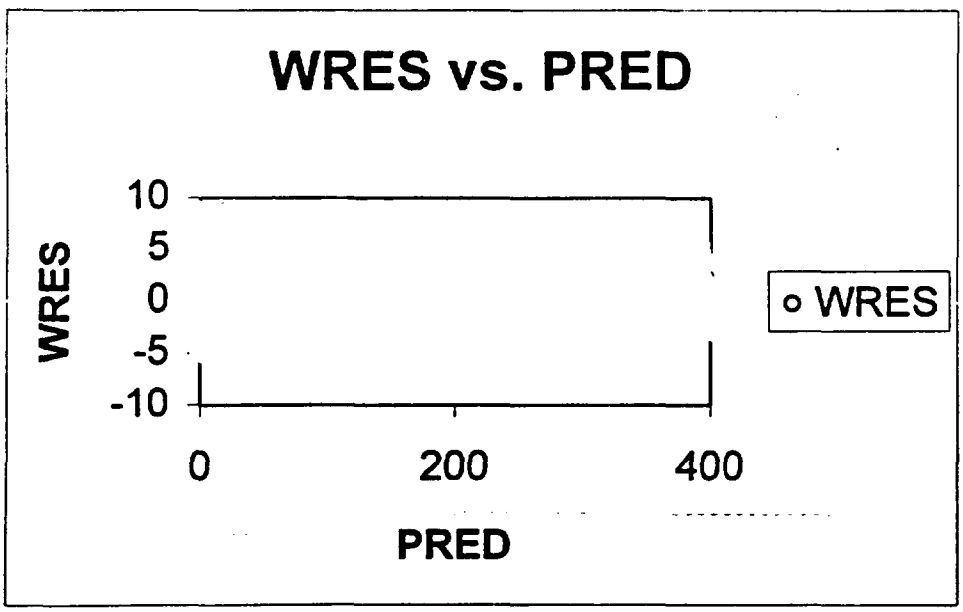
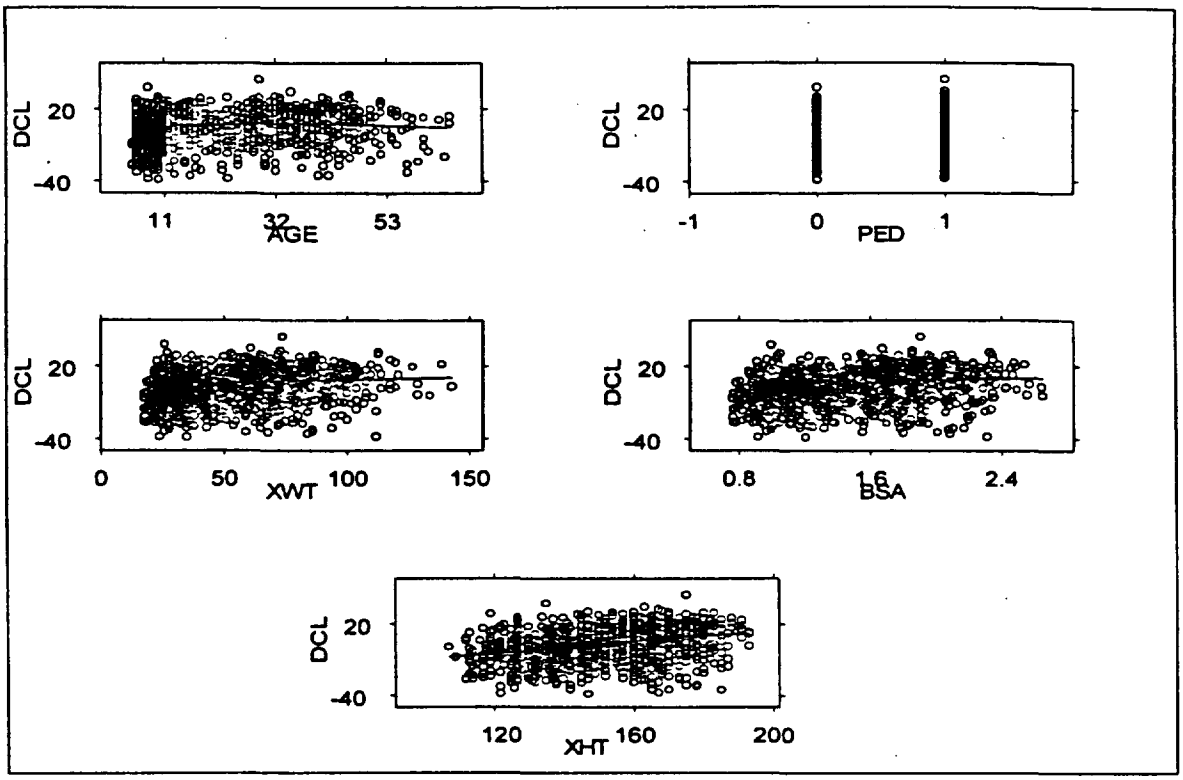


Figure 3 show the results of the covariates exploratory analysis for CL/F (results for V/F not shown, but are very similar). The residual of each individual's CL/F or V/F minus the "typical" or mean value was plotted against each of the covariates mentioned above. Overall, no strong relationships between any of the covariates and CL/F or V/F could be shown. Nevertheless, an attempt was made to add BSA , weight, PED, and height to each parameter. No improvement in the fit was obtained, indicating that these covariates explain little of the PK variability.

Figure 3: Residual CL/F values vs. covariates. For PED, 0= < 12 years old, 1=≥12. XWT and XHT are weight and height, respectively.



The final PK results are shown in Table 1. The result for CL/F in particular agrees well with the values found in other studies. The inter-subject variability in all of the parameters is somewhat large, but as discussed previously, can not be explained by any covariates. All three parameters are estimated with reasonable precision.

Table 1: Results of PPK analysis of data from K-98-0093-D and K-98-0119-D

Parameter	Typical Value (Interindividual CV%)	Precision (precision of CV)
CL/F (L/hr)		3.7% (27%)
*V/F (L)		6.7% (36%)
ka (hr^{-1})		21.7% (60%)

*covariance of CL/F and V/F is 51% (±38%)

These results disagree somewhat with Report K-96-0978-D, which was a population analysis of five studies in normal healthy volunteers (n=88) and pediatric SAR patients (n=14). The firm's analysis of these results show that the apparent oral clearance in the pediatric patients (30.3 L/hr) differs significantly from that in adults (50.7 L/hr). In this analysis, this difference is attributed to BSA. The reason for this discrepancy is difficult to determine, but a likely reason is the extremely small number of pediatric patients used

in K-96-0978-D. The reviewer's population analysis is considered to be more reliable, since it is based on many more subjects. Based on this analysis, there appears to be no reason, from a pharmacokinetics perspective, to adjust the dose in children aged 5-11 as compared to adults. There may be other reasons (e.g., pharmacodynamic or safety) to do so, however.

Conclusions

- Based on the reviewer's analysis, the pharmacokinetics of fexofenadine do not appear to differ substantially between adults and children.
- From a pharmacokinetics perspective, there appears to be no reason to adjust the dose in children aged 5-11 as compared to adults. There may be other reasons (e.g., pharmacodynamics or safety) to do so.

/S/ 7/9/99

Michael J. Fossler, Pharm.D., Ph.D.

Pharmacometrics Scientist
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

CC: NDA 20-872, HFD-850(Lee, Metz, Lesko)

AUG 3 1 1998

Clinical Pharmacology & Biopharmaceutics Review

NDA 20-872
Fexofenadine HCl 30, 60, 120 and 180 mg Tablets (Allegra®)

Hoechst Marion Roussel, Inc.
10236 Marion Park Drive
P.O. Box 9627
Kansas City, MO 64134-0627

Type of Submission:
New NDA, 3S
Suitability for filing
Submission Date:
07/17/98

Reviewer:
Brad Gillespie, PharmD

Background

Fexofenadine HCl (Allegra) is an H_1-receptor antagonist indicated for the treatment of seasonal allergic rhinitis. The sponsor received FDA approval for Allegra capsules on July 25, 1996. The sponsor has developed 30mg , 60mg, 120mg and 180mg lactose-free fexofenadine HCl tablets as an alternative to the capsules. They propose that these tablets will be indicated for treating the symptoms of seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU) in adults and children age 6 years and up.

The sponsor has conducted a complete safety and efficacy program in support of the proposed adult indications and have proposed using the pediatric rule to support registration in that population. Additionally, they have included human pharmacokinetic (PK) studies designed to link the proposed to the approved products, assess the effect of food on the bioavailability of ALLEGRA tablets, and characterize the disposition of fexofenadine in a pediatric population (aged 7-12 years).

In this review, the Human Pharmacokinetics section of the application will be reviewed to ensure that it is complete and is organized properly to permit a timely and efficient review.

Comments

1. The sponsor has conducted single- and multiple-dose pharmacokinetic studies designed to describe the disposition of the drug in human volunteers.
2. The sponsor has provided information demonstrating that 30, 60, 120 and 180 mg tablets are compositionally proportional. Additionally, they have provided mean tablet data showing similar *in vitro* behavior in four different dissolution media. They are requested to submit complete individual tablet data for all tablet strengths in all media so that these similarities can be investigated more completely.
3. The sponsor has completed food effect studies with both the 120 and 180 mg tablets.
4. The sponsor has conducted bioequivalence trials comparing their 180 mg tablet (1x180 mg) to three of the approved capsules (3 x 60 mg) and their 60 mg tablet (1x60) to the approved 60 mg capsule.
5. With regard to formulations, it appears that the pivotal clinical studies were conducted with the to-be-marketed tablet formulation. The pediatric study

(PJPR0037) used 30 and 60 mg capsules. The sponsor stated that the active/inactive ingredient ratio of these capsules is identical to that in the approved capsules.

6. The sponsor has provided detailed assay performance data for all of the pivotal pharmacokinetic studies.

Recommendation The Human Pharmacokinetics section of this NDA has been briefly reviewed by the Division of Pharmaceutical Evaluation II for the purposes of filing and has been found to be complete with the exception of the item described in Comment 2, above. This deficiency should be communicated to the sponsor in the form of an information request (IR) letter.

It is paginated and properly organized to allow an efficient and thorough review.

/S/ 8/28/98

Bradley K. Gillespie, PharmD
Division of Pharmaceutical Evaluation II

FT /S/ 08/31/98 Ramana Uppoor, PhD., Team Leader