CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

sNDA	19-962 SE5 #033
Submission Dates	05/15, 06/16 and 07/10/2006
PDUFA Goal Date	11/15/2006
Brand Name	Toprol-XL
Generic Name	Metoprolol succinate
Priority Designation	P
Applicant	Astra Zeneca
Submission	Pediatric Supplement
Therapeutic Class	Beta Blocker
Dosage Form & Strength	Extended release tablets 25, 50, 100, and 200 mg
Indication (proposed)	Hypertension
Proposed Dosing Regimen	1.0 mg/kg daily (initial) followed by titration
Intended Population	Pediatric patients
OCP Division	DCPI
OND Division	Cardiovascular and Renal Drug Products
Primary Reviewer	Robert O. Kumi, Ph.D.
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Briefing Date: 10/13/2006
Briefing Attendees: Peter Hinderling, Christine Garnett, Elena Mishina, Avi Karkowsky, Arzu Selen, Sandra Chow, Joga Gobburu, Atik Rahman, Dennis Bashaw, John Lazor and Chandra Sahajwalla

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1 EXECUTIVE SUMMARY

Astra Zeneca submitted NDA 19-962 SE5 #033 (pediatric supplement) to fulfill a FDA pediatric written request for TOPROL-XL, metoprolol succinate extended release tablets. Metoprolol, a beta blocker, is approved for hypertension, angina and heart failure in adults. In adults with hypertension the usual initial dosage is 25 to 100 mg daily (single dose) as monotherapy or in combination with a diuretic; this dosage is titrated at weekly intervals until optimum blood pressure reduction or control is achieved. The current application focuses on Toprol-XL use in pediatric patients six years and older. The initial proposed dosing in children six and older is 1.0 mg/kg; subsequently the dose is titrated based on clinical response.

Two clinical trials, Studies 307A (dose-response) and 307B (safety extension of 307A), were conducted in pediatric patients with hypertension to support the proposed labeling changes. The applicant conducted dose-response (n = 140 patients), population PK (n = 120 patients) and PK/PD (n = 65 patients) analyses using data from pediatric hypertensive patients receiving Toprol-XL in the mentioned studies. PK and PD measures estimated in the analyses or determined during the trials included: Ctrough, Cmax, AUC_{0-24}, CL/F, Tlag (lag time), ka (first order absorption rate constant), V2/F (volume of distribution in central compartment), Q/F (inter-compartmental clearance), ΔDBP (change in diastolic blood pressure, ΔSBP (change in systolic blood pressure), and ΔHR (change in heart rate). Selected covariates including age, body weight, gender, race, and Toprol-XL dose were evaluated for their potential impact upon PK parameters.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the information submitted to NDA 19-962 SE5 #033. The clinical pharmacology and biopharmaceutics information provided in the current submission is acceptable. However, the sponsor should note the following.

Comments to sponsor

A. In future studies with pharmacometric components you should consider the following:
   1. Collect sufficient (multiple) samples from individual subjects to allow assessment of inter-occasion variability and estimation of inter-individual variability (eta) for all relevant parameters.
   2. Placebo groups should be identically matched across all dose groups (e.g. same titration schedule and number of tablets) to minimize potential bias or apparent differences in the placebo effect.

B. Please address labeling changes and comments in the attached revised label (Page 19).

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

1. **Dose-Response**: A statistically significant dose-response did not exist for placebo (pooled)–corrected ΔSBP from baseline; however, the relationship was evident when placebo (specific-group) –corrected data were used.

2. **Proposed Pediatric Dosage:** Overall, information from the dose-response study suggests that Toprol XL is effective in the pediatric population. The optimal initial dose in mg/kg or the maximum safe and effective dose cannot be determined from the information provided. However, the 1.0 mg/kg (proposed by applicant) appears to be a reasonable initial dose; subsequent titration based on clinical response is acceptable. Relative to adults (assuming average adult weighs 70 kg), the proposed initial pediatric dose is in the range but closer to the high end of the usual initial adult dose: 0.36 – 1.43 (25 to 100 mg).

3. **Metoprolol Pharmacokinetics in Pediatric Patients**: Metoprolol PK in children (6 – 16 years old) were adequately characterized by a 2-compartment model with flip-flop, first-order absorption, and an absorption lag time using a population PK approach. The population PK model yielded precise parameter estimates. Estimated PK Measures (median values) were CL/F = 227.5 L/hr; V2/F = 96.1 L; Q/F = 675 L/hr; V3/F = 620 L; ka = 0.0467 hr^{-1}; and Tlag = 0.853 hr. Overall, the PK measures in children are of a similar magnitude as that in adults reported in the literature.

4. **Metoprolol Exposure in Children**: At the proposed pediatric initial dose, 1.0 mg/kg, average Cmin was ~ 12.2 ng/ml and average Cmin was ~ 24.6 ng/mL at the 2.0 mg/kg dose; however data were highly variable with CV > 100 %. The majority of samples were below the lower limit of quantitation at the lowest studied dose, 0.2 mg/kg. In adults (literature reports), average Cmin following 50 mg (~0.71 mg/kg) was ~ 8.5 ng/mL and ~ 22.6 ng/mL following 100 mg (~1.43 mg/kg).

5. **Covariates:** Sex, age, race, body weight, and Toprol-XL dose did not have a clinically significant effect on metoprolol PK.

6. **Population PK/PD Model:** Using a log-linear model or linear model, there were statistically significant relationships ($p < 0.005$) between the changes in SBP and DBP from baseline and measures of metoprolol plasma exposure (Ctrough, $AUC_{(0–24}$ and Cmax). However, the goodness-of-fit of the PK/PD models were generally poor and parameters were not precisely estimated in most models due to a high degree of variability in the blood pressure data. Based on the PK/PD analysis, plasma exposure (AUC) explains < 10 % of the response (reduction in systolic blood pressure). However, the PK/PD relationship suggests that there is a trend for increased response with increased exposure (dose driven), thus supporting dose titration.

Robert O Kumi, Ph. D. Date
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Concurrence
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2 Question Based Review

2.1 What are the general attributes of metoprolol?

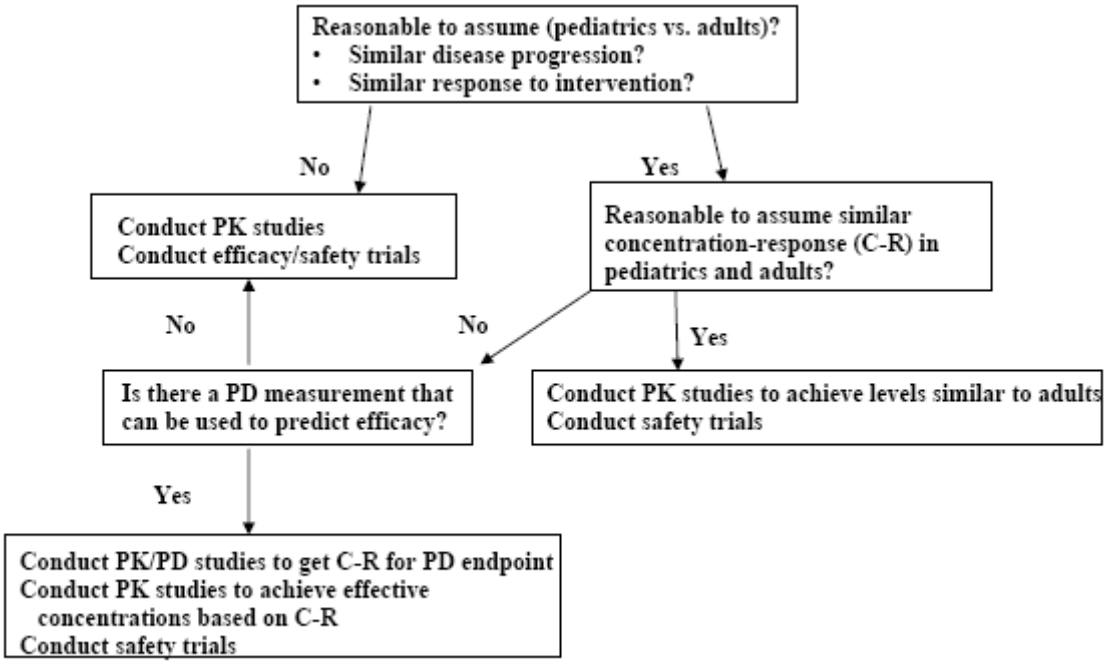
2.1.1 Regulatory Background

An original pediatric written request to support pediatric exclusivity was issued in October 1999. Subsequently, amendments were made to the original request and a final written request was submitted in October 2004. Key elements of the request follow:

1. Dose ranging trial in pediatric patients with hypertension (6 – 16 years old)
2. Pharmacokinetic sampling in the same range as those studied for effectiveness
3. Safety data from a controlled trial and 1-year open label treatment phase following the effectiveness trial
4. Summary of all available information on the safety of the drug in hypertensive patients.

The pediatric decision tree is depicted below: this decision paradigm is used to support the rationale for choosing which studies had to be conducted.

Pediatric Decision Tree (CDER MaPP 4000.4)



Disease Process: Cause of Hypertension in Children

Most children between 1 and 17 years old tend to have secondary forms of hypertension. In infants and younger children underlying renal or reno-vascular disease is frequently the cause for hypertension (80%), whereas essential hypertension is predominant in adolescents and adults. Therefore, the disease progression and response to the treatment in children and adults are not similar. Based on the Pediatric Decision Tree Guidelines safety and efficacy studies are required in the target population to establish the indication in the pediatric patient population.

2.1.2 Selected background information on metoprolol

Background on Metoprolol in Hypertension

Table 1: Snapshot of metoprolol clinical pharmacology and biopharmaceutic information*

Drug Class	Metoprolol is a ß1-selective (cardio selective) adrenergic receptor-blocking agent
Mechanism of Action (antihypertensive effect)	Multiple putative mechanisms: competitive antagonism of catecholamine at peripheral sites, reduction of sympathetic outflow to the periphery, or suppression of renin activity.
Approved Indications	Hypertension, Heart Failure and Angina Pectoris
Approved Formulations	1. Immediate Release (IR) – metoprolol tartrate 2. Toprol-XL is extended-release tablet of metoprolol as the succinate salt; it is also referred to as metoprolol in literature as controlled release (CR/Z0K)
Metabolism	Via CYP2D6 primarily
Absorption	Absolute oral bioavailability ~ 50 % following IR. Food does not affect metoprolol absorption using ER formulation
Distribution	Protein binding to albumin is about 12%.
Elimination	For IR, $t_{1/2}$ from 3 – 7 hours. Less than 5 % dose excreted unchanged in urine. No $t_{1/2}$ values for ER; this may be due to difficulty in separating absorption and elimination phases
Variability	Plasma levels are highly variable among subjects after oral administration.
PK/PD in children	Limited information in children; information obtained following administration of metoprolol tartrate (IR).

*****Please refer to NDA 19-962 for additional background information.

2.1.3 Proposed Formulation, Administration Route and Dosage

The formulation proposed for pediatric use is Toprol-XL; this formulation will be given orally at an initial dosage of 1.0 mg/kg once daily (QD). Subsequently the dosage will be titrated depending on clinical response. The maximum dosage studied was 200 mg QD. Toprol-XL is available as a 25 (scored tablet), 50, 100 and 200 mg tablet (b) (4)

2.2 What are the general clinical pharmacology characteristics of metoprolol succinate?

2.2.1 Design features of clinical studies used to support dosing in the target population

Two studies were conducted in hypertensive pediatric studies, Study 307A and 307B; the design features of these studies are summarized in Table 2.

Table 2: Study Designs

Study Name	Study 307A (D4020C00033)	Study 307B (D4020C00001)
Objective	Determine dose-response in children	Determine long-term safety
Doses	Toprol XL 0.2, 1.0 and 2.0 mg/kg QD (maximum 200 mg QD) and Placebo	Initial 25 mg QD then titrated to optimal clinical response (maximum 200 mg QD)
Design Feature	• 1-2 week placebo run-in period • Patients in 1.0 and 2.0 mg/kg groups dosed over 2 week period, but 0.2 mg/kg group received dose for 4 weeks	Patients continuing from 307A or new enrollees
PK Features	Ctrough (week 4)	Ctrough (last study visit) and serial PK in subset (n = 31)
Primary Measures/ Outcome	Change in placebo-corrected trough sitting BP from baseline at week 4*	Long-term safety using effective Toprol dose

* LOCF approach followed

2.2.2 Clinical response (efficacy) endpoints

Pharmacodynamics

- Primary variable

Sitting SBP determined at trough (24±4 hours, Visit 7) served as the primary efficacy assessment. The primary measure of effect was the placebo-corrected change from baseline to the end of treatment (Week 4) in trough sitting SBP. Each BP determination represented the mean of 3 readings with less than 7 mmHg between the highest and lowest value.

- Secondary variables

Secondary variables included trough sitting DBP and percentage of responders at Week 4.

2.2.3 Idenitifcation and measurement of metoprolol concentrations in plasma

Metoprolol appeared to be adequately identified and measured in Study 307A and 307B. A validated HPLC with tandem mass spectrometry method was used to quantify metoprolol. Key features of the assay were:

- limit of quantitation (LOQ) = 1 ng/mL.
- linear range = 1 to 1000 ng/mL
- Precision, measured by CV (%) ≤ 10.9%
- Accuracy measured by relative bias ranged from – 6 % to + 1.3 % .

Overall, the assay performance was acceptable.

2.2.4 Metoprolol exposure-response

The exposure-response evaluation revealed that:

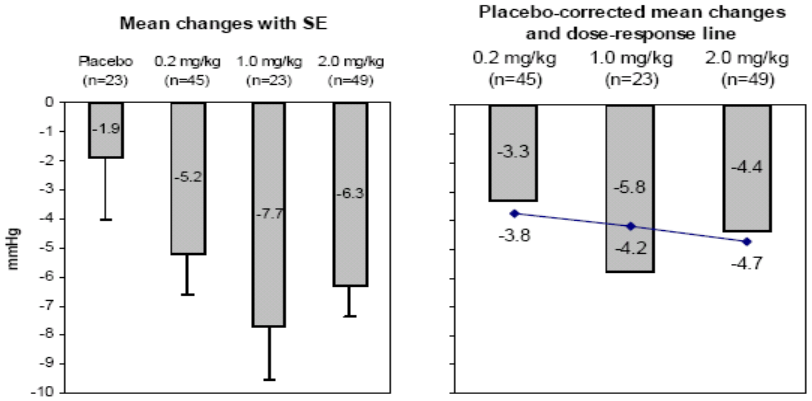
- There was no clear dose-response relationship for effectiveness (primary variable: change in sitting SBP) in the target patient population using the planned analysis (Sponsor's), but there was a dose-response for the secondary efficacy variable (Sponsor's)
- There was a dose-response relationship for effectiveness when group-specific placebo correction was employed (Reviewer's)
- The proposed initial dosage regimen and subsequent titration are supported by
    1) Existence of an exposure-response relationship for Ctrough and AUC, and SBP reduction
    2) Overall Toprol XL being more effective than placebo at reducing SBP and DBP
    3) For a given dose maximal efficacy occurring between 1 and 4 weeks after treatment initiation
- There was no clear dose-response relationship for safety .

2.2.4.1 Dose-Response Assessment using Primary Variable and Analyses

Sponsors Analyses: Primary Variable

The dose-response relationship for Study 307A is depicted in Figure 1. When pooled placebo data were used for correcting change in SBP, the slope of the curve is not different form zero ($p = 0.5371$ for dose ratio), suggesting that there is no dose response. By visual inspection it appears the lack of observed dose-response is mainly driven by a lower than expected response at the 2.0 mg/kg level. Patients assigned to the 1.0 mg and 2.0 mg/kg dose received drug for only 2 weeks whereas dose in the 0.2 mg/kg received the same dose for 4 weeks. It is unclear if this difference in titration schedule influenced the outcome.

Figure 1: Dose response for placebo-corrected change from baseline to Week4/LOCF for sitting SBP (ITT population)

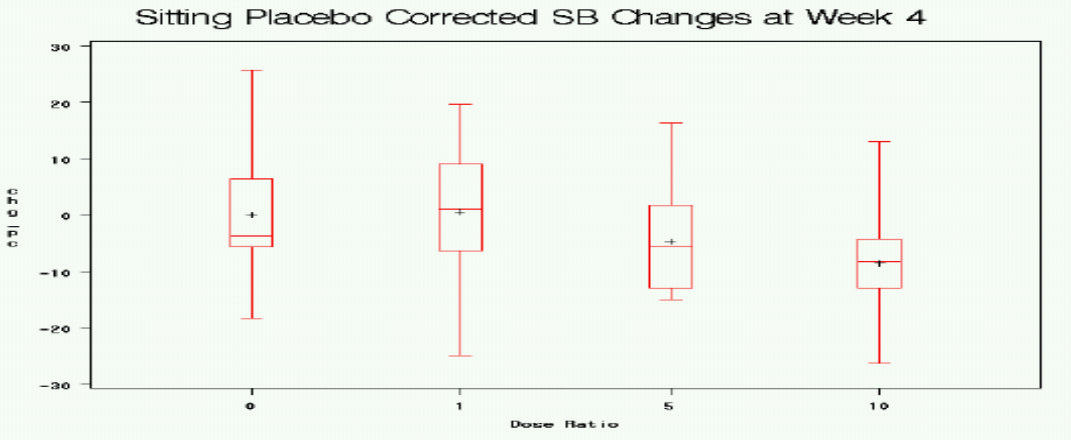


Note: For each treatment group, the standard error (SE) was calculated using the following formula: standard deviation ÷ square root of n.

Reviewer's Analysis: Primary Variable

When group-specific placebo corrected data were used for correcting change in SBP there was a statistically significant dose-response (Figure 2).

Figure 2: Placebo corrected changes in SBP (chg_pc) as a function of dose ratio (relative to 0.2 mg/kg)



In this procedure, data for subjects assigned to a given active group (e.g. 0.2 mg/kg) were corrected with placebo data (0.2 mg/kg). It should be noted that the group-specific placebo data appeared to follow a consistent trend, where the placebo effect decreased with increasing number of tablets. It is unclear if this titration/tablet-dependent placebo effect is valid or random. Overall, the apparent differential placebo effects suggest that the placebo group may have overly influenced the outcome of the dose-response analysis.

Two potential limitations of this Reviewer's supplemental analyses are:

1. Typically placebo effects are constant if randomization is appropriate; thus it is unclear if sub-setting the placebo group is reasonable and did not increase bias.
2. Additionally, sub-setting the placebo group leads to a reduced number of placebo subjects per dose group that may decrease the robustness of the regression findings.

2.2.4.2 Dose-Response Assessment using Secondary Variable and Analyses

Treatment Group Effects and Pairwise Comparisons for sitting SBP and DBP

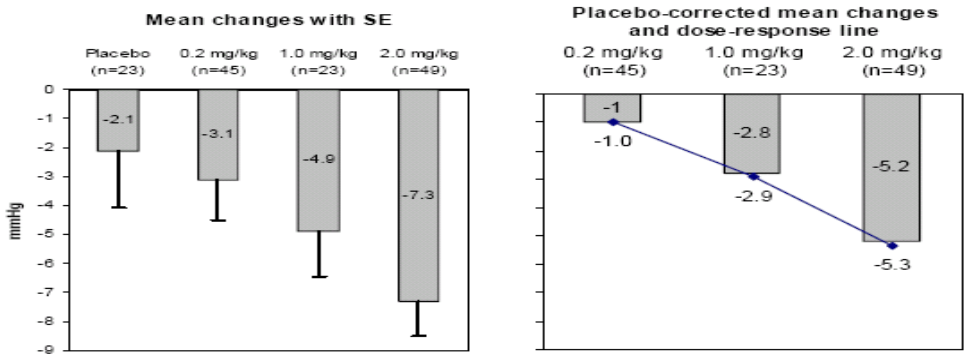
Key findings from the group and pair-wise comparisons are:

1. All active groups produced statistically significant reductions from baseline ($p < 0.02$) in sitting SBP ($|\Delta$ SBP$| > 5$ mmHg) and DBP ($|\Delta$ DBP$| > 3$ mmHg) at the Week 4/LOCF visit, whereas placebo ($p = 0.3133$) did not.
2. Overall, the mean change from baseline in sitting SBP ($|\Delta$ SBP$| = 4.256$) at Week 4/LOCF for the TOPROL-XL groups pooled was statistically significantly larger ($p=0.0351$) than that for the placebo group.
3. Pairwise comparisons between individual TOPROL-XL dose groups and placebo also revealed a statistically significant difference for the 1.0 and 2.0 mg/kg groups ($p=0.0270$ and $p=0.0492$, respectively); the 0.2 mg/kg group was not different from placebo.

Sponsor's Analyses : Secondary variable

A dose-response relationship was observed for the secondary efficacy variable (delta DBP), as depicted in Figure 3.

Figure 3: Mean changes (actual and placebo-corrected) from baseline to Week 4/LOCF for sitting DBP (ITT population)



Note: For each treatment group, the standard error (SE) was calculated using the following formula: standard deviation ÷ square root of n.

2.2.4.3 Dose-Response assessment based on subgroup analyses (per Sponsor) and time course

Subgroup Analyses

The sponsor conducted several exploratory subgroup analyses; however, these analyses were not reviewed critically and are not presented in this review as:

1. they do no impact the primary outcome or study objective
2. they are unlikely to be clinically useful due to the small number of patients per subgroup

However, one potentially useful group analyses involved the percentage of responders, as defined in Table 3. The responder analyses shows:

1) greater percentage of responders in active dose group relative to placebo
2) comparable response rates for all active dose groups suggesting similar efficacy across dose groups, despite different exposure (doses).

Table 3: Number and proportion of responders (ITT population)

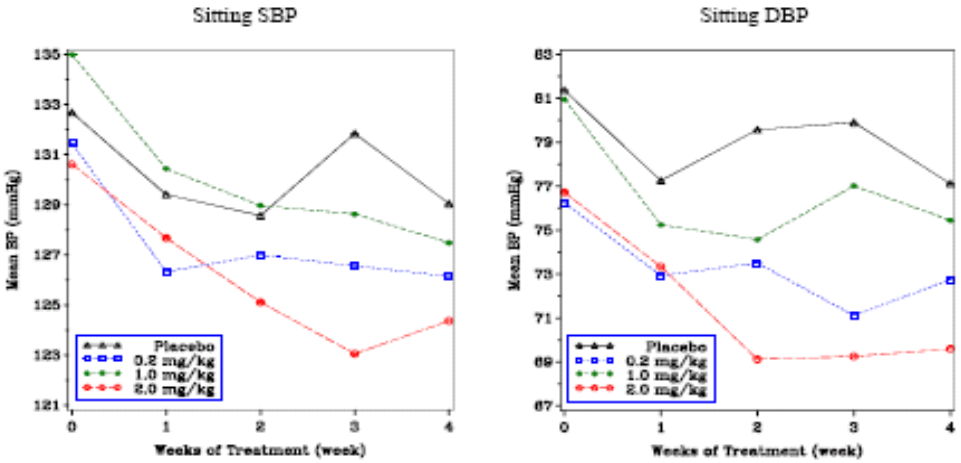
	N	Number of responders	Proportion of responders	95% CI
Placebo	23	6	0.261	0.0814, 0.440
TOPROL-XL 0.2 mg/kg	45	21	0.467	0.3209, 0.612
TOPROL-XL 1.0 mg/kg	23	10	0.435	0.2322, 0.637
TOPROL-XL 2.0 mg/kg	49	23	0.469	0.3297, 0.609
TOPROL-XL groups combined	117	54	0.462	0.3712, 0.551
Total	140	60	0.429	0.3466, 0.510

Note: Responders were defined as any patient whose sitting SBP and DBP was less than the 95th percentile at Week 4. Patients without a value at Week 4 were considered nonresponders.
CI confidence interval; ITT intention-to-treat.

Time course of effect (2- to 4-week treatment period)

Consistent with findings from other studies with metoprolol and some beta-blockers, apparent maximal reduction in blood pressure occurred between 1 and 4 weeks of treatment. The mean changes over time in sitting SBP and DBP are depicted in Figure 4.

Figure 4: Mean changes* over time for sitting SBP and DBP (ITT population)



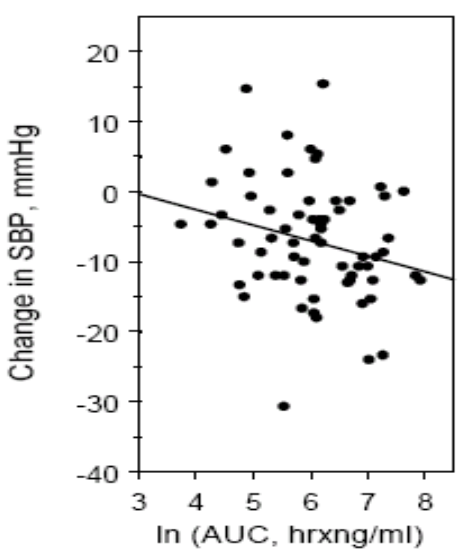
* Data points in plot are from absolute values (not taking baseline into account) and subjects in 1.0 and 2.0 mg/kg received drug after two weeks on 0.2 mg/kg.

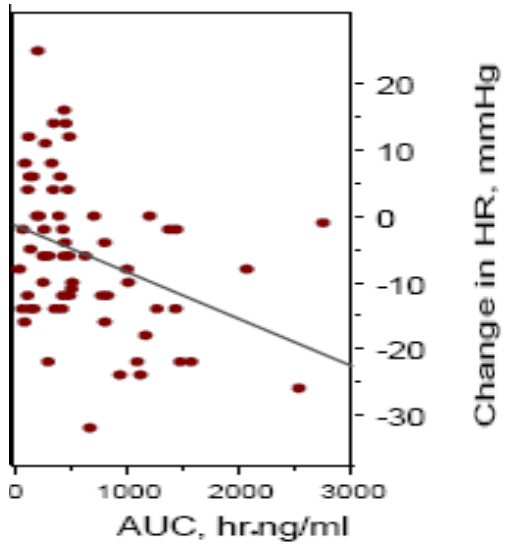
2.2.4.4 PK/PD Assessments

Overall there were statistically significant relationships between metoprolol exposure, particularly AUC, and SBP reduction as shown in Figure 5. Similar findings were observed for heart rate reduction Figure 6.

Change in SBP

Figure 5: Change in SBP vs. log (AUC) – per Sponsor **Figure 6: Change in HR vs. AUC**





The population PK/PD assessment evaluated the effect of PK exposure measures (AUC, Cmax and Ctrough) on various PD measures (change in SBP, change in DBP. However, only the AUC was considered reliably estimated. It is noted that AUC is a derived measure that may not bear as direct a relationship as Ctrough (observed value) on a given PD measure. However, Ctrough is related to AUC, particularly at steady-state. The equation relating AUC to change in SBP was:

$$E = E0 - 2.21 \times m \log AUC$$

Where E = change in SBP, E0 = baseline SBP, m = slope and AUC = area under plasma concentration-time curve

The regression analyses yielded the following: $p < 0.05$ for slope and $R^2 < 0.1$. The relatively low R^2 value suggests that the SBP data were highly variable and changes in SBP could not be accounted for entirely by AUC (exposure). Nevertheless, there is a relationship between effectiveness and AUC that indicates that increasing exposure potentially increases effectiveness; this finding supports dose titration.

Change in Heart Rate

The change in heart rate was defined as follows (Reviewer's regression analysis)

$$E = I - 2.21 \times m \log AUC$$

Where E = change in HR, I = intercept and m =and AUC are as previously defined

The regression analyses yielded the following: $p < 0.01$ for slope and $R^2 = 0.11$. The heart rate findings support metoprolol's known activity as a beta blocker.

Reviewer Note: PK/PD modeling with various hemodynamic measures
The modeling exercises indicated that there was no difference in the PK/PD modeling results using different hemodynamic data formats, such as change in the measurements, percent change in the measurements, or actual BP measurements.

2.2.4.5 Exposure-Safety Highlights (per Applicant)
According to the applicant Toprol XL was generally well tolerated in the pediatric population and there did not appear to be a clear dose-dependent effect in terms of severity or frequency of adverse events (tabulated below).

Category	TOPROL-XL treatment groups									
	Placebo (N=24)		0.2 mg/kg (N=46)		1.0 mg/kg (N=23)		2.0 mg/kg (N=49)		All patients (N=142)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
At least 1 treatment-emergent AE[a]	12	(50.0)	17	(37.0)	9	(39.1)	30	(61.2)	68	(47.9)
Drug-related AE	2	(8.3)	3	(6.5)	2	(8.7)	5	(10.2)	12	(8.5)
Serious adverse event	0		0		0		0		0	
Discontinued treatment due to AE	1	(4.2)	0		0		0		1	(0.7)
Death	0		0		0		0		0	

[a] A treatment-emergent adverse event (AE) is defined as an AE which began following the first dose of double-blind study medication.

2.2.4.6 Acceptability of sponsor's proposed regimen
The proposed initial dosage, 1.0 mg/kg QD, followed by titration according to clinical response appears reasonable based on the dose-response information, time course of maximal effect and exposure-response (AUC and SBP reduction) information. It is unclear if the proposed initial dose is optimal since a dose-response relationship was not established for the primary efficacy variable and response rates were comparable across dose groups. One should note that the proposed initial pediatric dosage is within the range of usual adult initial dosage: 25 – 100 mg (assuming 70 kg adult ~ 0.36 – 1.43 mg/kg).

The major unresolved issues are

- Absence of a clear dose-response relationship for the primary efficacy variable
- Unknown maximal dose in mg for initial therapy and titration/maintenance therapy
- Unknown optimal titration frequency

Although these major issues are not completely resolved, information provided in the submission provides adequate information to support the proposed dosage. In brief these limitations are addressed in part by adopting the following approaches:

- Therapy will be initiated at a dose that was more effective than placebo, yet was not the highest dose, thus providing a safety window
- Initial dosage (dose in mg) will be limited to a dose that produces exposure that is likely to be effective but does not exceed the highest studied dose (200 mg)
- Titration will be allowed at a frequency no greater than once a week, which is consistent with data obtained (time to peak activity) and previous information form metoprolol and other beta-blockers used in hypertension treatments.

2.2.4.7 PK/PD comparisons : Pediatric patients vs. adults

A priori PK/PD relationships are expected to differ between adults and children because the two populations have different disease processes (secondary hypertension in children vs. essential or primary hypertension in adults). Results of the pediatric modeling exercise showed that a log-linear model appeared to work better than other models for the relationship between SBP and DBP and exposure (AUC). In adults the Sigmoid Emax model has been successfully applied in PK/PD modeling exercises. It should be noted that the adult data were not reanalyzed for this review, so it is unclear if log-linear or linear models would be adequate.

As illustrated in Table 4, Toprol XL is effective in adults as well as in children and appears to be effective across a similar concentration range.

Table 4: PK/PD Comparisons- Pediatric Patients vs. Adults

	Pediatric Patients	Adults
Population	hypertensive	Typically healthy
Model	Log-linear	Sigmoid Emax
PD Markers	Placebo corrected SBP / DBP changes at trough	• Reduction in exercise heart rate (beta-blockade measure) • Placebo corrected SBP / DBP changes at trough
Effective/Therapeutic metoprolol concentrations	Most concentrations < 107 ng/mL	• EC_{50} = 105 nmol/L (28.1 ng/mL) • Emax achieved at concentrations above 400 nmol/L (107 ng/mL). • Range between 80 and 300 nM
Maximal mean BP Reduction at Studied Doses	• SBP reduction -6 • DBP reduction -5	• SBP reduction -10 • DBP reduction -4
Effectiveness of metoprolol relative to placebo	Generally more effective over the course of treatment	Generally more effective over the course of
Time course of effect	Maximal effect observed within 1 to 4 weeks after initiation of therapy	Maximal effect observed within 1 to 4 weeks after initiation of therapy
Utility in Poor CYP2D6 metabolizers (PMs)	Not evaluated	Poor metabolizers have a higher plasma concentration and a greater duration or degree of beta blockade, thus PMs may not need extended release formulations
Proposed Initial Dosage	1.0 mg/kg ~ 70 mg QD	25 to 100 mg QD

Overall, it appears the studied pediatric doses produce comparable changes in diastolic pressure but lower changes in systolic pressure. However, in pediatric patients it is unlikely that the maximal possible activity was achieved at the doses studied; thus, conceivably pediatric patients can achieve maximal effects comparable to adults at optimized pediatric doses. Three challenges in making definitive PK/PD comparisons between the pediatric (studied in this NDA) and adult population are as follows:

1. Study conditions differ- typically in adult studies HR is measured during exercise and not at rest
2. Results are obtained in healthy adult subjects rather than hypertensive patients
3. Insufficient numbers of studies have been reported in the literature that attempt to identify the relationship between metoprolol exposure and SBP or DBP effect in adults.

2.2.5 Pharmacokinetic characteristics of metoprolol

2.2.5.1 Metoprolol pharmacokinetics in pediatric patients

Metoprolol PK parameters obtained from the population PK analyses are summarized in Table 5.

Table 5: Metoprolol population PK parameter estimates (SE %) obtained using final population PK model

PK Parameter	Value
CL/F (L/hr)	227.5 (11.4 %)
V2/F (L)	96.1 (20.3 %)
V3/F (L)	620 (25.5 %),
Q/F (L/h)	675 (20.4)
Ka (hr^{-1})	0.0467 (19.2 %)
Tlag1 (hr)	0.853 (2.97)

The data in Table 5 are derived from a 2-compartment linear PK model with first-order elimination and flip-flop first-order absorption and lag time.

2.2.5.2 Metoprolol pharmacokinetic comparisons: pediatric patients vs. adults

PK Parameter Comparison

Overall, pediatric PK parameters obtained following administration of Toprol-XL are comparable (similar magnitude) to those in adults receiving IR metoprolol. Potential limitations of the stated comparison and finding include the use of different modeling approaches, populations, number of samples and number of subjects in the trials (Table 6).

Table 6: Comparative PK (children vs. adults)

Source	NDA 19962	Luzier et al	Taguchi et al	Plosker and Cissold and other sources
Model	2 Comp, 1st Order absorption		1 Comp	
Formulation	Toprol XL	IR	IR	IR
Population	Pediatric Hypertension	Healthy adults	Japanese geriatric	
Sampling	Intense and Ctrough	Intensive	Sparse	intensive
CL/F (L/hr/kg)	3.38	1.16 – 3.40	0.94	-
V2/F (L/kg)	1.28	2.70 – 3.98	4.52	-
V3/F	8.51	3.33 – 8.09	-	-
Q/F (L/hr)	8.99	2.82 – 6.94	-	-
$T_{1/2}$ (h)	3.51	-	-	3 - 6
Covariate Effects Based on CL/F*				
Age	None	-	Yes	Yes/No
Gender Effect	None	Yes	-	-
Race	None	-	-	-

* The applicant noted that pediatric data were compared to adult data from IR, where CL/F is dominated by the disposition function of metoprolol, therefore it may be complicated to compare adult data to pediatric data (Toprol XL), where CL/F is under a considerable influence from the release rate (input function) of the device. This appears to be a valid caveat. Using AUC and dosing information (Table 8), adult CL/F for Toprol-XL ~ 1.7 – 2.5 L/hr/kg

Exposure Comparison

Following administration of Toprol XL at comparable doses in mg, pediatric patients and adults generally had similar metoprolol exposure. Adult data from literature and archived clinical pharmacology and biopharmaceutics reviews are presented in Table 8 and pediatric data from

population PK modeling (Study 307A) are presented in Table 7. The main limitations of the cross-population comparison is the pediatric doses are over the 12.5 to 200 mg dose range, whereas adult data is for specific doses. However, reasonable comparisons can be made at the 100 mg dose level assuming the mean/median values in pediatric patients offer an acceptable approximation of exposure values and are representative of the central tendency of the data. In this case, the adult and pediatric data have comparable

1. exposure at 100 mg
2. degree of variability

Table 7: Bayesian estimates of metoprolol PK exposure for those patients included in the PK/PD analysis (N=65)*

Parameter	Median	Mean	SD	Max	Min
Dose (mg)	100	107.7	69.5	200	12.5
Observed trough plasma concentration (ng/mL)	10.8	21.3	29.3	167	1.28
Estimated C_{24} trough plasma concentration (ng/mL)	10.1	18.8	21.1	99.3	1.20
C_{max} (ng/mL)	25.2	32.6	25.8	123	2.19
$AUC_{(0-24)}$ (hr •ng/mL)	440	629	577	2745	42.2
T_{max} (hr)	5.25	5.32	2.42	9.75	1.50

[a] No interpatient variability in V_2/F in the model.

* includes only data where concentration > LOQ

Table 8: Metoprolol exposure in adults following administration of Toprol XL

	Cmax	Cmin	AUC
	Literature References		
50	17.9 – 19.0	8.6 – 10.4	286 - 351
100	9.6 – 75.9	10.7 – 30.5	533 - 1192
200	77.8 – 113.9	31.0 – 44.7	1392 - 1892
	FDA Archived Information		
50	17.9 ± 18.2	8.5 ± 13.8	286 ± 346
100	54.4 ± 43.6	22.6 ± 23.4	827 ± 766

2.2.5.3 Inter and intra-subject variability in metoprolol pharmacokinetic

Based on the values of the standard error (%) associated with PK parameters (Table 5), metoprolol PK exhibited low variability (SE % < 30). However, this estimate may not be reliable (under predicted) because concentrations < LOQ were not included in the analysis. Several subjects, particularly those receiving 0.2 mg/kg had concentrations < LOQ. In adults exposure is highly variable (CV > 70 %) as reflected in exposure estimates and wide exposure ranges Table 8.

Potential sources of variability following metoprolol administration (Toprol XL) in children include regio-selective absorption, incomplete gastric emptying, variable gastric motility, varying metabolic activity (CYP2D6) and inconsistent absorption. Some of these factors are also applicable to adults.

2.3 What Intrinsic Factors Affect Metoprolol Exposure-Response?

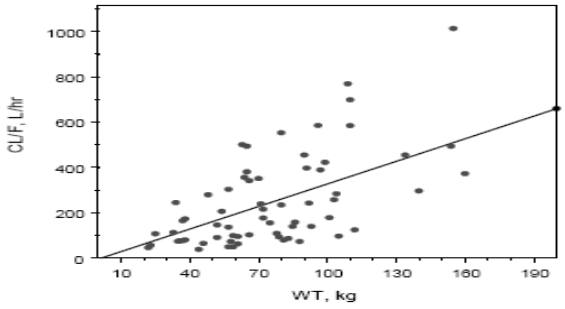
Based on the population pharmacokinetic model, weight was the only potentially clinically meaningful intrinsic factor that affected metoprolol exposure and hence response. Other intrinsic

factors such as age, height, gender, race and sex did not affect metoprolol exposure.

2.3.1 Effect of weight

The effect of weight on metoprolol CL/F are illustrated in Figure 7.

Figure 7: Variation of CL/F with weight obtained in population PK analysis



Note: Each point represents an individual Bayesian estimate of the corresponding CL/F . The line is derived from model expression CL/F =227.5+3.32*(WT−70) .

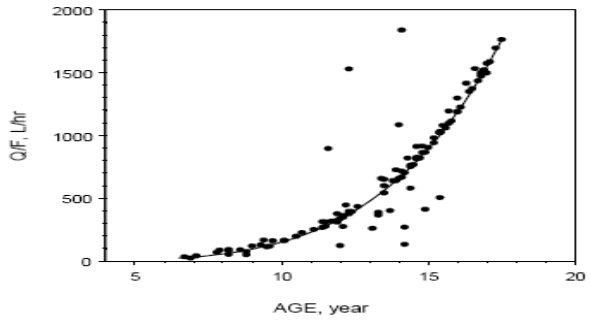
CL/F increased linearly with body weight: relative to a 70 kg individual, the CL of a 22 kg individual is 30 % lower. This decreased CL will result in an increased exposure (maximum 30 %) that does not pose additional safety concerns or appear clinically significant (tolerated in studies). It should be noted that exposure (AUC) accounted for an insignificant portion of the hemodynamic effect (poor correlation), thus the clinical implications of the impact of body weight on CL/F of metoprolol identified in the population PK modeling are limited. Consequently, dose adjustment is not required based on body weight. Furthermore, the maximum initial dose is 50 mg, thus subjects with weight > 50 kg will receive a maximum dose of 50 mg, diminishing the impact, if any, of weight-dependent clearance.

2.3.2 Effect of Age

The effect of age on Q/F, the inter-compartmental clearance, is illustrated in Figure 8.

Figure 8: Variation of Q/F with age obtained in population PK analysis

Observed and simulated dependence of distribution clearance of metoprolol on age (AGE)



The line was derived from the model expression $Q/F = 675*(AGE/14.0)^{4.41}$.

Q/F does not contribute significantly to overall clearance, therefore the reported finding does not appear clinically relevant. It should be noted that the observed Q/F-age relationship is atypical.

2.3.3 Effect of intrinsic factors on exposure-response: pediatrics vs. adults

As mentioned previously the only evaluated intrinsic factor that affected metoprolol exposure was body weight. In adults, age and gender effects have been reported, although there are conflicting reports on the age effect. The exposure in adult and pediatric population are both potentially affected by the CYP2D6 metabolizing status of the subject. Metoprolol is metabolized primarily in the liver by CYP2D6. The scientific literature reports several instances in adults of varying metoprolol exposure by poor and extensive CYP 2D6 metabolizers. In the pediatric studies (307A and 307B) there was one suspected poor metabolizer (Trough concentration was 2330 ng/mL), but the metabolic status (PM or EM) of this individual was not confirmed.

2.4 What extrinsic factors affect metoprolol exposure-response?

The role of extrinsic factors were not specifically evaluated in the pediatric population; however, one anticipates that extrinsic factors that affect adults should be applicable to children.

2.5 What analytical method was used in pediatric studies 307 A and 307B?

Please refer to section 2.2.3 .

3 DETAILED LABELING RECOMMENDATIONS

GENERAL

CLINICAL PHARMACOLOGY COMMENTS

Labeling

Attach annotated labeling with reviewer markings and list all proposed changes along with the reviewer comments.

Pertinent sections of the annotated labeling follow.

Rx only
Toprol-XL
(metoprolol succinate)
EXTENDED-RELEASE TABLETS
TABLETS: 25 MG, 50 MG, 100 MG, AND 200 MG

Clinical Pharmacology
Pharmacokinetics

1Module 5, Clinical Study Report section 5.1 (307B)
2Module 2, Clinical Overview section 1.2.2.1
3 Module 5, Population PK Report sections 2 and 4.5.1
4Module 2, Clinical Overview section 3.3
5Module 5, Population PK Report section 6.2.1

(b) (4)

Metoprolol apparent oral clearance (CL/F) increased linearly with body weight.5 Metoprolol pharmacokinetics have not been investigated in patients < 6 years of age.

Hypertension
Clinical Trials
Pediatric

6Module 5, Clinical Study Report sections 5.1 and 5.2 (307A)
7Module 5, Clinical Study Report, section 7.2.1 (307A)
8Module 5, Clinical Study Report section 7.2.2 (307A)
9Module 2, Clinical Overview section 4.2
10Module 5, Clinical Study Report 7.2.2.5 (307A)

(b) (4)

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Safety and effectiveness of TOPROL-XL have not been established in patients < 6 years of age. (b) (4)

ADVERSE REACTIONS
Hypertension and Angina
Pediatric
11Module 2, Clinical Overview sections 5.4 and 6
12Module 2, Summary of Clinical Safety section 6

No clinically relevant differences in the adverse event profile were observed for pediatric patients as compared with adult patients.11,12

Dosage and administration
Pediatric Hypertensive Patients ≥ 6 Years of age
13Module 2, Clinical Overview section 6

(b) (4) Dosage should be adjusted according to blood pressure response. Doses above 2.0 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)13

Reviewer Comments
1. It is not clear why a maximum initial dose of 50 mg was chosen; the sponsor should provide justification for this seemingly arbitrary cut-off.
2. A statement regarding the maximum recommended dose should be included
3. A table providing dosing guidelines as provided in Study 307A may be useful.

TOPROL-XL is not recommended in pediatric patients < 6 years of age (see CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS, Pediatric Use.)

4 APPENDICES

4.1 Sponsor's Proposed Label

17 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

4.2 Pharmacometrics Review

Office of Clinical Pharmacology Pharmacometrics Review

NDA/IND: 19-962
Volume: Not applicable; submitted electronically: POP PK Report in Section 5.3.3.5 (Network Path \\Cdsesub1\n19962\N_000\2006-05-15\hpbio\hupharm)
Compound: Metoprolol succinate
Submission Dates: 05/15/2006
Sponsor: Astra Zeneca
Pharmacometrics Reviewer: Robert Kumi, Ph.D.
Secondary Reviewer: Yaning Wang, Ph.D.

TABLE OF CONTENTS

Executive Summary

In NDA (b) (4) SE5 #033, the applicant, Astra Zeneca has proposed changes to the currently approved labeling for TOPROL-XL, metoprolol succinate extended release tablets. Metoprolol, a beta blocker, is approved for hypertension, angina and heart failure in adults. In adults with hypertension the usual initial dosage is 25 to 100 mg daily (single dose) as monotherapy or in combination with a diuretic; this dosage is titrated at weekly intervals until optimum blood pressure reduction is achieved. The current application focuses on Toprol-XL use in pediatric patients ≥ six years old. The initial proposed dosing in children six and older is 1.0 mg/kg; subsequently the dose is titrated based on clinical response.

Two clinical trials, Studies 307A (dose-response) and 307B (safety extension of 307A), were conducted in pediatric patients with hypertension to support the proposed labeling changes. The applicant conducted dose-response, population PK (n = 120 patients) and PK/PD (n = 65 patients) analyses using data from pediatric hypertensive patients receiving Toprol-XL in the mentioned studies.

Key Findings from the Dose-Response and Population PK/PD analyses follow.

1. **Dose-Response:** A statistically significant dose-response did not exist for placebo (pooled)–corrected ΔSBP from baseline; however, the relationship was evident when placebo (specific-group) –corrected data were used.
2. **PK Model:** Metoprolol PK in children were well characterized by a 2-compartment model with flip-flop, first-order absorption, and an absorption lag time. The model yielded precise parameter estimates.
3. **Covariates:** Sex, age, race, body weight, and Toprol-XL dose had no clinically significant effect on metoprolol PK.
4. **PK/PD Model:** Using a log-linear model or linear model, there were weak but statistically significant relationships between the changes in DBP and SBP, and measures of metoprolol plasma exposure (Ctrough, AUC_{0-24} and Cmax). Overall, parameters were not precisely estimated in most models due to a high degree of variability in the blood pressure data.

Overall Conclusions

1. Were metoprolol PK adequately characterized in the pediatric population?
Metoprolol PK in pediatric patients (n = 120, Age 6 to 17) were adequately characterized using a population pharmacokinetic approach. The population model was validated and qualified and comprised a 2-compartment open model, with first order absorption and absorption lag time.

2. Are there any covariates that influence metoprolol PK in pediatric patients with hypertension?
The two covariates that influenced metoprolol PK were weight and age: apparent oral clearance increased linearly with body weight and inter-compartmental clearance increased with age according to a power function. Other covariates, including race, sex, and metoprolol dose did not impact metoprolol kinetics.

3. Was a PK/PD relationship established between metoprolol dose or plasma exposure(AUC, Ctrough or Cmax) and hemodynamic measures (blood pressure)?
Using a simple linear regression model, no dose-response (reduction in placebo corrected systolic blood pressure, the primary outcome variable) was observed, although, a weak ($R^2 < 0.1$) but statistically significant ($p < 0.05$) PK/PD relationship was observed between metoprolol exposure measures and reduction in systolic blood pressure. The small R^2 value indicates metoprolol exposure could account for only a small portion of the hemodynamic effect. According to the model as exposure increased, there was greater reduction in blood pressure. However, only the relationship with AUC was considered reliable, as AUC was estimated with good precision (PK modeling), whereas Cmax was not.

4. Is there sufficient evidence to support effectiveness of Toprol XL in pediatrics and the initial proposed pediatric dosage?
Yes. Although dose-response was not established with SBP reduction (primary variable), suggesting that the effectiveness of the individual tested Toprol-XL doses could not be differentiated, the following information provides evidence to suggest that some Toprol-XL doses were more effective than placebo.

- Analysis of treatment group effects and pairwise comparisons suggested that overall, Toprol-XL demonstrated effectiveness in pediatric patients with hypertension: pooled Toprol groups vs. placebo ($p = 0.0351$) and relative to baseline each active Toprol-XL dose group decreased SBP whereas placebo did not.
- There was a dose-response relationship for reduction in diastolic blood pressure; typically, systolic and diastolic blood pressure effects mirror each other
- PK/PD findings (reduction in SBP and heart rate as a function of AUC) support metoprolol effectiveness (increased exposure led to increased effectiveness). The heart rate effect supports metoprolol's known beta blocking activity.
- Generally, Toprol-XL was effective in pediatric patients and adult patients at similar metoprolol exposure levels: 0.2 mg/kg in pediatrics was minimally effective because this dose yielded exposures lower than that obtained in adults at the lowest effect adult dose, 25 mg.

- The proposed pediatric dosage, 1.0 mg/kg is supported by the results from the dose-response study. Visual inspection and pairwise comparisons indicated that 1.0 mg/kg (placebo corrected) was statistically the most effective dose (greater efficacy than 0.2 mg/kg and 2.0 mg/kg) and was more effective than placebo ($p = 0.027$).

5. Will initial dosage adjustment be required for any pediatric patients, prior to titration?
No, dosage adjustment does not appear necessary prior to titration (typically one week after treatment begins). Based on the population PK model the only potentially relevant factor that could affect PK was body weight. CL/F increased linearly with body weight: relative to a 70 kg individual, the CL of a 22 kg individual is 30 % lower. This decreased CL will result in an increased exposure (maximum 30 %) that does not pose additional safety concerns or appear clinically significant (tolerated in studies). The proposed starting dose, 1.0 mg/kg, and doses up to 2.0 mg/kg (maximum 200 mg) were tolerated in the clinical trials (307A and 307B). Furthermore, exposure accounted for an insignificant portion of the hemodynamic effect (poor correlation), thus the clinical implications of the impact of body weight on CL/F of metoprolol identified in the population PK modeling are limited.

The proposal to start Toprol-XL at a low dose and titrate (b) (4) to a higher and tolerable dose until optimum BP reduction is achieved is reasonable. This is consistent with labeling for adults.

6. Was the PK/PD relationship influenced by covariates?
Insufficient data were available to make this assessment.

7. Are the PK and PK/PD of metoprolol in children comparable to that in adults?
PK values obtained in pediatric patients were generally in the same range as those reported in adults. Potential limitations of the comparison are the different modeling approaches, populations, number of samples and number of subjects in the trials (Table B).

It is difficult to make definitive PK/PD comparisons between the pediatric (studied in this NDA) and adult population because:

1. Study conditions differ- typically in adult studies HR is measured during exercise and not at rest
2. Results are obtained in healthy adult subjects rather than hypertensive patients
3. Insufficient number of studies have been reported in the literature that attempt to identify the relationship between metoprolol exposure and SBP or DBP effect in adults.

Table B: PK Comparisons (Pediatrics vs. Adults)

Source	NDA 19962	Luzier et al	Taguchi et al	Plosker and Cissold and other sources
Model	2 Comp, 1st Order absorption		1 Comp	
Formulation	Toprol XL	IR		IR
PK Analyses	Population	Standard/NCA	Population	Standard
Population	Pediatric	Healthy adults	Japanese geriatric	
Sampling	Intense and Ctrough	Intensive	Sparse	intensive
CL/F (L/hr/kg)	3.38	1.16 – 3.40	0.94	
V2/F (L/kg)	1.28	2.70 – 3.98	4.52	
V3/F	8.51	3.33 – 8.09		
Q/F (L/hr)	8.99	2.82 – 6.94		
Ka (h-1)	0.0467			
Tlag (h)	0.853			
T1/2 (h)	3.51			3 - 6
Tmax (h)				2.5 – 7.3
Covariate Effects on CL/F*				
Age	None		Yes	Yes/No
Gender Effect	None	Yes		
Race	None			

* The applicant noted that pediatric data were compared to adult data from IR, where CL/F is dominated by the disposition function of metoprolol, therefore it may be complicated to compare adult data to pediatric data (Toprol XL), where CL/F is under a considerable influence from the release rate (input function) of the device. This appears to be a valid caveat

It should be noted that the cause of hypertension in adults differs from that in children. Results of the pediatric modeling exercise showed that a log-linear model appeared to work better than other models for both SBP and DBP. In adults the Sigmoidal Emax model has been successfully applied. Using the Hill Equation (Sigmoidal Emax model) with EHR reduction (measure of beta blockade) as the PD marker: in adults EC50 = 105 nmol/L (28.1 ng/mL) and Emax is achieved at metoprolol plasma concentrations > 400 nmol/L (107 ng/mL). Placebo-corrected mean blood pressure changes (standing) associated with concentrations producing maximal blockade are -10 for systolic and – 4 for diastolic. In the pediatric study, the observed maximal mean reductions (placebo corrected) at the studied doses were approximately -6 for systolic and -5 for diastolic. Hence it appears the studied pediatric doses produce comparable changes in diastolic pressure but lower changes in systolic pressure. It should be noted that in the pediatric studies, only a few metoprolol plasma concentrations were > than 107 ng/mL. It is unlikely that the maximal activity was achieved at the doses studied, yet the Toprol doses appeared effective. The differential maximal effects may also be due to the difference in initial SBP (adults patients with hypertension tend to have higher initial BPs); in adult and pediatric studies there was a dependence of change in SBP on initial SBP.

Introduction

Summary

NDA (b) (4) SE5 #033 was submitted to seek approval of labeling changes to the currently approved labeling for TOPROL-XL. This labeling translates to a new Toprol-XL indication for pediatric patients (6 years and older) with hypertension.

Background on Metoprolol in Hypertension

The majority of the following information was obtained form a Review article (sponsor provided) by Plosker and Clissold [Drugs 43(3) 382-414, 1992)].

Table 1: Snapshot of Metoprolol Clinical Pharmacology and Biopharmaceutics

Drug Class	Metoprolol is a ß1-selective (cardio selective) adrenergic receptor-blocking agent
Mechanism of Action (antihypertensive effect)	Multiple putative mechanisms: competitive antagonism of catecholamine at peripheral sites, reduction of sympathetic outflow to the periphery, or suppression of renin activity.
Approved Indications	Hypertension, Heart Failure and Angina Pectoris
Approved Formulations	Immediate Release (IR) – metoprolol tartrate Controlled Release (CR/Z0K) Toprol-XL is extended-release tablet of metoprolol as the succinate salt.
Metabolism	Via CYP2D6 primarily
Absorption	Absolute oral bioavailability ~ 50 % following IR. Food does not affect metoprolol absorption using ER formulation
Distribution	Protein binding to albumin is about 12%.
Elimination	For IR t1/2 from 3 – 7 hours. Less than 5 % dose excreted unchanged in urine. No t1/2 values for ER; this may be due to difficulty in separating absorption and elimination phases
Variability	Plasma levels are highly variable among subjects after oral administration.
Age Effects	PK of metoprolol not affected by age (20 to 65 years), but concentration of active metabolite in subjects > 65 years about twice as high as those in younger, although metoprolol concentrations similar in two groups (Regardh et al).
PK/PD in children	Limited information in children and provided mainly after administration of metoprolol tartrate.

Summarized PK and PK/PD Information in Adults

Table 2: Reported PK Values in Adults (multiple references*)

Dosing regimen	C_{max} (nmol/L)	t_{max} (h)	C_{min} (nmol/L)	AUC (nmol · h/L)
CR/ZOK (od)				
50mg	67 to 71	5 to 6.3	32 to 39	1069 to 1312
100mg	36 to 284	2.9 to 7.3	40 to 114	1994 to 4459
200mg	291 to 426	2.5 to 4.6	116 to 167	5206 to 7075
300mg	665	4.1	343	12 368
400mg	837	3.4	278	12 920

*References include: Abrahamsson et al, Sandberg et al, Wieselgren et al

Table 3: PK/PD Information

Reference	Key Findings
Abrahamsson et al	Therapeutic level of ß1blockade (model- reduction in exercise heart rate or EHR) is between 80 and 300 nM
Sandberg et al	Toprol XL is designed to deliver metoprolol succinate at a near constant rate for about 20 hr
Wieselgren et al	In healthy males, maximal EHR ~ 14 % and minimum reduction ~ 9 % with 50 mg. Activity greater than placebo over 24 hour period
Dayer et al, Lennard et al, Jonkers et al	Poor metabolizers have a higher plasma concentration and a greater duration or degree of beta blockade. Potential implications for use of extended release, as may not be needed in PMs
Various sources	Toprol XL produces clinically and statistically significant reductions in blood pressure values compared to baseline values. The maximal blood pressure lowering effect for a given dose in adults is observed between 1 and 4 weeks of treatment. In 4 week trials with Toprol XL, the maximum decrease in supine BP was 20/9 and standing was 12/9 (unclear if at trough) At trough, following 4 weeks of 50 mg QD Toprol XL, relative to placebo the reduction in supine BP was 11/2 and 10/3 in Standing

Summary of sponsor's current analysis relevant to pharmacometrics and resulting claims

Dose-Response Analysis

A dose-response analysis was conducted using a simple linear regression model, where metoprolol dose in mg/kg was the independent variable

Week 4 placebo corrected change in blood pressure (diastolic or systolic) from baseline was the dependent variable (response)

Sponsor's Analysis Claims (Dose-Response Study)

Following administration of TOPROL-XL at doses of 12.5 to 200 mg once daily for up to 4 weeks, metoprolol

- Exhibited a significant dose-response relationship for DBP, but none for SBP
- Produced statistically significant and clinically meaningful reductions in SBP and DBP for some individual and/or pooled target dose groups (0.2, 1.0, and 2.0 mg/kg)

Population PK and PK/PD Analyses

The sponsor's population PK and PK/PD analyses involved the use of typical population PK approaches. Primarily SAS and NONMEM were used to run the analyses. In brief the sponsor pooled plasma concentration time data from patients in Study 307A (trough samples) and 307B (trough samples in most subjects and serial samples in a subset of patients) for the PK modeling. PK/PD (PD measured primarily as changes in blood pressure) data were from patients in Study 307A. These collective data were used in the population PK and PK/PD analyses.

Initially the sponsor identified the best PK structural population model by testing several pharmacokinetic models. This model was further refined by eliminating error terms (etas) that were not statistically significant. Subsequently the sponsor evaluated the effect of

covariates on the PK model and developed a final PK model. The goodness of the fit of the model was assessed with standard procedures. The final population model was used to simulate individual plasma concentration-time profiles and Bayesian estimates for Cmax and AUC for all patients. These simulated AUC and Cmax values and actual (observed) Ctrough were used in the PK/PD model. The PK/PD model was developed in a similar manner as the population PK model. Initially, the best PK/PD base model was identified and the model refined until a final PK/PD model was identified.

Sponsor's Analysis Claims (Population PK and PD Modeling)

1. A 2-compartment PK model with first-order elimination and flip-flop first-order absorption and lag time best fit metoprolol concentration-time data obtained from the studied pediatric hypertensive patients.

2. The following tabulated parameter estimates were obtained using the final population PK model

CL/F	227.5 L/hr
V2/F	96.1 L
V3/F	620 L,
Q/F	675 L/h
Ka	0.0467 hr–1
Tlag1	0.853 hr

These PK values were generally in the same range as those reported in adults.

3. Sex, race, ideal body weight, and Toprol-XL dose have no significant effect on metoprolol pharmacokinetics. No covariate impacts V2/F, V3/F, Ka, or the Tlag of metoprolol. Age has no effect on metoprolol CL/F, and body weight has no effect on Q/F. Metoprolol CL/F increases linearly with body weight; however, no dose adjustment based upon body weight is necessary because dosage is titrated based on clinical response. Q/F is proportional to age; however, the increase in Q/F with age is not clinically relevant.

4. Weak, but statistically significant, relationships existed between DBP, SBP, and HR and some measures of metoprolol exposure (trough plasma levels, Cmax and AUC(0–24)). Because of high variability in the hemodynamic data, goodness-of-fit of the PK/PD models was generally poor and the resulting parameter estimates were not considered reliable. Extrapolation of these model parameters in the clinic for dose adjustment is not recommended.

5. No covariates had an impact on the parameters delineating the PK/PD relationship between metoprolol exposure and DBP, SBP and HR.

Objectives of the analysis

There are three specific goals of the PM analysis:

1. To evaluate the adequacy of the sponsor's dose-response analysis
2. To evaluate sponsor's population PK analysis and determine if PK labeling claims are acceptable

3. To evaluate sponsor's population PK/PD analyses and determine if the findings support the proposed dosing recommendation

Dose Response Analysis (Study 307A)

Title: Dose Ranging, Safety and Tolerability of TOPROL-XL® (metoprolol succinate) Extended-release Tablets (metoprolol CR/XL) in Hypertensive Pediatric Subjects: A Multicenter, Double-blind, Placebo-controlled, Randomized, Parallel-group Study

Study Duration: 30 May 2002 - 9 June 2004

Investigators (primary): Bonita E. Falkner, M.D. and Jonathan Sorof, M.D. 1800

Sites: Multiple locations (36 in US and 1 in Dominican Republic)

Table 1: Objectives and Outcomes for Study 307A

Objective	Summary outcome variables for analysis (including timepoint and population)
Primary	**Primary outcome variable**
To determine the dose range of TOPROL-XL in hypertensive pediatric patients	Trough sitting SBP. Placebo-corrected change from baseline to end of double-blind treatment (intention-to-treat [ITT] population using last observation carried forward [LOCF]) for sitting SBP. A significant dose response was concluded if the slope of the regression line differs from zero at 0.05 significance level.
Secondary	**Secondary outcome variables**
There were no specified secondary efficacy objectives, but additional BP variables were included in secondary analyses.	Trough sitting DBP. Placebo-corrected change from baseline to end of double-blind treatment (ITT population using Week 4/ LOCF) for sitting DBP. Trough sitting and standing SBP and DBP Change from baseline at each postbaseline visit (ITT population) Percentage of responders at Week 4 (ITT population)

DBP diastolic blood pressure; ITT intention-to-treat; LOCF last observation carried forward; SBP systolic blood pressure.

Study Design (FDA-approved Type A design)

This was a multi-center, international, double-blind, placebo-controlled, randomized, parallel-group study. The study included a screening visit, a 1- to 2-week single-blind, placebo run-in period during which all previous antihypertensive medications were discontinued, and a 4-week double-blind treatment period. At the end of the placebo run-in period, eligible patients with blood pressure (BP) measurements in the qualifying range were randomized in a 1:2:1:2 ratio to receive once daily, oral doses of placebo, TOPROL-XL 0.2 mg/kg, TOPROL-XL 1.0 mg/kg, or TOPROL-XL 2.0 mg/kg. TOPROL-XL doses of 12.5, 25, 37.5, 50, 75, 100, 150, or 200 mg were used to approximate the target doses. Patients in the placebo and TOPROL-XL 0.2 mg/kg groups received the target dose for 4 weeks, while patients in the TOPROL-XL 1.0 mg/kg and

2.0 mg/kg groups had their dose up-titrated (based on weight) to the target dose over the first 1 to 2 weeks of double-blind treatment.

Reviewer Note: Rationale on Study design

The inclusion of more patients in the TOPROL-XL 0.2 mg/kg and 2.0 mg/kg groups allowed better estimation of the dose response at the low and high ends of the dose range. The TOPROL-XL 1.0 mg/kg group, with fewer patients, provided a middle estimate that helped to describe the shape of the dose-response curve. However, having a fewer number of subjects may have contributed to variability. Inclusion of a placebo control group allowed for the quantification of treatment-related BP reductions after adjusting for placebo effect. It should be noted that the placebo groups were not identical as they followed different titration schedules and had a different number of tablets.

The 0.2 mg/kg dose is lower than the lowest approved adult dose on a mg/kg basis (assuming 70 kg adult weight), but the highest studied pediatric dose, 2.0 mg/kg (200 mg limit was placed) is lower than the highest studied adult dosage, 400 mg.

Table 2: Toprol Dosing Scheme for Study 307A

	Target dose of TOPROL-XL or matching placebo[a]		
Baseline weight (kg)	**0.2 mg/kg**	**1.0 mg/kg**	**2.0 mg/kg**
≤30	12.5	25	50
>30 to ≤45	12.5	37.5	75
>45 to ≤60	12.5	50	100
>60 to ≤80	12.5	75	150
>80	12.5	100	200

[a] Patients were supplied with 25- or 50-mg tablets to achieve target doses. The 12.5-mg dose was achieved by splitting the 25-mg tablet in half.

Table 3: Formulations used in 307A

Investigational product or other treatment	Dosage form and strength	Manufacturer	Formulation number	Batch number
Metoprolol CR/XL	Tablet, 25 mg	AstraZeneca Tablet Production	H0960-10-01	H0960-10-01-01 H0960-10-01-02
Metoprolol CR/XL	Tablet, 50 mg	AstraZeneca Tablet Production	H0638-09-03	H0638-09-03-09
Placebo to match metoprolol CR/XL 25 mg	Tablet	AstraZeneca Tablet Production	H1014-03-01	H1014-03-01-01 H1014-03-01-02

Investigational product or other treatment	Dosage form and strength	Manufacturer	Formulation number	Batch number
Placebo to match metoprolol CR/XL 50 mg	Tablet	AstraZeneca Tablet Production	H0695-04-01	H0695-04-01-07
Single-blind placebo	Tablet	AstraZeneca Tablet Production	H1014-03-01	H1014-03-01-02 H1014-03-01-03

All investigational products were to be kept in a secure place under appropriate storage conditions.

SPONSOR'S STATISTICAL ANALYSIS PLAN HIGHLIGHTS

- The primary analysis used an intention-to-treat (ITT) population which included all patients who received at least 1 dose of study medication and had baseline and at least 1 post baseline measurement. For this analysis, missing data were imputed using a last observation carried forward (LOCF) approach.
- A simple linear regression analysis was performed on the placebo-corrected change from baseline to Week 4/LOCF in sitting SBP and sitting DBP with dose ratio as the explanatory variable.
- The placebo correction for placebo-corrected changes from baseline to Week 4/ LOCF in sitting SBP and sitting DBP was performed by subtracting the mean change from baseline for the placebo group from the individual patient changes in the other treatment groups.
- ANOVA was performed with treatment group as the main factor for the changes from baseline to each post baseline visit in sitting SBP and DBP. This ANOVA model was used to construct pairwise comparisons of each active treatment versus placebo and the active treatment groups combined versus placebo.
- The percentage of responders at Week 4 was summarized by frequency counts, percentages, and 95% confidence intervals (CI) for each treatment group.
- Subgroup analyses were also performed on the changes from baseline at Week 4 in sitting SBP and DBP, and the influence of heart rate and baseline body mass index (BMI) on the mean changes from baseline to Week 4/LOCF in sitting SBP and DBP were examined using linear regressions.
- Trough plasma concentrations of metoprolol were summarized descriptively and the lower limit of quantitation (LLQ) was 1 ng/mL.
- Safety data were summarized using the safety population, defined as all patients who received at least 1 dose of study medication and were not lost to follow-up. No statistical analyses were performed on the safety data in this study.

Results

Patient Disposition

Per applicant patients recruited into this study were representative of a pediatric population with hypertension. The four treatment groups were balanced with respect to demographic and baseline characteristics (Tables 4 and 5). About 80 percent of the patients were considered 90 % compliant.

Table 4: Baseline Characteristics in Study 307A

		TOPROL-XL treatment groups			
	Placebo (N=23)	0.2 mg/kg (N=45)	1.0 mg/kg (N=23)	2.0 mg/kg (N=49)	All patients (N=140)
Age (years), n (%)					
≤12	9 (39.1)	20 (44.4)	7 (30.4)	22 (44.9)	58 (41.4)
>12	14 (60.9)	25 (55.6)	16 (69.6)	27 (55.1)	82 (58.6)
Age, years					
Mean (SD)	12.3 (3.2)	12.5 (2.7)	13.5 (2.5)	12.2 (2.8)	12.5 (2.8)
Median	13.0	13.0	13.0	13.0	13.0
Range	6.0 - 16.0	6.0 - 16.0	6.0 - 16.0	6.0 - 16.0	6.0 - 16.0
Sex, n (%)					
Male	13 (56.5)	35 (77.8)	16 (69.6)	34 (69.4)	98 (70.0)
Female	10 (43.5)	10 (22.2)	7 (30.4)	15 (30.6)	42 (30.0)
Race, n (%)					
Black	5 (21.7)	9 (20.0)	6 (26.1)	16 (32.7)	36 (25.7)
Nonblack	18 (78.3)	36 (80.0)	17 (73.9)	33 (67.3)	104 (74.3)
Caucasian	18 (78.3)	34 (75.6)	17 (73.9)	31 (63.3)	100 (71.4)
Asian	0	1 (2.2)	0	2 (4.1)	3 (2.1)
Other	0	1 (2.2)	0	0	1 (0.7)

Table 5: Sitting SBP and DBP measurements* at baseline

		TOPROL-XL treatment groups			
	Placebo (N=23)	0.2 mg/kg (N=45)	1.0 mg/kg (N=23)	2.0 mg/kg (N=49)	All patients (N=140)
Sitting SBP					
Mean (SD)	132.7 (8.9)	131.4 (9.0)	135.0 (8.0)	130.6 (9.6)	131.9 (9.1)
Median	133.3	131.3	136.0	130.0	132.0
Range	110.7 - 152.7	108.0 - 153.3	117.3 - 148.0	98.0 - 151.3	98.0 - 153.3
Sitting DBP					
Mean (SD)	81.4 (9.0)	76.3 (7.7)	81.0 (7.5)	76.7 (9.1)	78.0 (8.6)
Median	80.0	78.0	82.0	78.0	80.0
Range	66.0 - 99.3	57.3 - 90.7	62.0 - 91.3	60.0 - 92.0	57.3 - 99.3

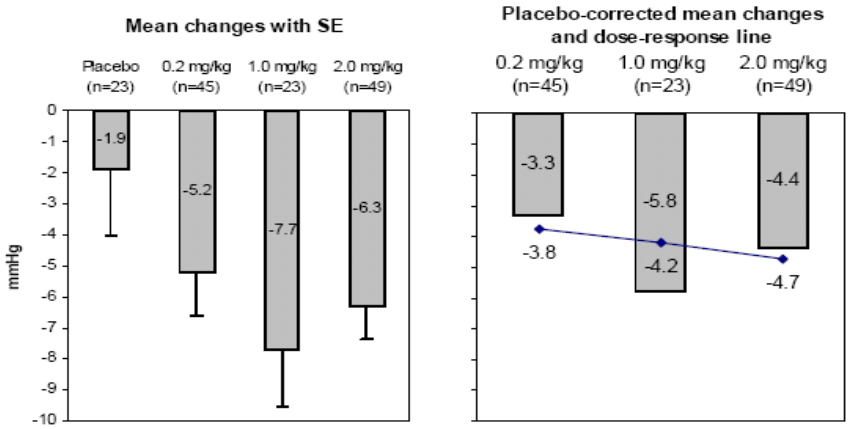
* Sitting and standing BP measurement were comparable (e.g. mean SBP for all patients- sitting = 131.9 and standing 130.6 with similar CVs ~ 9 %)

Primary Efficacy Variable

The results for the primary efficacy variable are illustrated in Figure 1.

Figure: Dose response for placebo-corrected change from baseline to Week4/LOCF for sitting SBP (ITT population).

Figure 1: Change in SBP from baseline as a function of Toprol XL dose



Note: For each treatment group, the standard error (SE) was calculated using the following formula: standard deviation ÷ square root of n.

Table 6: Linear regressions statistics used to assess Dose-Response

Trough sitting SBP	DF	Estimate	Standard error	P-value	95% CI
Model parameter					
Intercept	1	-3.6455	1.3357	0.0073	
Dose ratio	1	-0.1099	0.1945	0.5731	
Predicted values					
Dose ratio = 1		-3.7554	1.1840		-6.1006, -1.4102
Dose ratio = 5		-4.1950	0.7929		-5.7655, -2.6245
Dose ratio = 10		-4.7445	1.1679		-7.0578, -2.4311
Model statistics					
Mean square error	115	72.1860			
F statistic for model		0.3194		0.5731	
R-square		0.0028			

Note: Placebo is not included in the model. The individual values for patients in the active dose groups have been adjusted by subtracting the mean placebo change from baseline.
CI confidence interval; DF degrees of freedom; ITT intention-to-treat; LOCF last observation carried forward; SBP systolic blood pressure.

The results indicate that

- The slope of the curve is not different form zero (p = 0.5371 for dose ratio), suggesting that there is no dose-response relationship
- Most active treatment groups are more effective than placebo in reducing SBP

By visual inspection it appears the lack of observed dose-response is mainly driven by a lower than expected response at the 2.0 mg/kg level.

Potential issues affecting efficacy and pharmacokinetic results

- LOCF was required for eight patients, however, the LOCF approach did not greatly impact the outcome of the trial.
- Patients assigned to the 1.0 mg and 2.0 mg/kg dose received drug for only 2 weeks whereas dose in the 0.2 mg/kg received the same dose for 4 weeks.

Reviewer's Supplemental Dose-Response Analyses

The sponsor's dose-response analysis was successfully reproduced by this Reviewer using pooled placebo corrected data. A supplemental analysis was conducted using group-specific placebo corrected data. In this procedure, data for subjects assigned to a given Active Group (e.g. 0.2 mg/kg) were corrected with Placebo data (0.2 mg/kg). Group specific placebo data are presented in Table 7.

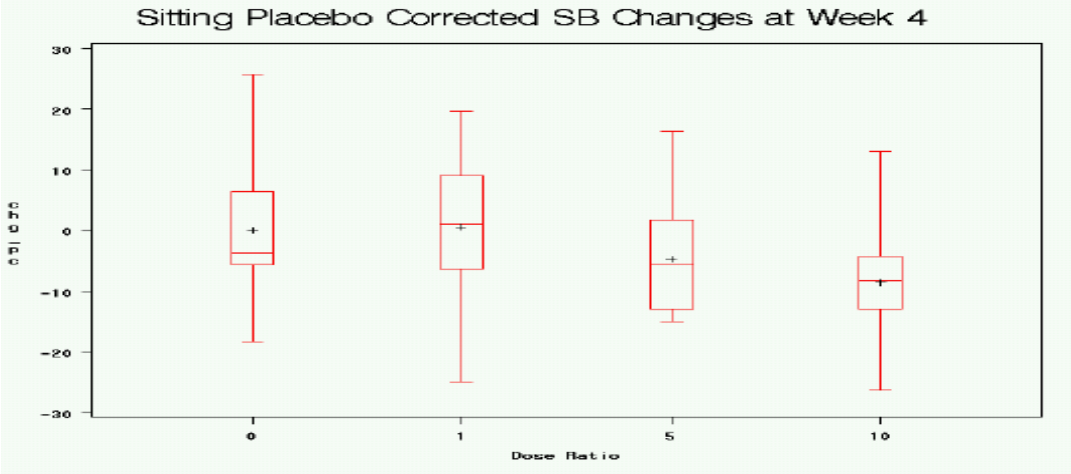
Table 7: Placebo-group specific data

Placebo Group	Frequency	Delta SBP
0.2 mg/kg	8	-5.67
1.0 mg/kg	6	-3.00
2.0 mg/kg	9	2.30

It should be noted that the group-specific placebo data appeared to follow a consistent trend, where the placebo effect decreased with increasing number of tablets. It is unclear if this titration/tablet-dependent placebo effect is valid or random. Overall, the apparent differential placebo effects suggest that the placebo group may have overly influenced the outcome of the dose-response analysis.

When active groups are corrected using group-matched placebo data, there is a statistically significant dose-response. The dose response using group-specific placebo data is illustrated in Table 8 and Figure 2.

Figure 2 : Placebo corrected changes in SBP (chg_pc on y axis) as a function of dose ratio



Potential Limitations of Supplemental Analyses

Typically placebo effects are constant if randomization is correct; thus it is unclear if subsetting the placebo group is acceptable and did not increase bias. Additionally, subsetting the placebo group leads to a reduced number of placebo subjects per dose group that may impact the regression analyses.

Table 8: SAS output for regression analyses using group-specific placebo corrections

The REG Procedure

Model: MODEL1
Dependent Variable: chg_pc

Number of Observations Read 117
Number of Observations Used 117

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	1910.83177	1910.83177	26.63	<.0001
Error	115	8251.09481	71.74865		
Corrected Total	116	10162			

Root MSE	8.47046	R-Square	0.1880
Dependent Mean	-4.30358	Adj R-Sq	0.1810
Coeff Var	-196.82365		

Parameter Estimates

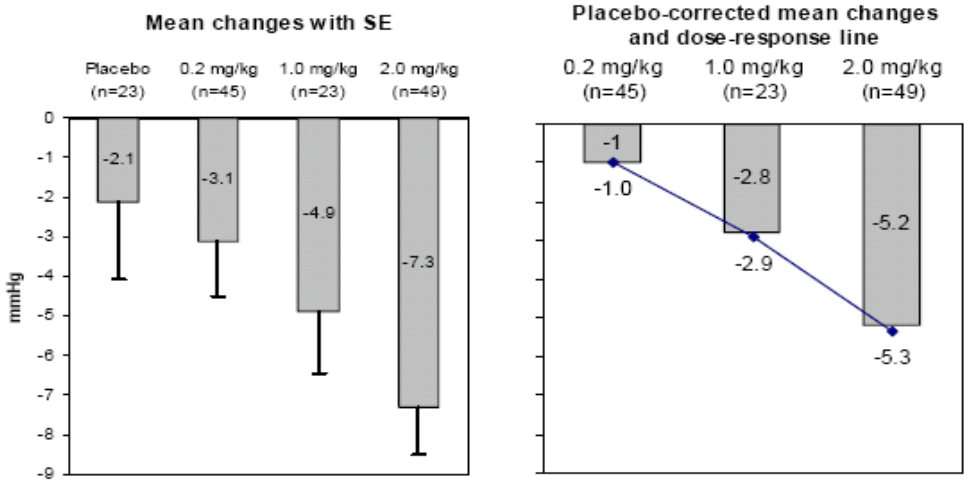
Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	1.25480	1.33166	0.94	0.3480
DOSRATIO	Dose Ratio	1	-1.00051	0.19387	-5.16	<.0001

Secondary variables

- ***Placebo-corrected change from baseline in sitting DBP***

The mean ± SD change (Week 4/LOCF) in sitting DBP is illustrated in Figure 3 and Table 9.

Figure 3: Mean changes (actual and placebo-corrected) from baseline to Week 4/LOCF for sitting DBP (ITT population)



Note: For each treatment group, the standard error (SE) was calculated using the following formula: standard deviation ÷ square root of n.

Table 9: SAS output for regression analyses for DBP with pooled placebo correction

Trough Sitting DBP	DF	Estimate	Standard Error	P-value	95% Confidence Interval
Model Parameter					
Intercept	1	-0.4943	1.3552	0.7160	
Dose ratio	1	-0.4850	0.1973	0.0155	
Predicted Values					
Dose ratio = 1		-0.9794	1.2012		-3.3588,1.4000
Dose ratio = 5		-2.9194	0.8044		-4.5129,-1.3260
Dose ratio = 10		-5.3446	1.1849		-7.6916,-2.9975
Model Statistics					
Mean square error	115	74.3069			
F statistic for model		6.0433			
F p-value		0.0155			
R square		0.0499			

Treatment group effects and pairwise comparisons for sitting SBP and DBP
Results of the treatment group effects at the Week 4/LOCF visit and the pairwise comparisons between each TOPROL-XL group and placebo for the change from baseline in sitting SBP and DBP are shown for the ITT population in Table 10.

Table 10: Treatment group effects for change in baseline to Week 4/LOCF for sitting SBP and DBP (ITT population)

	Sitting SBP (N=140)			Sitting DBP(N=140)		
Change from baseline	Least squares mean	P-value	95% CI	Least squares mean	P-value	95% CI
Placebo	-1.85507	0.3133	-5.4802, 1.7700	-2.11594	0.2503	-5.7404, 1.5085
TOPROL-XL 0.2 mg/kg	-5.15556	0.0001	-7.7472, -2.5639	-3.12593	0.0184	-5.7171, -0.5347
TOPROL -XL 1.0 mg/kg	-7.65217	0.0001	-11.2773, -4.0271	-4.92754	0.0081	-8.5520, -1.3030
TOPROL -XL 2.0 mg/kg	-6.26531	<0.0001	-8.7489, -3.7817	-7.48299	<0.0001	-9.9662, -4.9998
TOPROL -XL 0.2 mg/kg vs placebo	-3.3005	0.1453	-7.7567, 1.1558	-1.0100	0.6547	-5.4655, 3.4455
TOPROL -XL 1.0 mg/kg vs placebo	-5.7971	0.0270	-10.9238, -0.6704	-2.8116	0.2800	-7.9374, 2.3142
TOPROL -XL 2.0 mg/kg vs placebo	-4.4102	0.0492	-8.8045, -0.0159	-5.3671	0.0170	-9.7606, -0.9735
TOPROL -XL groups combined vs placebo	-4.2560	0.0351	-8.2102, -0.3019	-3.1889	0.1189	-7.2076, 0.8298

Note: Pairwise comparisons performed using an ANOVA model with 1 term for treatment group.
CI confidence interval; DBP diastolic blood pressure; ITT intention-to-treat; LOCF last observation carried forward; SBP systolic blood pressure.

Some key findings from the pair-wise comparison are as follows (Table 10):

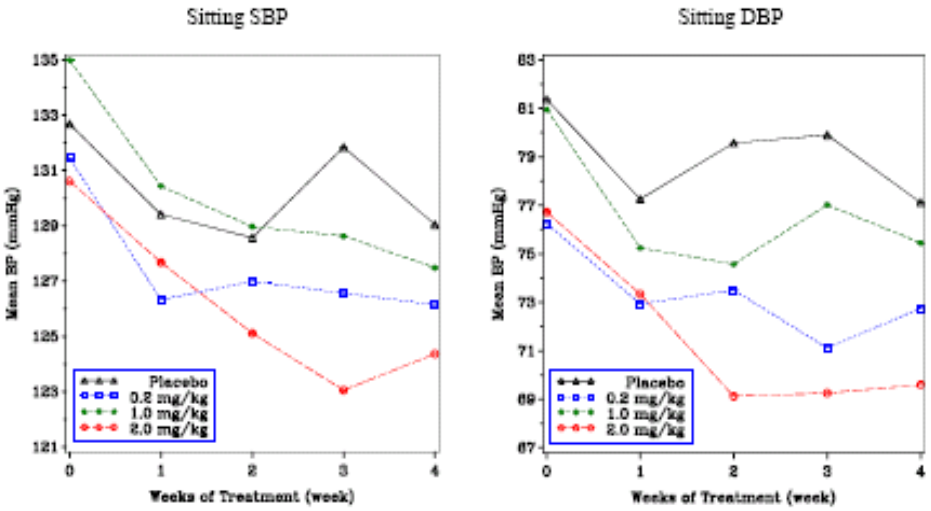
1. All active groups produced statistically significant reductions from baseline in sitting SBP and DBP at the Week 4/LOCF visit, whereas placebo did not.

2. Overall, the mean change from baseline in sitting SBP at Week 4/LOCF for the TOPROL-XL groups pooled was statistically significantly larger than that for the placebo group (p=0.0351).
3. Results of pairwise comparisons between individual TOPROL-XL dose groups and placebo also revealed a statistically significant difference for the 1.0 and 2.0 mg/kg groups (p=0.0270 and p=0.0492, respectively).

- ***Mean changes over time in sitting SBP and DBP***

Consistent with findings from other studies with beta-blockers, apparent maximal reduction in blood pressure occurred between 1 and 4 weeks of treatment

Figure 4: Mean changes* over time for sitting SBP and DBP (ITT population)



* Data points in plot are from absolute values (not taking baseline into account)

Subgroup Analyses

The sponsor conducted several exploratory subgroup analyses; however these analyses were not reviewed critically and are not presented in this review as:

1. they do no impact the primary outcome or study objective
2. they are unlikely to be clinically useful due to the small number of patients per subgroup

One potentially useful some group analyses involved the percentage of responders, as defined in Table 11

The responder analyses shows comparable response rates for all active dose groups suggesting similar efficacy across dose groups, despite different exposure (doses).

Table 11: Number and proportion of responders (ITT population)

	N	Number of responders	Proportion of responders	95% CI
Placebo	23	6	0.261	0.0814, 0.440
TOPROL-XL 0.2 mg/kg	45	21	0.467	0.3209, 0.612
TOPROL-XL 1.0 mg/kg	23	10	0.435	0.2322, 0.637
TOPROL-XL 2.0 mg/kg	49	23	0.469	0.3297, 0.609
TOPROL-XL groups combined	117	54	0.462	0.3712, 0.551
Total	140	60	0.429	0.3466, 0.510

Note: Responders were defined as any patient whose sitting SBP and DBP was less than the 95th percentile at Week 4. Patients without a value at Week 4 were considered nonresponders.
CI confidence interval; ITT intention-to-treat.

Pharmacokinetic Results

The Ctrough information obtained in the trial are summarized in Figure 6 and Tables 12 and 13 .

Table 12: Summary of Ctrough data (per applicant)

	TOPROL-XL treatment groups		
Concentration (ng/mL)	0.2 mg/kg	1.0 mg/kg	2.0 mg/kg
No. patients with evaluable data	12	15	40
Mean (SD)	4.5 (2.9)	13.9 (14.3)	28.3 (34.5)
Median	3.3	10.8	13.4
Range	1.3 – 15.7	1.3 – 57.1	1.4 – 167.0
Value <LLQ, n/N (%)	27/47 (57.4)	2/23 (8.7)	6/50 (12.0)
Value ≥LLQ, n/N (%)	13/47 (27.7)	15/23 (65.2)	41/50 (82.0)
None, n/N (%)	7/47 (14.9)	6/23 (26.1)	3/50 (6.0)

LLQ lower limit of quantitation; SD standard deviation.

Sixteen patients across the 3 TOPROL-XL groups did not have blood samples obtained for analysis of metoprolol concentrations. Based on the number of samples BLQ, there appeared to be very low concentrations in the lowest dose group. It appeared that Ctrough increased with dose. According to the applicant, these values are similar to those obtained previously in adults, especially at the 2 higher doses. Variability was high in all treatment groups (CV > 60 %).

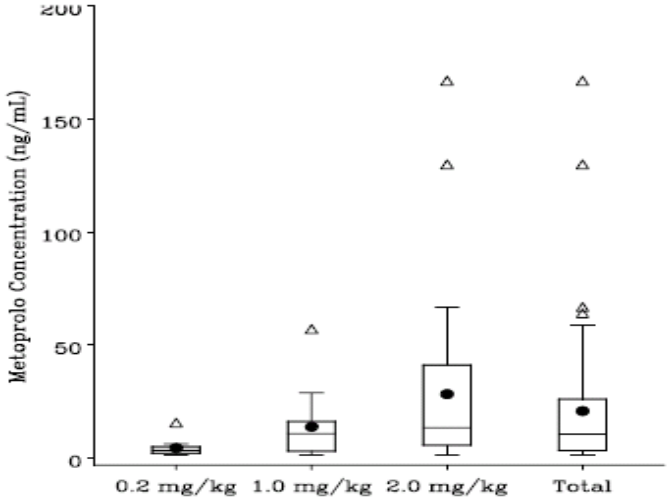
Table 12: Summary of Ctrough (Reviewer Generated) from all patients (samples < LOQ given value = 0)

Toprol XL Dose (mg/kg)	Number of subjects	Concentration (ng/mL)		
		Mean ± SD	Median	Range
0.2	39	1.37 ± 2.94	0.00	0 – 15.7
1.0	17	12.24 ± 14.16	8.45	0 – 57.1
2.0	46	24.62 ± 33.52	11.40	0 – 167.0

Reviewer Note

Overall, the plasma concentrations (exposure) for the 0.2 mg/kg dose group appear too low to be effective (close to LOQ). It is noted that adults typically have concentrations > LOQ at the lowest therapeutic dose, 25 mg (~ 4 ng/mL)

Figure 6: Boxplot of metoprolol Ctrough using samples > LLQ (per applicant)



Safety Results

According to the applicant Toprol XL was well tolerated in the pediatric population as tabulated below.

Category	Placebo (N=24)		TOPROL-XL treatment groups 0.2 mg/kg (N=46)		1.0 mg/kg (N=23)		2.0 mg/kg (N=49)		All patients (N=142)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
At least 1 treatment-emergent AE[a]	12	(50.0)	17	(37.0)	9	(39.1)	30	(61.2)	68	(47.9)
Drug-related AE	2	(8.3)	3	(6.5)	2	(8.7)	5	(10.2)	12	(8.5)
Serious adverse event	0		0		0		0		0	
Discontinued treatment due to AE	1	(4.2)	0		0		0		1	(0.7)
Death	0		0		0		0		0	

[a] A treatment-emergent adverse event (AE) is defined as an AE which began following the first dose of double-blind study medication.

Main Analyses Conclusions

- No dose response was observed for corrected SBP using pooled placebo data; however, using group-matched placebo data demonstrated a dose response
- Ctrough increased with dose
- Toprol 1.0 and 2.0 mg kg doses were more effective than placebo in reducing SBP
- The responder rate was comparable across all active dose groups and this rate was greater than that of placebo

Methods

Reviewer's Methods

Generally, this reviewer conducted the analyses in a manner similar to that of the sponsor to confirm the sponsor's findings.

Sponsor's Methods

Design

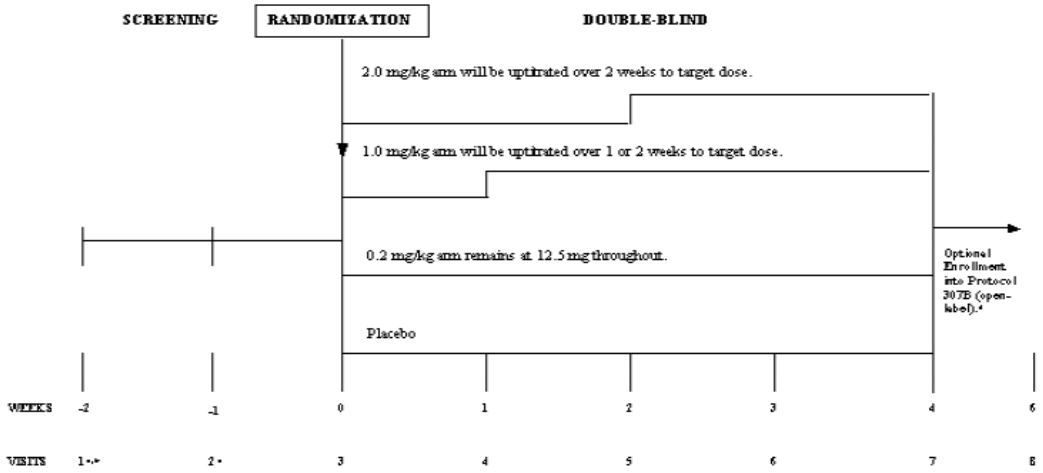
Study#1: 307A

Reviewer Note

This study was described in the Dose-Response Assessment (please refer to Page 7, Dose Response Analyses). Consequently, only highlights relevant to the population analyses will be included in this section.

Study 307A was a 4-week, multi-center, double-blind, placebo-controlled, randomized, parallel-group study. TOPROL-XL (metoprolol succinate) extended-release tablets were given to hypertensive pediatric patients. Patients were randomized to double-treatment with a once daily oral dose of placebo or Toprol-XL at 1 of 3 target doses: 0.2, or 2.0 mg/kg. The dose range for this study was 12.5 to 200 mg daily. Patients on placebo followed the same schedule as that for their active group comparators.

Study Flow Chart



[a] = Previous antihypertensive therapy must be stopped at this visit.
[b] = Patients who have been on previous antihypertensive therapy begin single-blind placebo run-in at Visit 1.
[c] = Patients who have newly diagnosed hypertension begin single-blind placebo run-in at Visit 2.
[d] = If not enrolling into Protocol 307B, then a Follow-up Visit for Protocol 307A takes place 2 weeks after cessation of study drug treatment.

Key Inclusion Criteria:

School age and adolescent children with reproducible SBP or DBP at or above the 95th percentile using height-adjusted charts for age and weight were eligible.

Study#2: 307B

Study 307B was a 52-week, multi-center, open-label study to determine the safety, and pharmacokinetics of TOPROL-XL (metoprolol succinate) extended-release tablets (metoprolol CR/XL) in hypertensive pediatric patients. The starting dose was 25 mg daily. The dose was increased every 2 weeks in increments of 25 mg or 50 mg based on tolerability until BP was controlled or the dose reached 200 mg.

Table 1: Study Assessments

	Open-label																		Follow-up
Week	0	2[a]	4	6[b]	8	10[b]	12	14[b]	16	20	24	28	32	36	40	44	48	52	54
Visit	1	2[a]	3	4[b]	5	6[b]	7	8[b]	9	10	11	12	13	14	15	16	17	18	19
General events/assessments																			
Informed consent/assent	X																		
Medical history	X[c]																		
Drug dispensing	X	X	X	X	X	X	X	X		X		X		X		X			
Drug accountability		X	X	X	X	X	X	X		X		X		X		X		X	
Urine drug and alcohol screen	X[c]																		
Urine pregnancy test	X[c]																	X	
Efficacy assessments																			
Blood pressure (sitting/standing)	X[c]	X	X	X	X	X	X	X		X		X		X		X		X	X[d]
Leg blood pressure[e]	X																		
Heart rate (sitting)	X[c]	X	X	X	X	X	X	X		X		X		X		X		X	X
Pharmacokinetic measurements																			
Serial metoprolol plasma sample[f]	Samples drawn after a single 25 mg dose of TOPROL-XL at any time between Visits 1 and 18																		
Trough metoprolol plasma sample																		X[g]	

[b] Optional visits for dose titration.
[c] The most current data were to be carried over for patients that were screened and/or randomized to Protocol 307A or enrolled in Protocol 307B (16-week). Adverse event assessments were only performed on patients who participated in Protocol 307A or Protocol 307B (16-week).
[d] One sitting blood pressure measurement for safety assessment only.
[e] Performed only in patients who did were not screened for participation in Protocol 307A.
[f] Following a 48-hour washout period, a subset of up to 30 patients had a total of 9 blood samples obtained at Hours 0, 1, 2, 3, 4, 6, 8, 10 and 24 after a single 25-mg dose of TOPROL-XL at any time during the study. This was treated as an unscheduled visit if performed at any time after Visit 1 and before Visit 18.
[g] All patients had a single trough plasma sample taken 24 hours after the last dose of open-label TOPROL-XL (Visit 18) with the exception of those patients who completed the serial pharmacokinetic portion of the study at Visit 18.
[h] Weight was measured at all visits, while height was only measured at Visits 1 and 18.

At the end of the 52-treatment period, all patients had BP measured and a trough plasma level taken 24 hours the last dose of Toprol-XL, with the exception of those patients who completed the serial portion at the final visit. Among the participants, a subgroup of approximately 30 patients was to participate in PK assessments of metoprolol requiring serial blood sampling at any time during the 52 weeks. A single dose of 25 mg of Toprol-XL was given orally to those participating patients after a 48-hour washout period. After the PK assessments, they returned to the main study protocol.

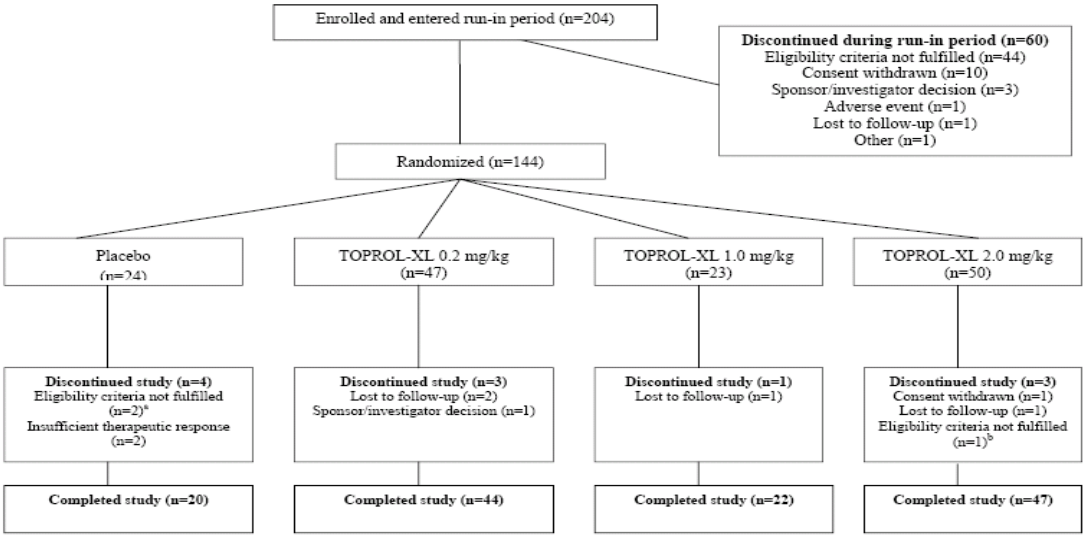
Data:

Study#1 307A:

4.1.1.1 Pharmacokinetics

A blood sample was to be collected at Visit 7 into a heparinized Vacutainer tube and obtained at 24 hours (±2 hour) following the last dose of study medication (i.e., trough measurement) for determination of plasma metoprolol concentrations.

Study Disposition Chart



[a] This includes the 1 patient who was reported to have discontinued the study for an adverse event on the adverse event page of the case report form.
[b] This patient did not receive study medication.

Table 2 : Study Demographics

	TOPROL-XL treatment groups								
	Placebo (N=23)		0.2 mg/kg (N=45)		1.0 mg/kg (N=23)		2.0 mg/kg (N=49)		All patients (N=140)	
Age (years), n (%)										
≤12	9	(39.1)	20	(44.4)	7	(30.4)	22	(44.9)	58	(41.4)
>12	14	(60.9)	25	(55.6)	16	(69.6)	27	(55.1)	82	(58.6)
Age, years										
Mean (SD)	12.3	(3.2)	12.5	(2.7)	13.5	(2.5)	12.2	(2.8)	12.5	(2.8)
Median	13.0		13.0		13.0		13.0		13.0	
Range	6.0 - 16.0		6.0 - 16.0		6.0 - 16.0		6.0 - 16.0		6.0 - 16.0	
Sex, n (%)										
Male	13	(56.5)	35	(77.8)	16	(69.6)	34	(69.4)	98	(70.0)
Female	10	(43.5)	10	(22.2)	7	(30.4)	15	(30.6)	42	(30.0)
Race, n (%)										
Black	5	(21.7)	9	(20.0)	6	(26.1)	16	(32.7)	36	(25.7)
Nonblack	18	(78.3)	36	(80.0)	17	(73.9)	33	(67.3)	104	(74.3)
Caucasian	18	(78.3)	34	(75.6)	17	(73.9)	31	(63.3)	100	(71.4)
Asian	0		1	(2.2)	0		2	(4.1)	3	(2.1)
Other	0		1	(2.2)	0		0		1	(0.7)

4.1.1.2 Pharmacodynamics

Primary variable

Sitting SBP determined at trough (24±4 hours, Visit 7) served as the primary efficacy assessment. The primary measure of effect was the placebo-corrected change from baseline to the end of treatment (Week 4) in trough sitting SBP. Each BP determination represented the mean of 3 readings with less than 7 mmHg between the highest and lowest value. Blood pressure was measured using a mercury sphygmomanometer with an appropriate size cuff positioned approximately at the level of the heart. Every effort was made to have the same individual measure the patient's BP throughout the study, if possible. At all post randomization visits, BP measurements were to be made at trough, defined as 24 hours (±4 hours) after receiving study medication. All measurements were to be determined prior to the patient taking the scheduled dose of study medication. In the

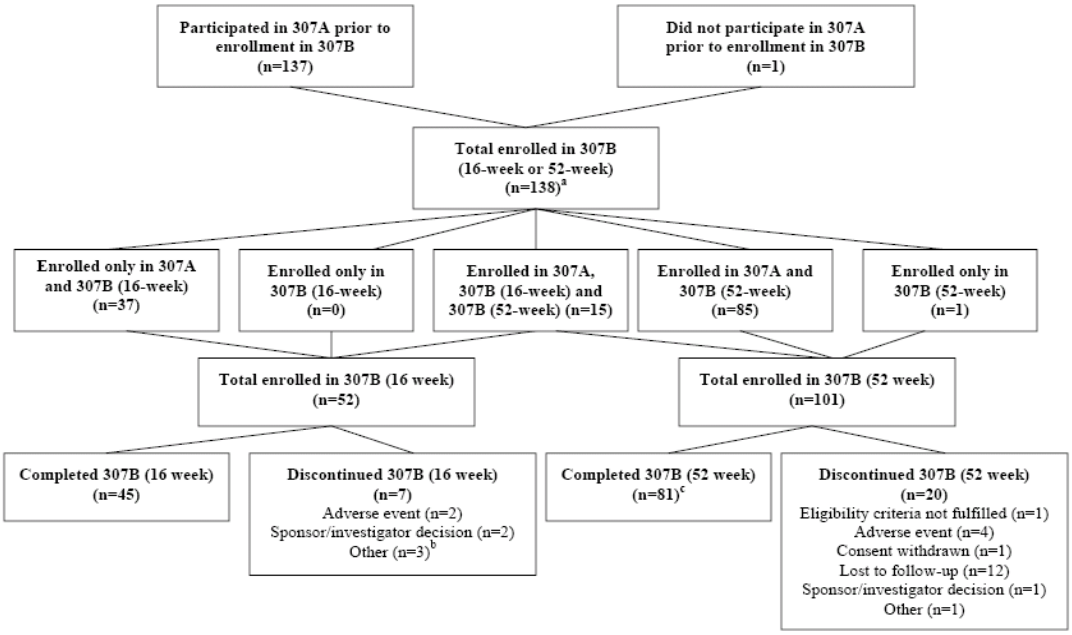
event that the patient accidentally took study medication on the day of the scheduled visit, the visit was to be rescheduled within 24 to 48 hours.

Study#2: 307B

4.1.1.3 Pharmacokinetics

A 48-hour washout period prior to sampling was required for all patients, including patients who entered the 52-week study and then decided to participate in the serial PK portion of the study. All patients were to have a 1.5-mL blood sample collected into a heparinized Vacutainer tube 24 hours (±2 hour) following the last dose of TOPROL-XL (i.e., trough measurement) at Visit 18 (or a the time of premature discontinuation), except for patients who participated in the serial PK portion of the study and had blood sampling performed at Visit 18. For patients participating in the serial PK portion of the study, blood samples (1.5 mL) were to be collected into heparinized Vacutainer tubes and obtained at Hour 0 (predose) and at 1, 2, 3, 4, 6, 8, 10, and 24 hours after administration of a single 25 mg dose of TOPROL-XL following a 48-hour washout period. After the last blood sample was obtained, the patient was to start/resume the prescribed dose of TOPROL-XL he/she was receiving prior to PK sampling.

Patient Disposition Chart (completion or discontinuation)



[a] A total of 138 patients were enrolled into 1 or both of the 16-week or 52-week studies for a total of 153 separate enrollment codes.
[b] These 3 patients were discontinued from the 16-week study in order to enter the 52-week study.
[c] Includes Patient No. 042-002, whose data were excluded from all analyses.

Overall, a total of 31 patients at 8 centers were enrolled in the serial PK portion of the study. Of these 31 patients, 27 had plasma concentration data available and were included in the analyses. Four patients were excluded from the analyses because their plasma concentrations were not quantifiable (Nos. 047-009 and 047-021) or because only whole blood samples were analyzed (Nos. 005-002, 005-003).

Table 3: Subject Demographics for Patients Providing Serial Blood Samples

Parameter	Tanner stage ≤3 (n=13)	Tanner stage >3 (n=14)
Age, years		
Mean (SD)	12.4 (2.1)	15.0 (1.5)
Median	12.4	15.0
Range	7.1 - 14.4	12.0 – 17.4
Sex, n		
Male	7	8
Female	6	6
Tanner stage, n		
1	1	
2	8	
3	4	
4		6
5		8
Weight, kg		
Mean (SD)	69 (19)	98 (26)
Median	66	96
Range	44 – 103	57 - 155

Missing Data

Twenty-six patients did not have blood samples obtained for analysis of metoprolol concentrations in either the 16-week (n=7) or 52-week (n=19) studies. Among patients with plasma samples, 14 (14%) in the 52-week study and 13 (13%) in the 16-week study had trough plasma metoprolol concentrations that were below the LLQ. Therefore, data from a total of 99 patients were included in this analysis.

Assay

Metoprolol plasma levels were assayed using high-performance liquid chromatography/ tandem mass spectrometric detection methods having limit of quantitation (LOQ) of 1 ng/mL. The method was validated in the linear range 1 to 1000 ng/mL. Precision was less than or equal to 10.9%. Accuracy ranged from 94.0% to 101.3%.

Pharmacodynamics

Not applicable.

Data Checking

SAS was used to format and check data. Additionally visual inspection of several randomly selected subject data was carried out.

Models

Overview
The sponsor's stated assumptions underlying this modeling analysis are:

1. Rich sampling data collected from 30 subjects in 307B Study can be used to adequately characterize the structural pharmacokinetic model of metoprolol.
2. Structural pharmacokinetic models of metoprolol at other dose strength are identical to that at 25 mg.
3. Metoprolol exhibits a linear pharmacokinetics in the dose ranges studied.
4. Steady-state pharmacokinetics of metoprolol has been reached at the time of blood sampling in Study 307A.
5. Metoprolol accounts for the blood pressure effect in the study.
6. Existing various disease states in the patients have no impact on the pharmacokinetics of metoprolol and pharmacodynamics of the blood pressure reduction in the study.
7. Concomitant medications, if existed, do not have any effects on the pharmacokinetics of metoprolol and pharmacodynamics of the blood pressure reduction in the study.

Reviewer Comment
The sponsor's assumptions appear reasonable based on existing metoprolol PK/PD information.

Pharmacokinetics

4.1.1.4 PK Structural Model

Several PK models were tested to identify the structural model. Flip-flop absorption was taken into consideration based on general PK characteristics following administration of sustained release tablets and observed data in the current study (serial PK samples).

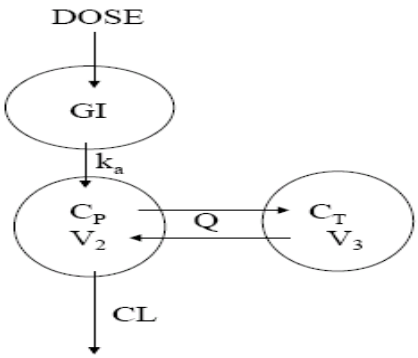
The models tested included linear 1- and 2-compartment PK models with the following characteristics (focused on flip-flop models):

- first-order absorption with and without absorption lag time (NONMEM subroutines ADVAN2 and ADVAN4);
- zero-order absorption with and without absorption lag time (NONMEM subroutines ADVAN1 and ADVAN3);
- simultaneous zero- and first-order absorption from the absorption compartment.

The models were parameterized in terms of CL/F and V/F

Ultimately the 2-compartment model with first order flip-flop absorption, an absorption lag time, and 2 residual error terms was selected as the structural model of metoprolol. The model scheme is presented in the following Figure 1.

Figure 1: PK Compartmental Model



CL apparent oral clearance; k_a first-order absorption rate constant; Q apparent intercompartmental distribution clearance; V_2 apparent volume of central compartment; V_3 apparent volume of peripheral compartment.

4.1.1.5 PK Covariate Model

Covariate models were developed to account for the potential impact of the following covariates and derived covariates on metoprolol PK:

Continuous variables

- Age (AGE, years)
- Body weight (WT, kg)
- Body surface area (BSA, m2) calculated from WT and HT (cm) using the height weight formula: BSA=0.024265 x WT 0.5378 x HT0.3964
- Ideal body weight (IBW, kg) calculated as: - Males: IBW=50+(HT–150)/2.5 and for Females: IBW=45+(HT–150)/2.5
- Dose (DOSE, mg of Toprol-XL)

Categorical variables

- Gender (SEX) - Male 0 - Female 1
- Race (RACE) - Caucasian 0 - Black 1 - Asian 2 - Other 3

PK covariate effects were modeled as follows.

Effects of continuous covariates (AGE, WT, BSA, IBW, and DOSE) were normalized to the corresponding median value across a dataset such that continuous covariates were related to structural PK parameters in a power function as described below:

$$PK\ parameter = PK\ typical\ value \bullet \left(\frac{Covariate\ value}{Median\ value\ of\ the\ covariate} \right)^{\theta}$$

where Θ is the fixed-effect parameter of a covariate estimated by the NONMEM program, covariate value is the observed covariate value, and PK typical value is the typical value of the PK parameter estimated by NONMEM. Effects of categorical covariates (SEX and RACE) are related to structural PK parameters by fractional changes of dummy variables:

$$PK\ parameter = PK\ typical\ value \bullet (1 + \theta \bullet covariate)$$

Where Θ is the fixed-effect parameter of a covariate estimated by the NONMEM program, covariate is the dummy variable value and modified in the control streams, and PK typical value is the typical value of this PK parameter as estimated by NONMEM.

Median values of all covariates in the dataset for population PK analysis are presented in Table A.

Table A: Summary of patient covariates and Toprol-XL doses in the data for population PK analysis

Parameter	Median	Mean	SD	Max	Min
Both studies (N=120)					
Age (year)	14.0	13.4	2.79	17.5	6.7
HT (cm)	163	161	15.9	192	115
WT (kg)	73.5	79.5	30.5	165	22.0
BSA (m^2)	1.88	1.89	0.445	2.94	0.856
IBW (kg)	57.9	58.0	15.3	88.6	17.8
Race: White/Black/Asian/Other			82/33/3/2[a]		
Sex: Male/female			79/41[a]		
Toprol-XL dose (mg): 200/175/150/100/75/50/37.5/25/12.5			32/1/14/17/11/15/2/15/13[a]		

[a] Classification by number of patients in each subgroup.

Two Steps were included in the modeling of covariates

Step 1: Forward Addition
The covariates were subjected to a stepwise forward selection algorithm using a likelihood ratio test based on a change in MOF values from the base model. A significant covariate reduced the MOF more than 6.60 (chi-square distribution, $p<0.01$, degrees of freedom [df]=1).

Step 2: Backward deletion (Excluding procedures for covariate effect)
The covariates in the full model acquired in Step #1 were subjected to a backward deletion algorithm; 1 covariate was deleted at a time, using a likelihood ratio test based on a change in MOF values. A covariate was determined to be statistically significant if the change in MOF after its deletion from the breakdown model was increased by more than 10.83 (chi-square distribution, $p<0.001$, df=1).

4.1.1.6 PK Random Variance Models

An exponential error model was used to characterize inter-patient variability based upon the assumption that random effects for PK parameters were not correlated among PK parameters. No other error models for eta were evaluated by the applicant or by this Reviewer. The retention of ETA values for each PK parameter in the structural model was confirmed by sequentially fixing each ETA value at zero, and comparing each resultant MOF with the MOF obtained when all ETA values were retained in the model (see Table 6).

The residual model was modeled by an additive model; two error terms were used, one for error associated with trough samples and the other with serial samples.

Reviewer Note
Use of an exponential model appears reasonable.

Pharmacodynamics

4.1.1.7 PK/PD Structural Model

The equations for the structural models are shown below:

Linear model: $E = m \quad X + Intercept$

Log-linear model: $E = m \quad \log(X) + Intercept$

Hill's sigmoid model without baseline: $E = \frac{E_{max} \; C_p^{\gamma}}{EC_{50}^{\gamma} + C_p^{\gamma}}$

Hill's sigmoid model with baseline: $E = \frac{E_{max} \; C_p^{\gamma}}{EC_{50}^{\gamma} + C_p^{\gamma}} + E_0$

where:

E	is the change in hemodynamic measurements.
X	is the observed metoprolol trough plasma concentration, C_{max} or $AUC_{(0-24)}$.
m	is the slope of the equation.
Intercept	is the intercept of the equation.
E_0	is the baseline effect.
E_{max}	is the maximum effect.
EC_{50}	is the concentration required to produce 50% of maximum effect.
γ	is an estimated parameter to empirically allow for sigmoidicity in the relationship
C_p	is the trough metoprolol plasma concentration.

The equation of the baseline model, which assumes that any change in the hemodynamic measurements between pretreatment and post-treatment is a constant, is delineated below:

Baseline model: $E = E_0$

1. Metoprolol Ctrough

The relationships between the observed metoprolol concentrations (Ctrough) and hemodynamic changes were investigated using 4 direct-link models, namely, a linear model, a log-linear model, and Hill's sigmoid Emax PK/PD model with and without a baseline.

2. The relationships between Cmax or AUC_{0-24} and hemodynamic changes were investigated using 2 direct-link models, a linear model and a log-linear model.

4.1.1.8 PK/PD Covariate Model

The inclusion and exclusion procedures of covariate effect on the selected PK/PD base model to obtain a selected final PK/PD model were identical to those in the covariate evaluation in the population PK models as described previously in PK Covariate Model.

Table B: Baseline demographic and covariate characteristics

Parameter	Median	Mean	SD	Max	Min
Age (year)	13.5	13.0	3.0	17.1	6.7
HT (cm)	163	158	17.2	183	115
WT (kg)	71.0	74.9	32.1	160.0	22.0
BSA (m^2)	1.81	1.81	0.480	2.91	0.856
IBW (kg)	51.6	52.0	7.32	63.2	36.0
ΔMAP (mmHg)	–6	–5.9	6.9	12	–19
ΔSBP (mmHg)	–7	–6.8	8.5	15	–31
ΔDBP (mmHg)	–6	–5.5	8.5	18	–22
ΔHR (beats/min)	–6	–5.8	11.5	25	–32
Race: White/Black/Asian/Other			43/20/1/1[a]		
Sex: Male/female			47/18[a]		
Toprol-XL dose (mg): 200/150/100/75/50/37.5/25/12.5			17/9/2/8/4/2/1/12[a]		

[a] Classification by number of patients in each subgroup.

4.1.1.9 PK/PD Random Variance Models

An exponential error model was used by the applicant to model inter-individual variability. The retention of a random effect parameter, ETA, in each selected PK/PD structural model was then evaluated by sequentially fixing each ETA value at zero, and comparing each resultant MOF with the MOF obtained when all ETA values were retained in the model ($p<0.05$). This step reduced over-parameterization by deleting unnecessary random-effect parameters from the structural model to obtain the base model.

Reviewer Note

The study design precludes assessment of inter-individual variability or random error because only one dose record was available per patient. Consequently, the model should not have included eta terms. It is noted that the sponsor ultimately dropped the eta term in the final model.

Model Selection

PK Initial Model Selection

PK Base Model to Final Model

The selection of the most appropriate PK base model for a metoprolol PK was based upon the following criteria: a significant reduction in MOF as compared to the baseline model and asymptotic chi-square distribution based on the likelihood ratio test, or AIC ($p<0.05$), as compared to the other structural models. This selected PK base model was then subject to a covariate evaluation. The population PK model bearing all surviving covariate parameters with statistical significance became the penultimate final model. If 1 of the body size parameters (WT, BSA, and HT) was not in the model, the penultimate final model became the final model. If body size parameters were in the model, they were sequentially replaced by other body size parameters in the regression submodel for each PK parameter. The best body size parameter was then selected on the basis of lowest MOF to form the final model.

PK Final Model Selection

Simulations and visual inspections based on goodness of fit plots were used to qualify and validate the model. The goodness-of-fit of the final model was evaluated graphically by comparing population and individual predictions of metoprolol concentrations with observed metoprolol concentrations along the line of unity, and by visual inspection of the following plots of population-weighted residuals (WRES) for the final population model:

1. Population-weighted residuals (WRES) versus population-predicted concentrations (PRED)
2. WRES versus time after first drug administration in each patient
3. WRES versus all covariates evaluated.

WRES were generally expected to be distributed homogenously around zero for PRED, time after administration, and covariates. For those 27 patients with serial samples, goodness-of-fit of the plasma concentration-time profile for each individual was visually inspected. The linear relationship between their AUClast values from the observed data and those from the simulated data (final model) was examined.

The predictive performance of the final population PK model including covariates was evaluated by comparing typical values of PK parameters with the mean of individual Bayesian estimates or individual values of PK parameters with the results from non-compartmental analysis for patients with serial samples. Steady-state metoprolol plasma concentration-time profiles from 0–24 hours at the interval of 15 minutes (0.25 hour) were calculated using the post hoc Bayesian estimated PK parameter obtained for 65 patients included in the PK/PD relationship using the following equation:

$$C_{p,t} = \frac{F\ K_a\ DOSE}{V_2}\left(\frac{(k_{21}-k_a)\ e^{-k_a T}}{(1-e^{-k_a \tau})(\alpha-k_a)(\beta-k_a)} + \frac{(k_{21}-\alpha)\ e^{-\alpha T}}{(1-e^{-\alpha \tau})(k_a-\alpha)(\beta-\alpha)} + \frac{(k_{21}-\beta)\ e^{-\beta T}}{(1-e^{-\beta \tau})(k_a-\beta)(\alpha-\beta)}\right.$$

where

Cp,t metoprolol plasma concentration (ng/mL) at time t (hour)

DOSE Toprol-XL dose (mg)

V_2 volume of distribution in the central compartment (L)

α rate constant for the distribution phase (hr^{-1})

β rate constant for the terminal elimination phase (hr^{-1})

k_{21} rate constant from the tissue compartment to the central compartment. It was obtained as: $\frac{Q}{V_3}$

τ dosing interval; ie, 24 hours

T time corrected with absorption lag time (hr); ie, $T = t - T_{lag}$

k_a first-order absorption rate constant (hr^{-1})

PK/PD Initial and Final Model Selection

A similar approach to that of PK model selection was adopted for PK/PD.
Each of the above-mentioned PK/PD models with random effects was identified by curve-fitting the dataset. Initial selection of the PK/PD structural model was based upon a significant reduction in MOF ($p<0.05$) as compared to the baseline model and reasonable PK/PD parameter estimates.

Software

Nonlinear mixed-effect modeling (NONMEM) software (Version V level 1.1, Globomax, Hanover, MD) was used in the population PK analysis. PK model fitting was accomplished using first-order (FO) approximation methods. For PK/PD model fitting, the first-order conditional estimation (FOCE) with eta-epsilon interaction method in NONMEM was used for all model runs.

SAS software (Version VIII, Cary, NC) was employed to prepare datasets according to the format required by the NONMEM program (Boeckmann et al 1991). Microsoft® Excel 2000 (Redmond, WA) and S-PLUS 2000 (Professional Release 2, MathSoft Inc, Cambridge, MA) were used to perform exploratory, graphical, exposure calculation, and statistical analyses. according to the format required by the NONMEM program (Boeckmann et al 1991). SAS command files, logs, and listings pertaining to data file conversion and merging were reviewed by an independent analyst. Datasets were stored in SAS data frames, combined, and exported to Excel, and then to ASCII files before fitting to the model.

Datasets were prepared and pooled in a NONMEM-compliant format using SAS software by the Programming Group, Clinical Information Sciences, at AstraZeneca, Wilmington, Delaware. SAS command files, logs, and listings pertaining to file conversion and merging were provided and found to be acceptable. The contents of both datasets (toprolkat.csv* for PK modeling and cppd2.csv for PK/PD modeling) were included.

toprolkat.csv* was not provided electronically in a SAS format; however this reviewer generated a similar dataset using the applicant's criteria.

Reviewer Comment
The software and data assembly methods appeared adequate.

Results and Discussion

Design Adequacy

Overall, the trial designs appeared adequate to evaluate metoprolol population PK and PK/PD in pediatric patients receiving Toprol XL. However, the design could have been further optimized by increasing the sampling points, particularly in the absorption phase. Due to the limited number of samples in the absorption phase, it was not possible to accurately characterize the absorption model: first order vs. zero order or mixed first and zero order. Additionally, collection of mainly trough samples limits the ability to accurately estimate measures such as Cmax that are not directly related to Ctrough, particularly if multiple compartments are present. Consequently, Cmax estimations are unlikely to be accurate. Finally, most patients provided only one trough sample, thus inter-individual variability could not be adequately captured and may have limited the utility of the modeling exercise, particularly in PK/PD where the random effect could not be accurately characterized. Ultimately, there was no random variable in the final PK/PD model (i.e. eta was set to zero).

Data Integrity

This reviewer checked the data visually by randomly selecting data from patients included in the population modeling and comparing to data in the study report (source data). Overall the data integrity appeared acceptable. The applicant observed the following guidelines that appeared acceptable.
No datum from any study participant with a protocol violation that was thought to materially impact the analysis was included.
The dataset contained data from only those study participants who could be evaluated; i.e., with all the last dosing date/time, blood sampling date/time, plasma drug concentrations, and demographic covariates.

Data that were excluded (n = 62 samples) from the model were as follows:
One sample from an apparent poor metabolizer
Two samples collected > 96 hours post dose
From 307B , 10 trough samples < LOQ
From 307A, 17 samples < LOQ
Thirty-samples from serial data that were < LOQ or whole blood samples

Model and Model Selection:

Base Model

4.1.1.10 Pharmacokinetic Model description

The base PK model was a standard two compartment model that incorporated lag time and flip-flop kinetics. The key features of the model were flip-flop was insured by making the value of ke > ka in the clearance equation. Additionally, lag time was restricted to a value of 2 hours or less and concentrations were log transformed; consequently all concentrations (F) = 0 were given individual predicted concentrations of zero. Finally there were two residual error terms, one for serial samples and the other for trough samples.

Key equations were as follows:

KA = THETA(1)*EXP(ETA(1))
V2 = THETA(2)*EXP(ETA(2))
CL = (THETA(1)*THETA(2)+THETA(3))*EXP(ETA(3))
Q = THETA(4)*EXP(ETA(4))
V3 = THETA(5)*EXP(ETA(5))
ALAG1=THETA(6)*EXP(ETA(6))

4.1.1.11 PK Parameter estimation results

Table 1: Summary of PK parameters in the metoprolol population PK base model (per applicant)

Parameter[a]	Explanation	Model-predicted value	Standard error of estimate (%)[b]
θ_1, K_a	First-order absorption rate constant (hr^{-1})	0.0475	16.9
θ_2, V_2	Apparent volume of central compartment, V_2/F (L)	180	29.9
θ_3, CL	Partial term in apparent oral clearance, CL/F (L/hr)	238	11.4
θ_4, Q	Apparent intercompartmental distribution clearance, Q/F (L/hr)	741	25.2
θ_5, V_3	Apparent volume of peripheral compartment (tissue), V_3/F (L)	661	27.4
θ_6, $ALAG_1$	Absorption lag time (hr)	0.818	7.52
ω_1^2, K_a	Variance of the first-order absorption rate constant	0.511	51.7
ω_2^2, CL	Variance of apparent oral clearance	0.747	15.3
ω_3^2, Q	Variance of apparent intercompartmental distribution clearance	6.70	74.2
ω_4^2, V_3	Variance of apparent volume of peripheral compartment	1.12	57.1
ω_5^2, $ALAG_1$	Variance of absorption lag time	0.0506	119
σ_1^2	Residual variance 1	0.0211	19.1
σ_2^2	Residual variance 2	0.232	36.0

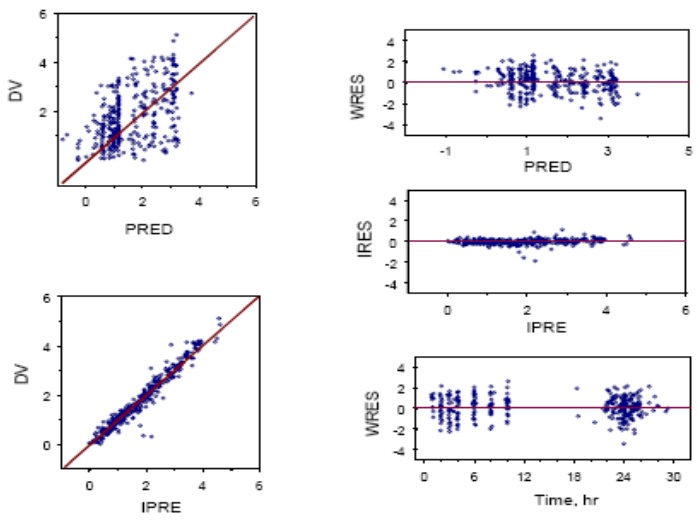
[a] PK parameters are referenced as theta (Θ) subscripted with the parenthetical index number in the NONMEM subroutine; ie, first-order absorption rate constant is Θ_1. Variances are referenced as omega-squared (ω^2) in the NONMEM subroutine.
[b] Standard error of estimate (%) was calculated as the percentage of the value obtained by dividing the standard error of the estimate by the parameter estimate.

4.1.1.12 Goodness of fit

The applicant provided the following goodness-of-fit plots (Figure 1).

Reviewer Note
The goodness-of-fit plots were reproduced by this Reviewer (see Appendix) with minor modifications.

Figure 1: Goodness of fit plots for Base Model



DV dependent variable, the natural logarithm of metoprolol plasma concentrations; PRED population-predicted metoprolol plasma concentrations; IPRE individual-specific prediction of metoprolol plasma concentrations; WRES weighted residual erros; IRES individual residual errors; Time elapsed time after the last dose.

Base PK Model Selection

The MOF values of all structural model candidates tested are presented in Table 2. Model selection was based primarily on MOF values, the lower MOF the better the model. The applicant reports that in general, MOF values generated by a conventional absorption model (i.e., absorption rate is faster than elimination rate) and a flip-flop absorption model (i.e., absorption rate is slower than elimination rate) were identical.

Reviewer Comment

The existence of flip-flop kinetics appears plausible based on data provided and general patterns for sustained release formulations. Consequently the use of flip-flop kinetics for the bulk of the modeling exercise appears reasonable.

General conclusions from the information in Table 2 are:
First order input is better than zero order input
Two compartment model is better than one compartment model
Lag time presence is better than lack of lag time
Two residual error terms are better than one residual error term
It should also be noted that several other models led to unsatisfactory completion of the run and were not considered further.

Table 2: Comparison of Structural PK Models

Model	MOF	ΔMOF	ΔAIC
The structural model: 2-CM first-order flip-flop absorption with absorption lag time	–53.92	–	–
1-CM first-order flip-flop absorption with absorption lag time	–29.12	24.8	16.8
1-CM first-order flip-flop absorption without absorption lag time	18.55[a]	72.47	60.47
1-CM zero-order flip-flop absorption with absorption lag time	34.23	88.15	80.15
1-CM simultaneous zero- and first-order flip-flop absorption with absorption lag times	18.02[a]	71.94	75.9
1-CM first-order flip-flop absorption with absorption lag time and bimodal distribution mixture model in CL	–36.59[a,b]	17.33	15.3
2-CM zero-order flip-flop absorption with absorption lag time	–17.11	36.81	36.81
2-CM simultaneous zero- and first-order flip-flop absorption with absorption lag times	–36.80[a]	17.12	29.2
2-CM first-order flip-flop absorption without absorption lag time	–34.21[a]	19.71	15.71
2-CM first-order flip-flop absorption with absorption lag time and bimodal distribution mixture model in CL	–54.15[a,b]	–0.23	3.77
2-CM first-order flip-flop absorption with absorption lag time and 1 residual error term	17.7	71.62	69.62
2-CM first-order flip-flop absorption with absorption lag time and variance term for V_2[c]	–53.92	0	2

[a] Program converged with a warning of "R MATRIX ALGORITHMICALLY NON-POSITIVE-SEMIDEFINITE BUT NONSINGULAR".
[b] Program converged with a warning of "PROGRAM TERMINATED BY FNLETA".
[c] V_2 is the apparent volume of central compartment.
ΔAIC change in Akaike Information Criteria relative to the identified structural model (ie, 2-compartment model with first-order flip-flop absorption and absorption lag time). Positive values indicate inferior models relative to the structural model; ΔMOF change in minimum value of objective function against the structural model; CM compartment; MOF minimum value of objective function.

Reviewer Comment
The selected structural model appears appropriate, based on the data.

Base Model
The deletion of ETA for V2 did not change the MOF value, suggesting that ETA for V2 should be deleted to avoid an over-parameterized warning (Table 3). This was consistent with the estimated parameter value of ETA for V2 being 6.48 x 10–9, a very small value. Therefore, the base model was selected by deleting the ETA for V2 from the structural model.

Reviewer Comment on Eta deletion for V2
Deletion of eta for V2 is acceptable based on the empirical data, however from a physiological perspective deletion of eta is problematic. Generally, one anticipates inter-individual differences in volume of distribution. In this case it appears that the error associated with V2 may have been randomly shifted to V3 and or Q terms, as the three

terms are interrelated. This potential shift in error is supported by the fact that the V2 eta value increases significantly (by several orders of magnitude- 10-5 vs. 100) when eta for Q and or V3 is fixed. However, when Q or V3 are fixed minimization is successful, but Q and V3 are not accurately estimated. Accounting for the possible error shift is a complex process and goes beyond the scope of this reviewer, thus deletion of eta associated with V2 was considered acceptable for the remainder of the modeling evaluation.

Table 3: Structural elements tested in the metoprolol population PK structural model (p < 0.005)

Elements	MOF	Change of MOF from structural model	ΔAIC
Structural model	–53.92	—	—
Structural model with the removal of ETA for:			
K_a	–32.62	21.3	19.3
V_2	–53.92	0	–2.00
CL	40.32	94.24	92.2
Q	–35.12	18.8	16.8
V_3	–46.84	7.08	5.08
ALAG1	–50.1	3.82	1.82

Final PK Model

4.1.1.13 Model description

The key feature of the final model is the inclusion of the covariate effects of age on Q and weight on CL in the population PK model.

Key Equations
CL = (THETA(1)*THETA(2)+THETA(3)+EWT)*EXP(ETA(2))
Q = THETA(4)*EAGE*EXP(ETA(3))

CL/F was estimated as $(\theta_1 \times \theta_2 + \theta_3 + \theta_7 (WT - 70)$, where θ_1, θ_2, θ_3, and θ_7 were 0.0467 hr^{-1}, 96.1 L, 223 L/hr, and 3.32, respectively.

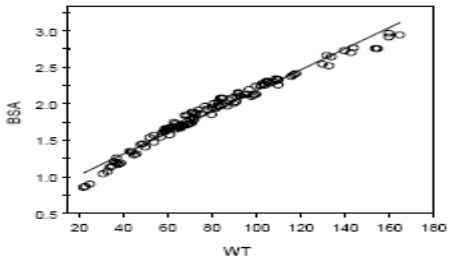
The typical value of apparent oral clearance of metoprolol was 227.5 (ie, $0.0467 \times 96.1 + 223 = 227.5$) L/hr for a study participant whose weight was 70 kg. CL/F increases linearly with body weight using a centering value of 70 kg, with a slope of 3.32.

Q/F was estimated as $\theta_4 \bullet (\frac{AGE}{14.0})^{\theta_8}$, where θ_4 and θ_8 were 675 L/hr and 4.41, respectively.

Including Covariate Effects
As previously described covariate effects were assessed by forward addition and backward deletion. Most covariates did not significantly change MOF; however, BSA significantly affected CL and Age affected Q. Consequently, these covariates were included in the penultimate final model.

Reviewer Note
BSA is derived form WT and HT covariates implying BSA is highly correlated to these two covariates (Figure 2); weight is the most suitable (practical covariate) as it is readily measured. Furthermore weight and BSA produced the same MOF (Table 4), whereas MOF with height was more positive (less significant).

Figure 2: Plot of BSA vs. Body Weight



The data in Table 4 support selection of the final model.

Table 4: Covariate elements tested in the metoprolol population PK penultimate final model (p<0.005)

Elements	MOF	Change of MOF from final model
Penultimate final model	–90.09	—
CL versus BSA	–67.33	22.76
Q versus AGE	–78.37	11.72

CL apparent oral clearance of metoprolol, CL/F; Q apparent intercompartment distribution clearance, Q/F.

Elements	MOF	Change of MOF from final model
Penultimate final model: CL versus BSA	–90.09	—
CL versus WT	–90.53	–0.44
CL versus HT	–76.36	23.73

The applicant acknowledges that mechanism(s) accounting for the impact of age on Q/F are not clear. However, since distribution clearance has little effect on metoprolol plasma exposure further investigation is not needed.

4.1.1.14 PK Parameter estimation results

As shown in Table 5, PK parameters were estimated fairly precisely by the final model.

Table 5: PK Parameter Estimates using Final Model

Parameter[a]	Explanation	Model-predicted value	Standard error of estimate (%)[b]
θ_1, K_a	First-order absorption rate constant (hr^{-1})	0.0467	19.2
θ_2, V_2	Apparent volume of central compartment, V_2/F (L)	96.1	20.3
θ_3, CL	Partial term in apparent oral clearance, CL/F (L/hr)	223	11.4
θ_4, Q	Apparent intercompartmental distribution clearance, Q/F (L/hr)	675	20.4
θ_5, V_3	Apparent volume of peripheral compartment (tissue), V_3/F (L)	620	25.5
θ_6, $ALAG_1$	Absorption lag time (hr)	0.853	2.97
θ_7	Linear coefficient of WT on CL/F	3.32	19.9
θ_8	Power coefficient of AGE on Q/F	4.41	13.6
ω_1^2, K_a	Variance of the first-order absorption rate constant	0.493	62.1
ω_2^2, CL	Variance of apparent oral clearance	0.613	15.7
ω_3^2, Q	Variance of apparent intercompartmental distribution clearance	6.71	53.5
ω_4^2, V_3	Variance of apparent volume of peripheral compartment	1.48	51.5
ω_5^2, $ALAG_1$	Variance of absorption lag time	0.0105	90.6
σ_1^2	Residual variance 1	0.0194	16.6
σ_2^2	Residual variance 2	0.225	36.0

[a] PK parameters are referenced as theta (Θ) subscripted with the parenthetical index number in the NONMEM subroutine; ie, first-order absorption rate constant is Θ_1. Variances are referenced as omega-squared (ω^2) in the NONMEM subroutine.

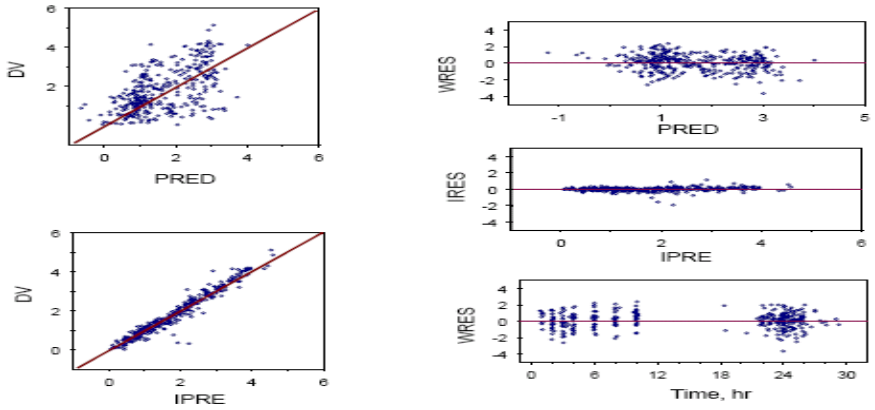
[b] Standard error of estimate (%) was calculated as the percentage of the value obtained by dividing the standard error of the estimate by the parameter estimate.

[c] The CV value was slightly high because of the small value of the variance estimate.

4.1.1.15 Goodness of fit

The goodness-of-fit plots provided by the applicant show good precision.

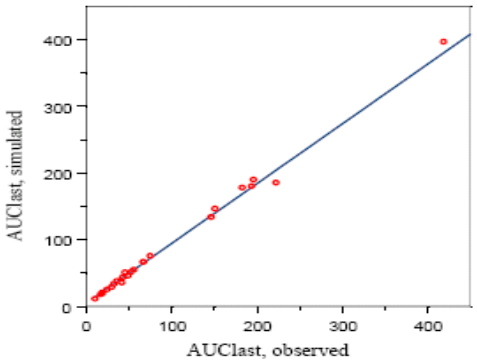
Figure 5: Goodness of fit plots for final PK model



PK Model Qualification

The post hoc Bayesian-estimated AUC (simulated) obtained for the 27 patients with serial plasma samples are plotted against the observed (AUCt). The correlation was high (R2 > 0.99).

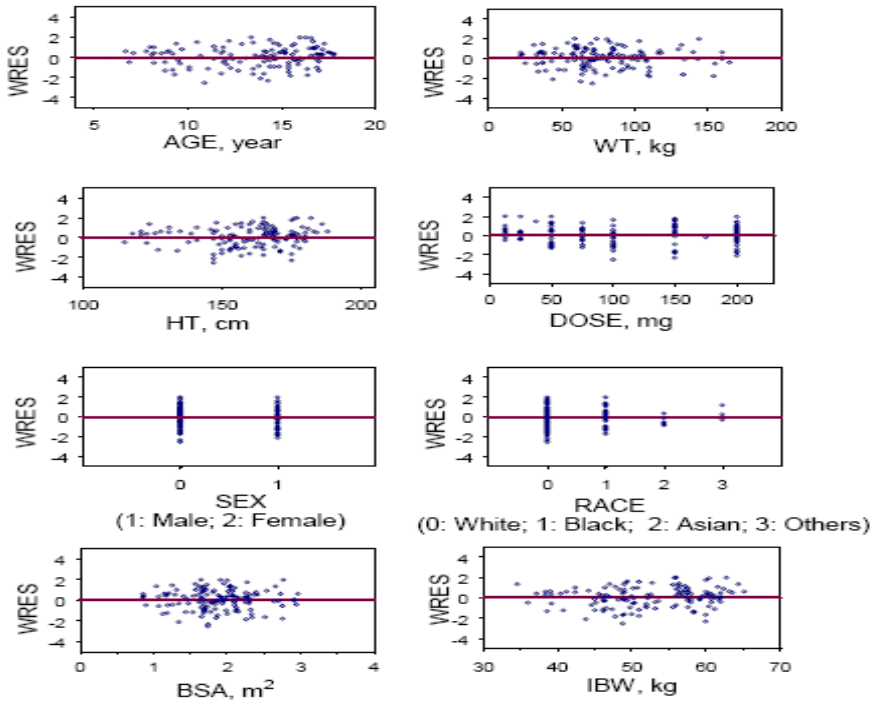
Figure 6: AUClast from observed data versus AUCt from model simulation* in the 27 patients providing serial plasma samples.



* Regression line Y= 4.514 + 0.8976 X R2 = 0.9957

The graphical validation of the final metoprolol population PK model validation against covariates evaluated is presented in Figure 6.

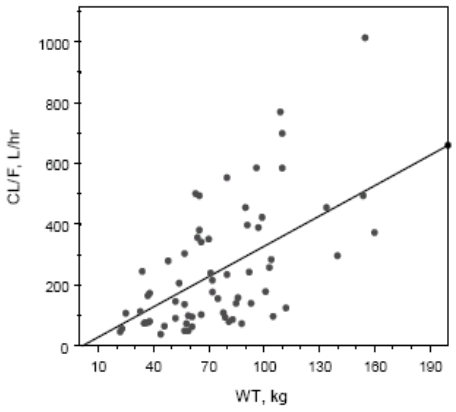
Figure 7: Graphical validation of covariates



There was no systematic bias in weighted residuals for any covariates evaluated, suggesting that the final model included all appreciable effects of available covariates (Figure).

The effects of weight on metoprolol CL/F are illustrated in Figure 8, where Bayesian post hoc estimates of CL/F are plotted against weight and overlaid by the model-predicted line. Overall, the model appeared to fit the data well.

Figure 8: Plot of CL/F vs. Body weight

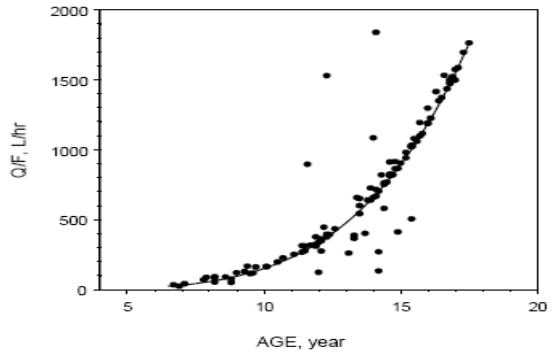


Note: Each point represents an individual Bayesian estimate of the corresponding CL/F . The line is derived from model expression CL/F =227.5+3,32*(WT–70) .

The effects of AGE on metoprolol Q/F are illustrated in Figure 9, where Bayesian post hoc estimates of Q/F are plotted against AGE and overlaid by the model-predicted line.

Figure 9: Plot of Q/F vs. Age

Observed and simulated dependence of distribution clearance of metoprolol on age (AGE)



The line was derived from the model expression $Q/F = 675*(AGE/14.0)^{4.41}$.

Reviewer Note
The applicant indicated that attempts to run the final model using the first-order conditional estimation method resulted in termination errors. Therefore, the parameter estimates obtained by the FO method were reported as the final parameter estimates.

Conclusion Regarding Population PK Modeling
Overall the sponsor's population PK modeling is acceptable.

PK/PD Model and Model Selection:

PK/PD Base Model
Pharmacokinetic/Pharmacodynamic Model description
The key feature of the model was a lack of random variance term for the slope, (since only single data points were available, per subject) and inclusion of baseline effect.

Key equations were as follows:
E0 = THETA(1)*EXP(ETA(1))
M = THETA(2)
Y = E0 + M*LOG(AUC) + EPS(1)

The control stream provided in the appendix is that for DBP (provided by sponsor). The control stream for SBP is comparable with appropriate substitution for BP type.

It should be noted that only the log-linear and linear PK/PD models were considered suitable for AUC and Cmax. For this review, only AUC estimates were considered reliable as Cmax estimates could not be accurately determined based on the sampling scheme. Consequently the remainder of this review focuses on AUC information although Ctrough and Cmax data are displayed for reference.

Bayesian estimates from PK modeling are summarized in Table 1.

Table 1: Bayesian estimates of metoprolol PK exposure for those patients included in the PK/PD analysis (N=65)

Parameter	Median	Mean	SD	Max	Min
Dose (mg)	100	107.7	69.5	200	12.5
Observed trough plasma concentration (ng/mL)	10.8	21.3	29.3	167	1.28
Estimated C_{24} trough plasma concentration (ng/mL)	10.1	18.8	21.1	99.3	1.20
C_{max} (ng/mL)	25.2	32.6	25.8	123	2.19
$AUC_{(0-24)}$ (hr •ng/mL)	440	629	577	2745	42.2
T_{max} (hr)	5.25	5.32	2.42	9.75	1.50

[a] No interpatient variability in V_2/F in the model.

PK/PD Model Selection (initial and final)

The log-linear model was adopted as the base model for this PK/PD relationship since it improved the MOF significantly (Table 2). The ETA parameter for the slope was pre-eliminated for the purpose of model parsimony. The intercept and slope in this log-linear model for AUC(0-24) did not bear ETA parameter; therefore, no covariates had impact on either parameter in the model.

Reviewer Note

The intercept should not have borne an eta term because individual subjects provided only one data point. Consequently, fixing eta to zero or deleting eta in the final model is appropriate. No further model development was required after eta was eliminated and the base model was equivalent to the final model.

Table 2: Base population PK/PD models tested for the change in SBP

	Model	MOF	ΔMOF	ΔAIC	p-value[a]
Observed C_p	Baseline model	341.770	-	-	
	Hill's model with a baseline	337.080	–4.69	1.31	>0.05
	Hill's model without a baseline	335.710	–6.06	–2.06	<0.05
	Log-linear model (selected model)	334.430	–7.34	–5.34	<0.05
	Linear model	338.100	–3.67	0.33	>0.05
Estimated C_{max}	Baseline model	341.770	-	-	
	Log-linear model	338.720	–3.05	–1.05	>0.05
	Linear model	338.710	–3.06	–1.06	>0.05
Estimated AUC	Baseline model	341.770	-	-	
	Log-linear model	337.760	–4.01	–4.01	<0.05
	Linear model	338.730	–3.04	–1.04	>0.05

[a] Probability was based on the value of ΔMOF and the degree of freedom from the chi-square table.

4.1.1.16 PK/PD Parameter estimation results

The final PK/PD parameter estimates are presented in Table 3.

Table 3 : Summary parameters in the final PK/PD model for the change in SBP using trough plasma level

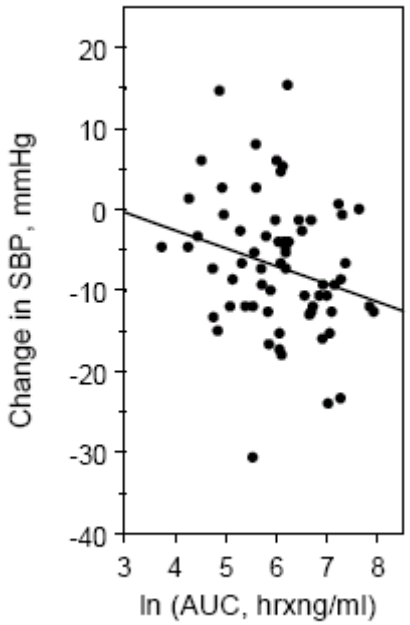
Parameter	Explanation	Estimate	SE (%)b
$AUC_{(0-24)}$			
θ_1, $E0_{AUC}$	Intercept of the log-linear relationship between DBP and $AUC_{(0-24)}$ of metoprolol	8.35	53.2
θ_2, M_{AUC}	Slope of the log-linear relationship between DBP and $AUC_{(0-24)}$ of metoprolol (mmHg•mL/hr/ng)	–2.38	30.0
ω_1^2, $E0_{AUC}$	Variance of intercept of the log-linear relationship between DBP and AUC of metoprolol	0.295	78.0
$\sigma 2$	Residual variance	38.8	30.2

[a] PK parameters are referenced as theta (Θ) subscripted with the parenthetical index number in the NONMEM subroutine; ie, E0 is Θ_1. Variances are referenced as omega-squared (ω^2) in the NONMEM subroutine.

[b] Standard error of estimate (%) was calculated as the percentage of the value obtained by dividing the standard error of the estimate by the parameter estimate.

Model Qualification
Based on the relatively low R^2 value and as shown in Figure, there is a poor correlation between change in SBP and log AUC.

Figure 1: Relationship between change in SBP and AUC (line generated from modeling)



Overall, goodness-of-fit of the model was considered to be poor, probably due to the high variability in the measurements. Consequently, the precision of the model parameter estimates was not considered to be very reliable. These parameters have little clinical usefulness and can be treated only as an indication of trends; i.e., more hemodynamic effects can be potentially achieved when high Toprol-XL doses are given. Clinical dose adjustment based on these PK/PD parameters is not recommended

Reviewer's Supplemental Analyses
A supplemental PK/PD analyses was conducted using simple linear regression since the population model did not improve the fit. Overall eta made an insignificant contribution to the overall model. The results of the analyses were similar to the population analyses. A series of regression analyses were conducted and are presented in Table 4.

The applicant notes that the preliminary modeling exercise found that there was no difference in the PK/PD modeling results using different hemodynamic data formats (i.e., change in the measurements, percent change in the measurements, or actual BP measurements). This finding was confirmed by this reviewer (see Table 4).

Table 4: Supplemental PK/PD Regression Analyses Conducted by Reviewer

Model (liner regression)	Intercept (I)	Slope (m)	R^2	Probability
RSBP = mISBP + I	39.57	-0.35	0.1626	0.009
PSBP = mISBP + I	25.24	-0.23	0.1252	0.0038
PSBP = mRSBP + I	0.005	0.74	0.9891	< 0.0001
RSBP = mlogAUC + I*	6.51	-2.21	0.060	0.0493
RSBP = mDose + I	-7.51	0.006	0.0026	0.6878
RSBP = mDose^ + I	-3.12	-1.11	0.04	0.2711
RSBP = mlogAUC + nISBP + I	53.03	-2.21 (m) -0.35 (n)	0.2230	0.001
RSBPplc = mAUC + I	-6.67	-0.003	0.0458	0.0871
RSBPplc = mlogAUC + I	4.61	-2.208	0.0600	0.0493
RPUL = mlogAUC + I	18.68	-4.05	0.1102	0.0069

Symbols in table
* similar to population PK model without eta term
ISBP- initial (baseline) SBP
Dose- in mg, where placebo is included as 0 mg
PSBP- percentage change of SBP without placebo correction
RSBP- change of SBP without placebo correction
RPUL- change in HR without placebo correction

Conclusion Regarding Population PK/PD Modeling
Overall the sponsor's population PK/PD modeling is acceptable. No dose adjustment conclusion can be made from this modeling; however an exposure-response relationship was established for AUC and reduction in SBP.

Discussion

The significance of the results
1. Provide estimates of PK measures and plasma exposure in pediatric population. These data can be compared to adult exposure to determine if exposure differences impact drug effectiveness. The main challenge in comparing pediatric data to adult data is different modeling schemes, formulations and methods were used in the two populations.

2. PK/PD findings are not sufficiently precise to provide a dose adjustment algorithm; however, the PK/PD analyses provides rationale for proposed titration as increasing exposure (doses) may improve efficacy (reduction in SBP). Ultimately, the risk-benefit analyses overrides PK/PD assessment for dose adjustment; drug will be titrated thus reliance on PK/PD information is not critical. The proposed dose, 1.0 mg/kg appears suitable, based on available information. It is unclear from the studies if there should be an initial maximum dose, although the sponsor has proposed 50 mg as the maximum initial dose. The proposed pediatric starting dose on a mg/kg basis is within the range of starting adult doses (25 – 100 mg), assuming an adult weighs 70 kg.

3. Cumulative information form dose-response study indicates that Toprol XL has effectiveness in children; however, the most effective dose is unclear. Since the drug can be titrated determining the initial optimal dose does not appear critical. As proposed by the applicant, dosing is started at a "low" dose that can be up-titrated, if needed.

4. The results did not adequately address the potential impact of CYP2D6 metabolic status for pediatric patients taking Toprol XL. There were an insufficient number of patients to make this assessment.

5. Covariate effects do not appear significant; only body weight significantly affects clearance. However, a worst case scenario can occur with a person that has a low body weight and is a poor metabolizer; this will result in very high, possibly supra-therapeutic exposure. Age does not impact apparent oral clearance, so an age-dependent dose adjustment is not needed for children over 6 years old. In essence all children over six years old can initiate therapy at 1.0 mg/kg.

The validity of the results

Overall the results produced by the sponsor appear valid and the sponsor used a sound modeling approach. However, alternative approaches that could have been adopted may have improved the outcome of the analyses. Three of these approaches are presented below:

1. Additional PK samples should have been collected during the absorption phase and throughout the dosing interval to improve the model's performance. Specifically additional samples collected during the absorption phase may have unambiguously identified the actual absorption input function (e.g. first order, zero order, mixed first and zero order). First order input was selected for the analyses, although the dosage form is reported to exhibit zero order kinetics in adults. It is possible that the input rate in children differs from that in adults, but unlikely. It should be noted that absorption kinetics in children is often erratic due to multiple factors (e.g. regio-selective absorption, incomplete gastric emptying and inconsistent absorption), so it is unclear if additional samples would have definitively identified the absorption function. However, additional, non-trough samples may have helped in estimating key PK measures such as V and Cmax. The final model did not have an eta associated with V, which is atypical. Collection of additional samples on different visits may have helped estimate potential inter-occasion variability. It should be noted that AUC was estimated precisely for subjects providing serial samples, but these subjects were not necessarily included in the PK/PD analyses. Ideally, the PK/PD modeling should have been conducted primarily in subjects who had accurate PK measures.

2. The PK/PD design could have been modified to potentially improve the utility of the analyses. Specifically there should have been better placebo matching procedures to minimize the potential impact of the placebo effect. This matching could have been improved by ensuring all patients on placebo had the same titration schedule and number of tablets. It is noted that the model had a poor predictive performance that was mainly attributed to the high degree of variability in the PD measures. Potentially, other PD markers could have been explored that have less inherent variability. One such marker is the degree of beta blockade using exercise heart rate (EHR) reduction; this marker has been used extensively for metoprolol in adult subjects. However, use of EHR in the pediatric setting may be challenging.

Recommendations

Labeling

Attach annotated labeling with reviewer markings and list all proposed changes along with the reviewer comments.

Pertinent sections of the annotated labeling follow.

Rx only
Toprol-XL
(metoprolol succinate)
EXTENDED-RELEASE TABLETS
TABLETS: 25 MG, 50 MG, 100 MG, AND 200 MG

Clinical Pharmacology
Pharmacokinetics

1Module 5, Clinical Study Report section 5.1 (307B)
2Module 2, Clinical Overview section 1.2.2.1
3 Module 5, Population PK Report sections 2 and 4.5.1
4Module 2, Clinical Overview section 3.3
5Module 5, Population PK Report section 6.2.1

(b) (4)

Metoprolol apparent oral clearance (CL/F) increased linearly with body weight.5 Metoprolol pharmacokinetics have not been investigated in patients < 6 years of age.

Hypertension
Clinical Trials
Pediatric

6Module 5, Clinical Study Report sections 5.1 and 5.2 (307A)
7Module 5, Clinical Study Report, section 7.2.1 (307A)
8Module 5, Clinical Study Report section 7.2.2 (307A)
9Module 2, Clinical Overview section 4.2
10Module 5, Clinical Study Report 7.2.2.5 (307A)

(b) (4)

(b) (4)

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Safety and effectiveness of TOPROL-XL have not been established in patients < 6 years of age. (b) (4)

ADVERSE REACTIONS
Hypertension and Angina
Pediatric
11Module 2, Clinical Overview sections 5.4 and 6
12Module 2, Summary of Clinical Safety section 6

No clinically relevant differences in the adverse event profile were observed for pediatric patients as compared with adult patients.11,12

Dosage and administration
Pediatric Hypertensive Patients ≥ 6 Years of age
13Module 2, Clinical Overview section 6

(b) (4) Dosage should be adjusted according to blood pressure response. Doses above 2.0 mg/kg (or in excess of 200 mg) once daily have not been studied in pediatric patients. (See CLINICAL PHARMACOLOGY, Pharmacokinetics.)13

Reviewer Comments
1. It is not clear why a maximum initial dose of 50 mg was chosen; the sponsor should provide justification for this seemingly arbitrary cut-off.
2. A statement regarding the maximum recommended dose should be included
3. A table providing dosing guidelines as provided in Study 307A may be useful.

(b) (4)

TOPROL-XL is not recommended in pediatric patients < 6 years of age (see CLINICAL PHARMACOLOGY, Pharmacokinetics and PRECAUTIONS, Pediatric Use.)

Comments to sponsor

In future pharmacometric studies you should consider the following:

1. collect sufficient (multiple) samples from individual subjects to allow assessment of inter-occasion variability and estimation of inter-individual variability (eta) for all relevant parameters
2. placebo groups should be identically matched across all dose groups (e.g. same titration schedule and number tablets) to minimize potential bias or differences in the placebo effect

Comments to medical reviewer

1. The sponsor has adequately characterized metoprolol PK in the studied pediatric population. The PK characterization could have been further optimized by obtaining additional samples over the entire dosing interval (e.g. during the absorption phase and elimination phase) on multiple occasions, rather than on one occasion primarily at trough.
2. A dose-response relationship could not be established using the protocol specified analysis approach. The outcome of the dose-response relationship appeared highly dependent on the "placebo effect", suggesting that the placebo group may not have been appropriate. One should consider re-evaluating the dose-response precisely matched placebo groups (e.g. all placebo patients have identical number of tablets and titration schedule).
3. Based on the PK/PD analysis, plasma exposure (AUC) explains < 10 % of the response (reduction in systolic blood pressure), thus has limited clinical utility. However, the PK/PD relationship suggests that there is a trend for increased response with increased exposure (dose driven).
4. Overall, information from the dose-response study suggests that Toprol- XL is effective in the pediatric population. The optimal initial dose, 0.2, 1.0 or 2.0 mg/kg or the maximum safe and effective dose cannot be determined from the information provided. It is noted that the 0.2 mg/kg dose is unlikely to be effective as plasma concentrations achieved at this dose are unlikely to be effective (most concentrations < LOQ and lower than effective adult concentrations). The 1.0 mg/kg (proposed by applicant) appears to be a reasonable initial dose. The labeling should reflect the regimens studied.

Appendix

```
$PROB Toprol base PPKmodel
$INPUT STUD ID DATE=DROP TIME AMT DV EVID SS II MDV TYPE
DOS AGE HT RACE SEX WT
$DATA toprolkat.csv
$SUBROUTINES ADVAN4 TRANS4
$PK CALFL=1
  KA   = THETA(1)*EXP(ETA(1))
  V2   = THETA(2)*EXP(ETA(2))
  CL   = (THETA(1)*THETA(2)+THETA(3))*EXP(ETA(3))
  Q    = THETA(4)*EXP(ETA(4))
  V3   = THETA(5)*EXP(ETA(5))
  ALAG1=THETA(6)*EXP(ETA(6))
  IF (ALAG1.GT.2) THEN
  ALAG1=2
  ENDIF
  S2=V2/1000
  T12=0.693*V2/CL

 $ERROR CALLFL=0
 IF (F.GT.0) THEN
 IPRE = LOG(F)
 ELSE
 IPRE = LOG(1)
 ENDIF
 IRES = DV - IPRE
 QQ=0
 IF (TYPE.EQ.2) QQ=1
 Y=IPRE+(1-QQ)*ERR(1)+QQ*ERR(2)

 $THETA
 (0.0012 0.0475  15);          1        KA
 (0.025 180 9500);             2     V2
```

```
(0.01 238 1000);              3  CL
(0.025  747 1000);          4       Q
(0.005 668 9600);           5       V3
(0.00002 0.82  2);          6       ALAG1

$OMEGA  0.5   0.01   0.7   1    1   0.04
;              7    8     9    10  11   12
;            KA   V2   CL  Q   V3  ALAG1

$SIGMA 0.05 0.1
$EST MSFO=msf MAX=9990 PRINT=10 POSTHOC; METHOD=1
$COV

$SCATTER IPRE VS DV
$SCATTER PRED VS DV
$TABLE ID TIME AMT IPRE IRES
 FILE=tab.txt NOPRINT ONEHEADER
$TABLE STUD ID CL V2 Q V3 KA T12 ALAG1 DOS AGE HT
 RACE SEX WT ETA1 ETA2 ETA3 ETA4 ETA5 ETA6
  FILE=prm.txt NOPRINT ONEHEADER FIRST
```

NONMEM truncated outputs for covariate evaluation to identify metoprolol final pharmacokinetic model

Step1 Inclusion (in ranked order)

File Name	MOF	TH1	TH2	TH3	TH4	TH5	TH6	TH7	ETA1	ETA2	ETA3	ETA4	ETA5	ERR1	ERR2
2CM ka Flip Lag 2ERR ETA2=0.out.txt[a]		-53.92	0.0475	180	238	741	661	0.818		0.511	0	0.747	6.7	1.12	0.0211	0.232
RACE~Q.out.txt		-53.92	0.0475	180	238	737	661	0.819	0.0245	0.512	0.748	6.7	1.12	0.0501	0.0211	0.232
RACE~V3.out.txt		-53.92	0.0475	181	238	743	660	0.819	0.00347	0.51	0.747	6.72	1.12	0.0504	0.0211	0.232
SEX~V3.out.txt		-53.94	0.0474	178	238	730	650	0.817	0.0412	0.508	0.75	6.66	1.12	0.0514	0.0211	0.232
RACE~CL.out.txt		-53.98	0.0475	179	241	737	659	0.819	0.0464	0.509	0.747	6.69	1.11	0.0495	0.0211	0.232
SEX~CL.out.txt		-53.98	0.0474	179	242	732	658	0.818	0.0447	0.506	0.75	6.68	1.11	0.0514	0.0209	0.23
IBW~KA.out.txt		-53.99	0.0481	179	238	741	652	0.819	0.24	0.517	0.752	6.86	1.19	0.0487	0.0211	0.23
RACE~ALAG1.out.txt		-54.19	0.0472	181	238	708	651	0.82	0.0376	0.519	0.75	6.56	1.2	0.0555	0.0212	0.228
DOSE~KA.out.txt		-54.26	0.0499	175	233	711	640	0.817	0.0664	0.537	0.723	6.78	1.13	0.0523	0.0208	0.227
AGE~KA.out.txt		-54.28	0.0476	178	238	742	653	0.82	0.333	0.533	0.75	6.85	1.24	0.0471	0.021	0.234
RACE~KA.out.txt		-54.28	0.0459	182	237	747	657	0.819	0.151	0.502	0.744	6.77	1.12	0.0499	0.0208	0.227
WT~KA.out.txt		-54.28	0.0827	178	232	742	653	0.82	0.333	0.532	0.75	6.87	1.24	0.0469	0.0203	0.23
BSA~V3.out.txt		-55.19	0.0484	274	238	818	574	0.758	0.953	0.539	0.722	9.95	1.77	0.119	0.0195	0.222
IBW~V3.out.txt		-55.33	0.0482	163	243	728	613	0.825	1.73	0.559	0.738	6.4	1.69	0.0422	0.0209	0.229
SEX~Q.out.txt		-55.75	0.0468	261	233	770	575	0.664	0.485	0.478	0.761	9.54	1.5	0.272	0.0213	0.23
IBW~ALAG1.out.txt		-55.99	0.0468	130	240	685	689	0.815	0.201	0.526	0.753	6.01	1.06	0.0242	0.0214	0.23
BSA~ALAG1.out.txt		-56.36	0.0467	255	236	674	599	0.678	0.441	0.538	0.743	8.6	1.43	0.128	0.0212	0.234
BSA~Q.out.txt		-56.61	0.0481	181	240	808	656	0.805	1.47	0.513	0.748	6.93	1	0.0654	0.0211	0.235
SEX~ALAG1.out.txt		-57.3	0.0472	128	240	776	704	0.638	0.388	0.511	0.749	8.26	0.85	0.0138	0.0213	0.231
WT~ALAG1.out.txt		-57.49	0.047	121	241	711	714	0.65	0.144	0.524	0.751	5.85	0.922	0.0258	0.0211	0.232
SEX~KA.out.txt		-57.55	0.041	193	239	786	686	0.819	0.501	0.513	0.723	6.66	1.02	0.0504	0.0197	0.226
BSA~KA.out.txt		-57.59	0.0452	175	239	751	594	0.823	1.08	0.593	0.713	8.2	1.59	0.0419	0.0211	0.227
DOSE~V3.out.txt		-58.12	0.0469	197	229	696	276	0.791	0.598	0.492	0.777	7.19	1.28	0.0779	0.0199	0.231
IBW~Q.out.txt		-58.75	0.0453	100	244	562	584	0.84	4.98	0.486	0.805	6.3	1.85	0.0215	0.0208	0.23

DOSE~ALAG1#.out.txt	-59.08	0.0473	175	233	758	642	0.0212	2.65	0.504	0.731	7.11	1.11	0.0426	0.0192	0.217
AGE~V3.out.txt	-59.77	0.0466	205	240	646	612	0.753	2.68	0.551	0.759	6.29	2.54	0.107	0.0204	0.216
DOSE~Q.out.txt	-59.77	0.0478	261	232	82.8	606	0.745	1.58	0.547	0.77	9.35	1.45	0.147	0.0192	0.217
WT~V3.out.txt	-59.77	0.0467	206	240	646	7.31	0.753	2.67	0.55	0.759	6.3	2.54	0.108	0.022	0.272
DOSE~CL.out.txt	-61.13	0.0443	150	251	572	555	0.809	0.165	0.42	0.686	6.43	0.861	0.0642	0.0202	0.228
AGE~CL.out.txt	-61.24	0.0471	176	252	722	635	0.814	0.957	0.502	0.733	7.24	1.28	0.0508	0.0202	0.228
WT~CL.out.txt	-61.24	0.0471	176	1260	722	635	0.814	0.957	0.502	0.733	7.24	1.28	0.0509	0.0212	0.233
AGE~ALAG1.out.txt	-62.34	0.047	171	239	756	694	0.724	0.488	0.529	0.743	7.19	0.928	0.127	0.0195	0.222
IBW~CL.out.txt	-62.48	0.0479	216	282	828	658	0.796	1.62	0.543	0.715	8.26	1.46	0.0711	0.0193	0.237
AGE~Q.out.txt	-67.33	0.0461	101	241	655	603	0.849	4.5	0.455	0.799	7.25	1.19	0.0127	0.0193	0.237
WT~Q.out.txt	-67.33	0.0461	101	241	1140000	604	0.849	4.5	0.456	0.8	7.24	1.19	0.0126	0.0194	0.229
BSA~CL.out.txt	-78.37	0.0482	206	245	801	595	0.803	1.63	0.542	0.594	9.17	1.51	0.0614	0.0211	0.232

[a] The base model

Step2 Inclusion (in ranked order)

File Name	MOF	TH1	TH2	TH3	TH4	TH5	TH6	TH7	TH8	ETA1	ETA2	ETA3	ETA4	ETA5	ERR1	ERR2
BSA~CL.out.txt	-78.37	0.0482	206	245	801	595	0.803	1.63		0.542	0.594	9.17	1.51	0.0614	0.0194	0.229
BSA~CL WT~Q.out.txt	-79.16	0.0484	201	244	811	593	0.799	1.61	0.423	0.536	0.594	8.95	1.43	0.0663	0.0196	0.23
BSA~CL AGE~CL.out.txt	-79.38	0.0484	210	239	828	604	0.804	1.95	0.468	0.55	0.57	9.28	1.46	0.0626	0.0197	0.233
BSA~CL IBW~CL.out.txt	-79.41	0.0483	201	224	793	605	0.806	2	0.853	0.534	0.572	8.56	1.37	0.0599	0.0201	0.235
BSA~CL WT~CL.out.txt	-80.23	0.0475	211	225	879	631	0.809	1.28	1.81	0.585	0.577	8.95	1.54	0.0557	0.0199	0.22
BSA~CL AGE~ALAG1.out.txt	-81.12	0.0482	205	245	833	615	0.749	1.61	0.197	0.565	0.59	9.75	1.41	0.0781	0.0196	0.228
BSA~CL DOSE~CL.out.txt	-81.86	0.0466	188	255	705	526	0.8	1.54	0.103	0.481	0.573	9.41	1.38	0.068	0.0197	0.249
BSA~CL AGE~Q.out.txt	-90.09	0.0471	94	244	661	626	0.853	1.57	4.39	0.472	0.622	6.69	1.32	0.0102	0.0193	0.231

Step 3 Exclusion

File Name	MOF	TH1	TH2	TH3	TH4	TH5	TH6	TH7	TH8	ETA1	ETA2	ETA3	ETA4	ETA5	ERR1	ERR2
BSA~CL AGE~Q.out.txt[a]	-90.09	0.0471	94	244	661	626	0.853	1.57	4.39	0.472	0.622	6.69	1.32	0.0102	0.0193	0.231
BSA~CL.out.txt	-78.37	0.0482	206	245	801	595	0.803	1.63		0.542	0.594	9.17	1.51	0.0614	0.0194	0.229
AGE~Q.out.txt	-67.33	0.0461	101	241	655	603	0.849	4.5		0.455	0.799	7.25	1.19	0.0127	0.0193	0.237

[a] The final model

File Name	MOF	ΔMOF	ΔAIC	TH1	TH2	TH3	TH4	ETA1	ETA2	ETA3	ERR1
C_{trough}											
Base model identification[a]											
Baseline model.out.txt	341.778			-6.84				0.00			70
M CP model.out.txt	338.1	-3.68	0.32	-5.16	-0.0687			0.351	4.24E-08		54.8
M CP model - ETAm.out.txt	356.62	14.84	16.84	-0.227	-0.216			10.2	0		102
M log CP model.out.txt	334.6	-7.18	-3.18	-0.153	-2.57			9.57	1.71E-09		58.3
M log CP model - ETAm.out.txt[d]	334.43	-7.35	-5.35	-0.0979	-2.59			14.9	0		58.3
RSBP Model 3.OUT.txt	334.71	-7.07	2.93	-35	29.9	0.2	8.55	0.07	3.11	0.305	0.00000443
RSBP Model 3 - ETAe0.OUT.txt	335.611	-6.17	1.83	-37.3	0.0681	0.307	23.3	0.0256	12.1	0	0.0000338
RSBP Model 3 - ETAec50.OUT.txt	334.88	-6.90	2.10	-35.3	22.3	0.191	9.18	0.0935	0	0.278	0.00000401
RSBP Model 3 - ETAemax.OUT.txt	336.899	-4.88	3.12	-38.5	0.152	0.246	21.2	0	6.13	0.002	44
RSBP Model 3 - ETAec50 -ETAemax.OUT.txt	337.08	-4.698	1.302	-59.4	0.00534	0.162	38.8	0	0.0197		35.5
RSBP Model 2.out.txt	335.71	-6.07	-0.07	-10.8	6.09	1.47		0.000000331	1.82		53.3
RSBP Model 2 -ETAemax.out.txt	335.71	-6.07	-2.07	-10.8	6.09	1.47		0	1.82		53.3
Covariate Evaluation for C_{trough} base model											
AGE~E0.out.txt	334.37	-0.06		-2.58	-1.84	4.15		0			63.1
BSA~E0.out.txt	336.23	1.8		-2.52	-1.71	-1.08		0			64.9
IBW~E0.out.txt	336.01	1.58		-0.0000304	-2.58	-27.1		0			64.7
RACE~E0.out.txt	334.27	-0.16		-0.0932	-2.58	-0.258		0			57.7
SEX~E0.out.txt	337.58	3.15		-0.392	-2.46	-0.428		0			56.5
WT~E0.out.txt	335.81	1.38		-2.65	-1.66	-0.757		0			64.5
C_{max}											
Base model identification[a]											
Baseline model.out.txt	341.778			-6.84				0.00			70
SBP Cmax.out.txt	338.71	-3.06	0.94	-4.22	-0.0734			0.45	1.57E-09		56.5
SBP Cmax - ETAm.out.txt	338.71	-3.06	-1.06	-4.22	-0.0734			0.45	0		56.5
SBP log(Cmax) - ETAm.out.txt	338.72	-3.05	-1.05	-0.419	-2.04			0			67.4
SBP log(Cmax).out.txt	338.72	-3.05	0.95	-0.419	-2.04			0.00000832	6.76E-22		67.4
AUC											
Base model identification[a]											
Baseline model.out.txt	341.778			-6.84				0.00			70
SBP log(AUC).out.txt	337	-4.77	-0.77	-6.43	2.22			0.381	0.119		15.2
SBP log(AUC)-ETAe0.out.txt	338.713	-3.057	-1.057	0	1.16			1	5.33E-13		67.3
SBP log(AUC)-ETAm.out.txt	341.777	0.007	2.007	--6.84	0			0.000357	1		70.7

[a] No appropriate model was identified.
[b] Model 3 is the Hill equation model with baseline, E_0. The γ, Hill's coefficient, does not bear an ETA, intersubject variability parameter.
[c] Model 2 is the Hill' equation model without a baseline, E_0. The γ, Hill's coefficient, does not bear an ETA, intersubject variability parameter.
[d] The base model.

```
$PROB Toprol base PPKmodel AGE 14.0 WT73.50 DOSE100 BSA1.877
$INPUT STUD ID DATE=DROP TIME AMT DV EVID SS II MDV TYPE
DOS AGE HT RACE SEX WT
$DATA toprolkat.csv
$SUBROUTINES ADVAN4 TRANS4
$PK CALFL=1
   ABSA=0.024265*WT**0.5378
   BBSA=ABSA*HT**0.3964
   BSA=BBSA
   IF (BBSA.EQ.0) BSA=1.877
   EWT =THETA(7)*(WT-70)
   EAGE= (AGE/14)**THETA(8)
   IF (SEX.EQ.0) IBW=50+(HT-150)/2.5
   IF (SEX.EQ.1) IBW=45+(HT-150)/2.5
  KA   = THETA(1)*EXP(ETA(1))
  V2   = THETA(2)
  CL   = (THETA(1)*THETA(2)+THETA(3)+EWT)*EXP(ETA(2))
  Q    = THETA(4)*EAGE*EXP(ETA(3))
  V3   = THETA(5)*EXP(ETA(4))
  ALAG1=THETA(6)*EXP(ETA(5))
  IF (ALAG1.GT.2) THEN
  ALAG1=2
  ENDIF
  S2=V2/1000
  K12=Q/V2
  K21=Q/V3
  KEL=CL/V2
  RR=K12+K21+KEL
  BETA=0.5*(RR-(RR**2-4*K21*KEL)**0.5)
  ALPHA=0.5*(RR+(RR**2-4*K21*KEL)**0.5)
  VSS=V2+V3
```

```
  T12B=0.693/BETA
 $ERROR CALLFL=0
 IF (F.GT.0) THEN
 IPRE = LOG(F)
 ELSE
 IPRE = LOG(1)
 ENDIF
 IRES = DV - IPRE
 QQ=0
 IF (TYPE.EQ.2) QQ=1
 Y=IPRE+(1-QQ)*ERR(1)+QQ*ERR(2)
$THETA
 (0.0012 0.0475  15);          1 KA
 (0.025 180 9500);           2     V2
 (0.01 238 1000);              3  CL
 (0.025 747 1000 );          4       Q
 (0.005 668 9600);           5       V3
 (0.00002 0.82  2);          6 ALAG1
(–0.05);             7 WT~CL
 (–3  0.1 5);              8
$OMEGA   0.5   0.7  1   1   0.04
$SIGMA 0.05 0.1
$EST MSFO=msf MAX=9990 PRINT=10 POSTHOC; METHOD=1
$COV
$SCATTER IPRE VS DV
$SCATTER PRED VS DV
$TABLE ID TIME DOS IPRE IRES AGE HT RACE SEX WT BSA IBW
 FILE=tab.txt NOPRINT ONEHEADER
$TABLE STUD ID CL V2 Q V3 KA ALAG1 ALPHA BETA T12B VSS
 DOS AGE HT RACE SEX WT BSA IBW ETA1 ETA2 ETA3 ETA4 ETA5
FILE=prm.txt NOPRINT ONEHEADER FIRST
```

Table 15 Control streams for final log-linear PK/PD model for the change in DBP using metoprolol Cmax as the measure of exposure

```
$PROB DBP LOGCMAX RDBP Data
$DATA cppd2.csv
$INPUT  ID TIME DOS IPRE=DROP IPRC DVCP=DROP CP=DROP AGE HT RACE SEX WT
BSA IBW IMAP=DROP ISBP=DROP IDBP=DROP IHR=DROP MAP=DROP SBP=DROP
DBP=DROP HR=DROP RMAP=DROP RSBP=DROP RDBP=DV RHR=DROP PMAP=DROP
PSBP=DROP PDBP=DROP PHR=DROP CMAX AUC=DROP
$PRED
E0=THETA(1)*EXP(ETA(1))
M=THETA(2)
Y=E0 + M * LOG(CMAX)+ EPS(1)
$THETA
–5.49 ; E0
0.01;M
$OMEGA
2
$SIGMA
20
$ESTIMATION MAX=9000 PRINT=10 NOABORT POSTHOC METHOD = 1 INTERACTION
$COVARIANCE
$TABLE ID ;EMAX EC50 GAM CP RDBP ETA1 AGE RACE SEX WT BSA IBW
 FILE=rmap.txt NOPRINT ONEHEADER
```

Truncated NONMEM reports for base model identification for PK/PD relationship in change of SBP (per sponsor)

File Name	MOF	ΔMOF	ΔAIC	TH1	TH2	TH3	TH4	ETA1	ETA2	ETA3	ERR1
C_{trough}											
Base model identification[a]											
Baseline model.out.txt	341.778			-6.84				0.00			70
M CP model.out.txt	338.1	-3.68	0.32	-5.16	-0.0687			0.351	4.24E-08		54.8
M CP model - ETAm.out.txt	356.62	14.84	16.84	-0.227	-0.216			10.2	0		102
M log CP model.out.txt	334.6	-7.18	-3.18	-0.153	-2.57			9.57	1.71E-09		58.3
M log CP model - ETAm.out.txt[d]	334.43	-7.35	-5.35	-0.0979	-2.59			14.9	0		58.3
RSBP Model 3.OUT.txt	334.71	-7.07	2.93	-35	29.9	0.2	8.55	0.07	3.11	0.305	0.00000443
RSBP Model 3 - ETAe0.OUT.txt	335.611	-6.17	1.83	-37.3	0.0681	0.307	23.3	0.0256	12.1	0	0.0000338
RSBP Model 3 - ETAec50.OUT.txt	334.88	-6.90	2.10	-35.3	22.3	0.191	9.18	0.0935	0	0.278	0.00000401
RSBP Model 3 - ETAemax.OUT.txt	336.899	-4.88	3.12	-38.5	0.152	0.246	21.2	0	6.13	0.002	44
RSBP Model 3 - ETAec50 -ETAemax.OUT.txt	337.08	-4.698	1.302	-59.4	0.00534	0.162	38.8	0	0.0197		35.5
RSBP Model 2.out.txt	335.71	-6.07	-0.07	-10.8	6.09	1.47		0.000000331	1.82		53.3
RSBP Model 2 -ETAemax.out.txt	335.71	-6.07	-2.07	-10.8	6.09	1.47		0	1.82		53.3
Covariate Evaluation for C_{trough} base model											
AGE~E0.out.txt	334.37	-0.06		-2.58	-1.84	4.15		0			63.1
BSA~E0.out.txt	336.23	1.8		-2.52	-1.71	-1.08		0			64.9
IBW~E0.out.txt	336.01	1.58		-0.0000304	-2.58	-27.1		0			64.7
RACE~E0.out.txt	334.27	-0.16		-0.0932	-2.58	-0.258		0			57.7
SEX~E0.out.txt	337.58	3.15		-0.392	-2.46	-0.428		0			56.5
WT~E0.out.txt	335.81	1.38		-2.65	-1.66	-0.757		0			64.5

AUC									
Base model identification[a]									
Baseline model.out.txt	341.778			-6.84		0.00			70
SBP log(AUC).out.txt	337	-4.77	-0.77	-6.43	2.22	0.381	0.119		15.2
SBP log(AUC)-ETAe0.out.txt	338.713	-3.057	-1.057	0	1.16	1	5.33E-13		67.3
SBP log(AUC)-ETAm.out.txt	341.777	0.007	2.007	--6.84	0	0.000357	1		70.7

[a] No appropriate model was identified.
[b] Model 3 is the Hill equation model with baseline, E_0. The γ, Hill's coefficient, does not bear an ETA, intersubject variability parameter.
[c] Model 2 is the Hill' equation model without a baseline, E_0. The γ, Hill's coefficient, does not bear an ETA, intersubject variability parameter.
[d] The base model.

Reported PD information^

Reference	Metoprolol regimen	Number of evaluable subjects	Maximum % decrease	Minimum % decrease
Feliciano et al. (1990a)	**OROS**			
	100mg daily	18	11	5
	200mg daily	17	16	12
	300mg daily	18	23	15
	400mg daily	18	25	18
	Conventional tablets			
	100mg daily	18	23	0
	100mg 2 times a day	17	25	6
	100mg 3 times a day	18	26	16
	100mg 4 times a day	18	29	21
Lücker et al. (1990)	**CR/ZOK**			
	100mg daily	16	13	8
	200mg daily	18	24	14
	300mg daily	18	27	22
	400mg daily	18	27	20
	Conventional tablets			
	100mg daily	16	23	2
	100mg 2 times a day	18	26	13
	100mg 3 times a day	18	29	24
	100mg 4 times a day	18	28	24
Wieselgren et al. (1990)	**CR/ZOK**			
	50mg daily	12	14	9
	Conventional tablets			
	50mg daily	12	19	< 1

^ Under metoprolol regimen CR/Z0K is Toprol XL

Table: Results of randomised double-blind comparative trials evaluating antihypertensive efficacy of metoprolol formulations or other antihypertensives

Reference	No. of pts	Study design	Dosage (mg)	Duration (weeks)	Responders (%)[a]	Decrease from baseline in blood pressure [systolic/diastolic (mm Hg)][b]	
						supine	standing
Metoprolol CR/ZOK							
Benesch et al. (1990)	102[c]	p	CR/ZOK 100 od	6		30/18	
			SR 200 od			33/20	
Carruthers et al. (1990)	28	m, p	CR/ZOK 100 to 200 od	8	93	20/19[d]	
	28		CT 50 to 100 bid		93	20/14[d]	
Dahlöf et al. (1988)	74	m, co	CR/ZOK 100 od	6	61	14/9	
	74		AT 50 od		61	13/10	
Dimenäs et al. (1990a)	35	p	CR/ZOK 100 od	4	51	12/9	12/9
	38		AT 50 od		60	9/9	10/9
Fagerberg et al. (1990)	22	co	CR/ZOK 200 od	3		10/6	
	22		AT 100 od			10/8	
Houtzagers et al. (1988)	91	m, p	CR/ZOK 100 to 200 od	12	83*	20/16[d]	
	86		CT 100 od or SR 200 od		69	21/15[d]	
Klein et al. (1990a)	97	m, p	CR/ZOK 50 to 100 od	8	89*	23/15	
	95		AT 50 to 100 od		74	19/14	
Krönig (1990)	30	p	CR/ZOK 100 od	8	97*	39/21	
	30		BIS 10 od		57	35/14	
Rydén et al. (1988)	13	p	CR/ZOK 100 od	4		20*/9	12/8
	14		CT 100 od			9/8	8/10
Walle et al. (1990)	60[c]	co	CR/ZOK 100 od	6		19/12	
			AT 100 od			19/14	
Metoprolol OROS							
Oldenbroek et al. (1990)	53	m, co	OROS 200 od	4	36	15/10	14/10
	53		SR 200 od		47	11/10	13/9
Wheatley & Murphy (1989)	31	p	OROS 200 to 400 od	12	78*	26*/18*	
	28		CT 100 to 200 bid		48	16/12	

a Criterion: diastolic blood pressure < 90 or 95mm Hg.
b Measured 24 hours after the last dose.
c Total number of evaluable patients in the study.
d Some measurements were taken in a resting seated position.
Abbreviations: p = parallel; m = multicentre; co = crossover; od = once daily; bid = twice daily; CR/ZOK = metoprolol controlled release/zero order kinetics; SR = metoprolol matrix-based sustained release; CT = metoprolol conventional tablet; AT = atenolol; BIS = bisoprolol; OROS = metoprolol oral osmotic system; * = statistically significant difference between therapies, $p < 0.05$.

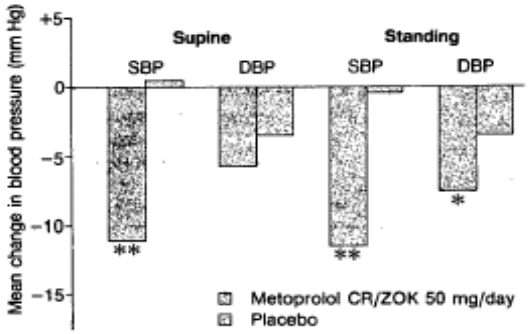


Fig. 8. Mean reductions in blood pressure 24 hours following the final dose after 4 weeks' therapy with metoprolol CR/ZOK 50mg daily or placebo in 62 patients with mild essential hypertension; SBP = systolic blood pressure, DBP = diastolic blood pressure (after Jäättelä et al. 1990). *Statistically significant difference versus placebo:* * $p = 0.035$; ** $p \leq 0.0001$.

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