CLINICAL PHARMACOLOGY REVIEW

NDA:	22-064, S017 (pediatric supplement)
Brand Name:	Xyzal®
Generic Name:	levocetirizine dihydrochloride
Indication:	Seasonal allergic rhinitis for children 2 to <6 years of age and perennial allergic rhinitis and chronic idiopathic urticaria for children 6 months to <6 yrs of age.
Formulation:	Oral solution
Strength:	5 mg/mL (proposed) 0.5 mg/mL (already marketed)
Proposed Dosing:	6 months to <1 year: 1.25 mg QD 2 to <6 years: 1.25 mg BID
Applicant:	UCB Inc.
OCP Division:	Clinical Pharmacology 2
Clinical Division:	Pulmonary and Allergy Products (OND-570)
Submission Date:	February 24, 2009
Reviewer:	Partha Roy, Ph.D.
Team Leader (Acting):	Sally Choe, Ph.D.
PM Reviewers:	Partha Roy, Ph.D. / Yaning Wang, Ph.D.
PM Team Leader:	Yaning Wang, Ph.D.

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1 Executive Summary

1.1 Background

Xyzal® (levocetirizine dihydrochloride, LCTZ), a histamine type-1 receptor antagonist, is currently approved in the U.S. for use in adults and children 6 years of age and older for the relief of symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria (CIU). Two dosage forms have been approved to date: the 5 mg tablets (NDA 22-064), and the 0.5 mg/mL oral solution (NDA 22-157). The present submission is intended to fulfill the PREA post-marketing commitments as well as the terms of the pediatric exclusivity Written Request issued on February 3, 2009. A 10-fold higher concentrated oral solution (5 mg/mL) designated as "oral drops" was developed to provide an additional liquid dosage form (b) (4)

The clinical program primarily consists of two adequate, well-controlled pediatric Xyzal safety trials (A00423 and A00426) in children below 6 years of age with SAR, PAR or CIU, and a population pharmacokinetics (Pop PK) data analyses. A00423 was conducted in infants 6 months to <12 months of age at a dose of 1.25 mg QD. A00426 was conducted in children 1 to <6 years of age at a dose of 1.25 mg BID (2.5 mg/day). The dose regimens studied in A00423 and A00426 were chosen based on the results of population pharmacokinetics data analysis A00422. An additional supplemental population PK analysis, A00422a, incorporated data from A00423 and A00426 to the database for study A00422. This supplemental Pop PK analysis was performed to further confirm the appropriateness of the dose regimens chosen for trials A00423 and A00426 and ultimately the final dosing recommendation in the product label. The dose regimens studied in A00423 and A00426 are the doses proposed for the pediatric population in the draft package insert labeling included in this submission. Xyzal efficacy in SAR, PAR and CIU has not been studied in children below 6 years of age, and is therefore supported by extrapolation of the efficacy demonstrated in the adult and adolescent population (NDA 22-064) using the PK data.

The oral drops formulation was used in both the pivotal clinical studies A00423 and A00426 as well as in a number of supporting clinical trials in the pediatric population ages 1 to <6 years, which formed the basis of the population PK analysis.

1.2 Recommendation

The Office of Clinical Pharmacology /Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 22-064 S017 submitted on February 24, 2009 and finds it acceptable provided that a mutually satisfactory agreement can be reached between the sponsor and the agency regarding the language in the package insert.

1.3 Summary of Clinical Pharmacology Findings

1.3.1 Age-appropriate pediatric formulation

The 0.5 mg/mL oral solution and the 5 mg/mL "oral drops" formulations of LCTZ were developed to allow flexible dosing for patients who may have difficulty swallowing solid oral dosage forms. According to the sponsor, both the liquid formulations are especially appropriate for administration to young children (<6 years of age).

(b) (4)

Bioequivalence was demonstrated between the LCTZ oral solution and oral tablet formulations in Study A00318, submitted under NDA 22-157. The clinical pharmacology reviewer concluded that the two LCTZ formulations (oral solution and oral tablet) are bioequivalent (see Dr. Partha Roy's Clinical Pharmacology NDA review dated 10/17/2007 under NDA 22-157).

There are no clinical trials submitted under any Xyzal-related NDAs that attempt to demonstrate BE between the two oral liquid formulations. The two oral liquid formulations (0.5 mg/mL and 5 mg/mL) are independently BE (b) (4) . Although the two liquid formulations differ in the active drug strength as well as type and amount of excipients, it is concluded that no BE study is required between the two formulations to accept the oral solution (0.5 mg/mL) as a viable alternative formulation in young pediatric population (i.e. <6 years of age). This is based on the following:

1. These two formulations are simple solutions and hence release of the drug substance from the solution is self-evident and that the solutions do not contain any excipient that significantly affects drug absorption.
2. These two oral liquid formulations are independently bioequivalent to the approved oral tablet formulation. Refer to Dr. Tien-Mien Chen's review dated 5/11/2009 under NDA 22-157 for additional details.
3. The pediatric clinical program is based on achieving comparable exposure between adults and children without the requirement for establishing BE.

1.3.2 Pediatric Dosing Recommendation

A population PK approach was utilized to characterize the pharmacokinetics of levocetirizine in the pediatric population and to provide dosing recommendations for subjects 6 months to <6 years of age. Study A00422, a retrospective population

pharmacokinetic analysis of levocetirizine from 9 studies in children and adults, was conducted using NONMEM at the recommendation of the FDA (see pre-NDA meeting minutes, 24 Jan 2007). After receiving the Written Request (03 Feb 2009), a supplemental population PK analysis, Study A00422a was conducted incorporating PK data from the pivotal trials A00423 and A00426 to the database employed in A00422 in order to confirm whether the model utilized in Study A00422 was adequate to provide dosing recommendations in children 6 months to <6 years of age. The model was then used to carry out Monte Carlo simulations of different dose regimens in children ages 6 months to <6 years. Levocetirizine concentrations were then predicted and summarized by computing the median and 5^{th}-95^{th} percentile values of concentrations, C_{max} and C_{min} per age category. The predictions were then compared with LCTZ concentrations simulated in adults following repeated administration of the recommended dose of 5 mg once daily.

Simulation in 6 to <12 month-old children:

For children 6 to <12 months of age, two dosing regimens were compared: once daily 1.25 mg and twice daily 1.25 mg (2.5 mg/day). As shown in Table 1, the median Cmax and Cmin values of a 1.25 mg once daily administration remained within the range (90% confidence interval) of concentrations in adults following once daily 5 mg dose (Cmax: 199 to 462 ng/mL and Cmin: 4 to 64 ng/mL).

In contrast, the median Cmax following 1.25 mg b.i.d. exceeded the adult range for the youngest children from 6 to <9 months old while the median Cmin values far exceeded the upper bound of the adult range for all sub-groups within the broad age-range of 6 to<12 months (i.e. 6-<7, 7-<8, 8-<9, and so on). Therefore the data strongly suggest that 1.25 mg once daily dosing regimen is more appropriate for 6 to <12 months old children.

Table 1. Predicted levocetirizine C_{max} and C_{min} values following administration of 1.25 mg LCTZ once daily (QD) and twice daily (BID) in 6- to <12-month-old infants

Age (months)	**Median Cmax (**5^{th}-95^{th} percentile**) (ng/mL)**		**Median Cmin (**5^{th}-95^{th} percentile**) (ng/mL)**	
	QD	**BID**	**QD**	**BID**
6 to <7	394 (261 – 584)	516 (347 – 758)	15 (2 – 59)	81 (20 – 219)
7 to <8	375 (254 – 568)	497 (334 – 735)	15 (2 – 57)	76 (19 – 205)
8 to <9	364 (246 – 547)	472 (317 – 689)	14 (2 – 59)	74 (18 – 199)
9 to <10	351 (236 – 529)	456 (311 – 677)	14 (2 – 57)	71 (18 – 191)
10 to <11	341 (227 – 511)	443 (299 – 659)	13 (2 – 54)	71 (18 – 186)
11 to <12	332 (224 – 498)	433 (295 – 646)	13 (2 – 52)	68 (18 – 180)

Simulation in 1 to <6 years-old children:

For children 1 to <6 years of age, three dosing regimens were compared: once daily 1.25 mg, twice daily 1.25 mg (2.5 mg/day) and once daily 2.5 mg. Since the median Cmax in children for 2.5 mg once daily was found to exceed the range of Cmax concentrations in adults (199 to 462 ng/mL), this dosing regimen was dropped from consideration. As shown in Table 2, for 1.25 mg twice daily administration, the 95th percentile of the Cmax values in children 1 to 3 years of age exceeded the range of Cmax concentrations in adults. The median Cmin values in children after twice daily dosing were shown to be more than 2-fold greater compared to median Cmin estimate in adults. Additionally, the 95th percentile of the Cmin values in all children ages 1 to <6 years exceeded the Cmin range in adults (4 to 64 ng/mL).

In contrast, for 1.25 mg once daily administration, 95th percentile for both Cmax and Cmin values in children did not exceed the corresponding 95th percentile of the adult range. Although the 5th percentile of the pediatric range dropped below that of the adult range for Cmin in all numerical ages within the age-range of 1 to <6 years (i.e. 1-<2, 2-<3, 3-<4 and so on), still this reviewer considered once daily dosing regimen to be the safer alternative compared to 1.25 mg twice daily regimen (2.5 mg daily dose), particularly when it is known that even half the marketed dose in adults, i.e. 2.5 mg once daily was considered efficacious per the approved Xyzal label for most patients.

Table 2. Predicted levocetirizine C_{max} and C_{min} values following administration of 1.25 mg LCTZ once daily (QD) and twice daily (BID) in 1- to <6-year-old children

Age (years)	**Median Cmax (**5th-95th percentile**) (ng/mL)**		**Median Cmin (**5th-95th percentile**) (ng/mL)**	
	QD	**BID**	**QD**	**BID**
1 to <2	299 (201 – 449)	375 (250 – 562)	12 (2 – 48)	63 (16 - 165)
2 to <3	264 (178 – 396)	324 (214 – 486)	11 (2 – 44)	56 (15 – 146)
3 to <4	240 (160 – 363)	294 (197 – 444)	11 (2 – 39)	51 (13 – 136)
4 to <5	218 (145 – 328)	267 (177 – 405)	10 (2 – 36)	48 (13 - 124)
5 to <6	199 (130 – 302)	245 (160 – 371)	9 (2 – 34)	44 (12 – 115)

This reviewer considered the sponsor's original labeling recommendation and has the following comments in justifying the once daily dosing recommendation:

1. Clearly, the median Cmin estimates in 2 to <6 years of age following 1.25 mg BID were substantially higher (2-3 fold) than the median Cmin value in adults following 5 mg QD. The sponsor likely focused on the higher Cmax value rather than the total exposure (including both Cmax and Cmin) as the benchmark for safety, which this reviewer does not agree. The primary concern for this drug is

somnolence, which may be related to extent of exposure and not only on Cmax. Therefore, the importance of keeping Cmin within the adult range can not be overlooked with respect to safety.

2. It is acknowledged that most subjects will have trough concentrations as low as half of that seen in adults dosed 5 mg once daily. However, it is reported in the adult clinical program (reference: Xyzal label) that 2.5 mg dose works equally well as the 5 mg dose for the PAR indication and also works for most patients for the SAR indication even though 5 mg provides numerically better efficacy for SAR indication.
3. Based on a pharmacokinetic study in children 6 to 11 years reported in the literature (Simons FER and Simons KJ: J Allergy Clin Immunol 2005; 116:355-61), LCTZ was shown to provide significant peripheral antihistaminic activity from 1 to 28 hours after a single dose. The PD effect (suppression of wheal and flare) initially lags behind plasma levocetirizine concentration but prolongs well past the time of rapidly declining plasma concentration, which is consistent with the counter-clockwise hysteresis loop found in adults for inhibition of histamine-induced wheal (refer to Dr. Partha Roy's Clinical Pharmacology Review dated 3/27/2007 in NDA 22064 for additional details). Therefore, it is concluded that the PD effect of the drug would be maintained for the entire 24-hour dosing interval even if there is a drop in systemic exposure towards the end of the dosing regimen for most of the subjects.

In conclusion, the dose recommendations proposed in this submission are a fixed dose related to age, with a dose of 1.25 mg LCTZ once daily for children 6 months to <6 years of age. This is in contrast to sponsor's dosing recommendation of 1.25 mg twice daily for age group of 1 to <6 years of age originally submitted as part of the proposed label at the time of NDA submission.

Labeling Negotiation

Once the above dosing recommendation was relayed to the sponsor as part of the label negotiation, the sponsor submitted a counter-proposal. The sponsor agreed with FDA's once daily dosing regimen recommendation, however, they wanted to provide a twice daily option for 2 to <6y old children with the following dosing recommendation for children 6 months to <6 years of age:

The recommended initial dose of XYZAL is 1.25 mg once daily. The 1.25 mg dose provides comparable exposure to that in adults receiving 5 mg. ***The dosage in patients 2 to 5 years of age can be increased to 1.25 mg given every 12 hours.*** *The 1.25 mg once daily dose should not be exceeded in children 6 to 23 months of age.*

Sponsor's Rationale for the counter-proposal

The sponsor rationalized their counter proposal based on the view that the most appropriate dose regimen for children is one that ensures that the maximum plasma concentrations (Cmax) are within the range seen in adult patients, while maintaining trough concentrations (Cmin) at or above the level seen in adults to ensure that efficacy is maintained throughout the dose interval.

Clearance (Cl/F) of LCTZ in children aged 1 to <6 years is approximately 1.7 fold greater than in adults when normalized for body weight, resulting in a half-life that is shorter than that is observed in adults. Therefore, a once daily dose regimen can result in low trough concentrations at the end of the 24-hour dose interval in children. The median Cmin (90% CI) for simulations of 1.25 mg once daily dosing in children 2 to <6 years were much lower than in adults (Table 2). In some children 2 to <6 years of age dosed 1.25 mg once daily, the trough values are likely to be half of that seen in adults dosed 5 mg once daily, which could lead to reduced efficacy, especially at the end of the dosing interval. Accordingly, more frequent dose administration was evaluated in order to reduce the peak to trough variation in plasma concentration within the dose interval while keeping peak concentrations at or below the levels seen in adults.

The C_{max} resulting from the 1.25 mg twice daily dose regimen in children aged 2 to <6 years old was generally similar to or within the C_{max} in adults given 5 mg once daily (Table 2). However, the 95th percentile for C_{max} in children aged 1 to <2y was much higher, i.e. 562 ng/ml so the 1.25 mg twice daily dose regimen is not recommended for the 1 to <2 year age group. These data showed that with respect to C_{max}, which is usually the most important parameter for safety, exposures similar to or below the normal adult exposure are produced by the 1.25 mg twice daily dose regimen for children aged 2 to <6 years of age.

Reviewer's response on sponsor's counter-proposal on pediatric dosing

Even though 1.25 twice daily may provide SAR efficacy benefit for those patients not responding to 1.25 mg once daily given the difference in SAR response between 2.5 mg and 5 mg for adults, the medical division felt the safety trial for 1.25 mg twice daily in 2-<6 years old children is not long enough to conclude the long term safety of this regimen (Please refer to the clinical division reviews on this). Moreover, all other age groups including the youngest group of pediatric patients (6 to <12 months) are being dosed as once daily. Having a twice daily option in 2 to <6 years old children may lead to confusion and possibly medication error within the wider pediatric population.

Therefore, this reviewer is recommending 1.25 mg LCTZ once daily for children 6 months to <6 years of age without providing the option of twice daily dosing for 2 to <6 years of age. For those patients not responding to LCTZ 1.25 mg once daily dosing, they have the option of switching to other antihistamines with the same indication.

2 Question Based Review

2.1 General Attributes/Background

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of Levocetrizine (Xyzal®) in pediatric patients?

LCTZ is currently approved as an oral tablet (5 mg) and an oral solution (0.5 mg/mL) for use in adults and children 6 years and older for the relief of symptoms associated with allergic rhinitis (SAR and PAR) and for the treatment of uncomplicated skin manifestations of CIU. The LCTZ oral tablet formulation (5 mg) was approved on May 25, 2007 (NDA 22-064). The LCTZ oral solution formulation (0.5 mg/mL), developed to provide a liquid dosage form alternative to the oral tablet, was approved on Jan 28, 2008 (NDA 22-157). A 10-fold concentrated liquid formulation of LCTZ (oral drops, 5 mg/mL) was developed to provide an additional liquid dosage form. (b) (4) The 0.5 mg/mL oral solution and the 5 mg/mL "oral drops" formulations of LCTZ were developed to allow flexible dosing for patients who may have difficulty swallowing solid oral dosage forms. The two liquid formulations are especially appropriate for administration to young children.

Initially, the sponsor planned to submit this pediatric supplement with clinical safety data in pediatric patients associated with the LCTZ asthma prevention program. At the pre-NDA meeting held on Jan 24, 2007, FDA advised that the existing safety database would only be considered as supportive data, since the majority of studies were not conducted in subjects in the intended to-be-treated population. In addition, the studies utilized a dose regimen (weight-based) that was different than the proposed dosage recommendation (fixed dose age-stratified). Further, FDA recommended UCB to conduct a population PK data analysis to justify the appropriateness of the age-stratified dosing recommendations. Based on the FDA pre-NDA recommendations, a retrospective population PK analysis and two placebo-controlled clinical safety studies in pediatric subjects ages 6 months to <6 years. The results of the population PK analysis (A00422) form the basis for the dose recommendation of a fixed dose related to age in the pediatric population of 6 months to <6 years of age.

The clinical program consisted of two Phase 3 pediatric safety studies, A00423 and A00426. In these safety studies, children with AR or CIU were exposed to LCTZ for 2 weeks. These studies were conducted in the US with the (b) (4) oral drops (5 mg/mL) formulation.

A written request was issued by the FDA on Feb 03, 2009 for pediatric trials down to age 6 months. Subsequent to the receipt of the Written Request (03 Feb 2009), a supplemental retrospective population PK analysis (A00422a) of LCTZ was performed. This analysis incorporated the data from the two pediatric safety studies (A00423 in children 6 to <12 months of age and A00426 in children 1 to <6 years of age) into the database from the original study, A00422. The objective of the A00422a analysis is to confirm the proposed dosing recommendations.

2.2 General Clinical Pharmacology

2.2.1 What are the pharmacokinetic characteristics of levocetirizine in pediatric and adult allergic rhinitis patients?

LCTZ plasma concentration-time data were modeled by non linear mixed effects modeling using NONMEM. In study A00422, a two-compartment model with first order absorption and first order elimination developed using data (rich and sparse) from nine clinical trials: 5 trials in pediatric population (1 to 11 years of age) and 4 trials in adults (18 to 55 years of age). Refer to Table 3 for a summary of study designs and available data.

Table 3. Summary of study designs and available PK samples in 9 trials included in the Pop PK analysis (study A00422).

Trial No.	Study Type	Population	Age (y)	Route, Dose, Form	Sampling	No. of samples
A221	BA/BE	24 healthy	20-55	Oral 10 mg SD Extemporaneous solution	Rich	287
A297	BA/BE	24 healthy	18-55	Oral 5 mg SD tablet & oral drops	Rich	670
A00318	BA/BE	24 healthy	19-54	Oral 5mg tablet & oral drops	Rich	690
A00419	TQT	52 healthy	18-46	Oral 5, 30 mg SD 5 mg tablets	Rich	936
Total adults		**124**	**18-55**			**2583**
A00309	Therapeutic	161 asthma free atopic	1-5	Oral 0.125 mg/kg BID 18 month 5mg/mL oral drops	Sparse	180
A00315	Therapeutic	15 cough	1-2	Oral 0.125 mg/kg BID 90-day 5mg/mL oral drops	Rich	106
A00384	Therapeutic (continuation of A00309)	21 from A00309	1-5	Oral 0.125 mg/kg BID 18 month 5mg/mL oral drops	Sparse	Counted under A00309
A00385	Therapeutic	26 AR	2-6	Oral 1.25 mg BID 4 weeks 5mg/mL oral drops	Sparse	26
PSM1216	Therapeutic	13 AR or mild concurrent asthma	6-11	Oral 5 mg SD tablets	Rich	136
Total children		**215**	**1-11**			**448**

AR = allergic rhinitis, BA/BE = bioavailability/bioequivalence, BID = twice daily

Later in study A00422a, the model is updated with sparse data from trials A00423 and A00426. It was parameterized in terms of absorption rate (KA), clearance (CL/F),

volumes of distribution of the central (V2) and peripheral (V3) compartments, and intercompartment clearance (Q). The effect of weight on CL/F, V2/F and V3/F was added to provide an allometric scaling of the parameters. The influence of age, body weight, body surface area, creatinine clearance, gender, and formulation (tablet or solution) was tested on the main PK parameters, i.e. related to the central compartment (KA, V2/F, CL/F).

The means and relative standard errors of the post-hoc PK parameters KA, CL/F, V2/F and V3/F estimated by NONMEM were calculated for each age sub-group and are presented in Table 4.

Table 4. Summary of the estimated PK parameters per age group

Age group	N	KA (h^{-1})	CL/F (L/hr)	V2/F (L)	V3/F (L)
0.5 to less than 1 year	27	3.1 (0.4%)	0.57 (4.6%)	4.0 (2.4%)	0.89 (2.1%)
1 to less than 2 years	24	3.1 (0.9%)	0.77 (6.1%)	4.4 (2.4%)	1.1 (1.8%)
2 to less than 4 year	185	3.1 (0.4%)	0.90 (2.2%)	5.9 (0.9%)	1.4 (0.8%)
4 to less than 6 year	63	3.1 (0.7%)	0.98 (3.5%)	7.1 (1.6%)	1.7 (1.3%)
6 to less than 16 year	19	3.0 (2.2%)	1.42 (7.2%)	9.7 (5.5%)	2.5 (5.3%)
Adults	124	3.1 (1.5%)	2.60 (1.9%)	20.4 (2.0%)	5.7 (1.1%)

Note: Mean and Relative Standard Error (RSE) in parenthesis

According to the final population PK model, the CL/F in the typical adult subject weighing 70 kg was estimated as 2.6 L/h or 0.62 mL/min/kg. Similarly, the steady state V/F was estimated to be the sum of V2/F (central) and V3/F (peripheral), i.e. 20.4 + 5.7 = 26.1 L or 0.37 L/kg in a typical adult subject weighing 70 kg (Table 4). These estimates are comparable to the values (CL/F = 0.63 mL/min/kg, V/F = 0.4 L/kg) reported in the approved Xyzal® label for adults.

The RSE of the mean parameter estimates are relatively low for each age category, and are all lower than 10%. The mean absorption rate constant is the same for all groups. The other parameters increase with age, which is mainly due to the dependence of these parameters on bodyweight, which is highly correlated with age in the pediatric population.

The median bodyweights in the database for children in the age sub-groups of 0.5 to <1 y, 1 to <2 y, 2 to <4 y, 4 to <6 y are 8.8 kg, 10.9 kg, 15.3 kg, 18.6 kg, respectively. Based on these bodyweights, the CL/F in each of these groups are calculated to be 1.08 mL/min/kg, 1.17 mL/min/kg, 0.98 mL/min/kg, 0.88 mL/min/kg. Similarly, the V/F in each age group are calculated to be 0.45 L/kg, 0.40 L/kg, 0.38 L/kg, 0.38 L/kg, respectively. It appears that weight-normalized estimates of CL/F were higher in children than in adults while weight-normalized estimates of V/F were relatively comparable to adults.

2.2.2 How does the systemic exposure in pediatric patients 6 months to <1 year and 1 to <6 years compare to that in adults following the sponsor proposed dosing regimens for these age-groups?

For children aged 6 to <12 months and 1 to <6 years, two dosing regimens were compared: administration of 1.25 mg oral solution of LCTZ once a day; and administration of the same dose twice daily. The population PK model was used to carry out Monte Carlo simulations of the different dose regimens in children aged 6 months to <6 years, using 2000 replicates with bodyweight values sampled from the distribution characteristics at a given age (National Health and Nutrition Examination Survey growth tables). The distribution of the simulated plasma concentration profiles was then compared to the distribution of 2000 adults receiving 5 mg once daily.

Simulation in 6 to <12 month-old infants:

For children 6 to <12 months of age, two dosing regimens were compared: once daily 1.25 mg and twice daily 1.25 mg (2.5 mg/day). As shown in Figure 1, the median Cmax and Cmin values of a 1.25 mg once daily administration remained within the range of concentrations in adults following once daily 5 mg dose (Cmax: 199 to 462 ng/mL and Cmin: 4 to 64 ng/mL). In contrast, the median Cmax following 1.25 mg b.i.d. exceeded the adult range for the youngest children from 6 to <9 months old while the median Cmin values far exceeded the 95th percentile of the adult range for all sub-groups within the broad age-range of 6 to<12 months (i.e. 6-7, 7-8, 8-9, and so on). Therefore the data seem to suggest that 1.25 mg once daily dosing regimen is more appropriate for 6 to <12 months old children.

Figure 1. Comparison of median (5th-95th percentile) peak (Cmax) and trough (Cmin) LCTZ plasma concentrations predicted in 6 to <12 months old infants following 1.25 mg LCTZ once daily dosing with the range (5th-95th percentile) of values predicted in adults following 5 mg LCTZ once daily dosing.

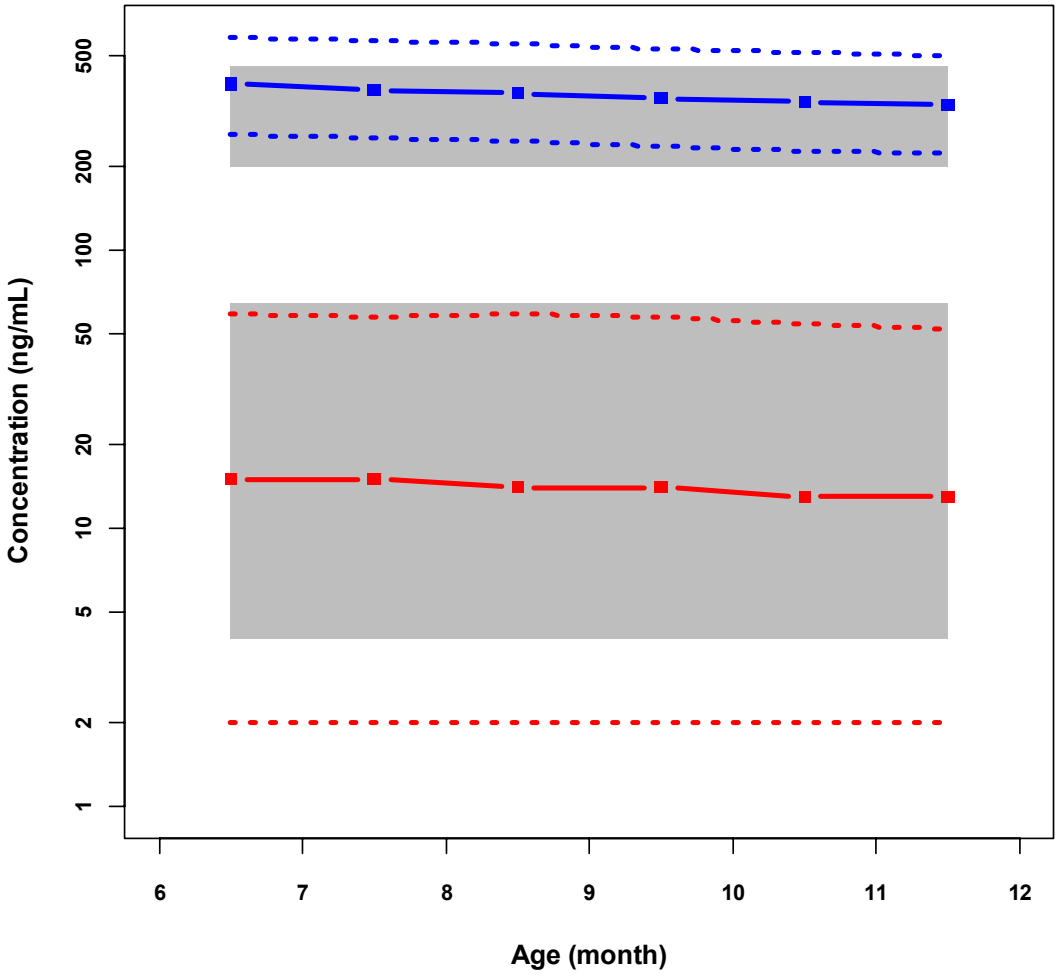
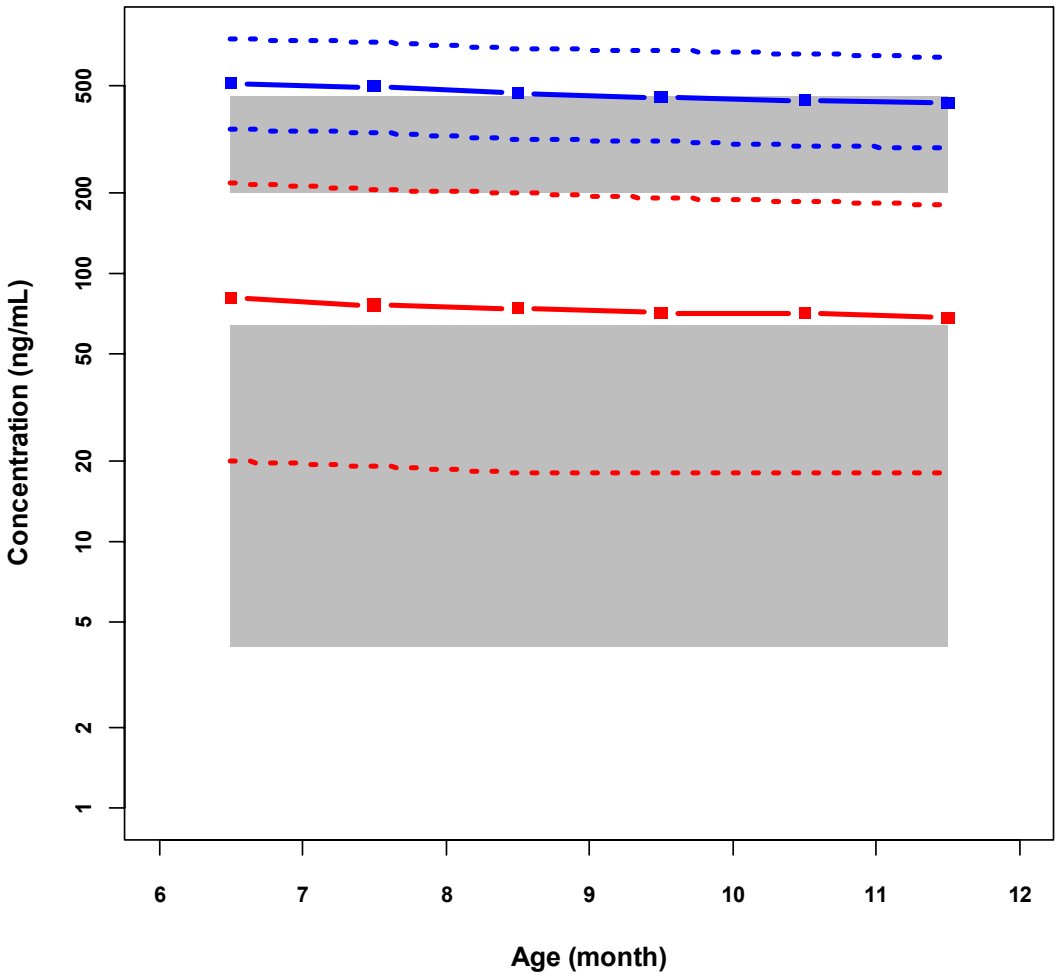


Figure 2. Comparison of median (5^{th}-95^{th} percentile) peak (Cmax) and trough (Cmin) LCTZ plasma concentrations predicted in 6 to <12 months old infants following 1.25 mg LCTZ twice daily dosing with the range (5^{th}-95^{th} percentile) of values predicted in adults following 5 mg LCTZ once daily dosing.



Simulation in 1 to <6 years-old children:

For children 1 to <6 years of age, three dosing regimens were compared: once daily 1.25 mg, twice daily 1.25 mg (2.5 mg/day) and once daily 2.5 mg. Since the median Cmax for 2.5 mg once daily dosing in the youngest children from 1 to <4 years old was found to exceed the range of Cmax concentrations in adults (199 to 462 ng/mL), this dosing regimen was promptly dropped from consideration (Table 5). For 1.25 mg twice daily administration, the 95th percentile of the Cmax values in children 1 to 3 years of age exceeded the range of Cmax concentrations in adults (Figure 3). Additionally, the 95th percentile of the Cmin values in all children ages 1 to <6 years exceeded the Cmin range in adults (4 to 64 ng/mL) as shown in Figure 3. For 1.25 mg once daily administration, the 95th percentile for both Cmax and Cmin values in children did not exceed the corresponding adult values (Figure 4). Although the 5th percentile of the pediatric range dropped below the adult value for Cmin in all numerical ages within the age-range of 1 to <6 years (i.e. 1-2, 2-3, 3-4 and so on) for 1.25 mg once daily dosing, still this regimen is considered the safer alternative compared to 1.25 mg twice daily regimen, provided there is no significant compromise of efficacy. Efficacy data in adults from the clinical development program of LCTZ (NDA 22064) suggested that 2.5 mg dose in adults is effective for most patients and with less sedation, which is reported to be the most common clinically-relevant, treatment-emergent adverse event in adults (≥12 years). Refer to Dr. Robert M. Boucher's review dated 04/03/2007 of original NDA 22064, for further details. Therefore, it is concluded by this reviewer that 1.25 mg once daily treatment will be more appropriate compared to 1.25 mg twice daily (i.e. 2-fold the daily dose) particularly since 2.5 mg dose in adults is effective for most patients.

In conclusion, the dose recommendations proposed in this submission are a fixed dose related to age, with a dose of 1.25mg LCTZ once daily for children 6 months to <6 years of age.

Table 5. Predicted Cmax, and Cmin following administration of LCTZ 2.5mg once daily in children 1 to <6 years old

Age (years)	**Median C_{max}, ng/mL** (5^{th}-95^{th} percentile)	**Median C_{min} ng/mL** (5^{th}-95^{th} percentile)
1-2	598 (401 – 898)	25 (4 – 97)
2-3	527 (355 – 792)	22 (4 – 87)
3-4	480 (320 – 726)	21 (4 – 79)
4-5	437 (290 – 655)	20 (4 – 73)
5-6	399 (260 – 603)	19 (4 – 68)
Adults (>16 years)	**302 (199 – 462)**	**20 (4 – 64)**

Figure 3. Comparison of median (5^{th}-95^{th} percentile) peak (Cmax) and trough (Cmin) LCTZ plasma concentrations predicted in 1 to <6 years old children following 1.25 mg LCTZ twice daily dosing with the range (5^{th}-95^{th} percentile) of values predicted in adults (grey area) following 5 mg LCTZ once daily dosing. [Solid line: median; dotted line: 5^{th}-95^{th} percentile]

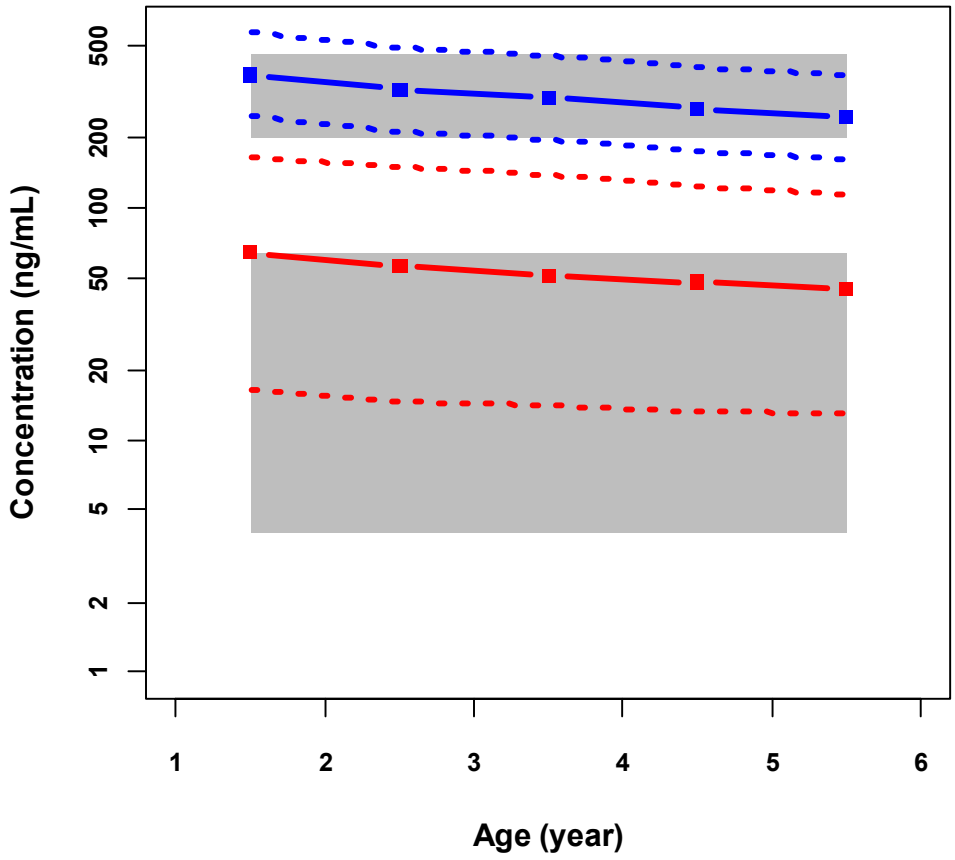
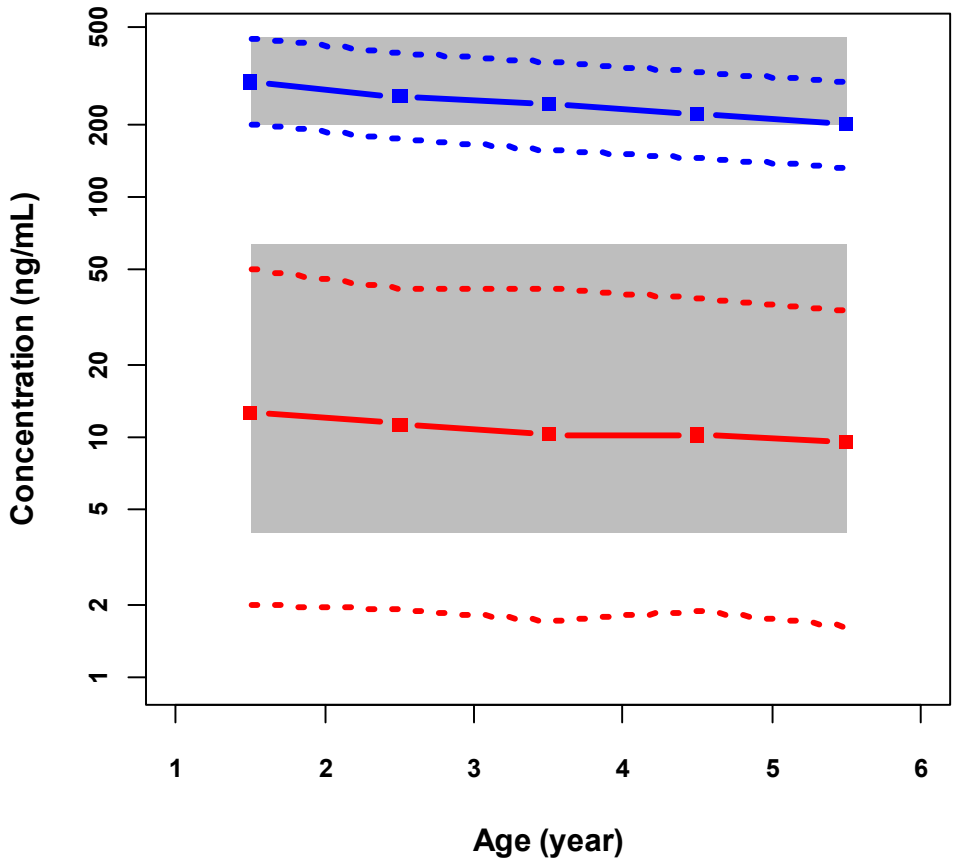


Figure 4. Comparison of median (5^{th}-95^{th} percentile) peak (Cmax) and trough (Cmin) LCTZ plasma concentrations predicted in 1 to <6 years old children following 1.25 mg LCTZ once daily dosing with the range (5^{th}-95^{th} percentile) of values predicted in adults (grey area) following 5 mg LCTZ once daily dosing. [Solid line: median; dotted line: 5^{th}-95^{th} percentile]



General Biopharmaceutics

2.3.1 What is the solubility and permeability of the drug substance?

Levocetirizine is a highly soluble (94.6 g/100 mL) and a moderately permeable (approximately 86% of radioactivity excreted in urine in a mass balance study) drug. The permeability of levocetirizine (P_{app}: 4.38×10^{-6} cm/s) was determined to be intermediate.

2.2.3 Is there any age-appropriate formulation for children 6 months to <6 years? What are the highlights of the age-appropriate formulation(s)?

The 0.5 mg/mL oral solution and the 5 mg/mL "oral drops" formulations of LCTZ were developed to allow flexible dosing for patients who may have difficulty swallowing solid oral dosage forms. Based on the quantitative composition of these two liquid

formulations, both are determined to be aqueous oral solution formulations. According to the sponsor, both these solution formulations are suitable dosage forms for use in young children (<6 years of age). The 0.5 mg/mL oral solution is already an approved formulation in adults and children 6 years and older. (b) (4)

There are no trials conducted to demonstrate BE between the two oral solution formulations. (b) (4)

Although the two solution formulations differ in the active drug strength as well as type and amount of excipients (Figures 5 and 6), it is concluded that no BE study is required between the two formulations to accept the oral solution (0.5 mg/mL) as a viable alternative formulation in young pediatric population (i.e. <6 years of age). This is based on the assumption that these two formulations are simple solutions and hence release of the drug substance from the solution is self-evident and that the solutions do not contain any excipient that significantly affects drug absorption (21 CFR 320.22(b)(3)(iii)). Refer to Dr. Tien-Mien Chen's review dated 5/11/2009 under NDA 22-157 for additional details.

Figure 5. Quantitative Composition of marketed oral solution (0.5 mg/mL)

Ingredient	Amount per mL (mg)	Function
Levocetirizine dihydrochloride	0.50	Active ingredient
Sodium acetate trihydrate, USP	(b) (4)	(b) (4)
Glacial acetic acid, USP		
Maltitol Solution, NF		
Glycerin (b) (4) USP		
Methylparaben, NF		
Propylparaben, NF		
Saccharin (b) (4) USP		
(b) (4) flavor (b) (4)		
Purified water, USP	qs	

Figure 6. Quantitative Composition of the proposed oral drops solution (5 mg/mL)

Ingredient	Amount per mL (mg)	Function
Levocetirizine dihydrochloride	5.00	Active ingredient
[redacted] (b) (4)		

2.2.4 Did the sponsor use the to-be-marketed formulation in the pivotal clinical trials? Is there any change in formulation during product development?

[redacted] (b) (4) oral drops formulation was used in the pivotal clinical trials. During development, the oral drops formulation was changed. Based on the results of antimicrobial testing, [redacted] (b) (4) of the original concentration. While the majority of the studies using oral drops [redacted] (b) (4) were conducted with the original formulation, [redacted] (b) (4) oral drops formulation was used in the two pivotal pediatric safety studies (A00423 and A00426). This formulation change is not considered to significantly impact the bioequivalence of the product. No BE study is required for this change (refer to the Quality Review for additional details).

2.3 Labeling Recommendations

Clinical Pharmacology has only one major edit. Since OCP/FDA's recommendation for dosing in 1 to <6 year old children is 1.25 mg BID and not 1.25 mg QD originally proposed by the sponsor, it has affected multiple parts of the label, primarily Dosage and Administration section both under the Highlights as well as the main body of the label, i.e. Full Prescribing Information (section 2).

The line-by-line editing of the proposed label is ongoing at the time of this review being filed. Attached is the draft label with initial FDA edits at the time this review is filed.

3 APPENDICES

3.1 PROPOSED PACKAGE INSERT

19 Page(s) of Draft Labeling has been Withheld after this page as B4 (CCI/TS)

17 Appendix 1 – Pharmacometric Review

Pharmacometrics Review

NDA:	22064 S017
Submission Date	24 February 2009
Type of Submission	Supplemental NDA for dosing in Pediatric Patients 6 months to <6 years of age
Generic Name	Levocetirizine Dihydrochloride
Brand Name	Xyzal®
Dosage Form	Oral Solution
Sponsor	UCB Inc.
PM Reviewer	Partha Roy, Ph.D., Yaning Wang, Ph.D.
PM Secondary Reviewer:	Yaning Wang, Ph.D.
PDUFA Date:	August 24, 2008

17.1 Executive Summary

Levocetirizine dihydrochloride (LCTZ, Xyzal®), a histamine type 1- (H1) receptor antagonist, is currently approved in adults and children 6 years of age and older for the treatment of symptoms associated with seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria (CIU). This supplemental New Drug Application (NDA) is intended to extend the age range of the approved indications down to 2 years for SAR and 6 months for PAR and CIU. Xyzal is currently approved in adults and children 6 years and older. The approved dosage is 5 mg once daily in adults and children 12 years and older and 2.5 mg in children 6 to <12 years of age.

For pediatric patients 6 months to <1y of age, the sponsor proposed a dosage regimen of 1.25 mg once daily. On the other hand, for pediatric patients 1 to <6y of age, the sponsor proposed a dosage regimen of 1.25 mg twice daily (i.e. 2.5 mg/day). To support the proposed doses and regimen in young children, the sponsor submitted the results of the population PK analysis (A00422) developed from observed PK data (rich and sparse) in subjects 1y and older, which form the basis for the dose recommendations proposed in this pediatric population (children <6y). These LCTZ doses were implemented in two 2-week Phase 3 pediatric safety studies, A00423 in children 6 to <12 months and A00426 in children 1 to <6y, in which sparse PK sampling was obtained. Subsequently, a supplemental retrospective population PK analysis (A00422a) of LCTZ was performed that incorporated the data from the two pediatric pivotal safety trials (A00423 and A00426) into the original study, A00422 to confirm the model used in study A00422 as well as provide additional support for the proposed dosing. The sponsor claimed that the proposed pediatric dosing of 1.25 mg once daily in infants 6 months to <1y and 1.25 mg twice daily in children 1 to <6y will match the exposure observed in adults taking 5 mg once daily.

After reviewing the submitted data and analysis, the Pharmacometrics Group in the Office of Clinical Pharmacology has the following findings:

- The submitted PK data was well documented and adequate for benchmarking safety based on comparative systemic exposure assessment.
- The sponsor explored both once daily as well as twice daily dosing scenarios in infants 6 months to <1y but did not explore the once daily dosing scenario in children 1 to <6y.
- The proposed dosing for LCTZ is following once daily regimen in all age groups except in children 1 to <6y of age, which raised the possibility of creating confusion and as a result, prescribing error. Therefore once daily dosing scenario was explored by the FDA in the age group of 1 to <6y.

Therefore, new analyses were conducted using pediatric and adult systemic exposure data. The population predicted pediatric clearance and volume of distribution after oral administration of LCTZ were found to be both dependent on body weight. The population PK model was used to carry out Monte Carlo simulations of different dosing scenarios including once and twice daily dosing of 1.25 mg and once daily dosing of 2.5 mg in children 1 to <6y of age.

Based on the results of these analyses, the proposed pediatric dose of 1.25 mg twice daily in children 1 to <6 years is not acceptable because simulated data in children was not fully contained within the exposure range in adults following a dose of 5 mg once daily in adults. Even though 1.25 mg twice daily dosing was studied in the safety study (A00426) for 2 to 6 years old children, the trial duration was not long enough to conclude the safety of this regimen in this population based on our medical team's opinion. Based on the simulation results and existing efficacy database of LCTZ in adults, the more appropriate dose for this pediatric age-group is 1.25 mg once daily. For those patients not responding to this regimen, they have the option to switch to other antihistamines with the same indication.

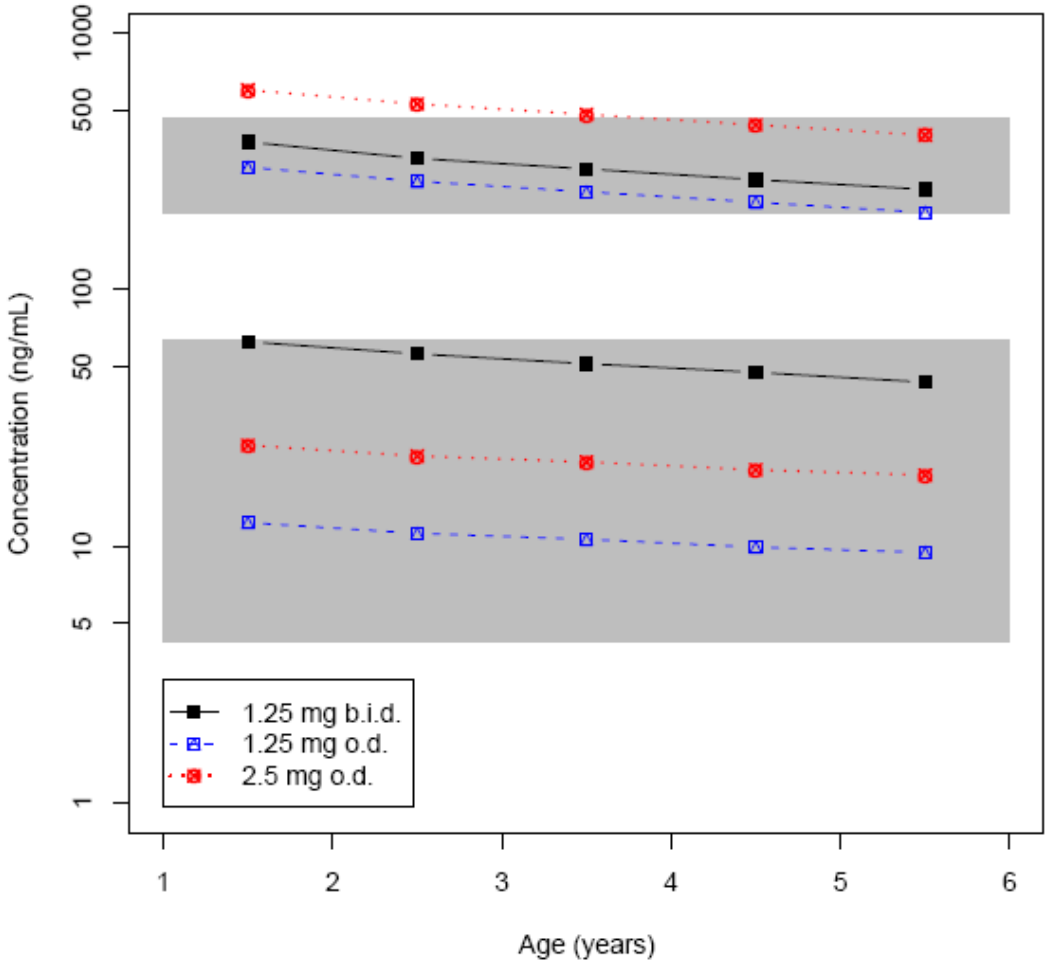
17.2 Key Questions

17.2.1 The sponsor proposed twice daily (BID) dosing for Xyzal® in children 1 to <6y of age while once daily (QD) dosing has been proposed/accepted for all other age-groups, i.e. 6 to <12 months and ≥6y. Does the data support the 1.25 mg BID dosing in children 1 to <6 years of age?

The objectives of pediatric dosing are two-fold: 1) to achieve concentrations that are comparable to concentrations in adults following 5 mg once daily dosing so that comparable efficacy can be extrapolated from adults, and 2) to not exceed the exposure observed in adults after multiple dosing of once daily 5 mg of Xyzal® in order to provide a benchmark for systemic safety. FDA repeated the population PK analysis using NONMEM conducted by the sponsor and re-run the simulations for different dosing scenarios including 2.5 mg and 1.25 mg once daily which was not initially submitted by the sponsor.

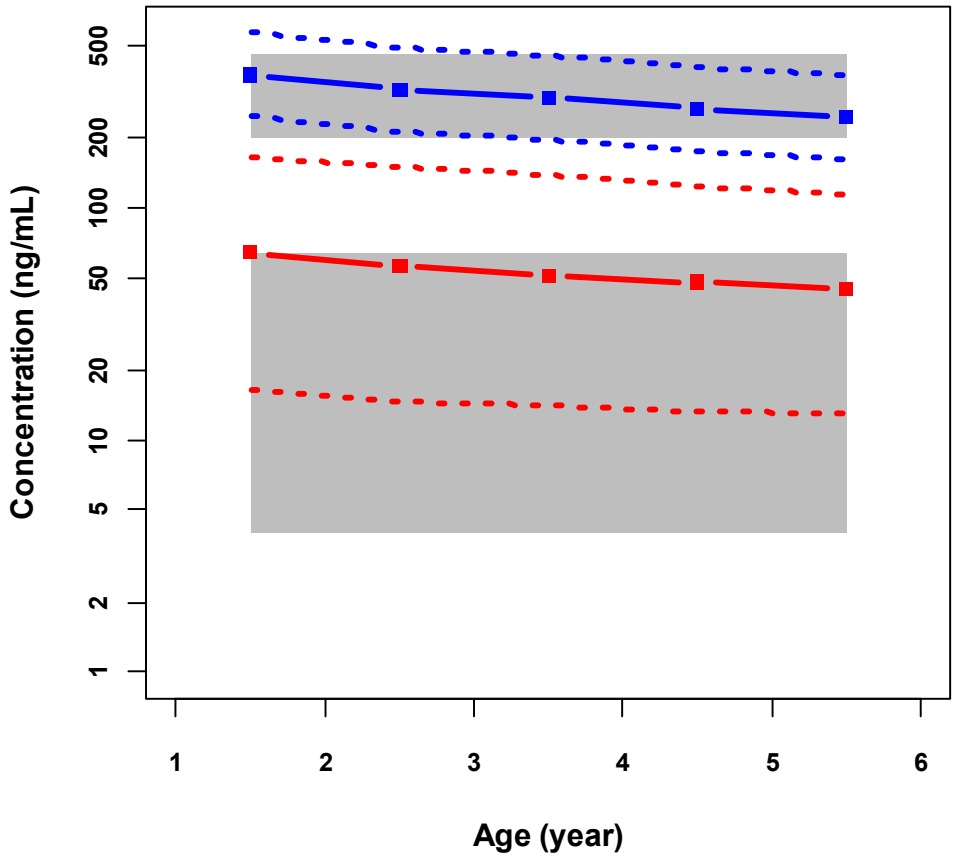
For the age-group of 1 to <6y, three dosing regimens were compared: once daily 1.25 mg, twice daily 1.25 mg (2.5 mg/day) and once daily 2.5 mg. As shown in Figure 1, the median Cmax for 2.5 mg once daily dosing in the youngest children from 1 to <4 years old was found to clearly exceed the range (5th to 95th percentiles) of Cmax concentrations in adults (199 to 462 ng/mL). Therefore, this dosing regimen was not considered for further evaluation.

Figure 1. Comparison of the median Cmax, Cmin predicted in children 1 to <6 years of age following different dosing scenarios to the 5th to 95th percentiles of the Cmax, Cmin predicted in adults receiving 5 mg once a day (grey area)



For 1.25 mg twice daily administration, the 95th percentile of the Cmax values in children 1 to <3 years of age exceeded the range of Cmax concentrations in adults (Figure 2). In addition, the 95th percentile of the Cmin values in all children ages 1 to <6 years far exceeded the Cmin range in adults (4 to 64 ng/mL) as shown in Figure 2.

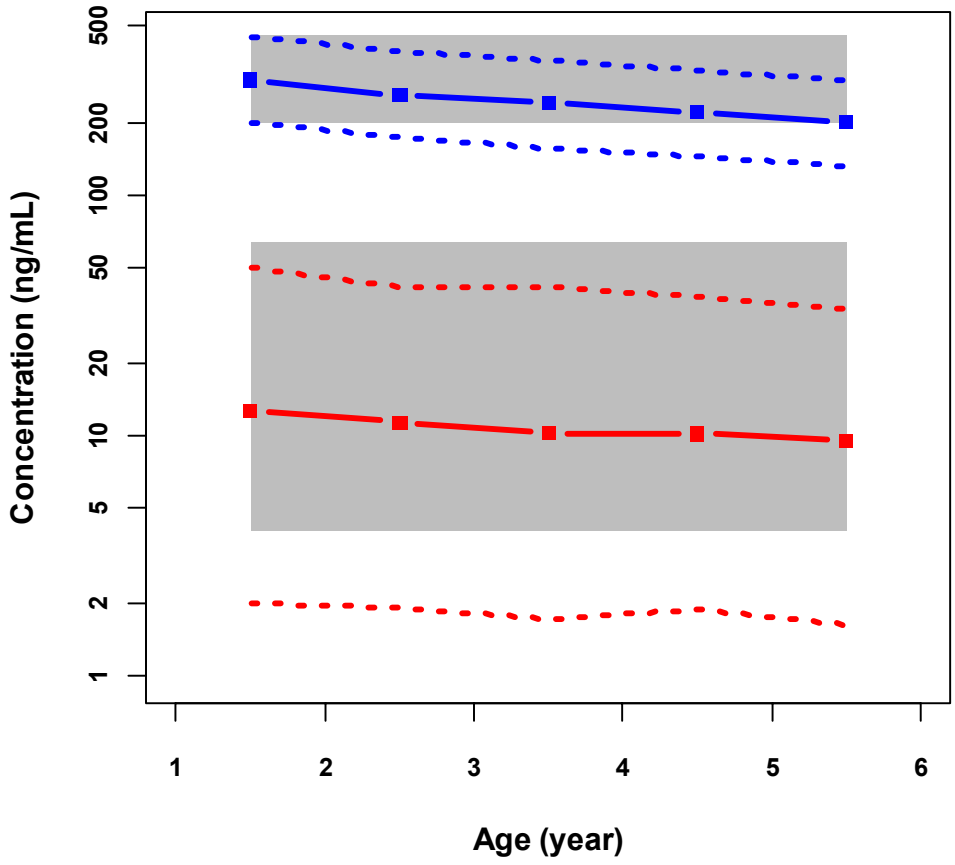
Figure 2. Comparison of median (5^{th}-95^{th} percentile) peak (Cmax) and trough (Cmin) LCTZ plasma concentrations predicted in 1 to <6 years old children following 1.25 mg LCTZ twice daily dosing with the range (5^{th}-95^{th} percentile) of values predicted in adults (grey area) following 5 mg LCTZ once daily dosing. [Solid line: median; dotted line: 5^{th}-95^{th} percentile]



For 1.25 mg once daily administration, the 95th percentiles of both Cmax and Cmin values in children did not exceed the corresponding adult values (Figure 3). Although the 5th percentile of the pediatric range dropped below the adult value for Cmin in all numerical ages within the age-range of 1 to <6 years (i.e. 1-2, 2-3, 3-4 and so on) for 1.25 mg once daily dosing, still this regimen is considered the safer alternative compared to 1.25 mg twice daily regimen, provided there is no significant compromise of efficacy. Efficacy data in adults from the clinical development program of LCTZ (NDA 22064) suggested that 2.5 mg dose in adults is effective for most patients with less sedation. Refer to Dr. Robert M. Boucher's review dated 04/03/2007 of original NDA 22064, for further details. Therefore, it can be concluded that 1.25 mg once daily treatment will be more appropriate compared to 1.25 mg twice daily (i.e. 2-fold the daily dose). For those patients not responding to 1.25 mg once daily dosing, 1.25 twice daily may provide SAR efficacy benefit given the difference in SAR response between 2.5 mg and 5 mg for adults. However, based on our medical team's opinion, the

safety trial for 1.25 mg twice daily in 2-6 years old children is not long enough to conclude that this regimen is safe for this age group.

Figure 3. Comparison of median (5^{th}-95^{th} percentile) peak (Cmax) and trough (Cmin) LCTZ plasma concentrations predicted in 1 to <6 years old children following 1.25 mg LCTZ once daily dosing with the range (5^{th}-95^{th} percentile) of values predicted in adults (grey area) following 5 mg LCTZ once daily dosing. [Solid line: median; dotted line: 5^{th}-95^{th} percentile]



17.2.2 Which covariates influence the PK of Xyzal?

The correlations between the PK parameters (KA, CL, Q, V2, V3) and the covariates were explored graphically. A large number of relevant covariates were tested that include age, bodyweight, body surface area, gender, creatinine clearance and formulation. Per sponsor's analysis of pooled PK data from 9 trials (5 pediatric and 4 adult), pediatric clearance and volumes of distribution (central plus peripheral) after oral administration of Xyzal® were both found to be dependent on body weight which is highly correlated with age and body surface area. Population predicted oral clearance (CL/F) and volumes of distribution

(V2/F and V3/F) in children were listed below in Table 1. All other covariates were found to be not significant for CL, V/2 and V3.

Table 1. Summary of the estimated PK parameters per age group: Mean and relative standard error in parenthesis

Age group	N	KA (h^{-1})	CL/F (L/hr)	V2/F (L)	V3/F (L)
0.5 to less than 1 year	27	3.1 (0.4%)	0.57 (4.6%)	4.0 (2.4%)	0.89 (2.1%)
1 to less than 2 years	24	3.1 (0.9%)	0.77 (6.1%)	4.4 (2.4%)	1.1 (1.8%)
2 to less than 4 year	185	3.1 (0.4%)	0.90 (2.2%)	5.9 (0.9%)	1.4 (0.8%)
4 to less than 6 year	63	3.1 (0.7%)	0.98 (3.5%)	7.1 (1.6%)	1.7 (1.3%)
6 to less than 16 year	19	3.0 (2.2%)	1.42 (7.2%)	9.7 (5.5%)	2.5 (5.3%)
Adults	124	3.1 (1.5%)	2.60 (1.9%)	20.4 (2.0%)	5.7 (1.1%)

Note: mean and relative standard error (RSE) in parenthesis

17.3 Background

Xyzal® (levocetirizine dihydrochloride, LCTZ), a histamine type-1 receptor antagonist, is currently approved in the U.S. for use in adults and children 6 years of age and older for the relief of symptoms of seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR), and the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria (CIU). The present submission is intended to fulfill the PREA post-marketing commitments as well as the terms of the pediatric exclusivity Written Request issued on February 3, 2009.

The clinical program primarily consists of two well-controlled pediatric Xyzal safety studies in children below 6 years of age with SAR, PAR or CIU, and a population pharmacokinetics data analysis. Study A00423 was conducted in infants 6 months to <12 months of age at a dose of 1.25 mg QD. Study A00426 was conducted in children 1 to 5 years of age at a dose of 1.25 mg BID (2.5 mg/day). The dose regimens studied in A00423 and A00426 were chosen based on the results of population pharmacokinetics data analysis A00422. An additional supplemental population PK analysis, A00422a, incorporated data from A00423 and A00426 was performed to further confirm the appropriateness of the dose regimens tested in the pivotal trials and ultimately the final dosing recommendation for approval. Xyzal efficacy in SAR, PAR and CIU has not been studied in children below 6 years of age, and is therefore supported by extrapolation of the efficacy demonstrated in the adult and adolescent population (NDA 22-064) using the PK data.

17.4 Sponsor's Analysis

17.4.1 Objective of the analysis

The objective of this analysis is to evaluate whether the Xyzal® pediatric doses of 1.25 mg once daily in 6 to <12 months of age and 1.25 mg twice daily in 1 to <6 years of age match systemic exposure in adults taking Xyzal® 5 mg QD i.e. the approved adult dose for treatment of allergic rhinitis and CIU.

17.4.2 Background

The clinical pharmacokinetic profile of LCTZ has been well documented from numerous studies conducted in healthy adults and allergic rhinitis patients. LCTZ is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hour after administration of the oral tablet. The accumulation ratio following daily oral administration is 1.12 with steady state achieved after 2 days. Peak concentrations are typically 270 ng/mL and 308 ng/mL following a single and a repeated 5 mg once daily dose, respectively. LCTZ can be administered without regard to food.

Following oral dosing, the average apparent volume of distribution is approximately 0.4 L/kg, representative of distribution in total body water. The plasma half-life in adult healthy subjects was about 8 to 9 hours after administration of oral tablets and 0.5 mg/mL oral solution, and the mean oral total body clearance for LCTZ was approximately 0.63 mL/kg/min. The major route of excretion of LCTZ and its metabolites is via urine, accounting for a mean of 85.4% of the dose. LCTZ is excreted both by glomerular filtration and active tubular secretion. Renal clearance of levocetirizine correlates with that of creatinine clearance.

17.4.3 Data

Study A00422

A retrospective population PK analysis of LCTZ was performed using rich and sparse data from 9 clinical studies in children (Trials A00309, A00315, A00384, A00385, and PSM1216) and adults (Trials A221, (b) (4) A00318, and A00419). The key objectives of the analysis were:

1. To characterize the pharmacokinetics of LCTZ in the pediatric population
2. To propose dosing recommendations for children aged 6 months to <6 years

These objectives were achieved through population PK modeling of LCTZ concentration-time data in 200 children and 124 adults, using NONMEM. A summary of demographic covariates are compiled in Table 2. One- and 2-compartment models with first-order absorption and first-order elimination were compared. Intersubject variability was set on each structural parameter related to the first compartment (absorption rate constant [KA], apparent clearance [CL/F], and apparent volume of distribution [V/F] of the first compartment). Proportional and proportional plus additive error models were tested for residual variability.

Table 2. Demographic variables of study participants (study A00422)

Age group	Number	Age (years)	Weight (kg)	Height (cm)	Body Surface Area (m^2)	Creatinine clearance (mL/min)
≤ 6 years	107 males 74 females	3.2 (1.1-6.0)	15.3 (8.9-25.0)	97.9 (77.0-123.0)	0.6 (0.4-0.9)	29.6 (12.9-51.1)
6 – 16 years	12 males 6 females	8.0 (6.2-11.0)	29.0 (20.0-43.8)	131.0 (118.0-143.8)	1.0 (0.8-1.3)	46.7 (44.8-56.3)
Adults	64 males 60 females	34.7 (18.4–55.4)	69.6 (46.2-95.8)	172.0 (153.0-199.0)	1.8 (1.4-2.3)	108.0 (69.4-174.4)

Study A00422a

The measured concentrations of A00423 and A00426 for which the time after last administration was available were added to the database of A00422. A summary of demographic covariates are compiled in Table 3. LCTZ plasma concentration-time data were modeled using NONMEM. It was assumed that the structural base model was the same as the one built in study A00422, ie, a 2-compartment model with first-order absorption and first-order elimination with the CL/F, V2/F and V3/F as function of weight. Intersubject variability was set on each structural parameter related to the central compartment (KA, CL/F, and V2/F). The effect of the following covariates was tested: age, WT, CLcr, gender, and formulation (liquid vs tablet).

Table 3. Demographic variables of study participants (study A00422a)

Age group	Number	Age (years)	Weight (kg)	Height (cm)	Body Surface Area (m^2)	Creatinine clearance (mL/min)
0.5 to <1 year	17 males 10 females	0.74 (0.53-0.99)	8.8 (7.1-11.0)	71.1 (66.0-76.7)	0.42 (0.36-0.48)	20.2 (17.0-24.1)
1 to <2 years	17 males 7 females	1.6 (1.12-1.98)	10.9 (8.9-14.1)	81 (73.9-88.5)	0.5 (0.44-0.59)	25.6 (22.4-31.9)
2 to <4 years	106 males 79 females	3.19 (2.02-3.99)	15.3 (11.6-20)	97.8 (82-110)	0.64 (0.51-0.78)	37.0 (26.9-47.5)
4 to <6 years	38 males 25 females	5.04 (4.01-5.99)	18.6 (14.3-27.3)	109.5 (96.5-123)	0.75 (0.62-0.94)	46.5 (35.6-58.1)
6 to< 16 years	12 males 7 females	8 (6-11)	29 (19.7-43.8)	129.8 (110-143.8)	1.02 (0.78-1.3)	53.1 (51.8-62.1)
Adults	64 males 60 females	34.7 (18.4-55.4)	69.6 (46.2-95.8)	172 (153-199)	1.83 (1.42-2.26)	108.3 (69.4-174.4)

17.4.4 Results & Discussion

17.4.4.1 Population PK Model – Study 00422

Both 1- and 2- compartment models were evaluated. The 2-compartment model was found to be superior to the 1-compartment model; the 2-compartment model improved the fit of the concentration profile for sampling times beyond 20 hours. The following parameters were characterized using the 2-compartment model:

KA, CL/F, apparent volumes of distribution of the central (V2/F) and peripheral (V3/F) compartments, and inter-compartment clearance (Q). The effect of WT on CL/F, V2/F, and V3/F needed to be taken into account in the base model.
The covariate analysis demonstrated statistically significant effects of: WT on Q, CLcr on CL/F, and formulation on KA. However, Monte Carlo simulations indicated that the effects of CLcr and formulation on exposure were negligible; thus, the model was reduced by removing these 2 covariates.

All the structural parameters of the final model were estimated with good precision, ranging from 3% to 27%, except for Q (56%). The intersubject variability was 25% for V2/F, 29% for CL/F, and 61% for ka. The residual variability was 28%.

The parameters of the final model were expressed as follows:
KA (h^{-1})=2.49
CL/F (L/h)=$0.99(WT/18.4)^{0.72}$
V2/F (L)=$7.38(WT/18.4)^{0.74}$
V3/F (L)=$1.53(WT/18.4)^{1.04}$
Q (L/h)=$0.15(WT/18.4)^{1.84}$

The internal predictive properties of the model were successfully evaluated using the jackknife method, with stratification per population (children or adults) and sampling density (rich or sparse sampling data).

Simulations

For children aged 6 to <12 months, 2 dosing regimens were compared: 1.25 mg oral solution of LCTZ once a day; and 1.25 mg twice daily. For children aged 1 to <6 years, 1 dosing regimen was investigated: administration of a 1.25 mg oral solution of LCTZ twice daily. The model was then used to carry out Monte Carlo simulations of the different dose regimens in children aged 6 months to <6 years, using 2000 replicates with WT values sampled from the distribution characteristics at a given age (National Health and Nutrition Examination Survey growth tables). The distribution of the simulated plasma concentration profiles was then compared to the distribution of 2000 adults receiving 5 mg once daily.

Simulations in 6- to 11-month-old infants
The simulation results (Figure 4, Table 4) in the 6- to <12-month age range must be considered with caution as no children in that age range were present in the database. It is thus possible that a covariate that may be important in infants could not be identified when constructing the model. For instance, CLcr is smaller in infants and this may affect the clearance of LCTZ. In the model, CLcr was not found to lead to important differences in the predicted concentrations when included in the model as a covariate. Even when using a low CLcr value, such as would be expected in a 6-month-old child and a WT value representative of a 6-month-old child, the predicted concentrations were very similar to those obtained

with the model without CLcr as a covariate. This is consistent with the observation that glomerular filtration rate reaches at least two-thirds of the adult value (per 1.73m^2) by the age of 6 months.

Figure 4. Comparison of the median levocetirizine Cmax and Cmin values predicted in 6- to 11-month-old children with the range of Cmax and Cmin values predicted in adults (semi-logarithmic scale)

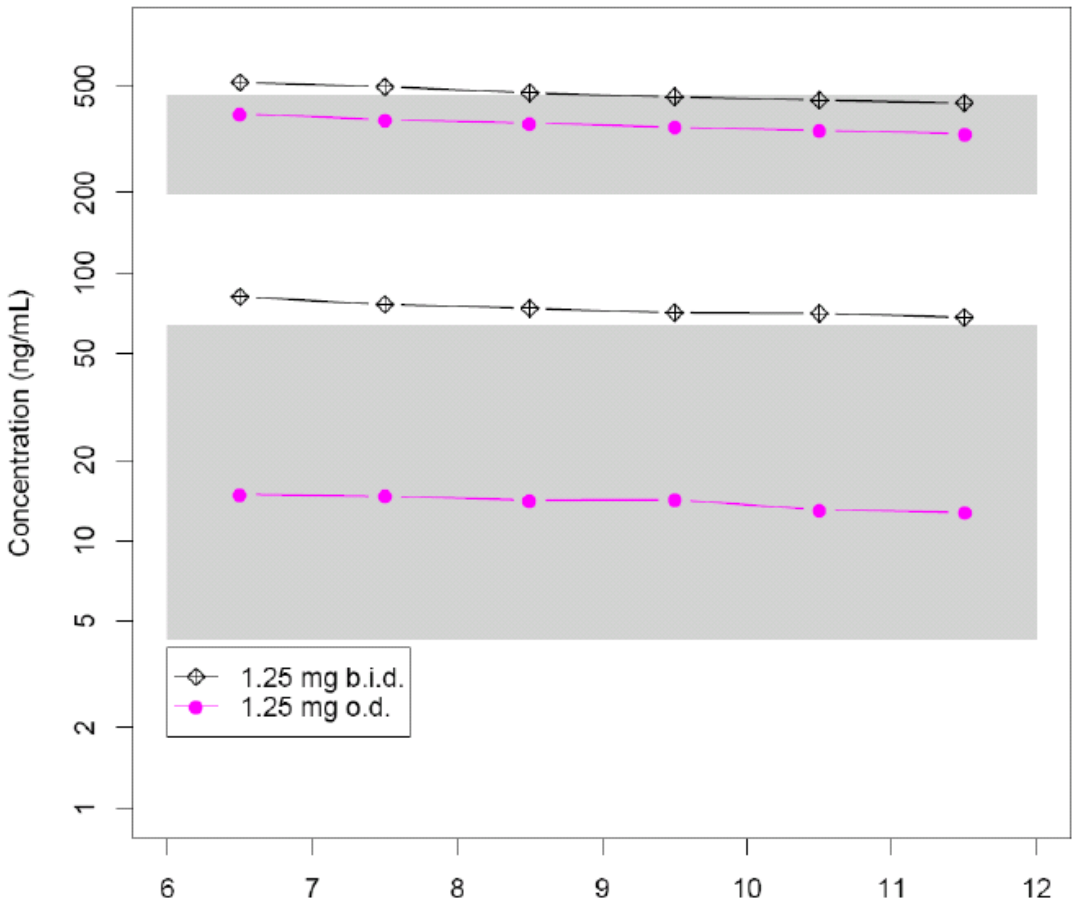


Table 4. Predicted levocetirizine Cmax, Cmin, and AUC values following administration of 1.25mg LCTZ once daily and twice daily in 6- to <12-month-old infants

Age (months)	Median C_{max} (5th – 95th percentile) (ng/mL)		Median C_{min} (5th – 95th percentile) (ng/mL)		Median $AUC_{24\ hrs}$ (5th – 95th percentile) (mg.h/L)	Median $AUC_{12\ hrs}$ (5th – 95th percentile) (mg.h/L)
	Once daily	Twice daily	Once daily	Twice daily	Once daily	Twice daily
6 to <7	394 (261 – 584)	516 (347 – 758)	15 (2 – 59)	81 (20 – 219)	2.4 (1.4 – 3.8)	2.4 (1.4 – 3.9)
7 to <8	375 (254 – 568)	497 (334 – 735)	15 (2 – 57)	76 (19 – 205)	2.3 (1.4 – 3.7)	2.3 (1.4 – 3.7)
8 to <9	364 (246 – 547)	472 (317 – 689)	14 (2 – 59)	74 (18 – 199)	2.2 (1.3 – 3.6)	2.2 (1.3 – 3.6)
9 to <10	351 (236 – 529)	456 (311 – 677)	14 (2 – 57)	71 (18 – 191)	2.2 (1.3 – 3.5)	2.1 (1.3 – 3.4)
10 to <11	341 (227 – 511)	443 (299 – 659)	13 (2 – 54)	71 (18 – 186)	2.1 (1.3 – 3.4)	2.0 (1.3 – 3.4)
11 to <12	332 (224 – 498)	433 (295 – 646)	13 (2 – 52)	68 (18 – 180)	2.0 (1.2 – 3.3)	2.0 (1.2 – 3.3)

The median Cmax and Cmin values were higher for LCTZ 1.25 mg twice daily administration than for the 1.25 mg once daily dosing regimen. The median Cmax values of the LCTZ 1.25 mg once daily administration remained within the 5th to 95th percentiles of the Cmax values in adults (199 to 462 ng/mL), whereas the median Cmax values following LCTZ 1.25mg twice daily administration exceeded the 95th percentile of Cmax in adults for the youngest children from 6 to 8 months old. The LCTZ 1.25mg once daily dosing appeared to be sufficient. Although it led to lower Cmin values, the median Cmin values remained within the 5th to 95th percentiles of predicted Cmin values for adults (4 to 64ng/mL). Subsequently, the 1.25mg once daily regimen appeared preferable for children aged 6 to <12 months.

Simulations in 1- to <6-year-old children
Simulations of levocetirizine concentrations in children between 1 and 5 years of age following administration of a daily dose of 2.5mg (1.25mg twice daily) of LCTZ were performed.

Figure 5. Comparison of the median Cmax and Cmin values predicted in 1-<6 year-old children with the range of Cmax and Cmin values predicted in adults (semi-logarithmic scale)

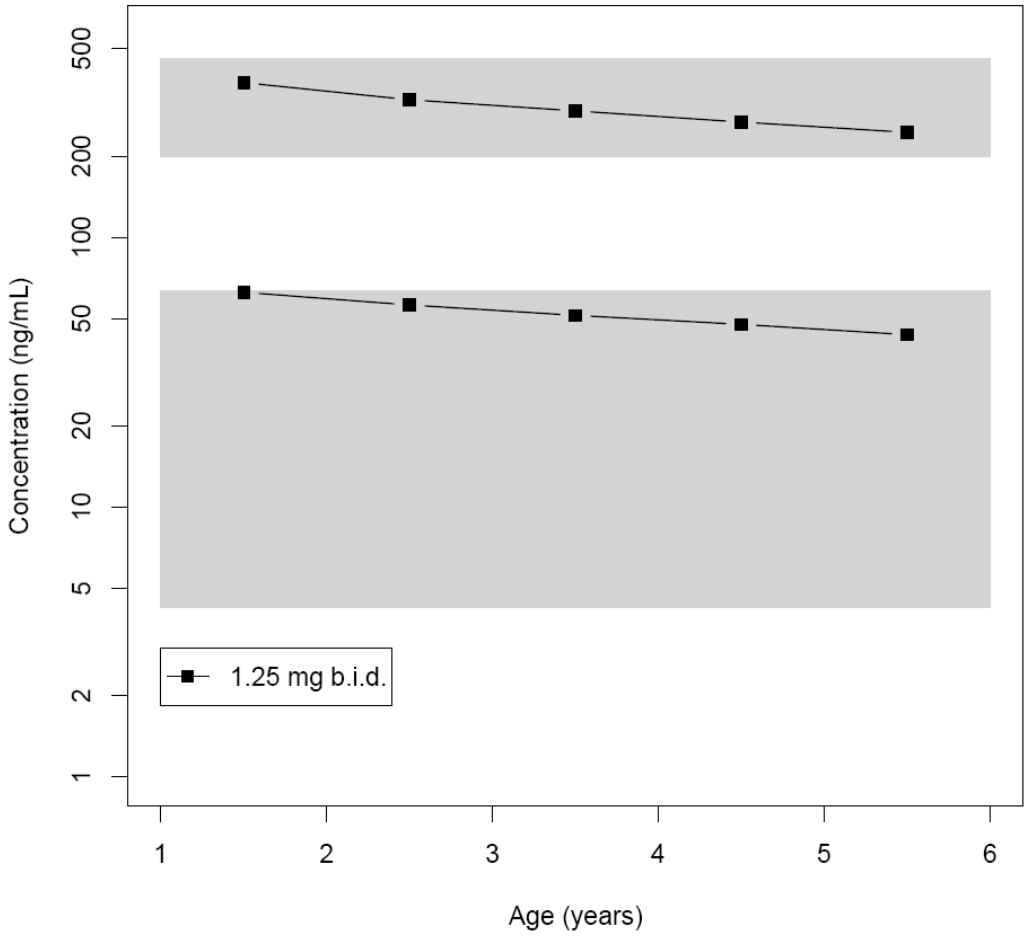


Table 5. Predicted levocetirizine Cmax, Cmin, and AUC values following administration of 1.25mg LCTZ twice daily in 1 to <6 year-old children

Age (years)	Median C_{max} (5th – 95th percentile) (ng/mL)	Median C_{min} (5th – 95th percentile) (ng/mL)	Median $AUC_{12\ hrs}$ (5th – 95th percentile) (mg.h/L)
1 to <2	375 (250 – 562)	63 (16 – 165)	1.8 (1.1 – 3.0)
2 to <3	324 (214 – 486)	56 (15 – 146)	1.6 (1.0 – 2.6)
3 to <4	294 (197 – 444)	51 (13 – 136)	1.5 (0.9 – 2.4)
4 to <5	267 (177 – 405)	48 (13 – 124)	1.3 (0.8 – 2.2)
5 to <6	245 (160 – 371)	44 (12 – 115)	1.2 (0.7 – 2.0)

The predicted median values for Cmax in children aged 1 to <6 years fell within the 5th to 95th percentiles of predicted Cmax values for adults. The predicted median values of Cmin in children aged 1 to <6 years were also within the 5th to 95th percentiles of predicted Cmin values in adults, even though in the upper part of the interval. Therefore, the dosing regimen of 1.25 mg twice daily was considered appropriate for children aged 1 to <6 years.

17.4.4.2 Population PK Model – Study 00422 addendum (00422a)

The data from A00423 and A00426 were added to the database employed in A00422 and a population PK analysis was undertaken.

The measured concentrations of A00423 and A00426 for which the time after last administration was available were added to the database of A00422.
LCTZ plasma concentration-time data were modeled using NONMEM. It was assumed that the structural base model was the same as the one built in study A00422, i.e., a 2-compartment model with first-order absorption and first-order elimination with the CL/F and V2/F and V3/F as function of bodyweight. Intersubject variability was set on each structural parameter related to the central compartment (ka, CL/F, and V2/F). The effect of the following covariates was tested: age, bodyweight (WT), CLcr, gender, and formulation (liquid vs tablet).

The performance of the model was evaluated by a visual and a numerical predictive check: simulations of the clinical studies were repeated 1000 times and the predictions were compared against the observations.

The effect of WT on the main parameters CL/F, V2/F, and V3/F was added to provide an allometric scaling of the parameters considering the large variability of subjects in the database. The covariate analysis investigated the effect of covariates on the main parameters of the model only, i.e., those related to the main compartment. It demonstrated a statistically significant effect of formulation on KA. However, Monte Carlo simulations indicated that the effect of this covariate on the concentrations was negligible; the model was thus reduced by removing this covariate.

The final model was the same as the base model and was close to the one obtained in Study A00422. The precision of the estimates, ranging from 3% to 16%, was improved compared to Study A00422 due to the expanded dataset.

The parameters of the final model were expressed as follows:
KA (h^{-1})=2.92
CL/F (L/h)=0.99 $(WT/18.4)^{0.72}$
V2/F (L)=6.94 $(WT/18.4)^{0.81}$
V3/F (L)=1.71 $(WT/18.4)^{0.90}$
Q/F (L/h)=1.53

The model was evaluated with goodness-of-fit plots (A00422a Section 10.1) and with individual time-concentration profiles comparing the predictions against the observations. A visual predictive check was also performed: 1000 simulations of the clinical studies were performed and the statistics of the predictions were compared with the observations.

Overall, 88% of the observations were found to be well fitted by the model. For the observations from the children 6 months to <6 years of age, 18% fell outside the 90% Prediction Interval, corresponding to 7% being underpredicted and 11% overpredicted. Since the model was employed to find a safe dosing regimen in children 6 months to <6 years of age, i.e., a dosage that did not lead to extremely high concentrations (higher than those expected in adults receiving 5mg daily), it is when it underpredicts the concentrations of LCTZ that it can cause problems. In this case, it was found to happen at a relatively low rate of 7%.

The population PK analysis (A00422a) undertaken after adding the data from A00423 and A00426 to the database of A00422 did not lead to the identification of an additional covariate that significantly influenced the parameters of the model compared to the model of Study A00422. The values of the parameter estimates were close to the ones obtained in Study A00422 and were achieved with better precision.

17.4.5 Sponsor's Conclusions

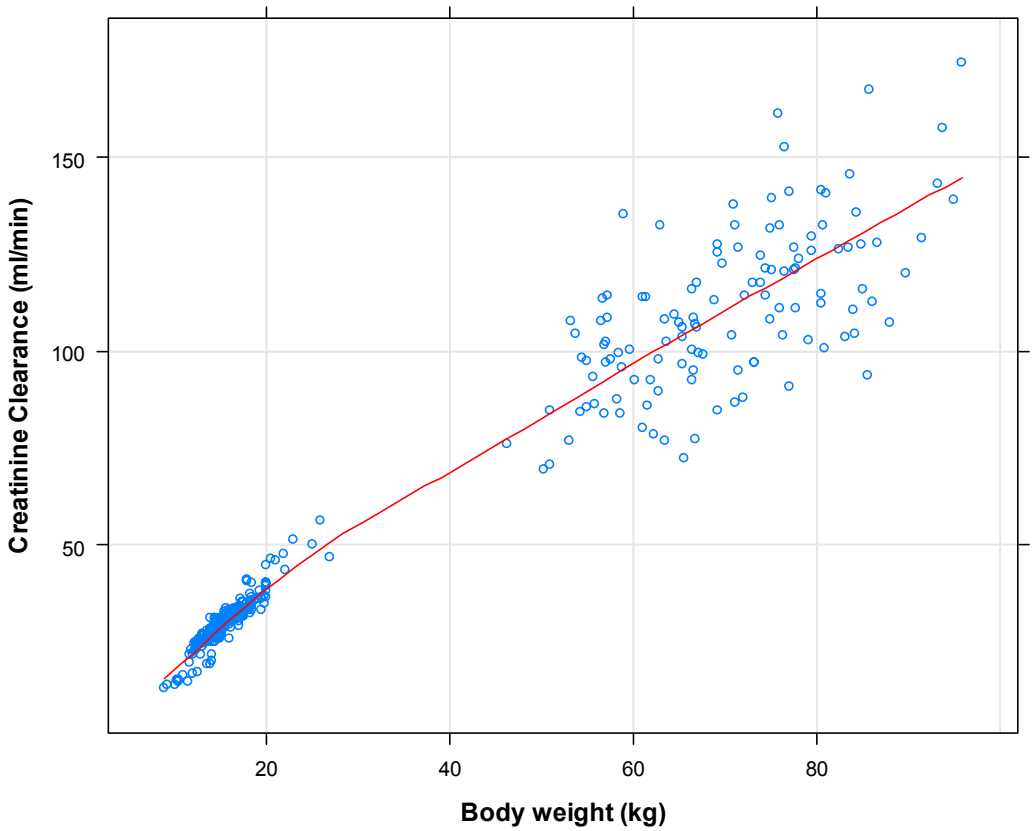
- Body weight was found to be the main parameter influencing the pharmacokinetics of LCTZ in the pediatric population.
- Following inclusion of body weight in the model, age, gender, form, CLcr and food were found to have a negligible additional influence on the pharmacokinetic of LCTZ.
- The model was then employed to identify dose adaptations for children aged from 6 months to 6 years that would result in the same peak and trough plasma concentrations as in adults receiving 5 mg levocetirizine once daily. In each successive age step, children body weights were sampled from the CDC/NHANES growth tables and were used in the

Monte-Carlo simulations of plasma concentrations. Finally, dosing regimens of 1.25 mg levocetirizine once a day for 6 to <12 months old children and 1.25 mg twice a day for 1 to <6 years old children were predicted to result in peak and trough concentrations in the range of the adult values at the current recommended dose 5 mg once daily.

Reviewer's comment:

Despite the fact that renal clearance plays an important role in the elimination of LCTZ, the sponsor removed CLcr from the covariate model for clearance. Even though this is not recommended from a mechanistic point of view, the sponsor demonstrated that the impact of CLcr on PK exposure is ignorable based on simulation as long as weight is included in the covariate model. This observation is explained by the high correlation between body weight and CLcr in the subjects included in the population PK analysis (Figure 6). However, it should be noted that this observation only applies to subjects with normal renal function because the sponsor's simulation only considered the renal function values within the normal range.

Figure 6. Relationship between creatinine clearance (CLcr) and body weight with loess smooth line



Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22064	SUPPL 17		XYZAL(LEVOCETIRIZINE DIHYDROCHLORIDE)TAB

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/s/

PARTHA ROY
08/14/2009

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08/14/2009

SALLY Y CHOE
08/14/2009