CLINICAL REVIEW

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Review Completion Date:

Established Name: Metoprolol extended release
Trade Name: Toprol-XL
Therapeutic Class: Beta blocker
Applicant: AstraZeneca

Priority Designation: S

Formulation: Extended Release formulation
Dosing Regimen: (b) (4) to 200 mg/day
Indication: Hypertension
Intended Population: Pediatrics

Table of Contents

Tables:

Figures:

1. EXECUTIVE SUMMARY

This submission consists of two studies in support of the use of Toprol-XL in pediatric patients. The data, as submitted, are insufficient to recommend a new indication for pediatric use for metoprolol.

Study 307A was an unbalanced, double-blind, placebo-controlled, dose-ranging study. Pediatric patients (aged 6-16 years), with either systolic or diastolic hypertension were randomized to treatment with either placebo or metoprolol, at approximate doses (based on 12.5 mg increments, the size of the scored portion of the Toprol-XL tablet) of 0.2, 1.0 and 2.0 mg/kg. The randomization to placebo: Toprol-XL 0.2 mg/kg: Toprol-XL 1 mg/kg: Toprol-XL 2.0 mg/kg was in a ratio of 1:2:1:2. The administered dose for the two highest randomized doses was titrated after one week (1 mg/kg Toprol-XL) or 2 weeks (2 mg/kg Toprol-XL). The primary metric of the study was the slope of placebo-subtracted sitting systolic blood pressure at trough at the end of the study. The sponsor's analysis did not include the placebo point in defining the slope. The primary analytic plan did not demonstrate a significant slope effect. The inclusion of the placebo-group to anchor the analysis of slope also did not produce a significant value (p= 0.135).

The sponsor performed several additional analyses including comparison of the high dose and mid dose to placebo. Both these analyses were nominally marginally significant.

Additional analyses were performed by Dr. Freidlin (biostatistics) and Dr. Kumi (biopharmaceutics). Although some, but not all, of these analyses were nominally statistically significant, demonstrating a blood pressure effect of Toprol-XL in children, the primary metric of the study was not statistically significant. Modeling of the data based on several models, resulted in some analyses, but not all, which indicate a significant effect of Toprol-XL in children. No modeling of blood pressure response to either concentrations or dose in adults is available to define the most appropriate analysis to be performed in children. There is, therefore, insufficient data to recommend that Toprol-XL be approved in children for the treatment of hypertension.

The concentrations of racemic metoprolol at the 0.2 mg/kg were largely below the LLQ. The median values of metoprolol (consisting of the active and inactive enantiomers) suggest that the 0.2 mg/kg dose might be considered as a pseudo-placebo. The trough concentrations for adults for a 50 mg, culled from the literature, are approximately 35 nmol/L (23 ng/ml). If one assumes linearity for the 25 g dose, the resultant value for the lowest approved antihypertensive dose in adults would be approximately12 ng/ml or an order of magnitude greater than that observed in the pediatric study. There was approximately twice the number of subjects in the 0.2 mg/kg dose group than in placebo, to assess blood pressure effects, suggesting a better estimate for the effect of the 0.2 mg/kg dose than placebo effect. The 0.2 mg/kg dose could reasonably be treated as a pseudo-placebo. Consequently, the proposed analytic plan that excluded the placebo in the analysis

should not be dismissed as totally illogical, since the lowest dose (0.2 mg/kg) may adequately serve as the placebo.

Study 307B was a 52-week open-label extension study. Subjects could enter this study by any one of several routes. The vast majority of subjects were enrolled after participating in study 307A. The initial protocol only planned to maintain follow-up for 16 weeks. The protocol was subsequently amended that follow up would be for 52 weeks. There were 138 patients who enrolled either into the 16 or 52 week extension. Of those enrolled, there were 27 who prematurely discontinued either the 16 week or 52 week extension. There were 45 patients who completed the 16 week extension (not re-enrolling to complete 52 weeks) and 81 who completed the 52-week extension.

Adverse events did suggest either unusual or drug-related concerns. The most frequent events were headache and URI. Most of the adverse events are common events in a pediatric population.

There were no laboratory events or shift from baseline in laboratory measurements of concern.

Heart rates at values below 50 BPM were measured in 3 patients during the double-blind phase of the study (measured at trough). During the open-label phase there were 5 subjects with heart rate values measured under 50 BPM. The decrease in heart rate likely reflects an extension of the β-blockade effect.

There were small but clear changes in measures of ECG repolarization,. These changes are of uncertain accuracy, due to the uncertainties of the correction when heart rate is substantially decreased. In addition, given, the long-history of use of Metoprolol (as an IR or XL formulation), there does not appear to be a significant risk of proarrhythmic events with its use in adults.

1.1 Recommendation on Regulatory Action

The study was appropriately performed. The sponsor fulfilled the pediatric written request requirements and pediatric exclusivity was granted to the sponsor. The study, however, was not convincing in demonstrating that Toprol-XL produced a blood pressure effect in children. The stipulated primary end point, the placebo-corrected, dose-related systolic blood pressure effect (without the 0, 0 point anchor) was not significant. Including the 0,0 point did not result in a significant drug effect on systolic blood pressure.

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

There are no recommendations for post-marketing risk-management activities.

1.2.2 Required Phase 4 Commitments.

There are no recommendations for phase 4 commitments.

1.2.3 Other Phase 4 Requests

There are no recommendations.

1.3 Summary of Clinical Findings

The primary metric of the study was sitting blood pressure measured at the interdosing interval after 4 weeks of treatment (the high dose only had two weeks at that dose). The primary analysis was the dose-response relationship of the placebo-subtracted linear response excluding the placebo group. There was no significance to the dose-response relationship.

1.3.1 Brief Overview of Clinical Program

A single efficacy, dose-response study did not convincingly demonstrate a blood pressure effect in the studied population. A single long term extension study in the same population did not indicate any unusual safety issues.

1.3.2 Efficacy

The single study was a placebo-controlled, unbalanced, parallel group, dose-ranging study. The primary efficacy measurement was not significant.

1.3.3 Safety

Safety was largely derived from the parallel dose-response study 307A and the open-label extension study, 307B.

1.3.4 Dosing Regimen and Administration

The dosing regimen used in the randomized study was based on categorical levels of 0.2, 1.0 and 2.0 mg/kg. In actuality, the dose was limited by 12.5 mg dosing gradations, the size of the scored portion of the 25 mg Toprol-XL tablet. The actual dose that any subject received, on a mg/kg basis, could deviate from the categorical doses.

1.3.5 Drug-Drug Interactions

Not applicable.

1.3.6 Special Populations

Not applicable.

2. INTRODUCTION AND BACKGROUND

2.1 Product Information

Toprol-XL is currently approved in the USA for the treatment of angina, heart failure and hypertension.

2.2 Currently Available Treatment for Indications

There are no other beta-blockers approved for the treatment of pediatric hypertension. There are drugs from other anti-hypertensive classes that are currently approved for the treatment of hypertension in children.

2.3 Availability of Proposed Active Ingredient in the United States

The drug is approved and marketed as Toprol-XL.

2.4 Important Issues With Pharmacologically Related Products

Not applicable.

2.5 Presubmission Regulatory Activity

The submission of the pediatric supplement was 15 May 2006. There were three additional submissions on 16 June 2006 (response to statistical inquiry), 10 June 2006 (response to statistical inquiry) and 31 August 2006 (labeling and packaging).

The sponsor put together a useful table of their interaction with the Agency. The dates and the specifics of the interaction are shown below.

Figure 1: Interactions of AstraZeneca and the Division with respect to the pediatric written request.

Date	Summary
10/1/1999	AstraZeneca requests guidance information for the treatment of hypertension in pediatric patients with Toprol-XL® (metoprolol succinate) Extended Release Tablets.
10/19/1999	FDA issues a Written Request on the use of metoprolol succinate to reduce blood pressure in pediatric patients.
2/20/2001	AstraZeneca faxes brief background information on the formulation of the Toprol-XL extended release tablet and the need to use the commercial IV solution (metoprolol tartrate) for use in the younger age groups, and requests a telephone conference.
3/1/2001	AstraZeneca provides 3/1/2001 meeting minutes whereby the FDA accepts the proposal to use the IV formulation in the two youngest age groups for the PK study.
12/6/2001	AstraZeneca submits draft PK Protocol 308 for review for the pediatric exclusivity program to IND 40,602 (Serial No. 200).
12/20/2001	AstraZeneca submits draft Protocols 307A and 307B to IND 40,602 (Serial No. 203) for review.
1/15/2002	Teleconference between AstraZeneca and the FDA to discuss the designs of Protocols 307A and 307B. AstraZeneca discusses use of data from studies 307A and 307B to build a pharmacokinetic model to show blood pressure response. AstraZeneca submits meeting minutes of the teleconference to IND 40,602. [CV.000-095-010]
2/21/2002	AstraZeneca submits original Protocols 307A and 307B to IND 40,602 (Serial No. 208).
5/6/2002	AstraZeneca requests a time extension to the deadline for the 3 pediatric studies (Protocols 307A , 307B, and 308) per the Written Request.
5/17/2002	AstraZeneca submits amendments to Protocols 307A and 307B to IND 40,602 (Serial No. 216).
5/24/2002	FDA amends the Written Request concerning the reporting section and in addition grants a time extension to October 19, 2005.
7/3/2002	FDA reissues the Written Request under the "Best Pharmaceuticals for Children Act". No other terms of the Written Request are altered.
8/22/2002	AstraZeneca submits correspondence concerning Protocols 307A, 307B, and 308 their submission dates and status.
9/20/2002	AstraZeneca submits an amendment to Protocol 307A to IND 40,602 (Serial No. 227).

Date	Summary
11/8/2002	AstraZeneca discusses with the FDA by telephone, the changes to the Written Request. Specifically, the FDA informs AstraZeneca that single dose PK data collected independently from efficacy assessment are no longer necessary.
11/13/2002	AstraZeneca requests a meeting with the FDA regarding the PK requirement changes and the implication to the current Written Request. AstraZeneca formally requests an amended Written Request.
11/15/2002	AstraZeneca submits a request for an amended Written Request to IND 40,602 (Serial No. 232) based on the PK requirement changes.
12/18/2002	FDA amends the Written Request, which removes the requirement for a PK study in children less than six years of age (Protocol 308), inclusion of the collection of PK sampling from children enrolled in the effectiveness study, and specification of a 1-year duration for the long-term safety study.
3/3/2003	AstraZeneca submits the Statistical Analysis Plan for Protocol 307A, in accordance with the amended Written Request dated 12/18/02. The Statistical Analysis Plan for Protocol 307A is also submitted to IND 40,602 (Serial No. 241).
3/25/2003	AstraZeneca submits a protocol amendment to Protocol 307B to IND 40,602 (Serial No. 243) in response to the amended Written Request dated 12/28/02.
3/26/2003	AstraZeneca informs the FDA that the pediatric program has been revised based on the requirement for an open-label safety study of 1 year and requests an extension of 12 months to October 19, 2006.
4/8/2003	FDA issues an amended Written Request, changing the reporting section, and grants an extension until October 19, 2006.
11/26/03	AstraZeneca submits a protocol amendment to Protocol 307B to IND 40,602 (Serial No. 254) to expand the timeframe in which the PK assessment can be performed.
5/7/2004	FDA issues an amended Written Request, which requires reports to include more specific information on racial and ethnic minorities.
8/4/2004	AstraZeneca submits a Statistical Analysis Plan for 307B.
10/5/2004	FDA issues an amended Written Request which changed the word "must" to "should" regarding the categorization of the designations for race and ethnicity.
10/28/2004	AstraZeneca submits an amendment to the Statistical Analysis Plan for Protocol 307A. This amended Statistical Analysis Plan is also submitted to IND 40,602 (Serial No. 264).
12/16/2004	AstraZeneca submits a briefing document along with a request for a pre-sNDA meeting with the FDA to discuss the pediatric exclusivity program.
2/3/2005	AstraZeneca receives meeting minutes from the FDA documenting the 1/26/2005 teleconference to discuss the sNDA for the pediatric exclusivity program.
2/7/2005	AstraZeneca submits sponsor meeting minutes from the FDA teleconference dated 1/26/2005 to discuss the sNDA for the pediatric exclusivity program.

2.6 Other Relevant Background Information

Not applicable.

3. SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The product is currently approved. No additional CMC data was required.

3.2 Animal Pharmacology/Toxicology

The product is currently approved. No additional pharmacology toxicology data was requested.

4. DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The data that was used for the determination of efficacy and safety from clinical studies were submitted.

4.2 Tables of Clinical Studies

The submission consists of one clinical study 307A and a long-term extension study, 307B.

4.3 Review Strategy

The review was a joint medical-statistical review. The strategy that was employed was standard. We had access to the line listings for efficacy and safety. Since the primary metric of efficacy excluded the placebo effect, several additional analyses including that performed by the statistician and the biopharmaceutist were considered prior to recommending an action.

4.4 Data Quality and Integrity

The official report is pending. A preliminary report indicates no concern with the integrity of the data from the two sites that were inspected.

4.5 Compliance with Good Clinical Practices

Pending DSI report.

4.6 Financial Disclosures

The sponsor submits two forms 3454 both dated April 22, 2005, asserting no financial arrangements with the investigators.

5. CLINICAL PHARMACOLOGY.

The final biopharmaceutic review is still pending. A DRAFT review was consulted in constructing this document.

5.1 Pharmacokinetics

The final biopharmaceutic review is still pending.

5.2 Pharmacodynamics

The final biopharmaceutic review is still pending

5.3 Exposure-Response Relationships

The final biopharmaceutic review is still pending.

6. INTEGRATED REVIEW OF EFFICACY

There was only a single efficacy study. It is reviewed in this document.

6.1 Indication

We do not recommend making labeling changes to include a pediatric indication. The results, however, are not sufficiently negative to require the Division to insert restrictive pediatric labeling.

6.1.1 Methods

There was only a single efficacy study that served as the basis for analysis and for the recommendation.

6.1.2 General Discussion of Endpoints.

The choice of end point, sitting systolic blood pressure at the interdosing interval after 2-4 weeks of treatment at several doses, was appropriate. The vast majority (88-93%) of those enrolled had systolic hypertension. The percent of patients with diastolic hypertension was substantially less (23-53%). The approximate doses of Toprol-XL that were included in the study were 0.2, 1.0 and 2.0 mg /kg. The actual dose, however, was limited by the gradation of the dose contained in a scored portion of the marketed Toprol-XL tablet. Subjects were randomized in a 1: 2: 1: 2 ratio to placebo and the 0.2, 1.0 and 2.0 doses of metoprolol. The pre-specified analytic plan was to demonstrate a dose-response,

based on the categorical doses for the placebo-subtracted linear dose-response relationship. This analysis did not include the placebo point within the calculation. The result of that analysis was not significant. Including the placebo point as a 0, 0 anchor point did not afford a statistically significant result.

Additional analyses such as two point comparison of the higher dose and mid dose versus placebo were nominally marginally significant (p~0.05).

Other analyses that were consulted in forming this conclusion included E_{max} model and log linear response, based on the actual dose (on a mg/kg basis). In addition, a PK-PD model was also performed based on concentrations that were collected from several studies within the pediatric program. The kinetics and dynamics (from study 307A) were modeled the analyzed by several plausible models. Only some of these analyses were nominally significant.

6.1.3 Study Design

Study 307A was an unbalanced, placebo-controlled, randomized, blinded, dose-ranging study in pediatric patients whose age ranged from 6-16 years old. At least half the subjects were to be ≤ Tanner 3 maturity. The primary metric of the study was sitting systolic blood pressure, measured immediately prior to dosing in the clinic (trough), at the end of 2-4 weeks treatment at a targeted dose.

6.1.4 Efficacy Findings

The results of the study indicate a small blood pressure effect of the treatments. The effect on this and other metrics of the study are shown below. The primary metric of the study is sitting SBP.

Table 1: Dose related effects on sitting SBP and DBP and standing SBP and DBP (mean ± SD)

	Placebo (N=23)	Toprol-XL mg/kg 0.2 (N=45)	1.0 (N=23)	2.0 (N=49)
Sitting SBP				
Baseline	**132.7 ± 8.9**	**131.4 ± 9.0**	**135.0 ± 8.0**	**130.6 ± 9.6**
Change	**-1.9 ± 10.2**	**-5.2 ± 9.5**	**-7.7 ± 8.9**	**-6.3 ± 7.4**
Sitting DBP				
Baseline	81.4 ± 9.0	76.3 ± 7.7	81.0 ± 7.5	76.7 ± 9.1
Change	-2.1 ± 9.4	-3.1 ±9.5	-4.9 ± 7.5	-7.3 ± 8.3
Standing SBP				
Baseline	131.3 ± 11.5	129.7 ± 8.0	133.7 ± 8.5	129.5 ± 9.3
Change	0.0 ± 10.9	-3.9 ± 9.5	-7.1 ± 9.4	-6.7 ± 7.3
Standing DBP				
Baseline	83.1 ± 9.3	78.8 ± 9.3	82.2 ± 8.8	78.7 ± 8.8
Change	0.2 ± 9.7	-3.3 ± 7.5	-5.0 ± 9.5	-5.9 ± 8.4

The primary analytic plan was a non-zero slope of placebo-controlled, dose ranging study for systolic blood pressure that was not anchored by the placebo point. The effect was not significant. Including the placebo-group did not afford a significant effect. Blood pressure measurement of sitting DBP and standing SBP and DBP were nominally significant by the initial proposed analytic method.

6.1.5 Clinical Microbiology.

Not applicable

6.1.6 Efficacy Conclusions

There is insufficient information to conclude that Toprol-XL is beneficial in pediatric patients with hypertension. There is a sufficient trend of a blood pressure effect as to not include language dissuading physicians from the administration of this drug to pediatric patients.

7. INTEGRATED REVIEW OF SAFETY

The safety was derived from the short (4-week), placebo-controlled period and the one-year open label extension.

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths.

7.1.2 Other Serious Adverse Events

There was one serious adverse event during the placebo-controlled study. The patient had elevated blood pressure for which she was treated with furosemide. During the open-label extension, there were two serious adverse events. One subject developed pneumonia and a second subject developed menometorrhagia.

7.1.3 Dropouts and Other Significant Adverse Events

During the double-blind, placebo-controlled study there were no patients who discontinued due to an adverse event. During the long-term extension there were two subjects who discontinued due to adverse events in the cohort recruited in the 16-week extension and another 4 patients who discontinued from the cohort of the 52-week extension. The reason for discontinuation included asthma, dizziness with lightheadedness, nightmares, bradycardia, diarrhea, and tiredness

7.1.3.3 Other significant adverse events

None.

7.1.4 Other Search Strategies

7.1.5 Common Adverse Events

There were no unusual or unanticipated adverse events. The vast majority of events were common occurrences in this aged population. There were a few events that appear to reflect excessive β-blockade effects.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor characterized the adverse events appropriately. It is unclear which method of classifying adverse events was utilized. The events were characterized by system class and higher order terms (suggests a Medra classification).

7.1.5.3 Incidence of common adverse events

The most common adverse events are common in this aged pediatric patient population.

7.1.5.4 Common adverse event tables

The most frequent adverse events during the double-blind portion fo the study are shown below.

Table 2: Overall adverse events in greater than 5% in any group N (%)

Term	Placebo	Toprol-XL (target dose, mg/kg)		
	N=24	0.2 (N=46)	1.0 (N=23)	2.0 (N=49)
Number with > 1 AE	12 (50%)	17 (37%)	9 (39%)	3 (61%)
Nervous system	5 (21%)	8 (17%)	6 (26%)	8 (16%)
Headache	4 (17%)	5 (11%)	5 (22%)	5 (10%)
Dizziness	1 (4%)	1 (2%)	1 (4%)	3 (6%)
Infection and infestation	4 (17%)	4 (9%)	0	11 (22%)
Upper respiratory tract Infection	1 (4%)	2 (4%)	0	6 (12%)
Respiratory thoracic and mediastinal disorders	3 (13%)	3 (7%)	4 (17%)	6 (12%)
Cough	2 (8%)	1 (2%)	1 (4%)	1 (2%)
Pharyngolaryngeal pain	0	0	3 (13%)	0
Gastrointestinal disorders	1 (4%)	1 (2%)	2 (9%)	7 (14%)
Diarrhea	1 (4%)	0	0	3 (6%)
General disorders and administration site conditions	1 (4%)	2 (4%)	2 (9%)	5 (10%)
Pyrexia	0	0	1 (4%)	4 (8%)

7.1.5.5 Identifying common and drug-related adverse events

The adverse events likely attributed to drug are the extension of its pharmacologic activity. Several subjects had substantial bradycardia.

7.1.5.6 Additional analyses and explorations

Not relevant.

7.1.7 Laboratory Findings

There were no unusual laboratory adverse events in this modest-sized database.

7.1.7.1 Overview of laboratory testing in the development program

Laboratory values were collected at baseline and at the end of treatment during the double-blind and open-label extension studies.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

There were no signals of laboratory change related to treatment.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Blood pressure at trough was the primary metric of the study and was adequately measured.

Heart rate below 50 BPM was observed in three subjects during the placebo-controlled study. There was a change, relative to placebo, of approximately 11 BPM for the two highest dose groups. (The effect of either of the two high dose groups versus the low dose group was only approximately 2 BPM). During the open label extension there were drops on therapy of 3.7 to 6.2 BPM from entry during the 16-weeks study and 52-week study, respectively.

Growth and weight were followed during the long term extension. There was an increase of 3 cm in the total group. Since the study population consists of pre-pubertal and pubertal patients the growth rate would be highly variable. A better analysis would have been Z-scores.

7.1.8.3 Standard analyses and explorations of vital signs data

See above.

7.1.8.3.1 Analyses focused on measures of central tendencies

See above

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

See above.

7.1.9 Electrocardiograms (ECGs)

ECGs were captured at baseline and at end of treatment. The timing of the measurement is unclear but likely did not capture peak effects. Toprol-XL alters heart rate and there are inherent difficulties in correcting repolarization rates under circumstances where heart rates are substantially altered. The drug has a long clinical history and torsades de pointes events do not appear to be a problem with metoprolol. Nevertheless, there were changes in QTcB (Bazett's correction) and QTcF (Fridericia's correction) in a dose related manner.

Table 3: Repolarization parameters for study 307A.

			Targeted dose Toprol-XL (mg/kg)					
	PBO		0.2		1.0		2.0	
QT interval, msec	357 ± 39	-2.8 ± 21	362 ± 28	7.5 ± 22	358 ± 32	21 ± 32	360 ± 30	13. ± 27
QTcB interval, msec	413 ± 24	-9.4 ± 19	408 ± 19	-5.2 ± 17	403 ± 21	6.4 ± 19	405 ± 22	-1.9 ± 21
QTcF* interval, msec	393 ± 26	-6.6 ± 16	393 ± 15	-1.0 ± 15	389 ± 20	11.0 ± 18	390 ± 19	2.4 ± 19

* Calculated by Dr. Freidlin by the formula of Fridericia $QTcf=QT/RR^{1/3}$

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7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The only interpretable data is derived from the placebo-controlled study.

7.1.9.4 Additional analyses and explorations

None.

7.1.10 Immunogenicity

Not relevant

7.1.11 Human Carcinogenicity

See current labeling.

7.1.14 Human Reproduction and Pregnancy Data

See current labeling.

7.1.15 Assessment of Effect on Growth

Growth and weight were followed during the long term extension. There was an increase of 3 cm in the total group. Since the study population consists of pre-pubertal and pubertal patients the growth rate would be highly variable. A better analysis would have been Z-scores.

7.1.17 Postmarketing Experience

The sponsor submits additional information from publications. Most of these studies include case reports in seriously ill populations and are difficult to separate out any adverse events caused by the underlying disease process form those that are drug related. A retrospective study assessing the use of rather low doses infusion of immediate release metoprolol in patients with severe traumatic brain injury indicated no obvious adverse event on the survival of these patients.

In addition to a review of the literature, AstraZeneca queried physicians as to their use of metoprolol in a pediatric population. Eight physicians responded. AstraZeneca also screened their adverse event reports for those dealing with children (less than 18 years).

7.2 Adequacy of Patient Exposure and Safety Assessments

In conjunction with he large amount of data from the use of Toprol-XL in adults, the modest exposure during the clinical trial database is adequate to construct a labeling.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The data sources for the assessment of safety include the placebo-controlled dose-ranging study, a one-year follow-up extension, publications, a small physician use survey and the information contained in the AstraZeneca's adverse event database.

7.2.1.1 Study type and design/patient enumeration

The study was limited to pediatric patients. At least 50% of those enrolled were to be less sexually developed than Tanner Stage III.

7.2.1.2 Demographics.

The demographics for those enrolled in the placebo-controlled study are shown below.

Table 4: Demographics of those entering study 307A.

	Placebo (n=23)	Toprol-Xl		
		0.2 m/kg (n=45)	1.0 mg/kg (N= 23)	2.0 mg/kg
Age mean ± SD, years % < 12 years	12.3 ± 3.2 39%	12.5 ± 2.7 44%	13.5 ± 2.5 30%	12.2 ± 2.8 41%
Gender % male	57%	78%	70%	69%
Race: Caucasian/Black/Asian Other %	78/22/0/0	76/20/2/2	74/26/0/0	63/33/4/0
Tanner stage (≤ 3), n %	10 (44%)	27 (60%)	10 (44%)	23, (47%)
Weight, kg mean ± SD [range]	84 ± 35 [26 to 162}	80 ± 29 [25 to 154}	84 ± 31 [23 to 160]	80 ± 31 [22 to 155]
Height, cm Mean ± SD	159 ± 19	161 ± 17	162 ± 13	157 ± 16
BMI kg/m^2, mean ± SD	32 ± 10	30 ± 8	31 ± 9	31 ± 11
Type of HBP None/DBP/SBP/Both %	0/9/49/44	2/7/76/16	4/9/44/44	0/12/61/27

7.2.1.3 Extent of exposure (dose/duration)

The major exposure was during the open-label extension. The mean duration of exposure in that study was 354 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Other data that were used for the evaluation of safety include the sponsor's review of the literature, the results of a physician's survey and an analysis of the adverse event contained in AstraZeneca's safety database.

7.2.3 Adequacy of Overall Clinical Experience

In conjunction with the large exposure in adults, the pediatric experience in this application is sufficient for conclusions to be drawn of the safety of Toprol-XL in pediatrics.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The metabolic fate of metoprolol is adequately described in current labeling. The quantitative analysis of metoprolol in the pediatric studies was not stereospecific.

7.2.8 Assessment of Quality and Completeness of Data

Line listings for the double-blind placebo-controlled study and long-term safety database were available for review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

None.

7.4 General Methodology

Standard methodology was used.

7.4.1.1 Pooled data vs. individual study data

Not applicable.

7.4.1.2 Combining data

Not applicable.

7.4.2 Explorations for Predictive Factors

Not applicable.

7.4.2.1 Explorations for dose dependency for adverse findings

A greater proportion of subjects in the high dose group had adverse events than in placebo and low dose group. The numbers were however small and caution should be exercised in assigning a dose effect.

7.4.2.4 Explorations for drug-disease interactions

Not applicable.

7.4.2.5 Explorations for drug-drug interactions

Not applicable.

7.4.3 Causality Determination

Toprol-XL is currently approved both for the treatment of hypertension, angina and for heart failure. The safety profile derived from study 307A and 307B do not indicate any unusual pediatric adverse events.

8. ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The doses studied ranged from 0.2 mg/kg to 2.0 mg/kg (as a categorical value) the actual values based on subjects weight were somewhat different. There was no convincing efficacy effect on blood pressure. No dosing recommendation can be made.

8.3 Special Populations

There did not appear to be major differences in effects in considering gender, race or Tanner $\leq$ or > 3. There were too few patients to determine whether the effect or safety differs by any demographic parameter.

8.4 Pediatrics

The population under consideration is those between 6 to 16 years old with elevated blood pressure. Although there was a trend to blood pressure effect, the study did not appear to be convincing.

8.6 Literature Review

The sponsor performed a literature search. The information adds little to the decision process.

8.7 Postmarketing Risk Management Plan

None.

8.8 Other Relevant Materials

None

9. OVERALL ASSESSMENT

9.1 Conclusions

There does not appear to be consistent information to recommend use of Toprol-XL in pediatrics. There is also insufficient information to indicate that attempts to use Toprol-XL in children would be fruitless. We do not recommend any labeling changes.

9.2 Recommendation on Regulatory Action

We do not recommend changing the label.

9.3 Recommendation on Postmarketing Actions

There is no additional post-marketing information needed, unless the sponsor plans to repeat the study.

9.3.1 Risk Management Activity

Not applicable.

9.3.2 Required Phase 4 Commitments.

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

We do not recommend any labeling changes.

9.5 Comments to Applicant

The applicant should be informed that the totality of the data are not convincing that Toprol-XL is effective in pediatric patients.

10. APPENDICES

10.1 Review of Individual Study Reports

See below.

10.2 Line-by-Line Labeling Review

No labeling changes are suggested.

Other Pertinent Information

REFERENCES

Study number: D4020C00033 (307A).

Study 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:

Dates of study:

Initial protocol: Dated 14 February 2002.
Protocol amendment #1: Dated 6 May 2002.
Protocol amendment #2: 28 August 2002.
First patient enrolled 30 May 2002.
Last patient completed 9 June 2004.
Statistical analytic plan: 15 January 2002.
Statistical analytic plan amendment: 18 October 2004.

Amendment # 1- Since the entry criteria is based on either having systolic or diastolic hypertension, this amendment defines the specifics for eligibility and the measurements that are required, based on whether SBP or DBP is the qualifying measurement.

The sponsor also altered the laboratory assessment substituting measurements of fructose amine (glycated albumin) for glycolated hemoglobin.

Amendment # 2:

Removed the criteria related to > 90^{th} percentile for either SBP or DBP. The 95% percentile remains as a criteria for enrollment.

Amendment to statistical plan:

- Changed personnel.
- Re-defined the per-protocol population.
- Re-defined safety population to include only those known to have taken at least one dose of treatment.
- Described the statistics to be displayed for the primary efficacy variables to the following: predicted mean value, SE of predicted mean value, 95% CI around predicted mean value.
- Redefined the time-windows for the various visits.

- Described the secondary analyses. The secondary endpoints e.g., each dose compared to placebo as being underpowered to assess a drug effect.
- Defined exploratory analyses of interest to the "study team".
- Deleted the Appendices to the SAP.

Inclusion Criteria:

Subjects are to be between 6 and 16 years old at the time of screening. Females are to have a negative pregnancy test. No more than 50% of those enrolled can be > Tanner stage 3. The protocol required an informed consent signed by guardian, and if applicable, an assent signed by the patient. Patients should have either SBP or DBP > 95% percentile age and gender corrected.

Exclusion criteria:

Patients are excluded:

- For secondary hypertension (e.g., Cushing's syndrome, pheochromocytoma, and hyperthyrpoidism).
- Have a SBP of > 20 or DBP > 10 mm Hg greater than 95th percentile appropriate for age and gender.
- Bradycardia (HR < 55 BPM).
- Have liver enzyme elevation (> 1.5 x ULN).
- Be pregnant or breast feeding.

Have a history of :

- Asthma, recurrent pulmonary disease or cystic fibrosis.
- Hypersensitivity to beta-blockers.
- Bleeding or coagulation disorders.
- Insulin-dependent DM.
- Cardiac disease, valvular disease, heart failure, arrhythmias. Have conduction disturbances (e.g., 2nd or 3rd degree AV block).
- Concomitant medications that interact with Toprol-XL (e.g., catecholamine depleting medications, CYP2D6 substrates).
- History of alcohol or drug abuse or non-compliant with run-in medication.

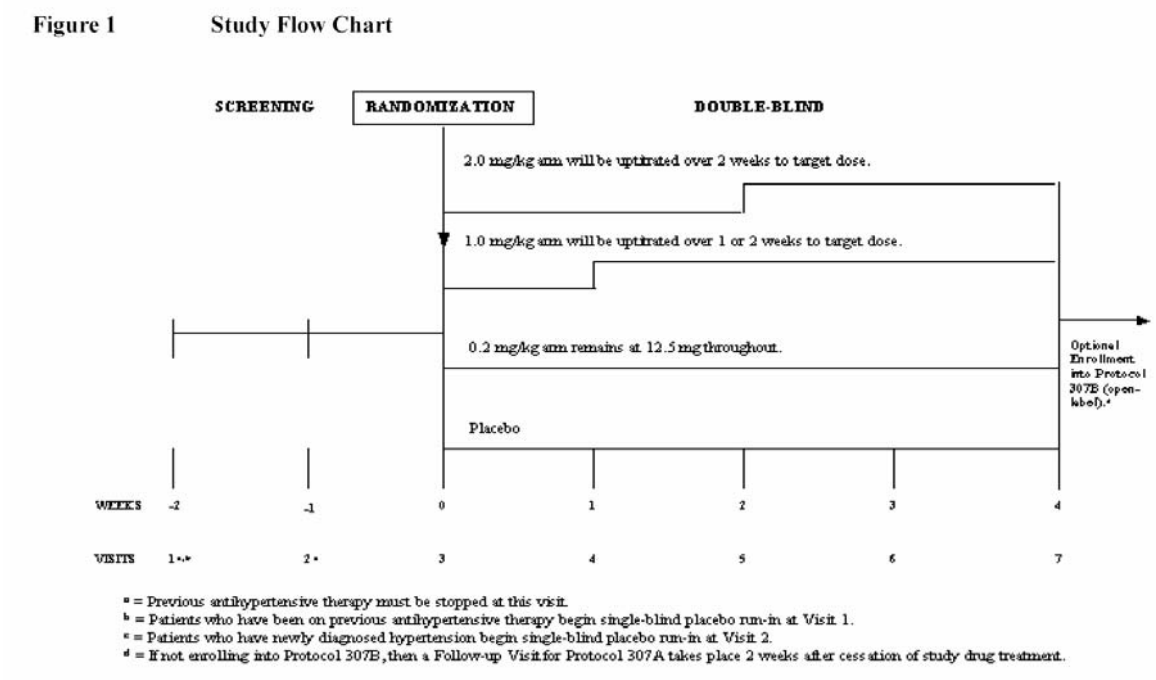
Procedures:

The study consisted of three periods:

- A one week screening period.
- A one-week single placebo blind run-in period.
- A four-week double-blind treatment period. During this period there was a one (1 mg/kg dose) or two week (2 mg/kg dose) titration period. Treatment at the targeted dose, therefore, ranged from two to four weeks.

For those with previously diagnosed and treated hypertension, the washout period could be one week, if at that time, the sitting SBP or DBP was > 95th percentile. If the blood pressure was below 95th percentile, the washout period could be extended an additional week.

Figure 2: Flow diagram, study 307A.



Dose:

Doses were targeted to 0.2, 1.0 or 2.0 mg/ kg. Since the 25-mg tablet of Toprol-XL could be split in half, there was somewhat more flexibility in the mg/kg dose. The table below shows the relationship between weight, the targeted dose and the actual dose on a mg/kg basis.

Table 5: Dose and actual dose based on weight for study 307A.

Weight range	Weight (kg)	Toprol-XL targeted dose					
		0.2 mg/kg		1.0 mg/kg		2.0 mg/kg	
		Dose	Act mg/kg	Dose	Act mg/kg	Dose	Act mg/kg
≤ 30 Kg	20	12.5	0.63	25	1.25	50	2.5
	30	12.5	0.41	25	0.83	50	1.7
> 30 to ≤ 45 kg	35	12.5	0.36	37.5	1.1	75	2.1
	40	12.5	0.31	37.5	0.94	75	1.9
	45	12.5	0.28	37.5	0.83	75	1.7
>45 to ≤ 60 kg	50	12.5	0.25	50	1.0	100	2.0
	55	12.5	0.23	50	0.91	100	1.8
	60	12.5	0.21	50	0.83	100	1.7
> 60 to ≤ 80 kg	65	12.5	0.19	75	1.15	150	2.3
	70	12.5	0.18	75	1.07	150	2.1
	75	12.5	0.17	75	1	150	2.0
	80	12.5	0.16	75	0.94	150	1.9
> 80 kg	90	12.5	0.14	100	1.1	200	2.2
	100	12.5	0.13	100	1.0	200	2.0
	110	12.5	0.11	100	0.91	200	1.8
	120	12.5	0.1	100	0.83	200	1.7
	130	12.5	0.09	100	0.77	200	1.5
	140	12.5	0.08	100	0.71	200	1.4
	150	12.5	0.08	100	0.67	200	1.3

The actual mg/kg dose could vary by almost a log-unit considering the lighter and heavier children those treated with the 0.2 mg/kg dose. The actual dose that a subject received in the higher dose groups was more likely centered around the proposed targeted dose.

Procedures:

The specific procedures are shown below.

Figure 3: Procedures planned for study 307A.

	Screening			Double-blind therapy				F/U
		PBO run-in	Random					
End of week	-2	-1	0	1	2	3	4	6
Visit #	1	2	3	1	5	6	7	8
Informed consent, Med History, BP (leg), urine and alcohol screen	X							
12-lead ECG, Complete P/E, Labs, Urine pregnancy test,	X						X	
Brief physical exam		X	X	X	X	X		X
Blood pressure (sitting and standing), concomitant meds, Heart rate sitting	X	X	X	X	X	X	X	X
Randomization			X					
Drug dispensation	X	X	X	X	X	X		
Drug accountability		X	X	X	X	X	X	
Trough plasma concentration of metoprolol							X	
Adverse events		X	X	X	X	X	X	X

The subject is to take the days medication at the same time of day but at the end of each clinic visit. As such the measurement of vital signs seems to reflect trough effect. The investigator is to measure blood pressure, in triplicate, both in the sitting and standing positions. The same cut-off for BP measurements (Korotkoff IV or V sound) will be used for all measurements.

Post study, there was no plans for down-titration of drug. Patients would be seen 2-weeks post treatment. Patients successfully completing the study could be enrolled in the long-term extension study (#307B).

Pharmacokinetics:

A single blood sample at visit #7 at 24 + 2 hours after dosing for measurements of metoprolol levels was planned. (b) (4)

Randomization:

Patients are to be enrolled in a 1: 2: 1: 2 ratios to placebo: Toprol-XL 0.2 mg/kg: Toprol-XL 1 mg/kg: Toprol-XL 2 mg/kg. Randomization is to be performed by a central IVRS (interactive voice response system) system. Eligible patients were stratified by weight.

Blinding:

Identical placebo pills to the active drug would be supplied. For emergency purposes, the site could un-blind the treatment. There were different sized placebos, corresponding in size to that of the active treatment.

Primary Efficacy measurements:

The primary question addressed by the study is whether the slope, representing placebo-corrected changes in sitting SBP from baseline, to the end of treatment as a function of target dose ratio, is different from zero.

Two populations are to be analyzed. These are the "intent to treat" population, for which missing data will be imputed by a LOCF method, and a 'per protocol' population for which only those completing the study without major protocol violations is included. No imputation of data for the per-protocol population is to be performed.

Baseline is defined by the last measurement taken prior to randomization.

Treatment groups will be handled as a categorical variable (0.2, 1 and 2 mg/kg and not the actual mg/kg of dose received). The primary analysis is a linear regression of the placebo-subtracted values of the treatment groups. The slope of the regression line, when the treating dose is assumed to be proportionate to target dose, is to be tested by an F-test at a 0.05 level of significance. A supportive analysis is to be performed employing the weight adjusted dose.

The primary statistical method is to be an analysis of variance (ANOVA), with treatment as the main factor, for assessing the change from baseline. This ANOVA model was used to construct the pair-wise comparison between each of the Toprol-XL groups and placebo.

Secondary measurements:

The primary question addressed by the study is whether the slope, representing placebo-corrected changes in sitting DBP from baseline to the end of treatment as a function of target dose ratio, is different than zero.

- The same analyses as employed for SBP will be employed for DBP.
- Are there differences comparing both SBP and DBP comparing each active group to placebo?
- Assessment of the safety profile.

Power calculation:

The sponsor powered the study to detect a difference in 8 mm Hg comparing the upper dose (10x) to the low dose (1x). The calculation assumes that the slope =0.9 and the SD of 12 mm Hg, the study would, therefore, require 120 patients. Assuming

approximately 15% of the patients prematurely discontinue, the sponsor increases the study participation to 144 subjects to be randomized 24: 48: 24: 48 to placebo and the three Toprol-XL groups.

Results:

Investigators and Sites:

The investigators and sites are shown below.

Table 6 : Investigators and sites study 307A.

	Investigator and sites	PBO	Torprol-XL mg/kg		
			0.2	1.0	2.0
001	Bonita Falkner, M.D., Thomas Jefferson University; Philadelphia, PA.	0	2	1	1
002	Howard Trachtman, M.D., Schneiders Children's Hospital; New Hyde Park, NY.	2	0	2	0
003	Donald L. Batisky, M.D., Colombus Children's Hospital; Colombus, OH.	2	6	2	7
004	Ronald Portman, M.D., University of Texas Medical Center; Houston, TX.	2	2	2	2
005	Vijay Kusnoor, M.D., Southeast Texas Cardiology Associates; Beaumont, TX.	2	9	6	8
007	Noosh Baqi, M.D., State University of New York Health Science Center; Brooklyn, NY.	-	-	-	-
008	Mazen Arar, M.D., University of Texas Health Science Center; San Antonio, TX.	0	4	0	3
009	Joseph Flynn, M.D., Montefiore Medical Center; Bronx, NY.	2	0	0	0
010	Tej Mattoo, M.D., Children's Hospital of Michigan; Detroit, MI.	-	-	-	-
012	Jorge Ramirez, M.D., Nemours Children's Clinic; Orlando, FL.	0	2	1	0
013	Irene Restaino, M.D., Monarch Medical Research; Norfolk, VA.	1	1	1	4
014	Richard E. Neiberger, M.D., University of Florida, School of Medicine; Gainesville, FL.	2	1	0	0
016	Frank Tenney, M.D., Children's Hospital Outpatients Center; Greenville, SC.	0	0	0	1
017	Stephen Daniels, M.D., Children's Hospital Medical Center; Cincinnati, OH.	1	0	0	0
018	Robert Cunningham, M.D and Deepa Chand, M.D., Cleveland Clinic Foundation; Cleveland, OH.	0	1	0	1
020	John W. Foreman, M.D., Duke University Medical Center; Durham NC.	1	0	0	0
023	Jeffrey Blumer, M.D, Rainbow Babies and Children's Hospital; Cleveland, OH.	2	1	0	3
024	Isabella Roberti, M.D., Saint Barnabas Medical Center; Livingston, NJ.	0	0	1	0
026	Eduardo Garin, M.D., University of South Florida; Tampa, FL.	1	2	0	0
027	Janice E. Sullivan, M.D., and Lawrence R. Shoemaker, M.D., University of Louisville; Louisville, KY.	-	-	-	-
028	Gaston Zilleruelo, M.D., Jackson Memorial Hospital; Miami, FL.	0	0	0	0
031	Ana L. Paredes, Miami Children's Hospital; Miami, FL.	1	1	0	2
032	Shermine Dabbagh, DuPont Hospital for Children; Wilmington, DE.	-	-	-	-
033	Russell Chesney, M.D., Le Bonheur Children's Medical Center; Memphis TN.	-	-	-	-
034	Joseph R. Sherbotie, University of Utah School of Medicine; Salt Lake city, UT.	0	2	0	0
035	Majid Rasoulpour M.D., Connecticut, Children's Medical Center; Hartford, CT.	0	0	0	2
037	James Musgrave, M.D., Honolulu, HI.	0	0	0	1
039	Carlos Ruiz, M.D, University of Illinois at Chicago; Chicago, IL.	0	0	1	0
042	Keith M. Weiner, M.D., Orange County Pediatric Cardiology Group; Orange, CA.	1	0	0	0
043	Randall Jenkins, M.D., Northwest Pediatric Kidney Specialists, LLC; Portland. OR.	1	3	1	4
044	Michael Seidner, M.D.; Landsdale, PA.	0	1	1	0
045	Louis Peterson, M.D.; Kansas City, MO.	-	-	-	-
046	Charles Gist, M.D., and Deane Baldwin, M.D., University of Arkansas Medical Center; Little Rock, AK.	0	0	2	2
047	Lydie Hazan, M.D.; Marina del Rey, CA.	2	8	2	9
048	Jeffrey Karasik, M.D.; Clarkstown Pediatric Associates; Nanuet, NY.	-	-	-	-
049	Elliot Seigal, M.D., Clarkstown Pediatric Associates; New City ,NY.	-	-	-	-
050	Maria Pamaran, M.D.; Bellflower, CA.	-	-	-	-
051	Ivan Goldsmith, M.D.; Las Vegas, NV.	-	-	-	-
101	Jesus Feris-Iglesias, M.D., Dr. Robert Reid Cabral Infantil Hospital; Santo Domingo, Dominican Republic.	1	1	0	0

There were 28 sites (1 outside the USA) that enrolled patients for this study.

Formulations:

The following were the formulations and lot numbers for medications used during the study.

Table 7: Formulations and lot numbers used during study 307A:

Toprol –XL 25 or 50 mg	H0960-10-01-01; H0960-10-01-02; H0638-09-03-09
Toprol –XL 25 or 50 mg placebo	H1014-03-01-01, H1014-03-01-02; H 0695-04-01-07
Placebo during single-blind run in phase 25 mg	H1014-03-01-02
Placebo to match 25 mg metoprolol-XL	H0960-10-01-01, H0960-10-01-02
Placebo to match 50 mg metoprolol-XL	H0638-09-03-09

The 25 mg dose was scored to allow dose levels of 12.5 and 37.5 mg.

Patient Disposition:

The patient disposition is shown below. There were no patients that discontinued due to an adverse events.

Table 8: Disposition of patients during study 307A:

Entered run in period	N= 204			
Randomized	N= 144			
	Placebo	Toprol-XL- target dose		
		0.2 mg/kg	1.0 mg/kg	2.0 mg/kg
	24	47	23	50
Discontinued	4	3	1	3
Eligibility not fulfilled	2	0	0	1
Insufficient therapeutic response	2	0	0	0
Lost to follow-up	0	2	1	1
Sponsor/investigator decision	0	1	0	0
Consent withdrawn	0	0	0	1
Completed	20	44	22	47
Per protocol population	19	39	21	43
Reason Non-qualifying BP	0	2	1	1
4 week sitting BP values missing	5	6	1	6
Safety population	24	46	23	49

Demographics at baseline:

The demographics for those enrolled are shown below.

Table 9: Demographic characteristics of patients enrolled into study 307A:

	Placebo (n=23)	Toprol-Xl		
		0.2 m/kg (n=45)	1.0 mg/kg (N= 23)	2.0 mg/kg
Age mean ± SD, years % < 12 years	12.3 ± 3.2 39%	12.5 ± 2.7 44%	13.5 ± 2.5 30%	12.2 ± 2.8 41%
Gender % male	57%	78%	70%	69%
Race: Caucasian/Black/Asian Other %	78/22/0/0	76/20/2/2	74/26/0/0	63/33/4/0
Tanner stage (≤ 3), n %	10 (44%)	27 (60%)	10 (44%)	23, (47%)
Weight, kg mean ± SD [range]	84 ± 35 [26 to 162}	80 ± 29 [25 to 154}	84 ± 31 [23 to 160]	80 ± 31 [22 to 155]
Height, cm Mean ± SD	159 ± 19	161 ± 17	162 ± 13	157 ± 16
BMI kg/m^2, mean ± SD	32 ± 10	30 ± 8	31 ± 9	31 ± 11
Type of HBP None/DBP/SBP/Both %	0/9/49/44	2/7/76/16	4/9/44/44	0/12/61/27

There were differences comparing the demographics of the treatment groups. There were more females in the placebo group. There were fewer sexually immature individuals (≤ Tanner 3) in the 0.2 mg/kg group. Most patients in all groups had evidence of systolic hypertension (sum of SBP + both) ranging from 88-93%. DBP (DBP + both) differed between treatment groups ranging from 23-53%. The choice of SBP change as the primary metric of the study appears appropriate.

Previous antihypertensive medications:

Table 10: Previous antihypertensive medications study 307A.

Placebo (n=4)	Atenolol (2), nifedipine (1), felodipine (1)
Toprol-XL 0.2 mg/kg (n= 12)	Lisinopril (2), Amlodipine (3), Atenolol (2), Captopril (1), Enalapril (1), Hydrochlorothiazide (1), Irbesrtan (1), Losartan (1)
Toprol-XL 1.0 mg/kg (n=4?)	Lisinopril (2), Felodipine (1), amlodipine (1)
Toprol-XL 2.0 mg/kg (n=14)	Lisinopril (3), Amlodipine (2), Benazapril (1), Clonidine (2), Captopril (1), Enalapril (2), Lotrel (1), Ramipril (1), Valsartan (1).

There was previous use of antihypertensive medication in approximately 25% of those enrolled. Four subjects were previously treated with β-blockers.

Efficacy measurements:

The efficacy effects (primary metric of interest in bold) are shown below.

	Placebo (N=23)	Toprol-XL mg/kg 0.2 (N=45)	1.0 (N=23)	2.0 (N=49)
Sitting SBP				
Baseline	**132.7 ± 8.9**	**131.4 ± 9.0**	**135.0 ± 8.0**	**130.6 ± 9.6**
Change	**-1.9 ± 10.2**	**-5.2 ± 9.5**	**-7.7 ± 8.9**	**-6.3 ± 7.4**
Sitting DBP				
Baseline	81.4 ± 9.0	76.3 ± 7.7	81.0 ± 7.5	76.7 ± 9.1
Change	-2.1 ± 9.4	-3.1 ±9.5	-4.9 ± 7.5	-7.3 ± 8.3
Standing SBP				
Baseline	131.3 ± 11.5	129.7 ± 8.0	133.7 ± 8.5	129.5 ± 9.3
Change	0.0 ± 10.9	-3.9 ± 9.5	-7.1 ± 9.4	-6.7 ± 7.3
Standing DBP				
Baseline	83.1 ± 9.3	78.8 ± 9.3	82.2 ± 8.8	78.7 ± 8.8
Change	0.2 ± 9.7	-3.3 ± 7.5	-5.0 ± 9.5	-5.9 ± 8.4

Primary analysis:

The proposed primary analysis was a non-zero slope limited to the three active doses for sitting SBP.

Toprol –XL, at the target doses of 0.2, 1.0 and 2.0 mg /kg, did not show a statistically significant slope effect with the slope of -0.11 $\pm$ 0.19 mm Hg/ unit dose increase; p=0.6)

Additional Analyses:

An analysis that includes the placebo group in defining a non-zero slope in the dose response relationship for sitting SBP was not significant (p=0.13). An analysis using weight adjusted dose was also not significant (see Figure 4 below)

Comparisons of each of the Toprol- XL doses to placebo:

Comparing each of the two highest Toprol-XL doses to placebo was nominally significant (without correcting for multiple comparisons) (p=0.027 and p=0.049, respectively). The prospective analytic plan considered these analyses as exploratory since the sponsor did not presume adequate power for the individual dose comparisons with placebo. Pooling all treatment groups and comparing the result to placebo indicated a moderately significant effect (p=0.04).

Sitting Diastolic blood pressure:

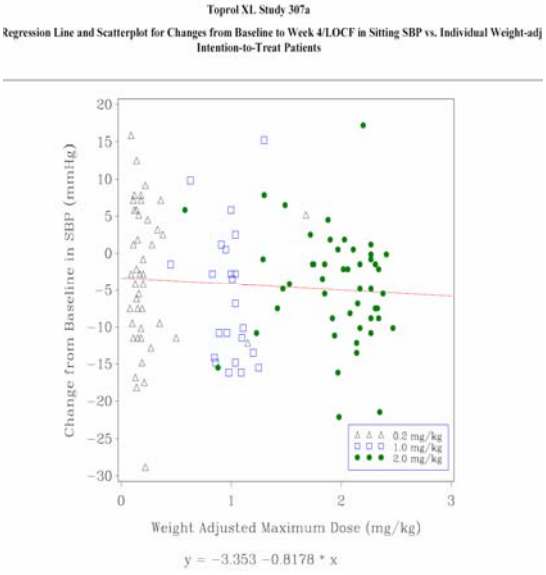
There was a statistically significant effect in considering the placebo-subtracted dose-response for active doses (p=0.02) .The weight adjusted dose compared to diastolic blood pressure effect was statistically significant (see Figure 4).

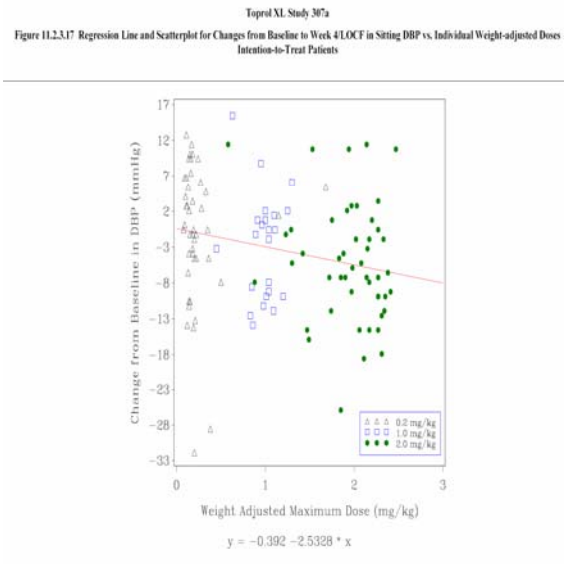
Only the high dose differed statistically from the placebo group (p=0.02). Pooling all treatment groups and comparing the results to placebo indicated no significant effect (p>0.1).

Standing Measurements:

Both standing systolic blood pressure effects and standing diastolic blood pressure effects were nominally significant for the slope effect (including the anchor point 0, 0) at levels of 0.01 and 0.004, respectively.

Figure 4: Linear regression based on actual dose received on sitting SBP and DBP, study 307A.





Pharmacokinetic/Pharmacodynamic analyses:

The pharmacokinetic-pharmacodynamic relationship between metoprolol concentrations (racemic) and blood pressure effect was performed by Dr. Kumi. His analyses as well as the sponsor's analyses are explored after the kinetic analyses.

Outcome based on demographics:

The table below lists the effect on both SBP and DBP based on race, Tanner stage ($\leq$ Tanner 3) and gender. In general, none of the demographic groups substantially deviates for the population as a whole. There were, however, far too few subjects to discriminate effects in the different treatment groups.

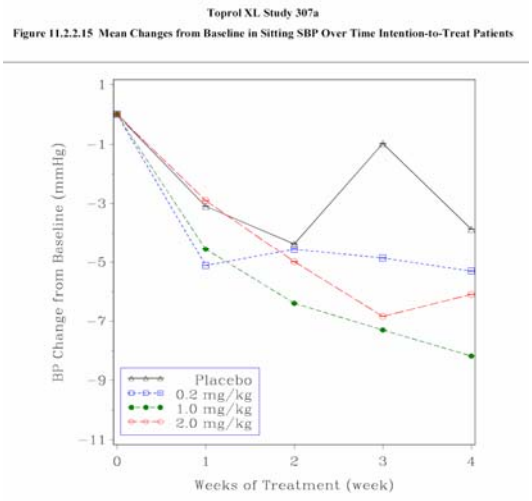
Table 11: Subgroup analyses based on demographic parameters, study 307A;

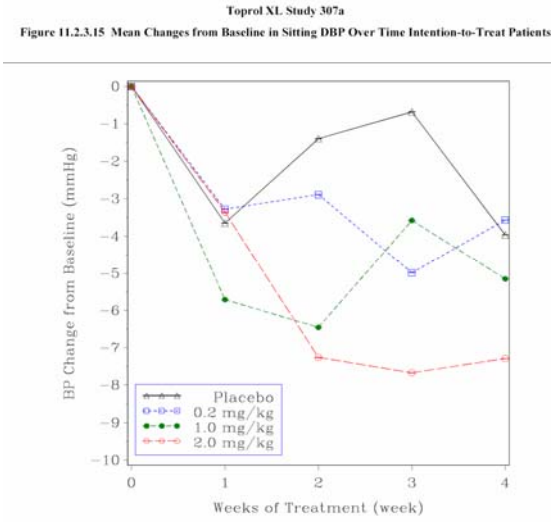
Demography		PBO	0.2	1.0	2.0
Overall	SBP	-1.9 ± 10 [23]	-5.2 ± 10 [45]	-7.7 ± 9 [23]	-6.3 ± 7 [49]
Overall	DBP	-2.1 ± 9 [23]	-3.1 ± 10 [45]	-4.9 ± 8 [23]	-7.3 ± 8 [49]
Black [N]	SBP	-0.8 ± 10 [5]	-6.5 ± 11 [9]	-4.2 ± 10 [6]	-6.4 ± 9 [16]
Non-black[N]		-2.1 ± 11 [18]	-4.8 ± 9 [36]	-8.9 ± 8 [17]	-6.2 ± 6 [33]
Black [N]	DBP	-0.9 ± 12 [5]	-2.3 ± 8 [9]	-4.0 ± 8 [6]	-7.9 ± 9 [16]
Non-black[N]		-2.4 ± 9 [18]	-3.3 ± 10 [36]	-5.3 ± 7 [17]	-7.3 ± 8 [33]
Tanner ≤ 3[N]	SBP	-0.6 ± 14 [10]	-5.2 ± 9 [27]	-6.4 ± 11 [10]	-6.0 ± 7 [23]
Tanner > 3		-2.8 ± 6 [13]	-5.1 ± 11 [18]	-8.6 ± 9 [13]	-6.5 ± 8 [26]
Tanner ≤ 3[N]	DBP	-1.8 ± 12 [10]	-3.6 ± 11 [27]	-5.1 ± 10 [10]	-7.0 ± 8 [23]
Tanner > 3		-2.3 ± 7 [13]	-2.4 ± 7 [18]	-4.8 ± 6 [13]	-7.9 ± 9 [26]
Male [N]	SBP	-0.9 ± 13 [13]	-6.0 ± 10 [35]	-6.2 ± 10[16]	-7.0 ± 8 [34]
Female [N]		-3.1 ± 5 [10]	-2.3 ± 5 [10]	-11.0 ± 6 [7]	-4.5 ± 5 [15]
Male [N]	DBP	-0.8 ± 12 [13]	-3.5 ± 9 [35]	-6.3 ± 8[16]	-7.4 ± 8 [34]
Female [N]		-3.9 ± 4 [10]	-1.8 ± 11 [10]	-1.7 ± 6 [7]	-7.7 ± 10 [15]

Time course of effects (in weeks):

The weekly effect on blood pressure is shown below for SBP and DBP. The effect of the 1.0 mg/kg dose should be assessed at or after week 2. The effect of the 2.0 mg/kg dose should be seen, in full, at weeks 3 and 4. The variability in effect was large but the full effect is likely to be seen at weeks 3. The time course on sitting measurements of DBP and SBP is shown below.

Figure 5: Weekly time course of sitting SBP and DBP, study 307A.





Pharmacokinetics:

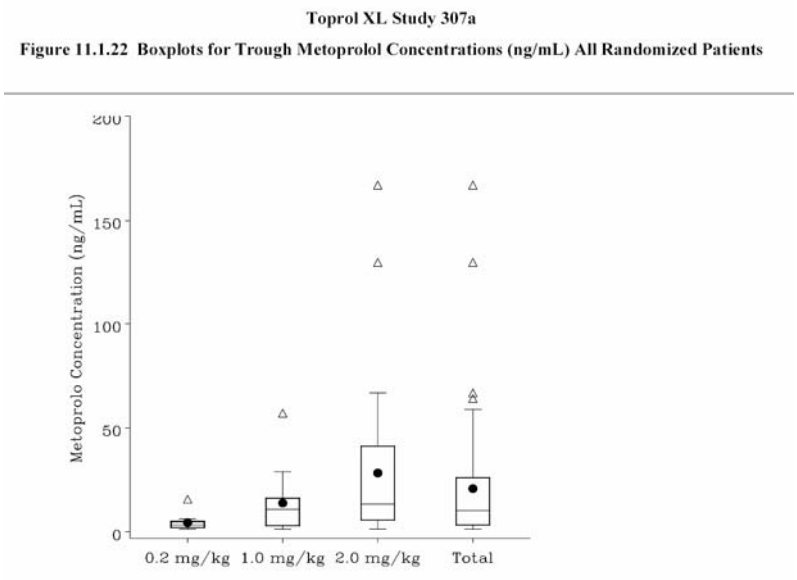
The data below reflect values measured in those samples above the LLQ. Censoring values below the LLQ, particularly in the 0.2 mg/kg dose group, makes the measurement less than reliable. Only racemic metoprolol was measured. The distribution of concentrations for those with measured values are shown in Figure .

Table 12: Pharmacokinetics of trough measurements, study 307A:

	Toprol-XL dose mg/kg		
	0.2	1.0	2.0
No of patients	45	23	49
Number not drawn	7	6	3
Number not valid	1	0	1
Value < LLQ	27	2	6
Number with values	12	15	40
Values, ng/ml	4.5 $\pm$ 2.9	13.9 $\pm$ 14	28.3 $\pm$ 35
C_{trough} measurements <LLQ treated as 0*	1.4 $\pm$ 3	12.2 $\pm$ 14	24.6 $\pm$ 34

- Per Dr. Kumi's Draft review

Figure 6: Distribution of measurements for metoprolol , limited to those above LLQ in study 307A



The value at the 0.2 mg/kg dose appears unreliable. There were a substantial number of pharmacokinetic measurements below limit of quantification. There appears to be a skewed distribution at the higher doses. The upward bar is much larger the lower bar.

Safety:

Duration of exposure:

The duration of exposure to the various doses is shown below:

Table 13: Duration of exposure, Study 307A:

	Placebo (n=24)	Target dose of Toprol-XL mg/kg		
		0.2 (n=46)	1.0 (N=23)	2.0 (N= 49)
Duration of exposure mean $\pm$ SD	27.5 $\pm$ 7	28.6 $\pm$ 2	28.8 $\pm$ 2	29.0 $\pm$ 4

Deaths, Dropouts, Discontinuations and Adverse events listed as "severe" in intensity:

There were no deaths or serious adverse events in this study. One 14-year old black female (weight=60 kg) discontinued for elevated blood pressure 138/192 (baseline 140/90). She was treated with furosemide for three days with a decrease in the elevated blood pressure.

There were two subjects, both randomized to the 2.0 mg/kg group of Toprol-XL both had headaches listed as "severe" in intensity.

Overall Adverse events:

Overall adverse events in greater than 5% in any group N (%)

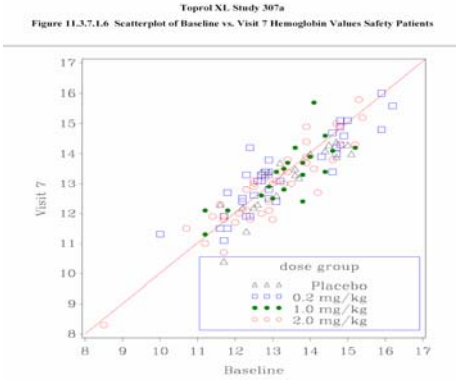
Table 14: Overall adverse events by targeted dose, Study 307A.

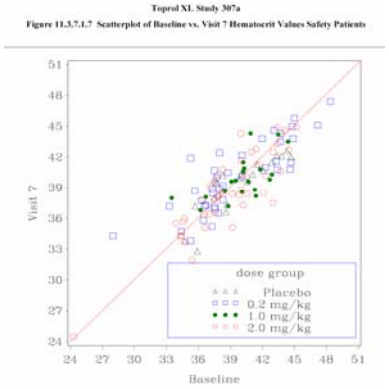
Term	Placebo	Toprol-XL (target dose, mg/kg)		
	N=24	0.2 (N=46)	1.0 (N=23)	2.0 (N=49)
Number with > 1 AE	12 (50%)	17 (37%)	9 (39%)	30 (61%)
Nervous system	5 (21%)	8 (17%)	6 (26%)	8 (16%)
Headache	4 (17%)	5 (11%)	5 (22%)	5 (10%)
Dizziness	1 (4%)	1 (2%)	1 (4%)	3 (6%)
Infection and infestation	4 (17%)	4 (9%)	0	11 (22%)
Upper respiratory tract Infection	1 (4%)	2 (4%)	0	6 (12%)
Respiratory thoracic and mediastinal disorders	3 (13%)	3 (7%)	4 (17%)	6 (12%)
Cough	2 (8%)	1 (2%)	1 (4%)	1 (2%)
Pharyngolaryngeal pain	0	0	3 (13%)	0
Gastrointestinal disorders	1 (4%)	1 (2%)	2 (9%)	7 (14%)
Diarrhea	1 (4%)	0	0	3 (6%)
General disorders and administration site conditions	1 (4%)	2 (4%)	2 (9%)	5 (10%)
Pyrexia	0	0	1 (4%)	4 (8%)

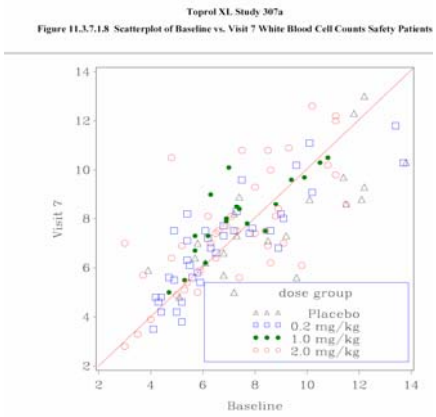
Laboratory:

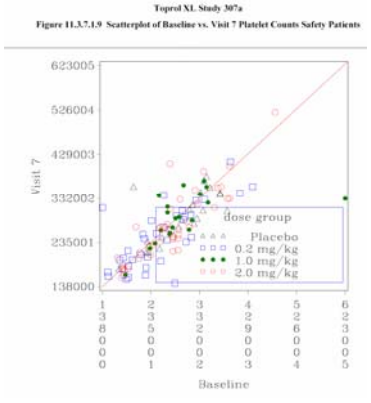
A scatter plot for the various laboratory measurements comparing baseline to end of treatment values are shown below. There did not appear to be any unusual values of concern.

Figure 7: Shift diagram of laboratory measurements, study 307A.

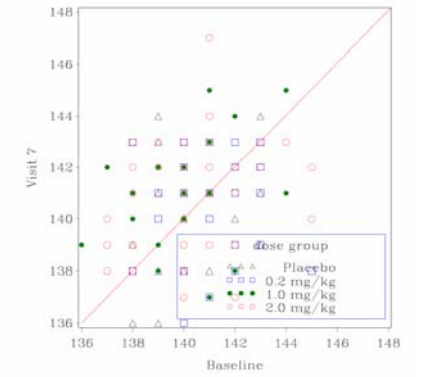




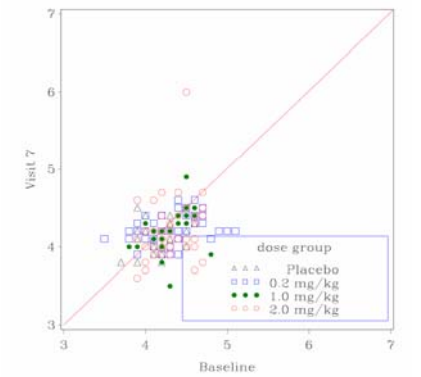




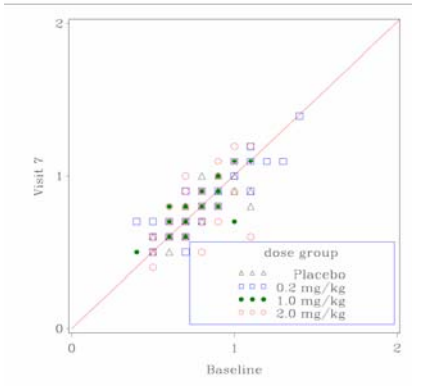
Toprol XL Study 307a
Figure 11.3.7.1.18 Scatterplot of Baseline vs. Visit 7 Sodium Values Safety Patients



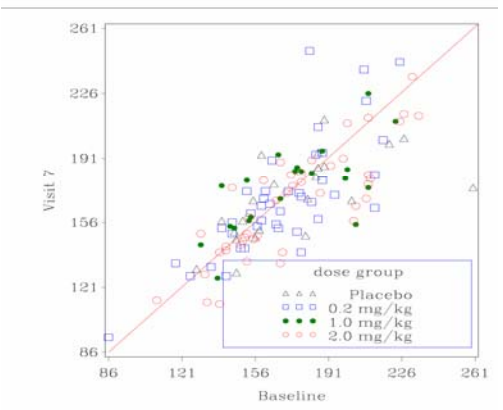
Toprol XL Study 307a
Figure 11.3.7.1.23 Scatterplot of Baseline vs. Visit 7 Potassium Values Safety Patients



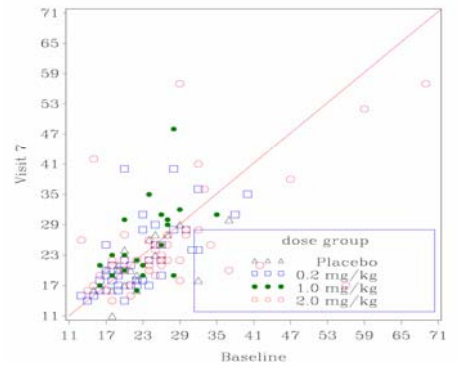
Toprol XL Study 307a
Figure 11.3.7.1.21 Scatterplot of Baseline vs. Visit 7 Creatinine Values Safety Patients



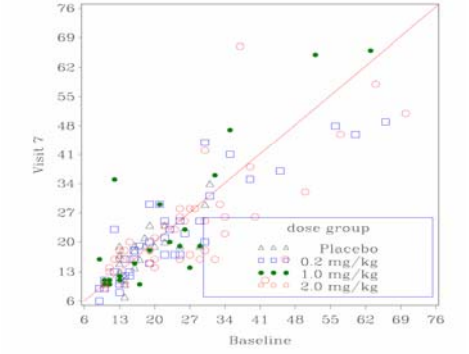
Toprol XL Study 307a
Figure 11.3.7.1.28 Scatterplot of Baseline vs. Visit 7 Total Cholesterol Values Safety Patien

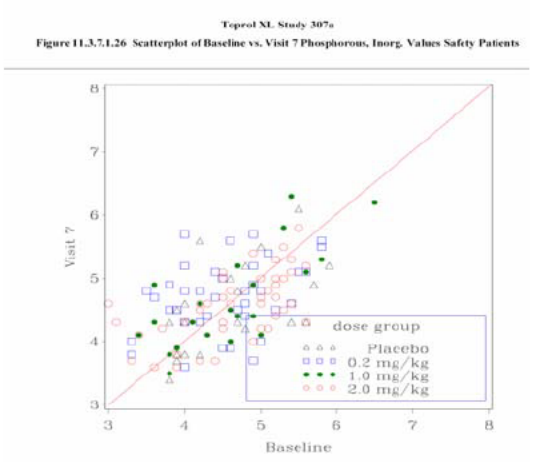


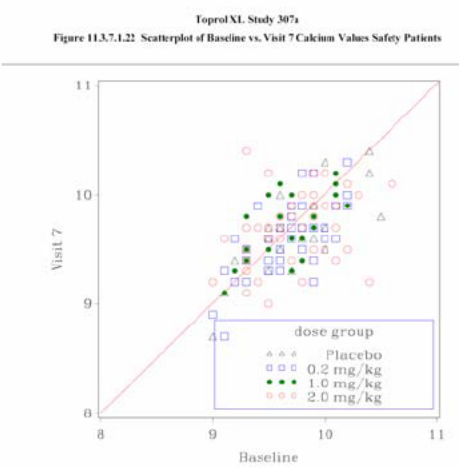
Toprol XL Study 307a
Figure 11.3.7.1.24 Scatterplot of Baseline vs. Visit 7 AST Values Safety Patients



Toprol XL Study 307a
Figure 11.3.7.1.25 Scatterplot of Baseline vs. Visit 7 ALT Values Safety Patients







ECG:

ECGs were recorded at baseline and end-of treatment, week 4 of double-blind period. The timing of the measurements, relative to dosing, is not stated but the description of the procedures during the visits would strongly suggest the ECG measurements reflect trough effect. Baseline measurements and change from baseline are shown below.

Table 15: ECG parameters for study 307A (Mean ± SD).

Parameter	Placebo (n=20-22)		Torprol-XL target dose (mg/kg)					
			0.2 (N=44)		1.0 (N=21- 22)		2.0 (n=47)	
	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change
Heart rate, BPM	82.7 ± 18	-2.5 ± 12	78.6 ± 16	-5.2 ± 9	78.2 ± 15	-6.5 ± 13	78.1 ± 14	-6.6 ± 12
PR interval, msec	144 ± 18	0.7 ± 9	144 ± 16	0.5 ± 11	152 ± 18	-1.3 ± 11	146 ± 43	-3.6 ± 35
QRS duration, msec	88.4 ± 11	-0.9 ± 6	88.1 ± 14	0.9± 10	89.0 ± 12	3.8 ± 8.0	88.0 ± 10	1.7 ± 6
QT interval, msec	357 ± 39	-2.8 ± 21	362 ± 28	7.5 ± 22	358 ± 32	21 ± 32	360 ± 30	13. ± 27
QTcB interval, msec	413 ± 24	-9.4 ± 19	408 ± 19	-5.2 ± 17	403 ± 21	6.4 ± 19	405 ± 22	-1.9 ± 21
QTcF* interval, msec	393 ± 26	-6.6 ± 16	393 ± 15	-1.0 ± 15	389 ± 20	11.0 ± 18	390 ± 19	2.4 ± 19

Analysis performed by Dr. Freidlin using the formula $QTcF = QT/ RR^{1/3}$ (Friderecia's correction)

There is a dose-related effect to change in heart rate consistent with a bet-blockade effect. There appears to be an effect on QT and QTc intervals. The QTc interval is the correction of Bazett. Dr. Freidlin calculated the correction in repolarization by the method of Friderecia.

Vital signs:

Blood pressures were the primary metric of the study and were analyzed above. Heart rate was also captured at what appears to be trough drug effect. The sponsor notes three subjects with resting heart rate less than 50 BPM during the study (these were likely trough measurements). These subjects all had baseline measurements in the upper 50s at baseline and the decline ranged from 7-10 BPM from the baseline measurement.

The heart rate effect at each of the clinic visits are shown below:

Table 16: Change in heart rate by week (mean ± SD), study 307A:

	Placebo		Toprol-XL target dose mg/kg					
			0.2		1.0		2.0	
	N=		N=		N=		N=	
Baseline	24	86 ± 13	46	82 ± 11	23	83 ± 13	49	83 ± 12
Change from baseline								
Week 1	23	2.2 ± 12	44	-3.6 ± 10	23	-4.3 ± 8	46	-2.7 ± 12
Week 2	22	0.9 ± 10	45	-2.8 ± 9	22	-4.3 ± 8	47	-3.0 ± 10
Week 3	22	4.0 ± 9	43	-2.0 ± 13	19	-3.1 ± 10	41	-6.0 ± 13
Week 4	20	5.4 ± 12	44	-3.7 ± 10	22	-6.5 ± 10	47	-5.5 ± 13

Study number 307B

Study title: A Safety, Tolerability and Pharmacokinetics Study of Toprol-XL (Metoprolol Succinate) Extended-release Tablets (Metoprolol CR/XL) in Hypertensive Pediatric Subjects: A Multicenter, Open-Label Extension of Protocol 307A.

The study is a long-term, open-label, safety study on the use of Toprol-XL in pediatric patients with hypertension. A sub-study explored the pharmacokinetic profile of Toprol-XL as a single 25-mg dose (after 48 hours of washout).

There was a major amendment that was submitted on 12 March 2003 that increased the duration of open-label exposure to assess safety from 16 to 52 weeks. The primary metrics of the overall study were safety and for the sub-study the primary metrics of interest were pharmacokinetic parameters.

Subjects could enter the study through several routes.

- Directly from their completion of study 307A.
- Subjects who prematurely discontinue study 307A for reasons other than adverse events.
- Subjects ineligible for entry into study 307A, because their blood pressure exceeded the upper cutoff limits.
- Subjects declining to participate in study 307A, but who fulfill the entry criteria for 307B.
- Subjects who are currently involved in the original 16-week 307B study may switch over to the longer term study (52-week study).
- Subjects who have completed the 16-week 307B study may enroll as new patients in the 52-week 307B study. The patients could not now take part in the pharmacokinetic assessment sub-study.

Inclusion criteria:

The pool of patients from enrollment is defined above. In addition these subjects must:

- Be of either gender between the ages of 6-16 years old (at the time of screening).
- If female, have a negative pregnancy test within three weeks of starting open-label therapy
- Signed a consent (by guardian) and assent (by child, if appropriate).
- Have hypertension as defined by the population from which the subjects are culled.

Exclusion criteria:

The subject must not:

- Be pregnant or breast feeding.
- Have secondary hypertension (Cushing's syndrome, pheochromocytoma, renal stenosis and hyperthyrpoidism).
- Have a SBP of > 20 or DBP > 10 m Hg greater than 95th percentile.
- Bradycardia (HR < 50 BPM).
- Have liver enzyme abnormality (> 1.5 x ULN).
- Have history of alcohol or drug abuse or non-compliant with run-in medication.

Or have a history of:

- Asthma, recurrent pulmonary disease or cystic fibrosis.
- Hypersensitivity to beta-blockers.
- Bleeding or coagulation disorders.
- Insulin-dependent DM.
- Have cardiac disease, valvular disease, heart failure, arrhythmias. Have conduction disturbances (2nd or 3rd degree AV block).
- Use of concomitant medications that interact with Toprol-XL (e.g., catecholamine depleting medications, CYP2D6 substrates).

Procedures:

Visits are scheduled every other week for the first 16 weeks, then every 4 weeks for the duration of the 52 weeks of the study. At the end of the study, a follow-up visit is planned after two weeks. At baseline (week 0) and at each of the clinic visits, the investigator will measure blood pressure and heart rate. The timing of these measurements appears to reflect trough values (immediately prior to the dosing in clinic). Safety assessments e.g., laboratory and ECGs were only performed at baseline and end of the open-label phase.

The timing of the procedures is shown below.

Figure 8: Procedure schedule, study 307B.

Protocol 307B Study Plan

	Open-Label [a]																	Follow Up
End of Week	0	2	4	6 [b]	8	10 [b]	12	14 [b]	16 [b]	20	24 [b]	28	32 [b]	36	40 [b]	44	48 [b]	52	54
Visit Number	1	2	3	4 [b]	5	6 [b]	7	8 [b]	9	10	11	12	13	14	15	16	17	18	19
Informed Consent	X																		
Medical History	X[c]																		
12-lead ECG	X[c]																	X	
Complete Physical Exam	X[d]																	X[d]	
Brief Physical Exam		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]		X[d]		X[d]		X[d]		X[d]			X[d]
Blood Pressure (sitting and standing)	X	X	X	X	X	X	X	X		X		X		X		X		X	X[g]
Leg Blood Pressure	X[c]																		
Heart Rate (sitting)	X	X	X	X	X	X	X	X		X		X		X		X		X	X
Laboratory Assessments	X[c]																	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug Dispensation	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	
PK Plasma sample	X[e]																X[f]	X[f]	
AE Assessment	X[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a - Visits are scheduled every 2 weeks during up titration and every 4 weeks thereafter. b - Optional visits for dose titration. c - The most current subject data should be carried over for subjects that were screened and/or randomized in Protocol 307A; AE assessments will be done only on subjects who participated in Protocol 307A. d - Weight will be measured at the Complete and Brief Physical Exams. Height will be measured at Visit 1 and Visit 18. e - A subset of up to 30 subjects (up to 15 per age group) will have 9 PK samples drawn (hours 0, 1, 2, 3, 4, 6, 8, 10 and 24 after a single dose of metoprolol CR/XL either at the beginning or 307B or at the very end of treatment). f - All subjects will have one PK sample drawn 24 ± 2 hours after last dose of metoprolol CR/XL. g - One Sitting BP for safety assessment only. h – these visits are telephone contacts, but may be clinic visits at the discretion of the investigator.

Dose:

The initial daily dose of Toprol-XL was 25 mg. The daily dose could be increased by 25-50 mg at each clinic visit to achieve acceptable blood pressure control. The maximal allowed daily dose is 200 mg. Should adequate control of blood pressure not be attained at this dose, other non-β-blocker anti-hypertensive medications could be added.

Pharmacokinetics:

Blood samples for pharmacokinetic measurements were collected following a 48-hour washout period (for those treated with metoprolol in study 307A) after a single 25-mg dose, at the following times: 0, 1, 2, 3, 4, 6, 8, 10 and 24 hours after the dose. The analysis was limited to the parent drug

Statistics:

The study is descriptive in nature for the assessment of safety. The pharmacokinetic metrics of interest are k_{el}, $T_{1/2}$, AUC and C_{max}. The values will only be defined by subjects who had measureable levels of metoprolol.

The study plans to have 80 subjects complete the one-year exposure.

Results:

Investigators and sites:

The investigator and sites were the same to those who enrolled subjects during study 307A.

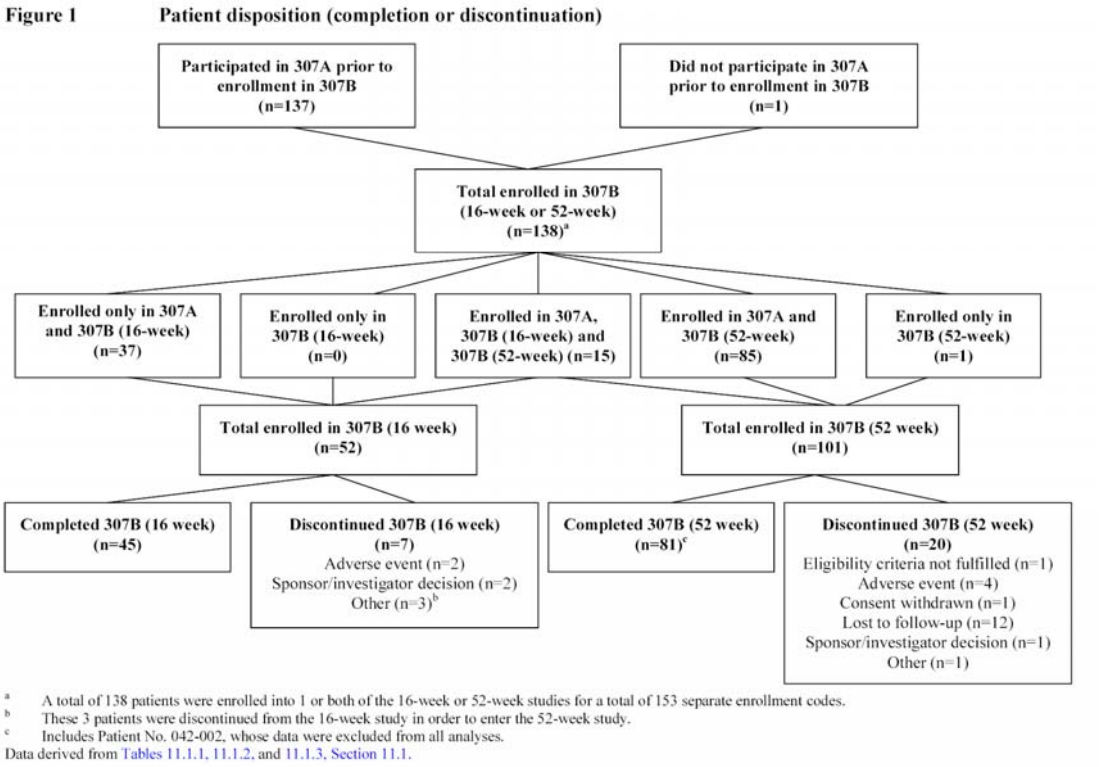
Table 17: Investigators and sites study 307B

	Investigator and sites:	16-wk	completed	52 week	completed
001	Bonita Falkner, M.D., Thomas Jefferson University; Philadelphia, PA.	3	3	1	1
002	Howard Trachtman, M.D., Schneiders Children's Hospital; New Hyde Park, NY.	-	-	3	2
003	Donald L. Batisky, M.D., Colombus Children's Hospital; Colombus, OH.	7	7	12	10
004	Ronald Portman, M.D., University of Texas Medical Center; Houston, TX.	-	-	9	8
005	Vijay Kusnoor, M.D., Southeast Texas Cardiology Associates; Beaumont, TX.	17	17	11	9
007	Noosh Baqi, M.D., State University of New York Health Science Center; Brooklyn, NY.	-	-	-	-
008	Mazen Arar, M.D., University of Texas Health Science Center; San Antonio, TX.	4	4	4	3
009	Joseph Flynn, M.D., Montefiore Medical Center; Bronx, NY.	1	1	2	2
012	Jorge Ramirez, M.D., Nemours Children's Clinic; Orlando, FL.	2	2	1	1
013	Irene Restaino, M.D., Monarch Medical Research; Norfolk, VA.	4	4	3	3
014	Richard E. Neiberger, M.D., University of Florida, School of Medicine; Gainesville, FL.	2	-	3	3
017	Stephen Daniels, M.D., Children's Hospital Medical Center; Cincinnati, OH.	-	-	1	1
018	Robert Cunningham, M.D and Deepa Chand, M.D., Cleveland Clinic Foundation; Cleveland, OH.	1	-	1	1
020	John W. Foreman, M.D., Duke University Medical Center; Durham NC.	2	2	1	1
023	Jeffrey Blumer, M.D, Rainbow Babies and Children's Hospital; Cleveland, OH.	4	2	1	1
024	Isabella Roberti, M.D., Saint Barnabas Medical Center; Livingston, NJ.	-	-	1	1
026	Eduardo Garin, M.D., University of South Florida; Tampa FL.	1	-	-	-
028	Gaston Zilleruelo, M.D., Jackson Memorial Hospital; Miami, FL.	-	-	2	2
031	Ana L. Paredes, Miami Children's Hospital; Miami, FL.	-	-	3	2
034	Joseph R. Sherbotie, University of Utah School of Medicine; Salt Lake City, UT.	2	2	3	3
035	Majid Rasoulpour M.D., Connecticut, Children's Medical Center; Hartford, CT.	-	-	1	-
037	James Musgrave, M.D., Honolulu, HI.	1	1	1	1
039	Carlos Ruiz, M.D, University of Illinois at Chicago; Chicago, IL.	-	-	1	1
042	Keith M. Weiner, M.D., Orange County Pediatric Cardiology Group; Orange, CA.	-	-	1	1
043	Randall Jenkins, M.D., Northwest Pediatric Kidney Specialists, LLC; Portland. OR.	1	-	7	6
044	Michael Seidner, M.D., Landsdale, PA.	-	-	2	1
046	Charles Gist, M.D., and Deane Baldwin, M.D., University of Arkansas Medical Center; Little Rock, AK.	-	-	3	3
047	Lydie Hazan, M.D., Marina del Rey CA.	-	-	20	11
101	Jesus Feris-Iglesias, M.D., dr. Robert Reid Cabral Infantil Hospital, Santo Domingo, Dominican Republic.	-	-	2	2

Patient Disposition:

The sponsors diagram for patient disposition is shown below.

Figure 9: Patient flow diagram, study 307B.



[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.
Data derived from Tables 11.1.1, 11.1.2, and 11.1.3, Section 11.1.

Only one patient entered the long-term extension without treatment in study 307A. There were 52 patients who entered the 16-week extension phase only and either completed that portion of the study or who were discontinued from that portion of the study. There were 101 patients who entered the 52-week long term extension phase.

Demographics:

The mean $\pm$ SD; and median [range] age, in years, of those entering study 307B was 13.1 $\pm$ 2.5; median= 14.0 [7-17]. The study enrolled predominantly male (66%), The racial distribution of Caucasian: Black: Asian: other (%) were 72 (72%): 23 (23%): 3 (3%): 2 (2%). Of those enrolled in the open-label extension, 39% were $\leq$ Tanner 3. The mean $\pm$ SD weight was 86 $\pm$ 32 kg. With respect to BMI 64% of those enrolled were at or above the 95th percentile.

Dose:

The dosing during the open-label study is shown below. At baseline, the mean dose was greater than the proposed 25-mg daily dose. Over time the dose increased and leveled off somewhere between 32 and 52 weeks.

Table 18: Dose by week (mean + SD), study 307B.

	N	Average dose	Median [range]	Dose mg/kg	Median [range] mg/kg
Day 1 (baseline)	100	37 ± 33	25 [12.5-200]	0.5 ± 0.3	0.1 - 2.3
Week 16	95	97 ± 64	75 [25-200]	1.2 ± 1.0	0.2 -5.7
Week 32	91	108 ± 67	100 [25-200]	1.3 ± 1.0	0.2 -5.4
Week 52	81	114 ± 69	100 [25-200]	1.3 ± 1.0	0.2-5.6
LOCF week 53	100	112 ± 69	100 [25-200]	1.3 ± 1.0	0.2-5.6

Blood pressure effect.

The time course of blood pressure changes from the initial randomization is shown below (Tables 19 and 20)

SiSBP

Table 19: Sitting systolic blood pressure by duration of treatment in study 307B.

	52-week study			16-week study		
	N=	Mean ± SD	Change	N=	Mean ± SD	Change
307A randomization	88	132 ± 8.4	--------	48	133 ±9	----
Entry into 307B	87	127 ± 10.9	-5.3 ± 8.5	48	129 ± 11	-4.3 ± 10
Week 16	56	125 ± 11	-8.0 ± 9.0	41	126 ± 11	-7.4 ± 9
Week 16 LOCF				41	126 ± 11	-7.3 ± 9
Week 32	76	124 ± 11	-8.4 ± 9.2			
Week 52	72	124 ± 11	-7.4 ± 9.8			
Week 52 LOCF	88	125 ± 10	-7.4 ± 9.5			

SiDBP

Table 20: Sitting diastolic blood pressure by duration of treatment, study 307B.

	52-week study			16-week study		
	N=	Mean ± SD	Change	N=	Mean ± SD	Change
307A randomization	88	78 ± 8	--------	48	77 ± 10	----
Entry into 307B	87	75 ± 10	-3.2 ± 10.0	48	75 ± 10	-2.4 ± 9
Week 16	56	73 ± 10	-5.2 ± 10.8	41	70 ± 9	-6.3 ± 11
Week 16 LOCF				41	71 ± 10	-5.9 ± 12
Week 32	76	72 ± 10	-6.7 ± 11.0			
Week 52	72	71 ± 9	-6.6 ± 9.5			
Week 52 LOCF	88	72 ± 10	-6.7 ± 9.9			

The data reflect the sponsor's assessment of BP drop from the original measurements obtained prior to enrolling into study 307A. The values only reflect those who persisted on therapy. In the absence of a placebo group and in the absence of a placebo-controlled randomized withdrawal phase, the values are not easily interpretable.

Pharmacokinetics:

The pharmacokinetic section of the study is best described by the biopharmaceutic reviewer (Dr. Kumi). I will, however, summarize the sponsor's analyses in a later section of this review.

Safety:

The dose during the open-label portion of the study is described in Table 18. The mean duration of exposure was 354 days.

Deaths, dropouts, discontinuations, and patients sustaining adverse events with intensity listed as "severe".

There were no deaths in the study. There were two patients who sustained serious adverse events.
Patient 005020, a 7-year old Caucasian male developed pneumonia.

Patient 047-005, a 15-year old female Caucasian had a serious adverse event of menometrorrhagia.

The following patients were discontinued:
Patient 047-029 was a 15-year old Caucasian male who discontinued on day 94 due to asthma (wasn't this an exclusion?). Maximum dose was 50 mg (0.4 mg/kg).

Patient 047-028 was a 13-year old Caucasian male who discontinued on day 271 due to dizziness and lightheadedness. The maximum dose was 200 mg (1.2 mg/kg).

Patient #035-002 was a 9-year old Caucasian male who discontinued on day 44 due to nightmares and anxiety exacerbation. The maximum dose was 25 mg (0.5 mg/kg).

Patient #026-001 was a 6-year old Caucasian male discontinued on day 11 due to bradycardia. Maximum dose was 25 mg (0.4 mg/kg).

Patient # 023-003 an 8-year old black female discontinued on day 12 due to diarrhea. The maximum dose was 25 mg (0.7 m/kg).

Patient #004-010 was a 13-year old Caucasian male who discontinued on day 245 due to tiredness. The maximum dose was 25 mg (0.7 mg/kg).

There were 5 subjects who temporarily discontinued therapy. Three of these subjects had gastrointestinal symptoms (stomach virus, vomiting, and nausea and emesis). One subject was previously described under serious adverse events and had menometorrhagia. The last subject had dizziness and hypotension.

There were six events with intensity listed as "severe". The events included headache (n-2), diarrhea (n=1), tear in right shoulder (n=1), menometorrhagia and anemia (n=1), and pneumonia (n=1). The adjusted doses in this group ranged from 0.8 to 1.9 mg/kg.

Overall Adverse events

Table 21: Adverse events, study 307B:

Event	Number (%)	Event	Number (%)
Any patient	83 (83%)	Diarrhea	7 (7%)
Headache	30 (30%)	Nasal Congestion	7 (7%)
URI	20 (20%)	Otitis Media	7 (7%)
Cough	19 (19%)	Dizziness	6 (6%)
Nasopharyngitis	13 (13%)	Abdominal pain upper	5 (5%)
Pharyngolaryngeal pain	12 (12%)	Dysmenorrhea	5 (5%)
Influenza	10 (10%)	Gastroenteritis, viral	5 (5%)
Pyrexia	10(10%)	Edema Peripheral	5 (5%)
Fatigue	9 (9%)	Vomiting	5 (5%)
Back Pain	8 (8%)		

Laboratory:

Blood for laboratory measurements were collected at baseline and at end of study. There were no major changes in either chemistry or hematology parameters.

Table 22: Baseline value and change from baseline in laboratory values, study 307B (mean ± SD)

Parameter	N=	Baseline	Change from baseline
Chemistry			
ALT (U/L)	81	21 ± 13	1.7 ± 9
AST (U/L)	79	23 ± 7	1.1 ± 8
Albumin (G/DL)	81	4.5 ± 0.3	0.05 ± 0.2
Alkaline Phosphatase (U/L)	81	203 ± 91	-25 ± 52
BUN mg/dL	81	12.0 ± 3	-0.4 ± 3
Bilirubin, total	81	0.46 ± 0.3	0.01± 0.2
Calcium mg/dL	79	9.6 ± 0.3	0.1 ± 0.4
Chloride meq/L	81	105 ± 2	-0.4 ± 2
Cholesterol, LDL mg/dL	81	42 ± 9	-1 ± 6
Cholesterol, total mg/dL	81	168 ± 30	1.2 ± 22
Creatinine mg/dL	81	0.8 ± 0.2	0.02 ± 0.1
Fructosamine uMol/L	78	214 ± 21	6 ± 23
Phosphorus, Inorg mg/dL	81	4.6 ± 0.7	-0.4 ± 0.7
Potassium meq/L	79	4.2 ± 0.3	0.03 ± 0.3
Protein, Total	81	7.4 ± 0.5	-0.06 ± 0.3
Sodium, meq/L	81	141 ± 2	0.11 ± 2.6
Hematology			
Hemoglobin g/dL	77	13.4 ± 1.2	0.2 ± 0.8
Hematocrit %	77	40.1 ± 3.1	0.3 ± 2.6
Platelet count per mm^3 x 10^3	77	268 ± 75	2.8 ± 44

ECG:

ECGs were done at baseline and end of therapy.

The sponsor notes no change in parameters from entry to end of 52-week treatment. For a large number of the subjects, the measurements include the effects during study 307A.

Table 23: ECG parameters, study 307B:

Parameter	Mean ± SD study 307B	Week 52-LOCF
Heart rate	72 ± 13	71 ± 14
PR-interval	144 ± 19	147 ± 18
QRS duration	88 ± 10	90 ± 11
QT interval msec	372 ± 30	375 ± 35
QTcB interval	404 ± 19	399 ± 37

Vital signs:

There were no changes in z-scores for BMI or height. The z-score is a deviation from normals. Since weight and height are age-dependent, it seems to be a reasonable way to express the effect of 1-year treatment.

Heart rate was measured at each visit or every other visits, see proceures.

There were five subjects with heart rates below 50.

- Patient 004-001 (a 14-year old C/M) had a heart rate of 64 prior to treatment in 307A, a heart rate of 61 during the first visit during study 307B. The lowest heart rate recorded was at the end of the study with a measured heart rate measured of 44 BPM. The maximum dose received was 50 mg (0.54 mg/kg).

- Patient 004-006 (13-year old C/M) had a heart rate of 80 prior to enrollment in 307A and a pulse of 60 upon entering study 307B. The maximum dose was 37.5 mg (0.85 mg/kg). The nadir of heart rate was 48 at end of study.

- Patient 012-004 (15 year old C/M) had a heart rate of 60 prior to enrollment into 307A and a minimal heart rate of 47 BPM at the end of the study. The maximum dose was 150 mg (1.8 mg/kg).

- Patient # 014-202 (14 year old B/M) had a pulse of 84 at baseline of study 307A, and a pulse of 54 upon entering study 307B. The maximum dose was 200 mg (2.4 mg/kg). The minimum pulse was 47 on day 365.

Pulse rates are shown below.

Table 24: Baseline pulse and change in pulse, study 307B (mean ± SD:

	N	307A entry	Week 16 LOCF	Change from 307A
16-week study	48	84.5 ± 13.4	80.8 ± 17.0	-3.7 ± 12
52-week study	88	83.2 ± 11.2	77.0 ± 12.5	-6.2 ± 14

Pharmacokinetics:

Pharmacokinetic data were collected in study 307A. During this study 67 patients had blood collected at trough to measure metoprolol levels. The doses of the Toprol XL (N=) are as follows: 12.5 mg (13), 25 (1); 37.5 (2); 50 (4); 75 (8); 100 (12); 150 (9); or 200 (18).

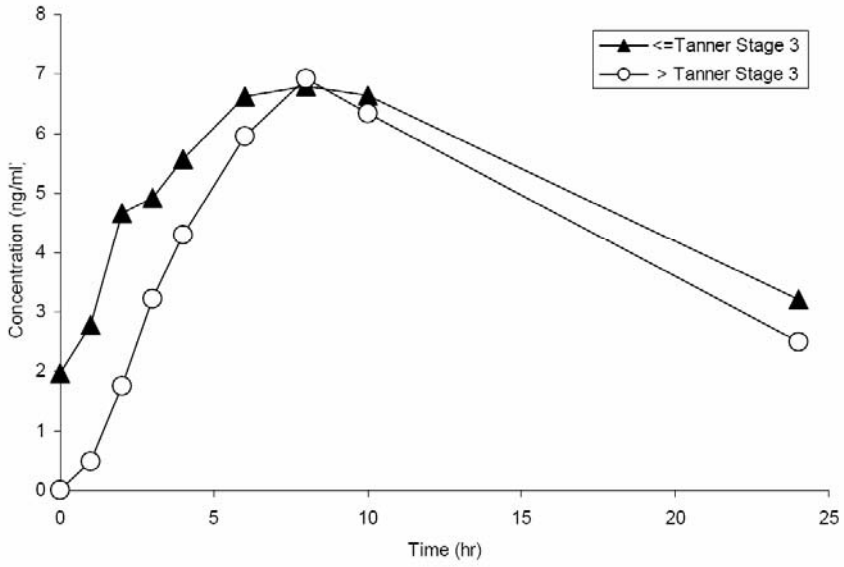
During study 307B there were 27 patients who had serial measurements of metoprolol concentrations after a 25-mg dose following a 48 hour washout period at the following times: 0, 1, 2, 3, 4, 8, 10 and 24 hours post-dose.

There were in addition 109 subjects who had trough samples drawn at the last visit. The dose (and number of patients) at the time of these samples were: 12.5 (13); 25 (1); 37.5 (2); 50 (4); 75 (8); 100 (12); 150 (9); or 200 (18). These patients include 56 patients who had trough values captured during study 307A.

The curve shape of those who received serial measurements (n=27) are shown below. The subjects should have been washed out for 48 hours prior to receiving a 25 mg dose. The reason for measurable metoprolol values at the zero time for the ≤ Tanner 3 subjects is unclear.

Figure 10; Pharmacokinetic profile for intense measurements study 307B.

Figure 3 **Mean plasma concentrations of metoprolol versus time following dosing with TOPROL-XL 25 mg (patients with evaluable serial PK samples)**



Data derived from Appendix 12.1.9, Table 3 of Pharmacokinetic Supportive Analyses.

The pharmacokinetic constants for males and females are shown below.

Table 25: Pharmacokinetic measurements for study 307B.

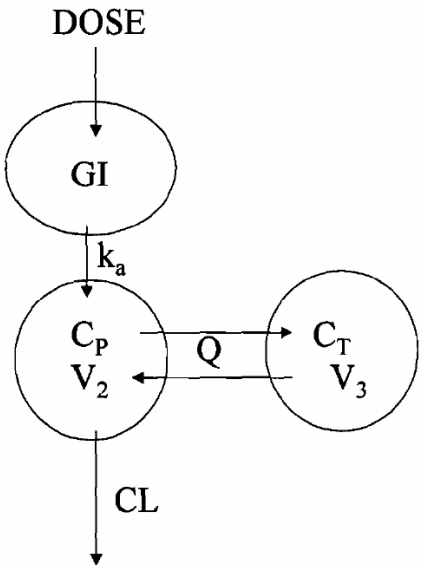
Table 18 **Summary of pharmacokinetic parameter estimates for metoprolol for male and female patients with evaluable serial PK samples**

Parameter	T_{max} (h)	C_{max} (ng/mL)	AUC_t (ng*hr/mL)
Males			
N	15	15	15
Mean (SD)	8.1 (5.3)	7.6 (8.3)	112.9 (143.6)
CV%	65.2	109.6	127.2
Geometric mean	7.7	5.2	65.7
Females			
N	12	12	12
Mean (SD)	6.7 (3.6)	6.8 (4.3)	89.0 (77.8)
CV%	54.2	63.1	87.4
Geometric mean	5.4	5.5	57.1

The final PK model is as shown below. There model assumes that absorption occurs with a variable lag time within the context of a two-compartment model. The absorption from the GI tract (Ka) is assumed to slower than clearance (flip-flop model). Of the covariates tested, age had an effect on the parameter reflecting time constants to the peripheral compartment (Q) and BSA had an effect on clearance (Cl/F). The following covariates did not alter the kinetic model: gender, race, ideal body weight and metoprolol dose. (See Dr. Kumi's review for additional data).

Figure 11: Final PK model.

Figure 1 Scheme of metoprolol population PK structural 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.

Several PK-PD models were evaluated. These models are shown below.

Figure 12: Equations employed in defining PK-PD model.

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_p

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

γ is an estimated parameter to empirically allow for sigmoidi in the relationship

C_p is the trough metoprolol plasma concentration.

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

Baseline model: $E = E_0$

The PK-PD models were tested for describing sitting SBP, DBP and HR.

The kinetic parameters, Cp, Estimated C_{max} and Estimated AUC_{0-24}, based on the AIC (Akaike information content) are shown in the Table.

It was generally easy to fit heart rate effect to any of several models using observed C_p, estimated C_{max} or estimated AUC_{0-24}. There was no significant effect for DBP using measured Cp values. DBP was significant only when the log-linear model for C_{max} or AUC_{0-24} was employed. SBP modeling was inconsistently significant. SBP was significant for the Hill model without baseline, with the log linear model and with AUC_{0-24} with the log-linear model.

Table 26: Model p-values for different measurements of pharmackinetic constants, with different pharmacodynamic models for SBP, DBP and HR.

		DBP	SBP	HR
Observed Cp	Hill's model with baseline	>0.05	>0.05	**<0.05**
	Hill's model without baseline	>0.05	**<0.05**	___
	Log linear mode	>0.05	**<0.05**	**<0.05**
	Linear model	>0.05	>0.05	**<0.05**
Estimated Cmax	Log linear model	**<0.05**	>0.05	**<0.05**
	Linear model	>0.05	>0.05	**<0.05**
Estimated AUC 0-24	Log linear model	**<0.05**	**<0.05**	**<0.05**
	Linear model	>0.05	>0.05	**<0.05**

Baaed on change in mean objective function (MOF) from baseline model and the degree of freedom from the chi-square table.

Note: This reviewer would have expected the measurement of blood pressure at trough, which was the measurements of this study, to be best correlated with Cp. Given the low concentrations at trough and low modeled AUC for the 0.2 mg/kg group it would appear that a linear model would be most appropriate. It is unclear why AUC correlates better with any parameter than Cp. It is possible that what is observed is the consequence of multiple model testing. There did not appear any data in adults to model SBP or DBP to offer a precedence for choosing one or another model. Consequently there is some uncertainty as to which of the various models would be most appropriate and whether any of the models define efficacy.

Additional safety:

In addition to the placebo-controlled database and long-term open-labeled extension, several other databases wee utilized to assess safety.

Publications: The sponsor detected 68 unique publications with reference to the pediatric population (any age from fetus to adolescent). There were 15 publications that the sponsor considered as of potential interest. There were no controlled studies. Case studies formed the bulk of these 15 publications.

Safety related issues were:

A 14-year old female with a history of hypertension and scheduled for repair of a mycotic aortic pseudoaneurism developed hemoptysis, suggesting an aorto-bronchial fistula during metoprolol treatment.

A 13-year old male with acute renal failure and hypertension demonstrated progressive renal failure while treated with metoprolol.

A 4-year old female with tuberous sclerosis and hypertension did not respond to metoprolol.

A 14-year old male with hypertension due to unilateral renal artery stenosis did not respond to metoprolol.

A 13-year old female developed intracranial hypertension 13 months after a renal transplant.

A 16-year old female treated with metoprolol and other medications was reported to have a single aberrant renal artery.

A 17-year old with SLE and renal disease was treated with multiple antihypertensive medications and developed an acute MI. She had triple vessel coronary artery disease.

One retrospective study assessed the effect of low dose metoprolol (0.3 mg/kg) in conjunction with clonidine in 41 pediatric patients with traumatic brain injury. Given the status of these patients there is little additional safety that is relevant to the use of metoprolol in the treatment of hypertension[1].

Additional databases:

A Physicians survey was carried out that involved nine physicians out of 28 that were solicitied by AstraZeneca who responded to the survey. The physicians were form the United States, New Zealand and Slovakia. There were 32 patients in the pediatric aged group of which four reported adverse events. The four adverse events detected from this survey were combined with the adverse events contained in AstraZeneca's database (n=15). There were a total of 19 events in this database.

The events are summarized below:

Case 2005UW14661a 12-year old female who was accidentally prescribed Toprol-XL 25 mg instead of Topamax (an anti-seizure medication), The maximum dose was 75 mg. She experienced chest pain, headache, dizziness, difficulty breathing and hands and feet turning blue. The symptoms are still ongoing,

Case 2005UW05149 a 13 year old male was hospitalized for asthma and pneumonia. He continued on metoprolol therapy

Case2004SE5518 was a serious overdose reported from a foreign source. A 16-year old female took 60 metoprolol 50-mg tablets (3000 mg) and 6 indapamide in an attempt to commit suicide. Symptoms were hypotension, bradycardia and somnolence. She recovered.

Case2003UW11764 an 11 year old female received Toprol-XL instead of Tegretaol. She sustained a seizure,

Case2001UW16611, a 2-year old ingested ½ a 100-mg metoprolol succinate tablet.

Case2000AH01318 a 25-year old male who took metoprolol succinate (? dose) and methylphenydate and sustained mild retinal artery occlusion. He subsequently recovered.

[1] Wahlstrom MR, Olivecrona M, Koskinen LOD, Rydenhag B, and Naredi S; Intensive care medicine; 2005; 31 (6) : 632-9.

Case 1999AU 12045 a 16 year old taking metoprolol succinate-maximum dose 50 mg daily. She was hospitalized for epigastric pain. Amylase levels were elevated. She had an appendectomy performed and an ovarian cyst excised.

There were 3 non-serious adverse events Case 2004UW23124 was a 15-year old female with marked bradycardia on metoprolol (42-50 BPM) . Baseline heart rate was in the 70s.

Case 2004UW23122 a 14-year old female experience hypertrichosis. Upon discontinuation of metoprolol, the hypertrichosis resolved.

Case 2004W23117 a 6-year old experienced facial edema. The patient recovered.

Other events reported as ingestion, increased weight, eneuresis, possible ingestion, alopecia, ingestion, amnesia, ingestion, depression.

These events do not appear to be interpretable as related to drug effects.

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/s/

Abraham Karkowsky
10/26/2006 08:21:01 AM
MEDICAL OFFICER
Fixed the typos, thanks.

Valeria Freidlin
10/27/2006 10:14:45 AM
BIOMETRICS

James Hung
10/27/2006 02:53:52 PM
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