CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-830/S008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Hiffiker
FEB 18 2000

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-830
Montelukast Chewable Tablets

BRAND NAME: Singulair

SPONSOR: Merck

SUBMISSION DATE:
05/06/99 (Serial No. SEI-008)
01/28/2000 (Serial No. BC)
11/18/98: IND —— Serial No. 114) /S/

REVIEWER: Tien-Mien Chen, Ph.D.

TYPE OF SUBMISSION: A Pediatric Supplement to An Approved NDA Code: 3S

TITLE: "Review of A Population Pharmacokinetic Study of A 4 MG Chewable Tablet in Pediatric Patients 2 to 5 Years Old"

BACKGROUND:

Montelukast is a specific and potent leukotriene ($cysLT_1$) receptor antagonist. Merck's NDA 20-829 [Singulair 10 mg montelukast film-coated tablets (FCT) for adults and adolescents 15 years and older] and NDA 20-830 [Singulair 5 mg montelukast chewable tablets (CT) for children 6 to 14 years old] were reviewed by the Agency and approved on 02/20/98. It is indicated for the prophylaxis and chronic treatment of asthma. The dosing regimen for adults and adolescents 15 years and older is one FCT given in the evening and that for children 6 to 14 years old is one CT also given in the evening.

Prior to the approval of Singulair 5 mg CT, a protocol (No. 066) had been submitted by the sponsor that was filed under IND —— (Serial No. 055) on 12/20/96. It was for studying montelukast in younger children 2 to 5 years old with asthma using a lower strength CT, 4 mg. Protocol No. 066 was reviewed on 01/30/97 by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). The comment of OCPB/DPE II for minor modification of the blood sampling schedule was incorporated in the revised protocol prior to its initiation. Study No. 066 had been completed and the report was submitted previously under IND ——

SYNOPSIS:

On 05/06/99, Merck filed a supplement to NDA 20-830 (Serial No. SEI 008) seeking approval for Singulair (montelukast) 4 mg CT. It is indicated for the prophylaxis and chronic treatment of asthma in children 2 to 5 years old. Please see the updated package insert in Attachment 1 for details. Submitted under Human Pharmacokinetics/Bioavailability (PK/Bio) section of NDA 20-830 supplement was Study No. 066 only. No clinical efficacy trial was conducted except a clinical safety trial No. 072 (an updated interim analysis as of June, 1999). The to-be-marketed 4 mg CT that was used in the Study Nos. 066 and 072 is compositionally and proportionally the same as the currently approved 5 mg CT.

For PK study No. 066, since limited volume of blood could be collected in these pediatric patients 2-5 years old (n=15), a population pharmacokinetic (PPK) approach was used. There were two distinct sampling schedules with 4 fixed time points per patient proposed to cover the entire plasma profile (up to 24 hr) for montelukast 4 mg CT dose as shown below in **Table 1**:

Table 1. Proposed Two Distinct Sampling Schedules

Time (hr)	**0**	**1.5**	**2**	**4**	**8**	**12**	**24**
Schedule A (n=8 patients)	X[1]	X		X		X	
Schedule B (n=7 patients)	X[1]		X		X		X

[1]. The sampling time =0 is obtained at the prestudy visit and not immediately before dosing.

The PK model was constructed based on previous PK data obtained from adults and children 6-14 years old. The NONMEM (nonlinear mixed-effects model) approach (in S-Plus program) was used to analyze the sparse montelukast plasma data in children 2-5 years old.

The objective of Study No. 066 was to verify the predicted mean AUC in children 2 to 5 years old when extrapolated down from mean AUCs in **1)** adults and children 15 years and older receiving a 10 mg FCT dose and **2)** children 6 to 14 years old receiving a 5 mg CT dose. In addition, it was for justifying the dose selection of a 4 mg CT dose for the chronic asthma clinical safety trial in this population (Study No. 072).

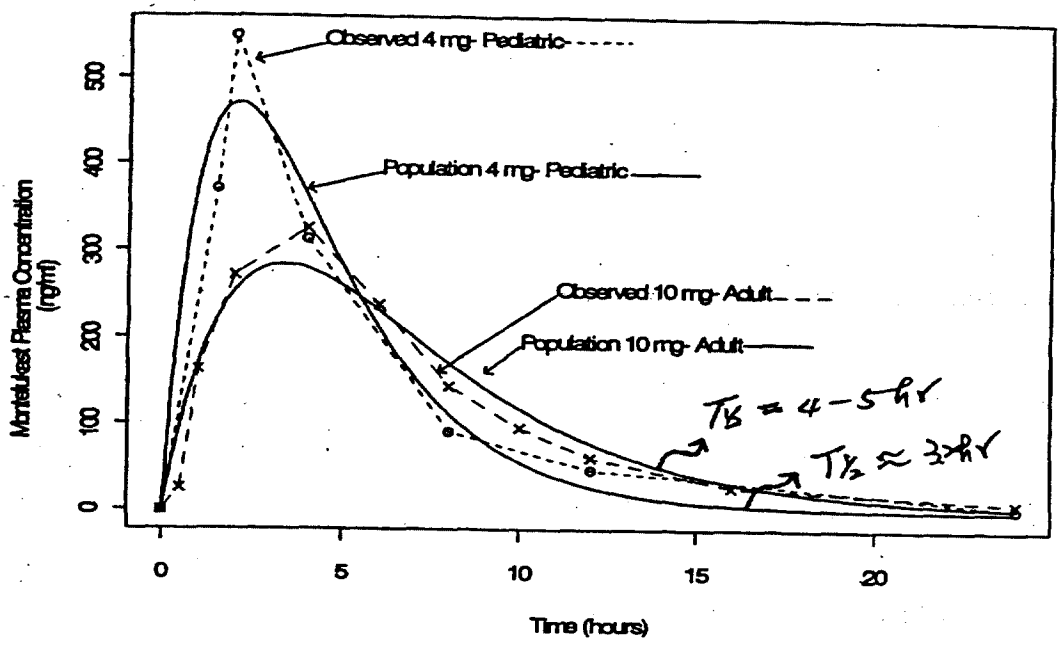
Results: The observed (mean) and predicted population plasma concentration profiles for montelukast 4 mg-CT in pediatrics 2-5 years old (Study No. 066) and the 10-mg FCT in adults (historical data, Study No. 034) are shown below in **Table 2** and **Figure 1**:

Table 2: Mean PK Parameters obtained from Study No. 066 as compared to Adult Historical Data (Study No. 034)

Parameter	**Study 034 (n=16 adults)**	**Study 066 (n=15 children)**
AUC(0-inf) (ng*hr/ml)	2595 ± 165[1]	2721 ± 164
Cmax (ng/ml)	284 ± 54	471 ± 65
Tmax (hrs)	3.4 ± 0.6	2.1 ± 0.3
$T_{½}$ (hrs)	4.09 ± 0.09	3.17 ± 0.20

[1]mean ± standard error (SE)

Figure 1: Observed (Mean) and Population Plasma Predicted Concentration Profiles for Montelukast 4 mg CT (No. 066) and 10 mg FCT (Historical Data; No. 034)



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The PPK analysis was consulted to and reviewed by Pharmacometrics group in the OCPB/DPE II in order to determine the appropriateness of Merck's PPK model analysis. The above PK data were reanalyzed independently by Dr. Fossler. It was concluded that the sponsor's PPK analysis is appropriate therefore, it is acceptable. Please see the consult review by Dr. Mike Fossler (plus individually fit PK profiles) in Attachment 2 for details.

The mean PK data obtained from Study No. 066 are consistent with the previous PK data obtained from children 6-14 years receiving a 5 mg CT dose (Study No. 039; **Table 3**).

Table 3: Mean PK parameters Obtained from Study No. 039

Treatment	N	$AUC_{0-\infty}$ (ng-hr/ml)	C_{max} (ng/ml)	T_{max} (hr)	$T_{1/2}$ (hr)
5-mg CT	19	2928[a] ± 904	495 ± 129	2.0 ± 1.3	3.7 ± 0.8

[a] Mean ± SD.

Mean plasma profiles obtained from the above Study No. 039 and those from adults receiving a 10 mg FCT dose (historical data, Study No. 034) are also shown below in **Figure 2** for comparison.

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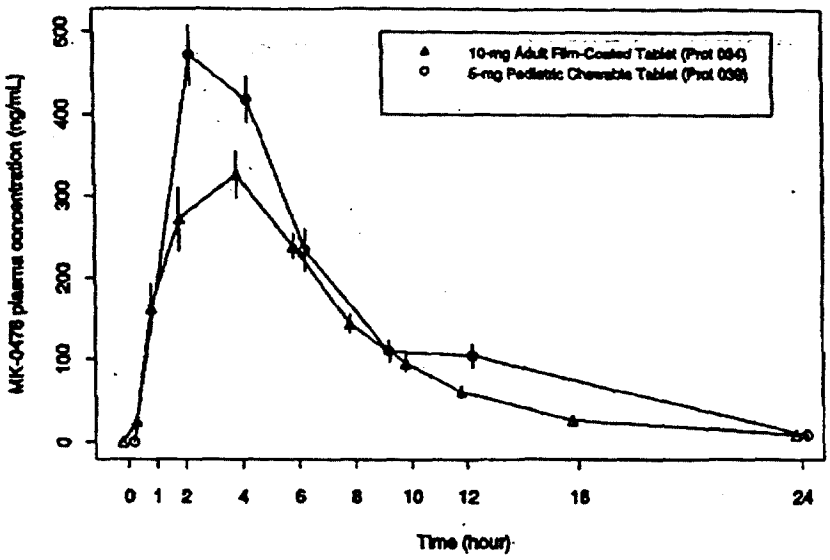
Figure 2: Mean Plasma Concentration Profiles for Montelukast 5 mg-CT in Pediatrics 6-14 Years Old (No. 039) and the 10-mg FCT in Adults (Historical Data; No. 034)



For the 10 mg FCT and 5 mg CT, the following dissolution method and specification were recommended previously:

900 ml of 0.5% sodium dodecyl sulfate (SDS) in water at 37°C
USP Apparatus 2 (Paddle) with 50 rpm
Specification: Q=————min

Submitted to the NDA supplement were dissolution data for three 4 mg CT stability batches (Nos. EXP9701, EXP9702, and EXP9703) that were manufactured at the commercial site, Wilson, NC. The mean % values of montelukast dissolved at 20 min (n=12) were 96, 101, and 97%, respectively. However, for the biobatch (No. MR-3393) that was manufactured at Merck's Frosst site in Canada and used in both the pivotal PK study (No. 066) and the clinical safety trial (No. 072), only mean dissolution data (at 10, 20, and 30 min) were provided. Upon request, additional dissolution data (6 individuals and mean ± standard deviation, SD) for batch No. MR-3393 were provided and reviewed. Also, in order to link the biobatch to the currently marketed 5 mg CT that is manufactured at the commercial site, Wilson, NC, the dissolution data of the currently marketed 5 mg CT was requested for comparison. The requested information was submitted on 01/28/2000 (Serial No. BC) for review. The results of dissolution comparison using the above dissolution methodology are shown below:

Table 4. Dissolution Data for the new 4 mg CT (biobatch from Frosst, Canada)

Biobatch No. MR-3393	% montelukast released		
	10 min	20 min	30 min
1			
2			
3			
4			
5			
6			
Mean ± SD	88.2 ± 4.4	99.7 ± 3.4	99.8 ± 3.3

Table 5. Dissolution Data for the currently marketed 5 mg CT (validation batch from the commercial site, Wilson, NC)

Validation batch No. 903541	% montelukast released		
	10 min	20 min	30 min
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Mean ± SD	92.5 ± 4.1	101.6 ± 2.2	102.8 ± 2.7

The above dissolution data are comparable between the 4 mg and 5 mg CT tablet batches. Finally, the HPLC assay method for montelukast in plasma used in Study No. 066 is the same as that used previously in the original NDA. The assay results for Study No. 066 had been submitted previously on 11/18/98 under IND —— (Serial No. 114). The summary of assay results are provided below:

I. Standard Curve: —— pg/ml (n=9)
Precision:
Intraday: CV% of ——
Interday: CV% of ——
Recovery: ——

II. QC: at —— pg/ml (n=2)
Precision:
Intraday: CV% of ——
Interday: CV% of ——
Recovery: ——

RECOMMENDATION:

Merck's NDA supplement that was submitted on 05/06/99 to NDA 20-830 (Serial No. SEI 008) for studying a 4 mg CT dose in children 2 to 5 years old, HPLC assay method submitted under IND —— (Serial No. 114) on 11/28/98, and additional dissolution information submitted on 01/28/2000 (Serial No. BC) have been reviewed by OCPB/DPE II. OCPB/DPE II is of the opinion that this NDA 20-830 pediatric supplement is acceptable. The following LABELING comment needs to be conveyed to the sponsor.

COMMENT TO MEDICAL OFFICER: (Need NOT be sent to the sponsor)

Children receiving a 4-mg CT had a similar systemic exposure (extent of absorption in terms of AUC) as compared to historical data for adults receiving a 10 mg FCT. However, when the mean C_{max} and T_{max} values are compared, children had a faster rate of appearance of montelukast plasma levels in the systemic circulation, i.e., a higher mean C_{max} and a smaller mean T_{max} (as presented in **Tables 2 and 3**).

The above differences may be expected since **1)** the CT was chewed before entering into the GI tract for further dissolution and/or absorption and **2)** children have smaller volume of distribution and a faster rate of elimination (shorter mean terminal $T_{1/2}$). The above data are consistent with the previous PK comparison between children 6-14 years old receiving a 5 mg CT dose and adults receiving a 10 mg FCT dose.

Since a flat dose-response relationship was previously observed in adult patients receiving montelukast FCT (10 mg dose QD up to 200 mg dose QD), it is unlikely that higher C_{max} values observed in children receiving 4 mg CT will affect the efficacy profiles of this drug. Also. the mean peak levels of montelukast in children 2-5 and 6-14 years old given proposed and labeled

dosed of montelukast are similar. Since montelukast at the labeled dose is considered safe in 6-14 year old children, the resultant higher mean peak level in 2-5 year old children compared to adults may not be a safety concern. However, it is still recommended that medical officer evaluate the safety data for children 2-5 years old receiving a 4 mg CT dose in light of higher C_{max} values observed compared to adults. If the safety profiles for children receiving a 4 mg CT dose are similar to **1)** adults receiving a 10 mg FCT dose and **2)** children 6-14 years old receiving a 5 mg CT dose, a higher mean C_{max} may be less of a safety concern.

LABELING COMMENTS: (Need to be sent to the sponsor)

The following is the FDA version of the **1)** Pharmacokinetics subsection under Clinical Pharmacology section and **2)** for Pediatric Use subsection under Precautions section.

1. Pharmacokinetics subsection under Clinical Pharmacology section:

Pharmacokinetics

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (C_{max}) is achieved in 3 to 4 hours (T_{max}). The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal in the morning.

For the 5-mg chewable tablet, the mean C_{max} is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

For the 4-mg chewable tablet, the mean C_{max} is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.

The safety and efficacy of SINGULAIR were demonstrated in clinical trials in which the 10-mg and 5-mg formulations were administered in the evening without regard to the timing of food ingestion.

The comparative pharmacokinetics of montelukast when administered as two 5-mg chewable tablets versus one 10-mg film-coated tablet have not been evaluated.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

Metabolism

Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.

In vitro studies using human liver microsomes indicate that cytochromes P450 3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of cytochromes P450 3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. Based on further *in*

vitro results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6 (see *Drug Interactions*).

Elimination

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Special Populations

Gender: The pharmacokinetics of montelukast are similar in males and females.

Elderly: The pharmacokinetic profile and the oral bioavailability of a single 10-mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency: Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI=7%, 85%) higher mean montelukast area under the plasma concentration curve (AUC) following a single 10-mg dose. The elimination of montelukast was slightly prolonged compared with that in healthy subjects (mean half-life, 7.4 hours). No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of SINGULAIR in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

Renal Insufficiency: Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Adolescents and Pediatric Patients: The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents ≥15 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients ≥15 years of age.

Pharmacokinetic studies show that the mean systemic exposure (in terms of AUC) of the 5-mg chewable tablet in pediatric patients 6 to 14 years of age is similar to that of the 10-mg film-coated tablet in adults. In a pharmacokinetic study in pediatric patients 2 to 5 years of age, the mean systemic exposure (AUC) of the 4-mg chewable tablet is also similar to that of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age and the 4-mg chewable tablet should be used in pediatric patients 2 to 5 years of age.

Drug Interactions

Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state:

- did not cause clinically significant changes in the kinetics of a single intravenous dose of theophylline (predominantly a cytochrome P450 1A2 substrate).
- did not change the pharmacokinetic profile of warfarin (a substrate of cytochromes P450 2A6 and 2C9) or influence the effect of a single 30-mg oral dose of warfarin on prothrombin time or the INR (International Normalized Ratio).

• did not change the pharmacokinetic profile or urinary excretion of immunoreactive digoxin.
• did not change the plasma concentration profile of terfenadine (a substrate of cytochrome P450 3A4) or fexofenadine, its carboxylated metabolite, and did not prolong the QTc interval following co-administration with terfenadine 60 mg twice daily.
Montelukast at doses of 100 mg daily dosed to pharmacokinetic steady state:
• did not significantly alter the plasma concentrations of either component of an oral contraceptive containing norethindrone 1 mg/ethinyl estradiol 35 mcg.
• did not cause any clinically significant change in plasma profiles of prednisone or prednisolone following administration of either oral prednisone or intravenous prednisolone.
Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for SINGULAIR is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.

2. Under Pediatric Use subsection of Precautions section:

Pediatric Use

Safety and efficacy of SINGULAIR have been established in adequate and well-controlled studies in pediatric patients 6 to 14 years of age. Safety and efficacy profiles in this age group are similar to those seen in adults. (See *Clinical Studies* and ADVERSE REACTIONS.) The safety of SINGULAIR 4-mg chewable tablets in pediatric patients 2 to 5 years of age has been demonstrated in an interim analysis of 314 pediatric patients in a 12-week double-blind, placebo-controlled study in approximately 650 patients (see ADVERSE REACTIONS). Efficacy of SINGULAIR in this age group is extrapolated from the demonstrated efficacy in adults 15 years of age and older and pediatric patients 6 to 14 years of age with asthma based on similar mean systemic exposure (AUC), and that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.

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/S/ 02/17/2000

02/01/2000
Tien-Mien Chen, Ph.D.
Division of Pharmaceutical Evaluation II

RD initialed by Ramana Uppoor, Ph.D. RU 02/01/2000

FT initialed by Ramana Uppoor, Ph.D. /S/ 02/18/2000

cc: NDA 20-830, HFD-570 (Gilbert-McClain, Hilfiker), HFD-870 (S.M. Huang, R. Uppoor, T.M. Chen), CDR (B. Murphy).

NDA 20-830 Pediatric Supplement
(Serial No. SEI-008)

Singulair 4 mg Chewable Tablets for Children 2 to 5 Years Old

ATTACHMENT 1

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SPONSOR'S PROPOSED PACKAGE INSERT

WITHHOLD 13 PAGES

Draft

Labeling

NDA 20-830 Pediatric Supplement
(Serial No. SEI-008)

Singulair 4 mg Chewable Tablets for Children 2 to 5 Years Old

ATTACHMENT 2

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DR. MICHAEL FOSSLER'S CONSULT REVIEW

Pharmacometrics Consult Review

~~NDA:~~	~~20-830~~
Montelukast 4 mg Chewable Tablets (Singulair®)	
Original Submission Date:	6 May 1999
Sponsor:	Merck
Type of Submission	Pediatric Supplement
Received by Pharmacometrics:	15 July 1999
Primary Reviewer:	Albert Chen
Medical Division:	HFD-570 (Pulmonary)
Pharmacometrics Scientist:	Michael J. Fossler

Submission

The submission dated 5/6/99 is a pediatric supplement for montelukast, a leukotriene antagonist proposed for the chronic treatment of asthma in children 2-5 years of age. Montelukast was previously approved in adults and children aged 6-14 on 2/20/98. Pharmacometrics was asked to assess the appropriateness of the study and the dosing recommendations based on the data.

Study Design

PROTOCOL TITLE/NO.: An Open, 1-Period, Single-Dose, Multicenter Study to Evaluate the Safety, Tolerability, and AUC $_{pop}$ (AUC Determined by a Non-Linear Mixed-Effect Model) of Montelukast Administered as a Chewable Formulation in 2- to 5-Year-Old Children With Asthma

INVESTIGATORS/STUDY CENTERS: One U.S. study center; 2 non-U.S. study centers

PRIMARY THERAPY PERIOD: 21MAR97 to 25APR97. In-house case report forms cutoff date was 15MAY97. The study is completed.
CLINICAL PHASE: —

DURATION OF TREATMENT: Single administration on Study Day 1; Poststudy Visit on Study Days 3 to 4.

OBJECTIVES:

1) To evaluate the safety and tolerability of a single 4-mg dose of montelukast (4-mg chewable tablet) in 2- to 5-year-old patients with asthma.

2) To evaluate the AUC $_{pop}$ of montelukast in 2- to 5-year-old patients with asthma.

3) To compare the AUC $_{pop}$ of montelukast in 2- to 5-year-old patients with historical adult data analyzed similarly (Protocol 034).

STUDY DESIGN: This was an open, 1-period, multicenter study (4 to 7 patients/center, 3 centers) to evaluate the safety, tolerability, and population area under the plasma concentration versus time curve (AUC$_{pop}$) of a single oral dose of 4 mg montelukast (chewable tablet [CT]) in 2- to 5-year-old patients with asthma. Since the volume of blood that could be collected in 2- to 5-year-old patients was limited, a population pharmacokinetic approach was used to estimate the pharmacokinetic parameters of interest.
To increase the number of time points available for analysis, there were 2 distinct plasma sampling schedules with 4 samples (3 mL each) for each schedule. Patients were randomly

assigned to 1 of the 2 sampling schedules according to their allocation number. Those assigned to Schedule A had samples drawn at 0, 1.5, 4, and 12 hours post-dose. Those assigned to Schedule B had samples drawn at 0, 2, 8, and 24 hours post-dose. The AUC_{pop} of montelukast was estimated using a 1-compartment pharmacokinetic model and compared with historical adult 10-mg (film-coated tablet [FCT]) data analyzed using the same model (Protocol 034).

DOSAGE/FORMULATION NOS.: Single oral administration of one 4-mg chewable tablet

DIAGNOSIS/INCLUSION CRITERIA: Two- to 5-year-old children with a history of physician diagnosed asthma. A total of 15 subjects (7 boys, 8 girls) aged 2-5 were enrolled in the study.

EVALUATION CRITERIA: Pharmacokinetic parameters (AUC_{pop}, peak plasma concentration [C_{max}], time to C_{max} (T_{max}), and half-life were estimated using 2 pharmacokinetic models. The AUC_{pop} in 2- to 5-year-olds was compared with the AUC_{pop} of historical adult data (10-mg film-coated tablet, Protocol 034). Safety and tolerability were evaluated by assessment of adverse experiences and laboratory data.

Analysis Methods

The resulting data were fit to the following model[1].

$$C(t) = \frac{e^{\phi_2} e^{\phi_3}}{e^{\phi_1}(e^{\phi_2} - e^{\phi_3})}(e^{(-\phi_3 * t)} - e^{(-\phi_2 * t)}) + \varepsilon$$

where:

c(t) is the montelukast plasma concentration at time t,

ϕ_1 is the negative log AUC, from time 0 to infinity

ϕ_2 is the log absorption rate constant,

ϕ_3 is the log elimination rate constant,

e is the exponential function,

ε is the error term in measuring the concentration at time t [c(t)] and is assumed to have a normal distribution with a mean value of 0 and a variance σ^2.

The absorption rate constant was fixed in the firm's analysis, since there were insufficient points in the absorption phase to estimate its value adequately. The population ϕ_1, ϕ_2, and ϕ_3, as well as the subject-specific ϕ_1 and ϕ_3, were estimated using the non-linear mixed-effect function (nlme) in S-Plus (statistical software from MATH Soft Inc., Version 3.4).

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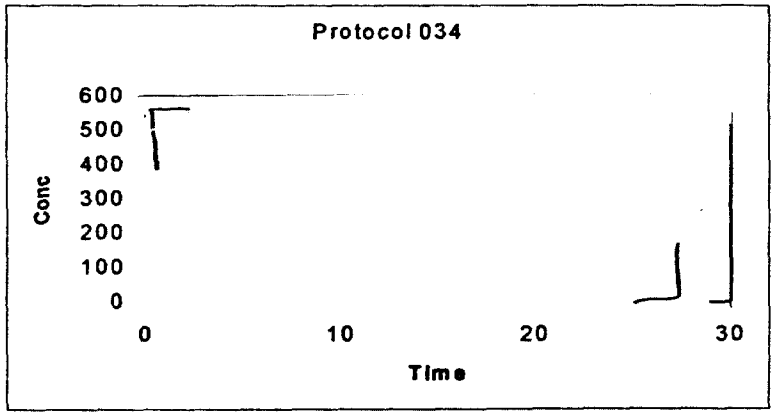
[1] This is the familiar 1 compartment model with first-order absorption; the term $e^{\phi 1}$ is equal to 1/AUC or kel*V/dose. The kel's cancel out, leaving the more familiar form.

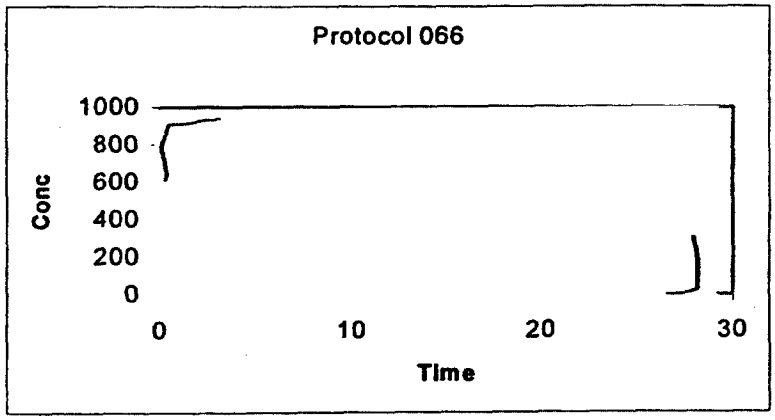
The model was externally validated by simulating AUC values after a 10 mg and 5 mg dose and comparing these values to actual data from two studies, one in adults using the 10 mg dose (Protocol 034) and one using the 5 mg dose in children aged 6-8 (Protocol 039).

Reviewer's Analysis

Although the reviewer feels that the approach taken by the firm is basically sound, there is an indication of significant lag-time occuring in both the adult and pediatric data (Figure 1). The firm did not take this into account in their model, and it is unclear to what extent this would affect the PK estimates, particularly Cmax and tmax. Therefore, the reviewer combined the data from Protocols 066 and 034 (adult data) and fit these data to a one compartment model with first-order absorption both with and without lag-time using NONMEM version V. The only covariate tested was PED, which equaled 1 if the data were from a child, and 0 if from an adult. This categorical classification was considered adequate since one would not expect that there would be much overlap between the two populations with regard to weight or other estimates of body size. In fact for the adults, the range studied was 57-98 kg, while for the children it was 12 – 21 kg. The age range for the adults was 18-27, while the range in the pediatric study was 2-5.

Figure 1: Individual concentration vs. time data from Protocol 034 (adults) and 066 (children). Both curves have a parabolic shape in the absorption phase, suggesting the presence of a lag-time.





The model-building procedure followed by the reviewer is as follows: A base model (without co-variates and without lag-time) was fit to the data. Lag-time was then added to the model to see if the fit was significantly improved. Finally, the covariate PED was added to CL/F and V/F in the following manner:

```
TVCL=THETA(2)*PED + THETA(7)*(1-PED)

TVV=THETA(3)*PED + THETA(8)*(1-PED)
```

Essentially, this fits a separate typical value of CL/F and V/F for each population (adults and children). The improvement in fit is then tested for significance in the usual way ($\chi^2 > 3.86$, α=0.05).

The final model was externally validated by the reviewer by simulating data from a single 5 mg dose of montelukast and comparing the results to the data in Protocol 039, which was a PK study in 19 children aged 6-8 given a single 5 mg dose of montelukast.

Results

Figure 2 shows the observed vs. predicted plot from the base model (without lag-time or PED). Figure 3 shows the individual residual parameter plots for CL/F and V/F plotted as a function of PED. From these plots it appears obvious that some accounting for body size is needed.

Table 1 shows a summary of the model-building process. The addition of lag-time to the model significantly improved the fit as anticipated, with a drop in the objective function of 66 points. The addition of PED to both CL/F and V/F was also warrented, as the fit significantly improved when this covariate was added.

Figure 2: Observed vs. predicted plot for base model. The solid line the the unit function (y=x).

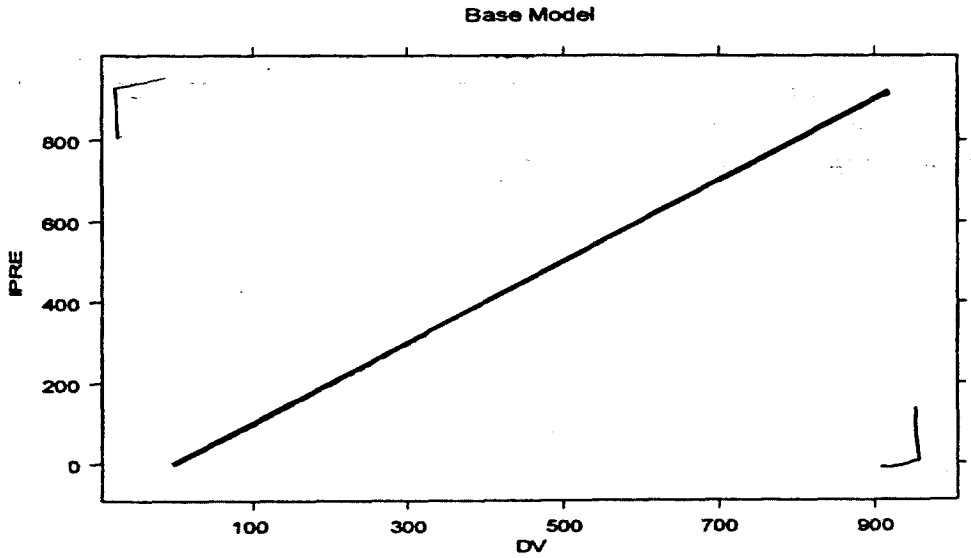


Figure 3: Residual CL/F and V/F plots as a function of PED for the base model, where 1=child and 0=adult.

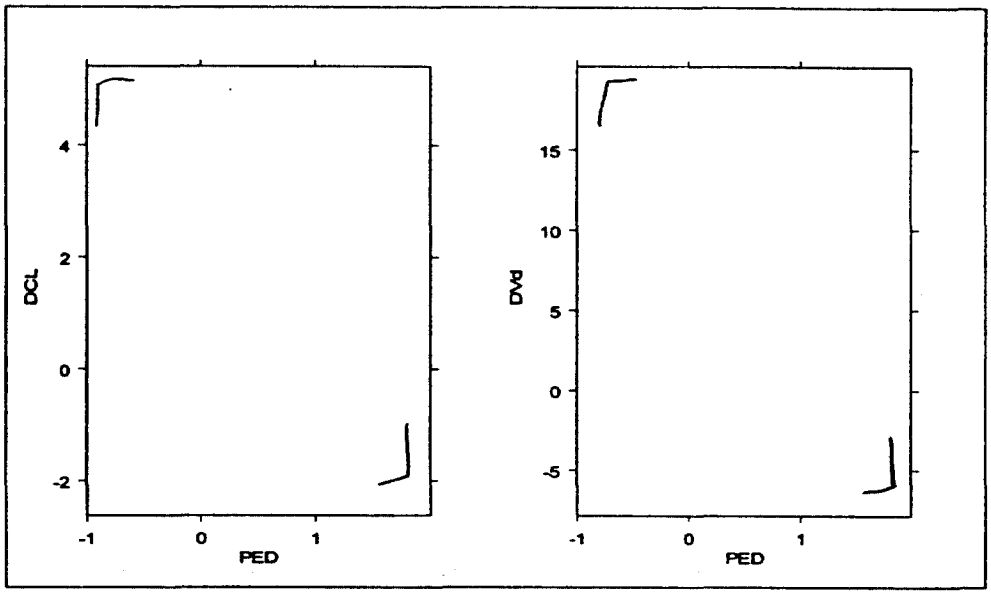


Table 1: Summary of NONMEM fitting procedure by reviewer.

Model	OF	Δ from previous model	Significantly improved over previous model
Base Model	1757	–	na
Base Model + lag time	1691	66	$p < 0.001$
Add PED to CL/F	1670	21	$p < 0.001$
Add PED to V/F	1599	71	$p < 0.001$

$\chi^2 = 3.84$, $\alpha = 0.05$

Figure 4 shows the observed vs. predicted fit for the final model. The individual observed vs. predicted plots are shown in the Appendix. For the most part, the fits are very good. Figure 5 depicts the results of a validation step in which pediatric data not used in the analysis (Protocol 039) were simulated using the model developed by the reviewer. These simulated data were compared to the actual data and are shown in Figure 5. The overall agreement is quite good.

Using these predicted values, estimates of AUC, Cmax and tmax were calculated, and compared with the adult data. This comparison is shown in Table 2. Overall, the results support the firm's conclusion that a 4 mg dose of montelukast in children give equivalent exposure as a 10 mg dose in adults. The slightly higher peak and shorter tmax in children as compared with adults is most likely due to formulation differences; the 4 mg tablet is a chewable formulation which might be expected to be absorbed faster than a conventional IR tablet.

Figure 4: Observed vs. predicted for the final model.

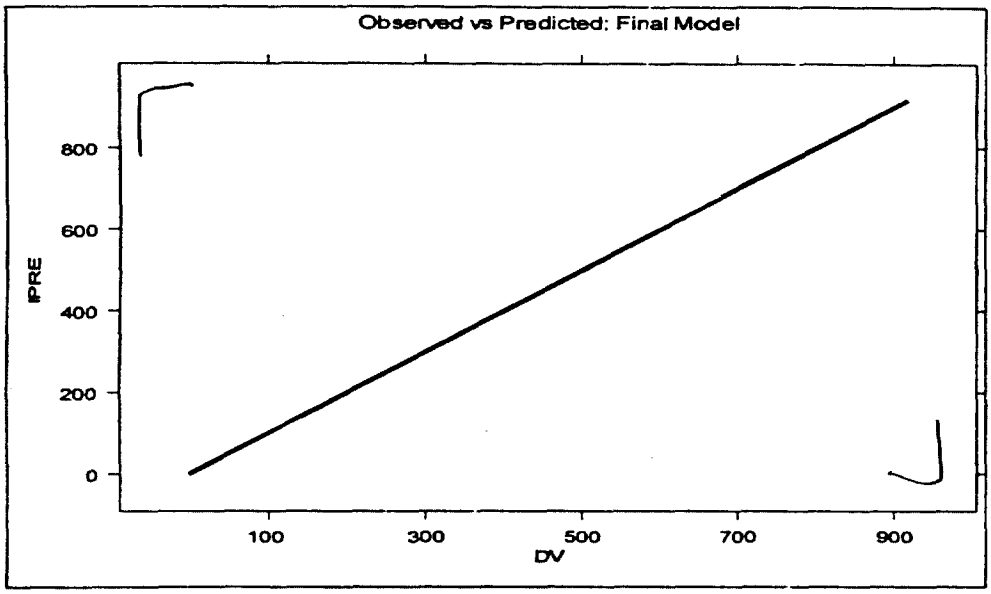


Figure 5: Results of simulating Study 039 using the reviewer-developed PK model and the comparison with the observed data. There is excellent agreement between the two.

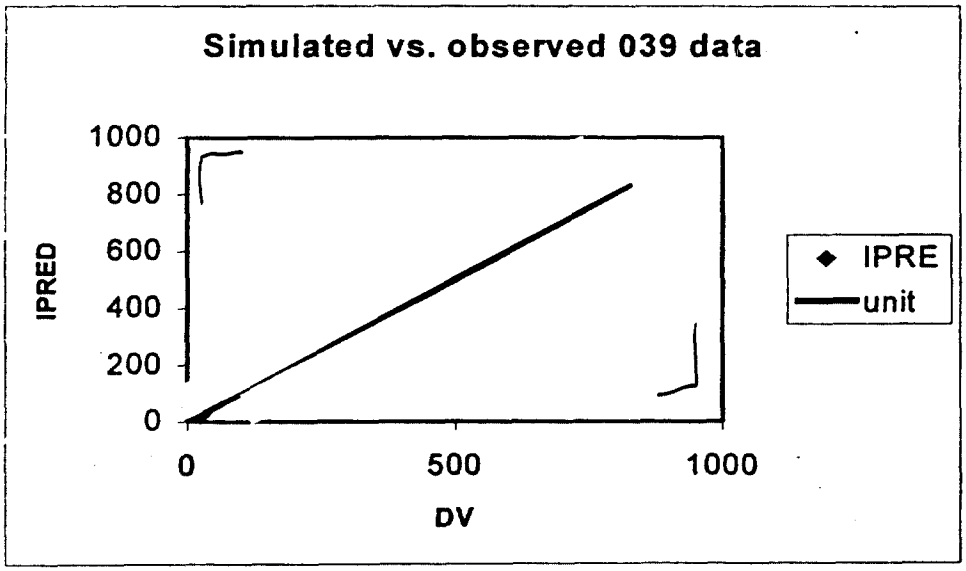


Table 2: Comparison of the PK of montelukast in adults given a single 10 mg dose with children aged 2-5 given a single 4 mg dose.

/S/

Parameter	Study 034 (n=15 adults)	Study 066 (n=15 children)
AUC(0-inf) (ng*hr/ml)	2592 ± 723	2669 ± 649
Cmax (ng/ml)	352 ± 102	480 ± 151
†tmax (hrs)	4.0	2.0
$t_{1/2}$ (hrs)	3.13 ± 0.25	2.4 ± 0.88

†median (range)

Reviewer Conclusions

- The firm has done a nice job of dose selection for the age group under study. Particularly good use was made of prior information in adults and older children. Lag-time should have been considered in the firm's original analysis.

- The data fully support the firm's conclusion that 4 mg of montelukast gives equivalent exposure in children aged 2-5 and 10 mg in adults and 5 mg in children 6-12.

/S/ 10/19/99

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