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MEDICAL REVIEW

CLINICAL REVIEW

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Reviewer Name	A.O.Williams, M.D.
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Established Name	Toprol XL /HCTZ
(Proposed) Trade Name	Metoprolol succinate and Hydrochlorothiazide
Therapeutic Class	β-blocker and Diuretic
Applicant	Astra-Zeneca LP
Priority Designation	S
Formulation	Tablets
Dosing Regimen	Individualized 25/12.5 to 200/25
Indication	Hypertension-not initial therapy

Intended Population: Patients with Essential Hypertension

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ON ORIGINAL

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1. EXECUTIVE SUMMARY

AstraZeneca, the sponsor, undertook development of a metoprolol succinate extended release (ER)/hydrochlorothiazide (HCT) combination product for the treatment of essential hypertension. The rationale for developing this product was based on previous observations that combined diuretic/beta-blocker pharmacologic therapy reduces the risk of cardiovascular and cerebrovascular incidents that often complicate the natural history of hypertension. To this end, an unbalanced factorial study (324, referred to as "ATTACH"), was initiated and completed. The data from 1,571 randomized patients exposed to the drug in this study were evaluated. The factorial, parallel group design of the study determined the effects of each individual drug across several dose levels as well as possible combinations. The unbalanced design placed more subjects in cells of pre-specified interest to provide greater precision for key comparisons. All cells, however, contributed to the overall response surface analyses.

The protocol title of Study 324 is as follows: "A phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group, factorial study of metoprolol succinate extended-release tablets (TOPROL-XL®), hydrochlorothiazide and their combination in patients with essential hypertension".

The patient population in the study included adults, ages 18 to 80 years, with essential hypertension and a pre-randomization diastolic blood pressure (DBP) between 95 and 114 mmHg inclusive. Patients with secondary hypertension, marked co-morbid illnesses, and contraindications to the study drugs were excluded.

A total of 2,831 patients were enrolled in study 324 of which 1,571 patients were randomized, Of the 1,571 patients randomized and stratified into 17 treatments groups, 1,559 were in the intent-to-treat (ITT) population, 1,339 in the per-protocol (PP) population, and 1,564 in the safety population. Demographics of the 1,571 patients showed 805 (51%) were males, 766 (49%) were females; 1,122 (71%) Caucasians and 400 (26%) Blacks. The mean duration of hypertension was 8.9 years and the mean average age was 53 years. Age distribution showed 1,324 (84%) patients to be under the age of 65 years, 217 (14%) were between the ages of 65 and 75 years, and 30 (2%) were over the age of 75 years.

The overall population was typical for patients with essential hypertension. The mean baseline blood pressure at randomization was 151/100 mmHg. The most common co-morbid cardiovascular medical conditions were dyslipidemia (38%) and Type II diabetes mellitus (10% of patients).

The treatment groups were balanced, *vis-a-vis* demographics, concomitant medication, co-morbidity etc. The 17 treatment groups were randomized to 16 various doses of metoprolol succinate extended release (25, 50, 100 and 200 mg), hydrochlorothiazide (6.25, 12.5 and 25 mg), and 9 of their combinations and placebo.

Of the randomized patients, 1,395 (88.8%) completed the study, 176 (11.2%) discontinued, 46 (2.9%) discontinued due to adverse events, 51 (3.2%) showed lack of therapeutic response, 45 (2.9%) were not willing to continue and 10 (1.2%) were lost to follow up.

A significant proportion of patients had co-morbidity including dyslipidemia and diabetes (48%) prior to randomization. This may explain some of the metabolic adverse events observed in the study. The metabolic (laboratory) adverse events of interest in this factorial study included hypokalemia, hyponatremia, dyslipidemia, hyperglycemia, and hyperuricemia.

A small clinical efficacy study (S 902) consisting of 47 ITT patients carried out in Sweden and Denmark in 1987 was also submitted to support the findings in ATTACH study. This clinical efficacy study used a combination product of metoprolol ER and HCTZ but had no dose ranging component or evidence of interaction. Therefore, this has limited value in characterizing efficacy of this combination product. Prior to the current NDA study under review there is no evidence whether there is interaction between the two components.

The goals of the current study was primarily to establish that both components did not interact, contributed to the treatment effect of the combination product and secondarily, to characterize the dose response relationship using response surface models. The sponsor also evaluated the antihypertensive efficacy of the combination product using responder frequency data.

The sample size of this study was adequate and provided greater than 95% power for performance of the global test (TAVE) for efficacy. By using the T_{AVE} statistic as the primary analysis, it was shown that at least 1 combination treatment exceeded the reductions of both monotherapy components of Toprol-XL and HCT for both trough SiDBP and SiSBP. These results were confirmed by the pairwise comparisons based upon the ANCOVA model, when even after adjustment for multiplicity, the Toprol-XL/HCT 100/12.5 mg treatment remained significantly better in reducing trough SiDBP and SiSBP than both the Toprol-XL 100 mg treatment and the HCT 12.5 mg treatment. Responder analyses also lent further support to efficacy of at least one combination tablet at certain doses being greater than its components.

Combining antihypertensive agents into a single drug product is an additional approach geared to improving drug therapy compliance by increasing dosing convenience. Such combination products, when they are available in a variety of dosage strengths, provide the clinician with considerable flexibility in individualizing a patient's treatment.

Conclusions:

- The factorial study, ATTACH, met its primary objective because the antihypertensive effect on trough SiDBP of at least 1 Toprol-XL/HCT combination was greater than both of its monotherapy components (TAVE statistic of –1.33, p-value 0.0015).

- The study also met the similar objective for trough SiSBP because the effect on trough SiSBP of at least 1 Toprol-XL/HCT combination was greater than both of its monotherapy components: (TAVE statistic –1.46, p= 0.0006).

- Table 53 below shows the results of the pairwise comparisons of each of the 9 combination treatment groups versus the placebo group in trough SiDBP from baseline to

week 8/LOCF. The mean differences ranged from –3.4 for the lowest strength combination group (Toprol-XL/HCT 25/6.25 mg) to –12.2 for the highest-strength combination group (Toprol-XL/HCT 200/25 mg). All 9 combination treatment groups had highly significantly reductions from baseline to Week 8/LOCF in trough SiDBP when compared to the placebo group (all p-values =0.0004).

- Each monotherapy component contributed to the combination's treatment effect albeit to different degrees as discussed below under additivity effects.

- There was no evidence of interaction between the 2 drug components (p=0.73).

- ANCOVA analyses demonstrated that all combinations were significantly better than placebo in reducing trough SiDBP and SiSBP. In pairwise comparisons of combinations versus their components, the decline in SiDBP was numerically greater for all combinations except for Toprol-XL/HCT 25/6.25 mg. Four treatment combinations (Toprol-XL/HCT 100/6.25 mg, 100/12.5 mg, 100/25 mg, and 200/25 mg) had significantly greater reductions than both of their respective components, at a nominal 0.05 significance level.

While statistical interpretation of these comparisons showed that 4 combination treatment groups of Toprol-XL/HCT (100/6.25 mg, 100/12.5 mg, 100/25 mg, and 200/25 mg) all had significantly ($p<0.050$) greater reductions from baseline in trough SiDBP compared to their respective monotherapy treatment groups, ***in a 5th combination treatment group, Toprol-XL/HCT 200/12.5 mg, SiDBP change was not significantly different from the Toprol-XL 200 mg group, but it was significantly greater than the HCT 12.5 mg group.***

- Pairwise comparisons also indicated that 4 low dose Toprol-XL/HCT combinations (25/6.25 mg, 25/12.5 mg, 50/6.25 mg, and 50/12.5 mg) were approximately as effective as at least 1 of the high dose monotherapies.

- All confidence limits for the combination product were negative, indicating that all studied treatments were desirable according to the regression model. For example, the Toprol-XL/HCT 25/6.25 mg treatment yielded, with 95% confidence, at least –0.56 mmHg more in the change from baseline to Week 8/LOCF in trough SiDBP than Toprol-XL 25 mg alone, HCT 6.25 mg alone, and placebo. Similarly, the Toprol-XL/HCT 100/25 mg treatment provided, with 95% confidence, at a minimum, an additional –1.53 mmHg over Toprol-XL 100 mg alone, HCT 25 mg alone, and placebo.

- Subgroup analyses showed greater reductions in females than males for both trough SiDBP and SiSBP. Black patients appeared to have smaller reductions than non-Black patients; however, increasing HCT dosage strengths appeared to cancel out this difference; Black patients responded somewhat better to HCT (Figures 6-9; Appendix 1).

Safety

- The safety population consisted of 1,564 patients who received at least 1 dose of the investigational product and for whom post-dose data is available. (7 patients less than 1,571 enrolled patients).

- Exposure data show that, on average, placebo run-in lasted 30 days, double-blind treatment 55 days, and down titration/follow-up lasted 15 days.

- Safety data show that no deaths occurred during the study.

- Headache was the most common reason (5 patients total) for treatment discontinuation. Other reasons occurred in 0.2% of patients or less, with most occurring in only 1 or 2 patients.

- An analysis of AEs found that 42% of patients had at least 1 treatment-emergent adverse event (TEAE); the most common of these were as follows: headache (6.2%), upper respiratory tract infection (3.9%), and nasopharyngitis (2.6%).

- An analysis of treatment emergent SAEs and discontinuations due to AEs show that the rates were low: 1.5% and 2.9%, respectively.

- Of the 45 patients (2.9%) who had treatment discontinued, 44 were also discontinued from the study (1 patient who received 6.25 mg HCT was reported as having an adverse event of headache and nervousness that led to treatment discontinuation but this patient was not discontinued from the study).

- Two SAEs occurred in more than 1 patient during the study: coronary artery disease (3 patients) and myocardial infarction (3 patients) (1 patient had both events). The coronary artery disease and MIs were not temporally related to abrupt cessation of beta-blocker treatment (1 MI occurred during down titration, and 2 MIs and 3 coronary artery diseases occurred either the last day of treatment or the day after treatment was stopped).
- The most common AEs leading to treatment discontinuation were headache (5 patients, 0.3%), with erectile dysfunction, fatigue, and hypertension each occurring in 0.2% of patients.

- Analyses show no notable clustering of adverse events in any 1 treatment group. Headache occurred at comparable frequencies across all treatment groups including placebo. There were no appreciable 'additive' safety findings with the possible exception of fatigue, which occurred at high dose HCT in combination with Toprol-XL, but particularly in combination with high dose (200 mg) Toprol-XL.

- Laboratory examination, as expected, identified a dose-related decline in serum potassium and increases in uric acid and BUN associated with HCT treatment and a suggestion of an increase in serum triglycerides. Toprol-XL was associated with a small

decline in HDL cholesterol and small increase in triglycerides. These laboratory findings associated with the individual agents were largely independent when used in combination with the possible exception of an additive effect on serum triglyceride.

- There was a dose-related slowing of heart rate with Toprol-XL and Toprol-XL combinations which is consistent with its known pharmacologic action but it was only notable at the higher (100 mg and 200 mg) doses.

- Metabolic adverse events of interest in this factorial study included: hypokalemia, hyponatremia, dyslipidemia, hyperglycemia, and hyperuricemia (See lab data below)

Analyses of laboratory data found the following abnormalities:

- serum potassium declined,

- serum uric acid and blood urea nitrogen increased with increasing doses of HCT, largely independent of the Toprol-XL dose;

- dose-related decline in HDL-cholesterol with Toprol-XL;

- Triglyceride levels increased with both HCT and Toprol-XL and the combinations tended to reflect the effects of both agents.

- Neither Toprol-XL, HCT, nor their combinations were associated with consistent changes in blood glucose whether for the whole patient population or for patients with diabetes.

- Neither Toprol-XL, HCT, nor their combinations were associated with consistent changes in serum sodium.

- Analyses of ECG and physical examinations data show the expected slowing of heart rate at higher doses of Toprol-XL but no patient was discontinued due to bradycardia.

Recommendation on Regulatory Action

Overall, this reviewer recommends approval of this combination fixed dose drug for the treatment of essential hypertension. Doses recommended include100/6.25 mg; 100/12.5 mg and 100/25 mg.

The fixed combination tablets planned for clinical use in the US include 3 tablet strengths: 25/12.5 mg, 50/12.5 mg, and 100/12.5 mg. The 100/12.5 mg tablet is scored and is divisible to 50/6.25 mg.

In accordance with federal regulations (US Code of Federal Regulations CFR 300.50), this study tested the hypothesis whether the antihypertensive effect of at least one combination tablet, i.e. 1 Toprol- XL/HCT combination was greater than both of its monotherapy components. It also examined the independent antihypertensive effects of each monotherapy and their combinations over a broad range of doses.

The trial established that metoprolol succinate extended release and hydrochlorothiazide both contribute to the antihypertensive effect, change from baseline to week 8 in sitting diastolic (p= 0.0015) and systolic (p=0.0006) blood pressure (see Table 1).

Overall, it can be concluded that Toprol-XL in combination with HCT is an effective antihypertensive treatment based on a large single factorial trial. The only minor down side of the trial was the failure of Toprol-XL/HCT 200/12.5 mg, to show significantly better efficacy in trough SiDBP change compared to Toprol-XL 200 mg. However, efficacy was significantly greater in this treatment group compared to HCT 12.5 mg group.

An assessment of additivity shows that the 2 drugs were less than fully additive at the extreme ends of the dosage range (particularly for the Toprol-XL/HCT 25/6.25 mg group and the 200/12.5 mg group) but the combinations with Toprol- XL 100 mg (Toprol-XL/HCT 100/6.25 mg, 100/12.5 mg, 100/25 mg) were almost fully additive.

1.2 Recommendation on Postmarketing Actions

Safety of this drug should be monitored closely by periodic safety reports with emphasis on the metabolic adverse events observed in this study. This should be reflected in the labeling. This has been addressed in the risk management activity proposed by the sponsor and agreed to by this reviewer.

1.2.1 Risk Management Activity Risk Mitigating Action Plan (Risk Map)

Risk intervention is a process used to reduce the safety risks associated with a drug. AstraZeneca has decided that the Prescribing Information will be their primary tool for communicating the risks associated with the combination tablet. In addition, several other programs will serve to inform and communicate to all stake holders the known risks associated with the combination product using periodic safety reviews, patient and physician education programs.

Although there are no new safety concerns reflected in the combination product that are not already known for the individual components, a pro-active program should be encouraged to monitor the metabolic abnormalities observed in this study among others. During the post-marketing period, AstraZeneca's Safety Surveillance Program should put a system in place to evaluate these risks.

Patient and physician educational materials will provide information on the proper usage of the product and the benefits and risks associated with the combined product. Consumers can access

the AstraZeneca Information Center to obtain information, make inquiries, or report any complaints including AEs.

1.2.2 Required Phase 4 Commitments: Not required

1.2.3 Other Phase 4 Requests: Not required

1.3 Summary of Clinical Findings

The study required approximately 1485 randomized patients and the design specified 4 sequential periods as shown in Figure 1 and Table 1. The primary efficacy measure was SiDBP and the primary measure of effect was the change from baseline to Week 8. Each BP was the mean of 3 BP readings and baseline was at the randomization visit (Day 0). Therefore, the sample size of the study was adequate and provided greater than 95% power for performance of the global test (TAVE) for efficacy.

This factorial study (324) was designed to study whether the BP lowering effects of 9 combinations of Toprol-XL/HCT exceeded that of its individual components and placebo. Given the prior experience with the existing metoprolol succinate extended release/HCT combination, and published studies of metoprolol tartrate/HCT, the combinations planned for Study 324 were expected to lower diastolic blood pressure (DBP) by a placebo-corrected range of approximately 3 to 15 mmHg (Study S-902 1992, Swedish /Danish Study by Westergren et al., 1994).

A total of 2,831 patients was enrolled in the factorial study and 1,571 patients were randomized. Of 1,571 patients randomized and stratified into 17 treatments groups, 1,559 were in the intent-to-treat (ITT) population, 1,339 in the per-protocol population, and 1,564 in the safety population. Males accounted for 51%; 49% of patients were women; 71% were Caucasian and 26% Black. Eighty four per cent (84%) of patients were less than 65 years of age with a mean age of 53 years (For demographics See section 6). The overall population was typical for patients with essential hypertension. The mean baseline blood pressure at randomization was 151/100 mmHg. The most common co-morbid cardiovascular medical conditions were dyslipidemia (38%) and Type II diabetes mellitus (10% of patients).

Eligible patients with BPs in the qualifying range (DBP between 95 and 114 mmHg, on 2 consecutive visits [Week –1 and Day 0]) began an 8-week double-blind treatment period with random allocation to 1 of 17 treatments, ie, 1 of 4 dose levels of Toprol-XL, 1 of 3 dose levels of HCT, 1 of 9 Toprol-XL/HCT combinations, or placebo. (Those patients assigned to receive 200 mg of Toprol-XL received 100 mg for 1 week before escalation to the 200 mg dose.) Patients returned for scheduled visits at 2-week intervals (±2 days) and had end-of-study procedures done at Week 8.

The mean duration of each treatment period was: run-in period 30 days, double-blind

treatment period 55 days, and the down-titration/follow-up period 15 days. Study patients entered a single-blind placebo 4 or 5 week run-in period prior to randomization into an 8-week double-blind treatment period that was followed by a 2-week down-titration/follow-up period.

By using the T_{AVE} statistic as the primary analysis, it was shown that at least 1 combination treatment exceeded the reductions of both monotherapy components of Toprol-XL and HCT for both trough SiDBP and SiSBP. The results of this analysis were confirmed by the pairwise comparisons based upon the ANCOVA model, when even after adjustment for multiplicity, the Toprol-XL/HCT 100/12.5 mg treatment remained significantly better in reducing trough SiDBP and SiSBP than both the Toprol-XL 100 mg treatment and the HCT 12.5 mg treatment. Responder analyses also lent further support to efficacy of at least one combination tablet at certain doses being greater than its components.

1.3.1 Brief Overview of Clinical Program

AstraZeneca, the sponsor, undertook development of a metoprolol succinate extended release (ER)/hydrochlorothiazide (HCT) combination product based on the facts that diuretic/beta-blocker pharmacologic therapy reduces the risk of cardiovascular and cerebrovascular incidents that may complicate hypertension. Furthermore, clinical outcome trials, such as ALLHAT and the two STOP (Swedish Trial in Old People) trials, have suggested a combination of diuretic/beta-blocker treatment reduced the risk for cardiovascular morbidity and mortality associated with hypertension, most notably, the risk for stroke and cardiovascular mortality.

Expert groups have recommended the necessity to combine antihypertensive agents with usually a thiazide diuretic. Such recommendations are based on the established effectiveness and safety of both agents and their predictable behavior in combination regimens. Furthermore, fixed-dose combination products may lead to better compliance (JNC 7 Report 2003). Fixed-dose combination tablets of metoprolol tartrate, an immediate release (IR) formulation, with HCT have been available since 1978 and a combination, specifically, of the ER succinate salt of metoprolol and HCT (100/12.5 mg) became available in 1989 and is an approved antihypertensive agent in 11 countries.

After discussions with the Division of Cardio-Renal Drug Products on January 24, 2003, the sponsor agreed to carry out studies that will further characterize the combination's dose response. This was addressed in this NDA submission by a single factorial clinical trial (ATTACH –Study 324 with 1571 patients).

In addition to the factorial study, a supportive study, (S-902; 47 ITT patients), conducted in Denmark and Sweden in 1987-88, that evaluated the antihypertensive effect of metoprolol succinate ER/HCT (100/12.5 mg) in comparison to a conventional metoprolol tartrate/HCT combination in a population remaining hypertensive in spite of treatment with HCT 12.5 mg daily was also submitted.

The factorial study, ATTACH, tested the hypothesis that the antihypertensive effect of at least 1 Toprol-XL/HCT combination was greater than each of the individual components, and examined

the independent antihypertensive effects of each agent and their combinations over the entire range of doses by dose response analysis (See Section 6 on Efficacy).

The sponsor is pursuing approval for commercial marketing of the tablet strengths of 25/12.5 mg, 50/12.5 mg, and 100/12.5 mg extended release tablets (metoprolol succinate and hydrochlorothiazide, respectively), and does not intend to pursue approval of the 25/6.25 mg extended release tablet of metoprolol succinate and hydrochlorothiazide, respectively, for commercial marketing. A lower dose combination tablet of metoprolol succinate ER/HCT 25/6.25 mg was developed and evaluated in the factorial study submitted in this NDA but is not planned for marketing.

The fixed combination tablets planned for clinical use in the US include 3 tablet strengths: 25/12.5 mg, 50/12.5 mg, and 100/12.5 mg. The 100/12.5 mg tablet is scored and is divisible to 50/6.25 mg.

The Chemistry, Manufacturing and Controls and Clinical information available for the formulated tablet of 25/6.25 mg and at this dosage is contained in this NDA as supportive information for the intended commercial extended release tablet strengths of 25/12.5 mg, 50/12.5 mg, and 100/12.5 mg of metoprolol succinate and hydrochlorothiazide, respectively.

Primary objective: The primary objective of the ATTACH study was to determine whether at least 1 Toprol-XL® (metoprolol succinate)-hydrochlorothiazide (HCT) combination exceeds the blood pressure (BP) lowering effects of its individual components.

Secondary objectives:

- To determine whether at least 1 Toprol-XL/HCT combination exceeded the BP lowering effects of its individual components with regard to the placebo-corrected mean change from baseline to Week 8 in trough sitting systolic blood pressure (SiSBP).
- To describe the dose effects of the individual drugs (Toprol-XL and HCT) and their combinations using response surface analysis in terms of the change from baseline to Week 8 in trough SiDBP and SiSBP.
- To compare each Toprol-XL/HCT combination to its components with regard to the change from baseline to Week 8 in trough SiDBP and SiSBP.
- To compare each combination to placebo with regard to the change from baseline to Week 8 in SiDBP and SiSBP.

Study design: This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group, unbalanced factorial study of 3 dose levels of HCT monotherapy and 4 dose levels of Toprol-XL monotherapy, and 9 of the Toprol-XL/HCT combinations over an 8 week period.

Population and sample size: These included adults, 18 to 80 years of age, with essential hypertension and a pre-randomization diastolic blood pressure (DBP) between 95 and 114 mmHg inclusive. Patients with secondary hypertension, marked co-morbid illnesses, and contraindications to the study drugs were excluded (See Inclusion and Exclusion criteria below).

A total of 2,831 patients was enrolled in the study and 1,571 patients were randomized, Of the 1,571 patients randomized and stratified into 17 treatments groups, 1,559 were in the intent-to-treat (ITT) population, 1,339 in the per-protocol population, and 1,564 in the safety population.

Table 1: Distribution of all randomized patients by dose-Study 324 (ATTACH)

	HCT	Toprol-XL dosage					Total
	dosage	0 mg	25 mg	50 mg	100 mg	200 mg	
All randomized patients, N	0 mg	152	89	94	96	52	1571
	6.25 mg	86	147	137	45	NA	
	12.5 mg	105	142	148	95	43	
	25.0 mg	48	NA	NA	42	50	

This sample size provided greater than 95% power for performance of the global test (TAVE).

The overall population was typical for patients with essential hypertension. The mean baseline blood pressure at randomization was 151/100 mmHg, 49% of patients were women, 71% were Caucasian and 26% Black and 84% of patients were less than 65 years of age (Mean age 53 years). The most common co-morbid cardiovascular medical conditions were dyslipidemia (38%) and Type II diabetes mellitus (10% of patients). For demographics see section 6.

1.3.2 Efficacy

The primary goal of the study was first to establish that both component treatments contribute to the combination and the secondary goal is to characterize the dose response relationship. This section describes the relationship based on response surface models.

- The factorial study, ATTACH, met its primary objective because the antihypertensive effect on trough SiDBP of at least 1 Toprol-XL/HCT combination was greater than both of its monotherapy components (TAVE statistic of –1.33, p-value 0.0015).

- The study also met the similar objective for trough SiSBP because the effect on trough SiSBP of at least 1 Toprol-XL/HCT combination was greater than both of its monotherapy components: (TAVE statistic –1.46, p= 0.0006).

- Each monotherapy component contributed to the combination effect albeit to different degrees as discussed below under additivity effects.

- Similar analyses of other secondary objectives show trough StDBP and StSBP and peak SiDBP and SiSBP changes from baseline to Week 8/LOCF. The results were generally consistent with the results for trough SiDBP and SiSBP.

- The ratio of trough to peak BP illustrates that most of all the BP lowering effect at peak drug effect was retained at trough.

- All confidence limits for the combination product are negative, indicating that all studied treatments were desirable according to the regression model adopted. For example, the Toprol-XL/HCT 25/6.25 mg treatment yielded, with 95% confidence, at least –0.56 mmHg more in the change from baseline to Week 8/LOCF in trough SiDBP than Toprol-XL 25 mg alone, HCT 6.25 mg alone, and placebo. Similarly, the Toprol-XL/HCT 100/25 mg treatment provided, with 95% confidence, at a minimum, an additional –1.53 mmHg over Toprol-XL 100 mg alone, HCT 25 mg alone, and placebo.

- According to subgroup analyses of both trough SiDBP and SiSBP, there was evidence that females had greater reductions than males. Additionally, Black patients appeared to have smaller reductions than non-Black patients; however, increasing HCT dosage strengths appeared to cancel out this difference; Black patients responded somewhat better to HCT.

- ANCOVA analyses demonstrated that all combinations were significantly better than placebo in reducing trough SiDBP and SiSBP. In pairwise comparisons of combinations versus their components, the decline in SiDBP was numerically greater for all combinations except for Toprol-XL/HCT 25/6.25 mg. Four treatment combinations (Toprol-XL/HCT 100/6.25 mg, 100/12.5 mg, 100/25 mg, and 200/25 mg) had significantly greater reductions than both of their respective components, at a nominal 0.05 significance level.

- Pairwise comparisons also indicated that 4 low dose Toprol-XL/HCT combinations (25/6.25 mg, 25/12.5 mg, 50/6.25 mg, and 50/12.5 mg) were approximately as effective as at least 1 of the high dose monotherapies.

- Trough to peak ratios for SiDBP and SiSBP had values close to 1 and changed little from baseline to Week 8/LOCF for all treatment groups, implying that treatment effects applied almost equally to both trough and peak blood pressures.

- Treatment effects expressed as categorical variables illustrate significantly greater proportions of patients responding to and controlled by active treatments than patients given placebo (Responder analyses).

- An assessment of additivity shows that the 2 drugs were less than fully additive at the extreme ends of the dosage range (particularly for the Toprol-XL/HCT 25/6.25 mg group and the 200/12.5 mg group) but the combinations with Toprol- XL 100 mg (Toprol-XL/HCT 100/6.25 mg, 100/12.5 mg, 100/25 mg) were almost fully additive.

1.3.3 Safety

- The safety population consisted of all patients (N= 1564) who received at least 1 dose of the investigational product and for whom post-dose data is available.

- Exposure data show that, on average, placebo run-in lasted 30 days, double-blind treatment 55 days, and down titration/follow-up lasted 15 days.

- Safety data show that no deaths occurred during the study.

- Headache was the most common reason (5 patients total) for treatment discontinuation. Other reasons occurred in 0.2% of patients or less, with most occurring in only 1 or 2 patients.

- An analysis of AEs found that 42% of patients had at least 1 treatment-emergent adverse event (TEAE); the most common of these were as follows: headache (6.2%), upper respiratory tract infection (3.9%), and nasopharyngitis (2.6%).

- The metoprolol succinate extended release and hydrochlorothiazide combination was evaluated for safety in 891 patients treated for hypertension in 2 clinical trials. In a placebo-controlled trial, 843 patients were treated with various combinations of metoprolol succinate (doses of 25 to 200 mg) and hydrochlorothiazide (doses of 6.25 to 25 mg). The frequency of adverse experiences reported with the combination was comparable to placebo. Adverse events, whether or not attributed to treatment, occurring in greater than 1% of patients treated with the combination product and at a rate equal to or greater than with placebo were: nasopharyngitis (3.4% vs 1.3%), fatigue (2.6% vs 0.7%), dizziness (2.6% vs 2.6%), back pain (1.7% vs 1.3%), and nausea (1.4% vs 0.7%). Adverse experiences were usually mild and transient in nature and resulted in discontinuation of therapy (2.7% vs 2.6% with placebo).

- An analysis of treatment emergent SAEs and discontinuations due to AEs show that the rates were low: 1.5% and 2.9%, respectively.

- Of the 45 patients (2.9%) who had treatment discontinuation, 1 patient who received 6.25 mg HCT with an adverse event of headache and nervousness that led to treatment discontinuation was not discontinued from the study.

- Two SAEs occurred in more than 1 patient during the study: coronary artery disease (3 patients) and myocardial infarction (3 patients) (1 patient had both events). The coronary artery disease and MIs were not temporally related to abrupt cessation of beta-blocker treatment (1 MI occurred during down titration, and 2 MIs and 3 coronary artery diseases occurred either the last day of treatment or the day after treatment was stopped).

- The most common AEs leading to treatment discontinuation were headache (5 patients, 0.3%), with erectile dysfunction, fatigue, and hypertension each occurring in 0.2% of patients.

- Analyses show no clustering of adverse events in any 1 treatment group. Headache occurred at comparable frequencies across all treatment groups including placebo. There were no appreciable 'additive' safety findings with the possible exception of fatigue, which occurred at high dose HCT in combination with Toprol-XL, but particularly in combination with high dose (200 mg) Toprol-XL.

- Laboratory examination, as expected, identified a dose-related decline in serum potassium and increases in uric acid and BUN associated with HCT treatment and a suggestion of an increase in serum triglycerides. Toprol-XL was associated with a small decline in HDL cholesterol and small increase in triglycerides. These laboratory findings associated with the individual agents were largely independent when used in combination with the possible exception of an additive effect on serum triglyceride.

- There was a dose-related slowing of heart rate with Toprol-XL and Toprol-XL combinations which is consistent with its known pharmacologic action but it was only notable at the higher (100 mg and 200 mg) doses.

- Metabolic Adverse events of interest in this factorial study included: hypokalemia, hyponatremia, dyslipidemia, hyperglycemia, and hyperuricemia (See lab data below).

Analyses of laboratory data found the following:

- serum potassium declined,

- serum uric acid and blood urea nitrogen increased with increasing doses of HCT, largely independent of the Toprol-XL dose;

- dose-related decline in HDL-cholesterol with Toprol-XL;

- Triglyceride levels increased with both HCT and Toprol-XL and the combinations tended to reflect the effects of both agents.

- Neither Toprol-XL, HCT, nor their combinations were associated with consistent changes in blood glucose whether for the whole patient population or for patients with diabetes.

- Neither Toprol-XL, HCT, nor their combinations were associated with consistent changes in serum sodium.

- Analyses of ECG and physical examinations data show the expected slowing of heart rate at higher doses of Toprol-XL but no patient was discontinued due to bradycardia.

- In general, the safety findings in Study 324 are to some extent similar to the safety profiles of the individual agents (HCT and Toprol-XL).

- There were no significant additional safety findings that could be attributed to their use in combination.

The trial investigators randomized 1571 patients (1570 unique patients – 1 patient participated twice). Definitions of the analysis sets are given below:

An ITT population was used for the efficacy analyses. The ITT population consisted of randomized patients with baseline and at least 1 post-baseline BP measurement and who took at least 1 dose of study medication. The primary time point for efficacy measures was Week 8. For patients in the ITT population with missing efficacy values at Week 8, the last observation during the double-blind period was carried forward (LOCF), whether or not the patient was on study treatment.

The ITT population included 1559 patients (1558 unique patients: 1 patient was randomized twice). Twelve patients were not included in the ITT population for the following reasons; patient did not take any double-blind medication (1 patient); no post baseline BP values (12 patients). (One patient had both these reasons.)

Safety summaries were based on all randomized patients who took at least 1 dose of study medication and had post baseline data available. The safety population included 1564 patients (1563 unique patients: 1 patient was randomized twice); patients were excluded from the safety population for the following reasons: patient did not take any double-blind medication (1 patient); no post baseline contact (6 patients).

Supporting analyses were also conducted with the observed data for the ITT population (ie, without LOCF) and with a PP population based on patients without any major protocol violations. The distribution of patients per treatment groups and by population groups are in Tables 2 and 3.

Ninety-one percent of ITT patients had trough SiDBP values at Week 8. For 144 patients (9%), the Week 8 value was imputed by carrying forward the last observation. For 43 patients, this was the Week 6 value; 44 patients, the Week 4 value; and 57 patients, the Week 2 value or earlier.

Table 2: Distribution of patients by dose groups-Study 324 - ATTACH

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Table 2 presents the number of patients planned per treatment group.

Table 2 Table of study treatments (number of patients per treatment)

Hydrochlorothiazide	Metoprolol succinate extended-release				
	0 mg	25 mg	50 mg	100 mg	200 mg[a]
0 mg	135	90	90	90	45
6.25 mg	90	135	135	45	0
12.5 mg	90	135	135	90	45
25.0 mg	45	0	0	45	45
Total number of patients=1485					

[a] Patients assigned 200 mg metoprolol succinate received 100 mg once daily for 1 week before escalation to 200 mg.

Table 3: Distribution of patients by population (ITT, PP. Safety) and treatment groups-Study 324

Table 11 Number of patients in each population and treatment group

Population	HCT dosage	Toprol-XL dosage					
		0 mg n (%)	25 mg n (%)	50 mg n (%)	100 mg n (%)	200 mg n (%)	Total n (%)
All randomized population, N	0 mg	152	89	94	96	52	1571
	6.25 mg	86	147	137	45	NA	
	12.5 mg	105	142	148	95	43	
	25 mg	48	NA	NA	42	50	
ITT population	0 mg	152 (100)	89 (100)	93 (99)	95 (99)	51 (98)	1559 (99)
	6.25 mg	86 (100)	144 (98)	136 (99)	45 (100)	NA	
	12.5 mg	104 (99)	141 (99)	147 (99)	94 (99)	43 (100)	
	25 mg	48 (100)	NA	NA	42 (100)	49 (98)	
Safety population	0 mg	152 (100)	89 (100)	94 (100)	95 (99)	51 (98)	1564 (100)
	6.25 mg	86 (100)	145 (99)	136 (99)	45 (100)	NA	
	12.5 mg	105 (100)	142 (100)	148 (100)	94 (99)	43 (100)	
	25 mg	48 (100)	NA	NA	42 (100)	49 (98)	
Per-protocol population	0 mg	125 (82)	77 (87)	82 (87)	82 (85)	44 (85)	1339 (85)
	6.25 mg	73 (85)	126 (86)	121 (88)	38 (84)	NA	
	12.5 mg	87 (83)	125 (88)	121 (82)	77 (81)	36 (84)	
	25 mg	44 (92)	NA	NA	37 (88)	44 (88)	

Data derived from Table 11.1.1.5.

Study design and flow chart

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, unbalanced factorial study examined the BP lowering effects of 3 dose levels of HCT, 4 dose levels of Toprol-XL and 9 Toprol-XL/HCT combinations over an 8 week treatment period.

The mean SiDBP values at study entry were similar across the 17 treatment groups with mean values ranging from 91.6 to 94.5 mmHg. Patients then proceeded into a 4- to 5-week placebo run-in period in which they were not allowed to take any other antihypertensive medications. At the time of randomization, trough SiDBP mean values had risen to a mean value of 100.1 mmHg overall, with mean values ranging from 98.4 to 101.0 mmHg across the treatment groups. Potentially eligible patients with essential hypertension underwent screening procedures. Those patients who were free of disqualifying findings entered a single-blind placebo run-in period of 4 weeks. (A 5th week was allowed for patients failing to meet entry BP criteria after 4 weeks.) (Figure 1).

Figure 1: Study Flow Chart

Figure 1 Study flow chart

Screening ≤2 weeks	**Placebo run-in** 4 or 5 weeks		**Treatment** 8 weeks					**Follow-up**[a] 2 weeks
Visit 1 Enrollment (Week –7 to –5)	Visit 2 (Week –5 or –4)	Visit 3 (Week –1)	Visit 4 (Day 0) Randomization	Visit 5 (Week 2)	Visit 6 (Week 4)	Visit 7 (Week 6)	Visit 8 (Week 8) End of treatment	Visit 9 (Week 10)
Patients with hypertension	Placebo run-in		Treatment group (see Table 2 for treatment groups)					

[a] Includes study down titration.

Eligible patients with BPs in the qualifying range (DBP between 95 and 114 mmHg, on 2 consecutive visits [Week –1 and Day 0]) then began an 8-week double-blind treatment period with random allocation to 1 of 17 treatments, ie, 1 of 4 dose levels of Toprol-XL, 1 of 3 dose levels of HCT, 1 of 9 Toprol-XL/HCT combinations, or placebo. (Those patients assigned to receive 200 mg of Toprol-XL received 100 mg for 1 week before escalation to the 200 mg dose).

Patients returned for scheduled visits at 2-week intervals (±2 days) and had end-of-study procedures done at Week 8.

Patients returned 2 weeks after Week 8 to complete the follow-up period. Study drug was down titrated during the follow-up period, although investigators had the option to add open-label antihypertensive treatment after the1st week of the follow-up period.

Investigators were permitted to conduct extra visits at any time during the study if needed for safety considerations.

Duration of treatment: Study patients entered a single-blind placebo 4 or 5 week run-in

period prior to randomization into an 8-week double-blind treatment period that was followed by a 2-week down-titration/follow-up period (See Figure 1).

Of the randomized patients 1,395 completed (88.8%), 176 (11.2%) discontinued, 46 (2.9%) discontinued due to adverse events, 51 (3.2%) showed lack of therapeutic response, 45(2.9%) were not willing to continue and 10 (1.2%) were lost to follow up (Table 4).

This study employed HCT in tablet strengths of 6.25 mg, 12.5 mg, and 25 mg. Although Appendix F of the protocol refers to a specific brand of HCT, the HCT tablets used for the study represented research formulations manufactured at AstraZeneca using HCT, United States Pharmacopeia (USP).

HCT 6.25 mg, 12.5 mg, 25 mg, and matching placebo tablets were white, circular, biconvex film coated tablet. All HCT active strengths and placebo matched in appearance.

The study also employed Toprol-XL in tablet strengths of 25 mg and 100 mg. The 25 mg Toprol-XL and matching placebo tablet were white, oval, biconvex, film-coated tablets, with a score on both sides. The 100 mg Toprol-XL and matching placebo tablet were white, circular, film-coated tablets with a score on 1 side.

Patient Disposition

The patient disposition, demographics and baseline characteristics are presented in the tables 4 -6 and 11 below.

Table 4: Patient disposition- all randomized patients - Study 324

Table 10 Patient disposition (all randomized patients)

	HCT dosage	Toprol-XL dosage					
		0 mg	25 mg	50 mg	100 mg	200 mg	Total
Randomized patients, N	0 mg	152	89	94	96	52	1571
	6.25 mg	86	147	137	45	NA	
	12.5 mg	105	142	148	95	43	
	25 mg	48	NA	NA	42	50	
Completed patients, n (%)	0 mg	128 (84.2)	79 (88.8)	82 (87.2)	84 (87.5)	45 (86.5)	1395 (88.8)
	6.25 mg	75 (87.2)	131 (89.1)	126 (92.0)	41 (91.1)	NA	
	12.5 mg	91 (86.7)	128 (90.1)	131 (88.5)	84 (88.4)	41 (95.3)	
	25 mg	46 (95.8)	NA	NA	38 (90.5)	45 (90.0)	
Discontinued patients, n (%)	0 mg	24 (15.8)	10 (11.2)	12 (12.8)	12 (12.5)	7 (13.5)	176 (11.2)
	6.25 mg	11 (12.8)	16 (10.9)	11 (8.0)	4 (8.9)	NA	
	12.5 mg	14 (13.3)	14 (9.9)	17 (11.5)	11 (11.6)	2 (4.7)	
	25 mg	2 (4.2)	NA	NA	4 (9.5)	5 (10.0)	
Discontinued due to							
Adverse event, n (%)	0 mg	4 (2.6)	3 (3.4)	1 (1.1)	3 (3.1)	5 (9.6)	46 (2.9)
	6.25 mg	0	3 (2.0)	3 (2.2)	1 (2.2)	NA	
	12.5 mg	6 (5.7)	4 (2.8)	7 (4.7)	4 (4.2)	0	
	25 mg	0	NA	NA	1 (2.4)	1 (2.0)	
Lack of therapeutic response, n (%)	0 mg	10 (6.6)	4 (4.5)	4 (4.3)	4 (4.2)	1 (1.9)	51 (3.2)
	6.25 mg	5 (5.8)	6 (4.1)	1 (0.7)	2 (4.4)	NA	
	12.5 mg	2 (1.9)	2 (1.4)	7 (4.7)	1 (1.1)	1 (2.3)	
	25 mg	1 (2.1)	NA	NA	0	0	
Patient not willing to continue, n (%)	0 mg	7 (4.6)	2 (2.2)	6 (6.4)	3 (3.1)	1 (1.9)	45 (2.9)
	6.25 mg	1 (1.2)	2 (1.4)	2 (1.5)	0	NA	
	12.5 mg	3 (2.9)	6 (4.2)	2 (1.4)	4 (4.2)	1 (2.3)	
	25 mg	1 (2.1)	NA	NA	1 (2.4)	3 (6.0)	
Patient lost to follow-up, n (%)	0 mg	3 (2.0)	0	1 (1.1)	1 (1.0)	0	19 (1.2)
	6.25 mg	1 (1.2)	4 (2.7)	2 (1.5)	1 (2.2)	NA	
	12.5 mg	1 (1.0)	2 (1.4)	0	2 (2.1)	0	
	25 mg	0	NA	NA	1 (2.4)	0	

Note: The denominator for percentages is the number of patients randomized.
Data derived from Table 11.1.1.2, Section 11.1.

Demographics

Demographics of the 1,571 patients, 805 (51%) were males and 766 (49%) were females, the mean average age was 53 years; there were 1122 (71%) Caucasians and 400 (26%) Blacks. The mean duration of hypertension was 8.9 years. Age distribution showed 1324 (84%) to be under the age of 65 years, 217 (14%) were between the ages of 65 and 75 years, and 30 (2%) over the age of 75 years (Table 5). There are no significant differences between all treatment groups.

About 13% of the US population is above the age of 65 years. The distribution of the patients in this study by age groups is fairly representative (16%) of the population (Table 7).

Table 5: Demographic and baseline characteristics- all randomized patients -Study 324

Table 12 Demographic and baseline characteristics (all randomized patients)

		HCT	Toprol-XL dosage					Total
		dosage	0 mg	25 mg	50 mg	100 mg	200 mg	
All randomized patients, N		0 mg	152	89	94	96	52	1571
		6.25 mg	86	147	137	45	NA	
		12.5 mg	105	142	148	95	43	
		25.0 mg	48	NA	NA	42	50	
Sex, n (%)	Men	0 mg	83 (55)	39 (44)	52 (55)	56 (58)	29 (56)	805 (51)
		6.25 mg	45 (52)	73 (50)	65 (47)	25 (56)	NA	
		12.5 mg	51 (49)	70 (49)	87 (59)	46 (48)	19 (44)	
		25.0 mg	22 (46)	NA	NA	22 (52)	21 (42)	
	Women	0 mg	69 (45)	50 (56)	42 (45)	40 (42)	23 (44)	766 (49)
		6.25 mg	41 (48)	74 (50)	72 (53)	20 (44)	NA	
		12.5 mg	54 (51)	72 (51)	61 (41)	49 (52)	24 (56)	
		25.0 mg	26 (54)	NA	NA	20 (48)	29 (58)	
Age, years, mean (SD)		0 mg	53 (12)	52 (11)	52 (11)	55 (11)	54 (10)	53 (11)
		6.25 mg	54 (12)	52 (11)	54 (11)	51 (11)	NA	
		12.5 mg	54 (11)	53 (11)	54 (10)	55 (11)	56 (11)	
		25.0 mg	53 (9)	NA	NA	51 (11)	50 (10)	
Race, n (%)	Caucasian	0 mg	109 (72)	65 (73)	62 (66)	71 (74)	39 (75)	1122 (71)
		6.25 mg	63 (73)	104 (71)	99 (72)	31 (69)	NA	
		12.5 mg	78 (74)	91 (64)	110 (74)	71 (75)	27 (63)	
		25.0 mg	35 (73)	NA	NA	32 (76)	35 (70)	
	Black	0 mg	41 (27)	22 (25)	27 (29)	24 (25)	11 (21)	400 (26)
		6.25 mg	21 (24)	39 (27)	34 (25)	12 (27)	NA	
		12.5 mg	23 (22)	44 (31)	33 (22)	20 (21)	15 (35)	
		25.0 mg	13 (27)	NA	NA	8 (19)	13 (26)	

Table 6: Demographic and baseline characteristics continued - Study 324

Table 12 Demographic and baseline characteristics (all randomized patients)

	HCT	Toprol-XL dosage					Total
Duration of hypertension (y), mean (SD)	0 mg	9.4 (9.2)	9.3 (8.3)	8.3 (9.4)	10.2 (9.7)	8.6 (9.1)	9.0 (8.9)
	6.25 mg	8.4 (8.0)	8.3 (9.0)	9.6 (8.9)	8.5 (10.4)	NA	
	12.5 mg	8.5 (8.8)	9.1 (8.4)	9.2 (9.1)	9.2 (8.9)	9.7 (11.6)	
	25.0 mg	8.5 (7.9)	NA	NA	9.4 (7.2)	8.4 (8.2)	
Trough SiDBP, mmHg, mean (range) at study entry	0 mg	94 (72-117)	92 (68-111)	93 (69-110)	92 (72-109)	94 (72-110)	93 (61-119)
	6.25 mg	92 (65-112)	94 (61-111)	94 (71-115)	93 (61-110)	NA	
	12.5 mg	93 (69-110)	93 (70-119)	93 (69-116)	92 (62-116)	92 (77-115)	
	25.0 mg	92 (71-109)	NA	NA	95 (80-110)	93 (64-118)	
Trough SiSBP, mmHg, mean (range) at study entry	0 mg	144 (113-188)	141 (112-183)	142 (109-172)	142 (112-181)	143 (109-180)	143 (91-211)
	6.25 mg	142 (91-180)	145 (101-181)	145 (103-211)	143 (102-171)	NA	
	12.5 mg	143 (114-185)	143 (109-178)	144 (101-176)	142 (109-188)	144 (115-170)	
	25.0 mg	141 (115-173)	NA	NA	145 (121-172)	144 (115-201)	
Trough SiDBP, mmHg, mean (range) at randomization	0 mg	100 (95-114)	100 (95-111)	100 (95-111)	100 (94-113)	100 (95-114)	100 (94-114)
	6.25 mg	100 (95-113)	100 (95-111)	101 (95-113)	100 (95-113)	NA	
	12.5 mg	100 (95-112)	100 (95-114)	101 (95-112)	100 (94-114)	98 (95-109)	
	25.0 mg	100 (95-112)	NA	NA	101 (95-111)	101 (95-113)	
Trough SiSBP, mmHg, mean (range) at randomization	0 mg	151 (119-179)	149 (124-179)	150 (126-178)	151 (125-177)	151 (130-177)	151 (119-179)
	6.25 mg	152 (124-175)	151 (129-177)	151 (127-179)	151 (125-179)	NA	
	12.5 mg	151 (122-176)	150 (119-179)	153 (128-179)	153 (133-179)	150 (130-176)	
	25.0 mg	151 (130-178)	NA	NA	154 (121-179)	149 (120-177)	

SiDBP Sitting diastolic blood pressure. SiSBP Sitting systolic blood pressure.
Data derived from Tables 11.1.2.1, 11.1.2.2, and 11.2.1, Section 11.1 and 11.2.

Table 7: Distribution of patients by age groups and Body mass Index- Study 324

Table 13 Distribution by age groups and body mass index (all randomized patients)

Demographic	HCT dosage	TOPROL XL dosage					Total
		0 mg	25 mg	50 mg	100 mg	200 mg	
Age							
<65 years, n (%)	0 mg	124 (82)	79 (89)	81 (86)	76 (79)	46 (89)	1324 (84)
	6.25 mg	68 (79)	130 (88)	109 (80)	40 (89)	NA	
	12.5 mg	88 (84)	122 (86)	126 (85)	72 (76)	34 (79)	
	25.0 mg	42 (88)	NA	NA	40 (95)	47 (94)	
65 to <75 years , n (%)	0 mg	23 (15)	8 (9)	13 (14)	20 (21)	6 (12)	217 (14)
	6.25 mg	15 (17)	14 (10)	24 (18)	4 (9)	NA	
	12.5 mg	14 (13)	19 (13)	19 (13)	20 (21)	8 (19)	
	25.0 mg	5 (10)	NA	NA	2 (5)	3 (6)	
≥75 years, n (%)	0 mg	5 (3)	2 (2)	0	0	0	30 (2)
	6.25 mg	3 (4)	3 (2)	4 (3)	1 (2)	NA	
	12.5 mg	3 (3)	1 (<1)	3 (2)	3 (3)	1 (2)	
	25.0 mg	1 (2)	NA	NA	0	0	
Body mass Index							
<30 kg/m^2, n (%)	0 mg	69 (45)	43 (48)	42 (45)	48 (50)	28 (54)	682 (43)
	6.25 mg	37 (43)	66 (45)	60 (44)	16 (36)	NA	
	12.5 mg	41 (39)	43 (30)	67 (45)	45 (47)	19 (44)	
	25.0 mg	20 (42)	NA	NA	16 (38)	22 (44)	
≥30 kg/m^2, n (%)	0 mg	83 (55)	46 (52)	52 (55)	48 (50)	24 (46)	889 (57)
	6.25 mg	49 (57)	81 (55)	77 (56)	29 (64)	NA	
	12.5 mg	64 (61)	99 (70)	81 (55)	50 (53)	24 (56)	
	25.0 mg	28 (58)	NA	NA	26 (62)	28 (56)	

Data derived from Table 11.1.2.1, Section 11.1.

Concomitant Medication and commonest medical conditions

There are no significant differences between the treatment groups that may influence the results. Table 8 presents the most common cardiovascular medical conditions in at least 2% of all randomized patients.

Table 9 presents the most common antihypertensive medication used in at least 10% of the patients at enrollment.

Table 10 presents the most common concomitant medication used in at least 10% of the patients during double blind treatment is presented in the table below. There is no excess of any type of concomitant medication during the double blind trial that may influence the results.

Table 8: Most common cardiovascular conditions among all randomized patients - Study 324

Table 14 Most common (in at least 2% of patients) cardiovascular medical conditions (all randomized patients)

Medical condition	HCT dosage	Toprol-XL dosage					Total n (%)
		0 mg n (%)	25 mg n (%)	50 mg n (%)	100 mg n (%)	200 mg n (%)	
Dyslipidemia including hypercholesterolemia, currently	0 mg	59 (39)	41 (46)	38 (40)	38 (40)	20 (39)	589 (38)
	6.25 mg	36 (42)	41 (28)	53 (39)	15 (33)	NA	
	12.5 mg	47 (45)	53 (37)	50 (34)	38 (40)	16 (37)	
	25.0 mg	20 (42)	NA	NA	14 (33)	10 (20)	
Diabetes mellitus, Type II	0 mg	9 (6)	6 (7)	9 (10)	9 (9)	3 (6)	150 (10)
	6.25 mg	9 (11)	11 (8)	18 (13)	6 (13)	NA	
	12.5 mg	15 (14)	13 (9)	12 (8)	7 (7)	9 (21)	
	25.0 mg	7 (15)	NA	NA	4 (10)	3 (6)	
Valvular heart disease, currently	0 mg	2 (1)	3 (3)	2 (2)	3 (3)	1 (2)	31 (2)
	6.25 mg	0	3 (2)	4 (3)	1 (2)	NA	
	12.5 mg	2 (2)	5 (4)	3 (2)	1 (1)	0	
	25.0 mg	0	NA	NA	1 (2)	0	

Data derived from Table 11.1.2.4, Section 11.1.

Antihypertensive medication usage for at least 10% of the patients at enrollment is presented in Table 9

Table 9: Most commonly used anti-hypertensive drugs in randomized patients at enrollment - Study 324

Table 16 Antihypertension medication usage for at least 10% of patients at study enrollment (randomized population)

Antihypertensive medication group	HCT dosage	Toprol-XL dosage					Total
(ATC code)		0 mg	25 mg	50 mg	100 mg	200 mg	
Angiotensin converting enzyme-inhibitors, plain	0 mg	20 (13.2)	15 (16.9)	17 (18.1)	19 (19.8)	9 (17.3)	269 (17.1)
	6.25 mg	10 (11.6)	20 (13.6)	25 (18.2)	7 (15.6)	NA	
	12.5 mg	16 (15.2)	28 (19.7)	34 (23.0)	17 (17.9)	8 (18.6)	
	25.0 mg	10 (20.8)	NA	NA	8 (19.0)	6 (12.0)	
Thiazides, plain	0 mg	18 (11.8)	11 (12.4)	11 (11.7)	15 (15.6)	8 (15.4)	211 (13.4)
	6.25 mg	13 (15.1)	17 (11.6)	20 (14.6)	10 (22.2)	NA	
	12.5 mg	13 (12.4)	18 (12.7)	24 (16.2)	16 (16.8)	5 (11.6)	
	25.0 mg	3 (6.3)	NA	NA	5 (11.9)	4 (8.0)	
Angiotensin II antagonists, plain	0 mg	22 (14.5)	12 (13.5)	12 (12.8)	14 (14.6)	5 (9.6)	208 (13.2)
	6.25 mg	14 (16.3)	17 (11.6)	18 (13.1)	8 (17.8)	NA	
	12.5 mg	13 (12.4)	17 (12.0)	19 (12.8)	10 (10.5)	4 (9.3)	
	25.0 mg	6 (12.5)	NA	NA	5 (11.9)	12 (24.0)	
β-blocking agents, selective	0 mg	15 (9.9)	13 (14.6)	12 (12.8)	13 (13.5)	7 (13.5)	206 (13.1)
	6.25 mg	13 (15.1)	17 (11.6)	22 (16.1)	7 (15.6)	NA	
	12.5 mg	13 (12.4)	12 (18.5)	18 (12.2)	12 (12.6)	6 (14.0)	
	25.0 mg	10 (20.8)	NA	NA	7 (16.7)	9 (18.0)	

ATC Anatomic, therapeutic, chemical classification.
Data derived from Table 11.1.2.15, Section 11.1.

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Table 10: Concomitant medication usage during double-blind treatment phase- Study 324.

Table 18 Concomitant medication usage in at least 10% of patients during double-blind treatment (randomized population)

Medication group (ATC code)	HCT dose	Toprol-XL dosage					Total
	mg	0 mg	25 mg	50 mg	100 mg	200 mg	
HMG COA reductase inhibitors	0	27 (17.8)	19 (21.3)	15 (16.0)	19 (19.8)	6 (11.5)	246 (15.7)
	6.25	18 (20.9)	17 (11.6)	24 (17.5)	4 (8.9)	NA	
	12.5	18 (17.1)	22 (15.5)	21 (14.2)	14 (14.7)	5 (11.6)	
	25.0	10 (20.8)	NA	NA	6 (14.3)	1 (2.0)	
Platelet aggregation inhibitors exclud heparin	0	28 (18.4)	14 (15.7)	14 (14.9)	15 (15.6)	4 (7.7)	238 (15.1)
	6.25	16 (18.6)	20 (13.6)	27 (19.7)	6 (13.3)	NA	
	12.5	16 (15.2)	21 (14.8)	27 (18.2)	12 (12.6)	6 (14.0)	
	25.0	3 (6.3)	NA	NA	4 (9.5)	5 (10.0)	
Anilides	0	22 (14.5)	10 (11.2)	15 (16.0)	8 (8.3)	4 (7.7)	232 (14.8)
	6.25	15 (17.4)	26 (17.7)	27 (19.7)	8 (17.8)	NA	
	12.5	11 (10.5)	23 (16.2)	29 (19.6)	15 (15.8)	5 (11.6)	
	25.0	5 (10.4)	NA	NA	3 (7.1)	6 (12.0)	
Propionic acid derivatives	0	25 (16.4)	13 (14.6)	7 (7.4)	9 (9.4)	6 (11.5)	216 (13.7)
	6.25	9 (10.5)	27 (18.4)	25 (18.2)	5 (11.1)	NA	
	12.5	15 (14.3)	14 (9.9)	25 (16.9)	12 (12.6)	3 (7.0)	
	25.0	8 (16.7)	NA	NA	3 (7.1)	10 (20.0)	
Multivitamins, plain	0	22 (14.5)	8 (9.0)	11 (11.7)	13 (13.5)	8 (15.4)	208 (13.2)
	6.25	11 (12.8)	17 (11.6)	18 (13.1)	4 (8.9)	NA	
	12.5	13 (12.4)	19 (13.4)	22 (14.9)	17 (17.9)	7 (16.3)	
	25.0	7 (14.6)	NA	NA	4 (9.5)	7 (14.0)	

ATC Anatomic, therapeutic, chemical classification.
HMG COA reductase inhibitors 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors.
Data derived from Table 11.1.2.19, Section 11.1.

Table 11: Distribution of patients by population and treatment groups - Study 324

Table 11 Number of patients in each population and treatment group

Population	HCT dosage	Toprol-XL dosage					
		0 mg n (%)	25 mg n (%)	50 mg n (%)	100 mg n (%)	200 mg n (%)	Total n (%)
All randomized population, N	0 mg	152	89	94	96	52	1571
	6.25 mg	86	147	137	45	NA	
	12.5 mg	105	142	148	95	43	
	25 mg	48	NA	NA	42	50	
ITT population	0 mg	152 (100)	89 (100)	93 (99)	95 (99)	51 (98)	1559 (99)
	6.25 mg	86 (100)	144 (98)	136 (99)	45 (100)	NA	
	12.5 mg	104 (99)	141 (99)	147 (99)	94 (99)	43 (100)	
	25 mg	48 (100)	NA	NA	42 (100)	49 (98)	
Safety population	0 mg	152 (100)	89 (100)	94 (100)	95 (99)	51 (98)	1564 (100)
	6.25 mg	86 (100)	145 (99)	136 (99)	45 (100)	NA	
	12.5 mg	105 (100)	142 (100)	148 (100)	94 (99)	43 (100)	
	25 mg	48 (100)	NA	NA	42 (100)	49 (98)	
Per-protocol population	0 mg	125 (82)	77 (87)	82 (87)	82 (85)	44 (85)	1339 (85)
	6.25 mg	73 (85)	126 (86)	121 (88)	38 (84)	NA	
	12.5 mg	87 (83)	125 (88)	121 (82)	77 (81)	36 (84)	
	25 mg	44 (92)	NA	NA	37 (88)	44 (88)	

Data derived from Table 11.1.1.5.

1.3.4 Efficacy

The primary efficacy measure was sitting diastolic blood pressure (SiDBP) and the primary measure of effect was the change from baseline to Week 8. Each blood pressure reading (BP) was the mean of 3 BP readings and baseline was at the randomization visit (Day 0).

Efficacy: Primary variable: Change from baseline to Week 8 in trough SiDBP.

Secondary outcome variables: Secondary measures of effect included the change from baseline to Week 8 in **trough** SiSBP, trough StSBP and StDBP, and **peak** SiSBP and SiDBP.

Patient population: The investigators randomized 1, 571 patients; 89% (n=1395) completed the study and 11% (n=176) discontinued for any reason; 2.9% (n=46) discontinued because of AEs. Treatment groups and number of patients in each group are presented below.

The factorial parallel group design determined the effects of each individual drug across several dose levels as well as possible combinations. The unbalanced design placed more subjects in

cells of pre-specified interest to provide greater precision for these key comparisons. All cells, however, contributed to the overall response surface analyses. There are no patients in cells 25/25 mg and 25/50 mg (Tables 12 and 13).

Table 12: Study treatment groups and distribution of patients per treatment cell- Study 324

Table 2 presents the number of patients planned per treatment group.

Table 2 Table of study treatments (number of patients per treatment)

Hydrochlorothiazide	Metoprolol succinate extended-release				
	0 mg	25 mg	50 mg	100 mg	200 mg[a]
0 mg	135	90	90	90	45
6.25 mg	90	135	135	45	0
12.5 mg	90	135	135	90	45
25.0 mg	45	0	0	45	45

Total number of patients=1485

[a] Patients assigned 200 mg metoprolol succinate received 100 mg once daily for 1 week before escalation to 200 mg.

Table 13: Distribution of patients by trough SiDBP at study entry and randomization-Study 324

Table 21 Descriptive statistics for trough SiDBP at study entry and randomization (all randomized patients)

		Toprol-XL dosage					
	HCT dosage	0 mg	25 mg	50 mg	100 mg	200 mg	Total
All randomized patients, N	0 mg	152	89	94	96	52	1571
	6.25 mg	86	147	137	45	NA	
	12.5 mg	105	142	148	95	43	
	25.0 mg	48	NA	NA	42	50	
Trough SiDBP							
-At study entry (Visit 1):							
Mean (SD)	0 mg	93.7 (8.6)	91.9 (8.7)	92.9 (9.0)	92.0 (7.8)	93.9 (8.7)	93.0 (8.9)
	6.25 mg	92.2 (8.5)	93.7 (9.3)	94.3 (9.6)	92.9 (10.1)	NA	
	12.5 mg	92.9 (9.1)	93.4 (8.9)	92.6 (8.9)	91.6 (9.3)	92.2 (8.2)	
	25.0 mg	91.7 (9.0)	NA	NA	94.5 (7.7)	92.5 (9.0)	
-At baseline, randomization							
Mean (SD)	0 mg	100.2 (4.4)	100.0 (4.1)	100.3 (4.1)	100.0 (3.9)	100.0 (4.7)	100.1 (4.2)
	6.25 mg	100.2 (4.5)	100.1 (3.8)	100.6 (4.7)	100.0 (4.6)	NA	
	12.5 mg	100.1 (4.1)	99.6 (3.8)	100.5 (4.4)	99.6 (4.0)	98.4 (3.4)	
	25.0 mg	99.8 (4.2)	NA	NA	101.0 (5.0)	100.7 (4.4)	

N Total number of patients in treatment group.
SiDBP Sitting diastolic blood pressure.
Derived from Table 11.2.1, Section 11.2.

Efficacy results

The study met its primary objective: the antihypertensive effect on trough SiDBP of at least 1 Toprol-XL/HCT combination was greater than both of its monotherapy components (TAVE statistic of –1.33, p-value 0.0015); the study also met the similar objective for trough SiSBP: the effect on trough SiSBP of at least 1 Toprol-XL/HCT combination was greater then both of its monotherapy components: (TAVE statistic –1.46, p= 0.0006).-Tables 14 - 19

Table 14: TAVE statistics for trough SiDBP from baseline to week 8 - ITT

Table 23 **T_{AVE} test results: changes from baseline to Week 8/LOCF in trough SiDBP (mmHg) (intent-to-treat population)**

	HCT dosage	Toprol-XL dosage			
Trough SiDBP		**25 mg**	**50 mg**	**100 mg**	**200 mg**
T statistics vs Toprol-XL monotherapy	6.25 mg	0.0020	–1.0228	–2.2929	NA
	12.5 mg	–1.8238	–1.7151	–3.4133	–0.0619
	25.0 mg	NA	NA	–2.7916	–2.3156
T statistics vs HCT monotherapy	6.25 mg	0.4136	–1.5847	–2.8217	NA
	12.5 mg	–0.1907	–1.1065	–3.0539	–1.8512
	25.0 mg	NA	NA	–2.3116	–4.0334
T_{AVE} statistic		–1.3269			
p-value		0.0015			

LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure.
Data derived from Table 11.2.2.1.5, Section 11.2.

While statistical interpretation of these comparisons must take into account that sample sizes (and power) differed for some contrasts, 4 combination treatment groups of Toprol-XL/HCT (100/6.25 mg, 100/12.5 mg, 100/25 mg, and 200/25 mg) all had significantly ($p<0.050$) greater reductions from baseline in trough SiDBP compared to their respective monotherapy treatment groups. ***In a 5th combination treatment group, Toprol-XL/HCT 200/12.5 mg, SiDBP change was not significantly different from the Toprol-XL 200 mg group, but it was significantly greater than the HCT 12.5 mg group (See Section 6: Review of Efficacy).***

Table 15: Pairwise comparisons for trough SiDBP from baseline to week 8- Study 324

Table 25 Pairwise comparisons for each combination to placebo, change from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)

Combination treatment group	Comparator treatment	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Placebo	–3.44	–5.34, –1.53	0.0004
Toprol-XL/HCT, 25/12.5 mg	Placebo	–5.66	–7.57, –3.74	<0.0001
Toprol-XL/HCT, 50/6.25 mg	Placebo	–5.79	–7.72, –3.86	<0.0001
Toprol-XL/HCT, 50/12.5 mg	Placebo	–6.59	–8.48, –4.69	<0.0001
Toprol-XL/HCT, 100/6.25 mg	Placebo	–8.48	–11.26, –5.71	<0.0001
Toprol-XL/HCT, 100/12.5 mg	Placebo	–9.25	–11.39, –7.10	<0.0001
Toprol-XL/HCT, 100/25 mg	Placebo	–9.27	–12.13, –6.42	<0.0001
Toprol-XL/HCT, 200/12.5 mg	Placebo	–8.49	–11.32, –5.66	<0.0001
Toprol-XL/HCT, 200/25.0 mg	Placebo	–12.19	–14.88, –9.50	<0.0001

Note: Based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction between Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure; CI Confidence interval; LL Lower limit; UL Upper limit.

Table 16: ANCOVA model for trough SiDBP from baseline to week 8-Study 324

Table 25 Pairwise comparisons for each combination to placebo, change from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)

Combination treatment group	Comparator treatment	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Placebo	–3.44	–5.34, –1.53	0.0004
Toprol-XL/HCT, 25/12.5 mg	Placebo	–5.66	–7.57, –3.74	<0.0001
Toprol-XL/HCT, 50/6.25 mg	Placebo	–5.79	–7.72, –3.86	<0.0001
Toprol-XL/HCT, 50/12.5 mg	Placebo	–6.59	–8.48, –4.69	<0.0001
Toprol-XL/HCT, 100/6.25 mg	Placebo	–8.48	–11.26, –5.71	<0.0001
Toprol-XL/HCT, 100/12.5 mg	Placebo	–9.25	–11.39, –7.10	<0.0001
Toprol-XL/HCT, 100/25 mg	Placebo	–9.27	–12.13, –6.42	<0.0001
Toprol-XL/HCT, 200/12.5 mg	Placebo	–8.49	–11.32, –5.66	<0.0001
Toprol-XL/HCT, 200/25.0 mg	Placebo	–12.19	–14.88, –9.50	<0.0001

Note: Based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction between Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure; CI Confidence interval; LL Lower limit; UL Upper limit.
Data derived from Table 11.2.2.1.12, Section 11.2.

Table 17: Raw and adjusted means for peak SiDBP from baseline to week 8 - ITT

Table 47 Raw and adjusted means for changes from baseline to Week 8/LOCF in peak SiDBP (mmHg) (intent-to-treat population)

Treatment group	N	Observed raw change		Adjusted change		
		Mean change	Standard error	Mean change	Standard error	95% CI LL, UL
TOPROL-X/HCTL, 100/6.25 mg	41	-14.87	1.25	-14.60	1.32	-17.18, -12.01
TOPROL-X/HCT, 100/12.5 mg	84	-15.69	0.97	-15.80	0.92	-17.60, -13.99
Toprol-XL/HCT, 100/25 mg	38	-14.66	1.39	-14.65	1.37	-17.33, -11.96
Toprol-XL/HCT, 200/12.5 mg	39	-13.11	1.34	-13.41	1.35	-16.06, -10.76
Toprol-XL/HCT, 200/25 mg	42	-14.23	1.35	-14.05	1.30	-16.60, -11.49

Note: Adjusted numbers were based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction between Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure; N Total number of patients in treatment group; CI Confidence interval; LL Lower limit; UL Upper limit
Data derived from Table 11.2.6.1.9, Section 11.2.

Factorial Design - Dose response relationships - construction of response surface models
The primary goal of the study was first to establish that both component treatments contribute to the combination and the secondary goal is to characterize the dose response relationship. This section describes the dose relationships based on response surface models.

The factorial design allowed summary estimates of the treatment effects. The factorial parallel group design determined the effects of each individual drug across several dose levels as well as possible combinations. The unbalanced design placed more subjects in cells of pre-specified interest to provide greater precision for these key comparisons. All cells, however, contributed to the overall response surface analyses.

This was used to address a second regulatory guidance to characterize dose response relationships by constructing response surface models. These dose response surface analyses were well described by a quadratic model for SiDBP and SiSBP (Figures 3 and 21). It was a better fit with a quadratic than a linear model suggesting that the trial included a wide range of doses that approached the top of the dose response curves. The model predicted BP reductions of 5.5/3.3 for the lowest (Toprol-XL/HCT 25/6.25 mg) after accounting for the placebo effect (Table 18). The dose response therefore supports the conclusion that not only are all combinations effective, but that there is a contribution from both components.

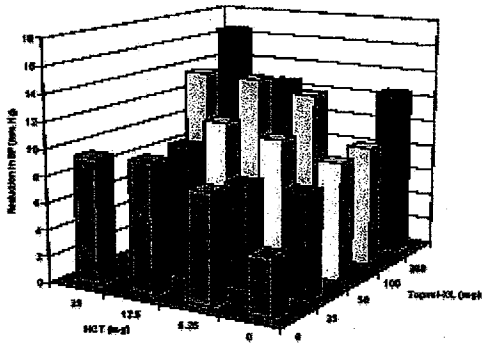
It also implies that a low dose combination may be a better alternative treatment than the individual agents, as the combination is predicted to yield a greater BP reduction. For example, the model predicts a placebo-corrected SiSBP/SiDBP decline of 2.0/1.4 mmHg if one treats with Toprol-XL 25 mg as monotherapy; 3.5/1.9 mmHg with HCT 6.25 mg as monotherapy, but 5.5/3.3 mmHg if one selects the Toprol-XL/HCT 25/6.25 mg combination (Table 18).

The response surface model that predicted placebo-corrected reductions in SiSBP/SiDBP ranging from 5.5/3.3 mmHg for the Toprol-XL/HCT 25/6.25 mg combination to 14.7/10.4 mmHg for the

200/25 mg combination, implied that all combinations would induce numerically greater SiDBP reductions than either of the components (Table 18).

Figure 2: Raw Mean reductions from baseline to week 8 in trough SiDBP - ITT

Figure S1 Raw mean reductions from baseline to Week 8/LOCF in trough SiDBP



The data are also described in Figure 2 based on an additive quadratic dose response surface model. The interaction between Toprol-XL and HCT in the model was not significant (p=0.73).

Figure S2 Dose response surface from the final polynomial regression of changes from baseline to Week 8/LOCF in trough SiDBP

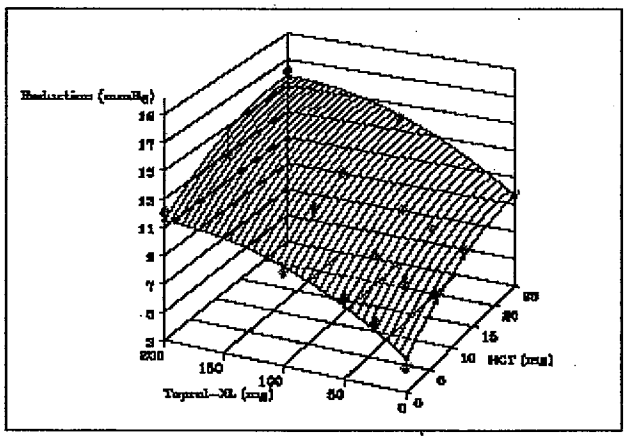


Figure 3: Dose response surface for trough SiDBP from baseline to week 8- ITT

The second regulatory guidance suggests to characterize dose response and Study 324 did so by fitting response surface models (Figure 3).

According to a regression model that contained both linear and quadratic terms for the dosage strengths of the 2 drugs, reductions in trough SiDBP and SiSBP increased with increasing doses of each drug. There was no significant interaction between the drugs (p=0.73) and the model predicted greater BP lowering with the combination than the components across the entire range of doses studied.

Table 18: Placebo corrected Predicted values for change from baseline in SBP/DBP

Table 1. Placebo-corrected Predicted Values for Change from Baseline in SBP/DBP

	TOPROL-XL Dosage				
HCT Dosage	**0 mg SBP/DBP**	**25 mg SBP/DBP**	**50 mg SBP/DBP**	**100 mg SBP/DBP**	**200 mg SBP/DBP**
0 mg	0/0	-2.0/-1.4	-3.7/-2.6	-6.1/-4.5	-7.0/-6.1
6.25 mg	-3.5/-1.9	-5.5/-3.3	-7.2/-4.5	-9.6/-6.4	10.5/-8.0
12.5 mg	-5.9/-3.3	-7.9/-4.7	-9.6/-5.9	-12.0/-7.8	-12.9/-9.3
25 mg	-7.7/-4.3	-9.7/-5.7	-11.4/-6.9	-13.8/-8.8	-14.7/-10.4

[a] Predicted values from a least-squares quadratic regression model.

Table 19: Mean differences between combination and comparator monotherapies- ITT- Study 324

Combination treatment group	Comparator monotherapy	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Toprol-XL, 25 mg	0.02	–2.19, 2.23	0.9858
Toprol-XL/HCT, 25/12.5 mg	Toprol-XL, 25 mg	–2.20	–4.42, 0.01	0.0516
Toprol-XL/HCT, 50/6.25 mg	Toprol-XL, 50 mg	–1.17	–3.37, 1.03	0.2986
Toprol-XL/HCT, 50/12.5 mg	Toprol-XL, 50 mg	–1.97	–4.14, 0.20	0.0753
TOPROL-X/HCTL, 100/6.25 mg	Toprol-XL, 100 mg	–3.63	–6.59, –0.67	0.0163
TOPROL-X/HCT, 100/12.5 mg	Toprol-XL, 100 mg	–4.39	–6.77, –2.01	0.0003
Toprol-XL/HCT, 100/25 mg	Toprol-XL, 100 mg	–4.42	–7.45, –1.39	0.0043
Toprol-XL/HCT, 200/12.5 mg	Toprol-XL, 200 mg	–0.27	–3.66, 3.12	0.8749
Toprol-XL/HCT, 200/25 mg	Toprol-XL, 200 mg	–3.98	–7.25, –0.71	0.0173
Toprol-XL/HCT, 25/6.25 mg	HCT, 6.25 mg	0.48	–1.75, 2.71	0.6718
Toprol-XL/HCT, 50/6.25 mg	HCT, 6.25 mg	–1.87	–4.12, 0.39	0.1046
Toprol-XL/HCT, 100/6.25 mg	HCT, 6.25 mg	–4.56	–7.57, –1.55	0.0030
Toprol-XL/HCT, 25/12.5 mg	HCT, 12.5 mg	–0.27	–2.39, 1.84	0.8000
Toprol-XL/HCT, 50/12.5 mg	HCT, 12.5 mg	–1.20	–3.30, 0.89	0.2613
Toprol-XL/HCT, 100/12.5 mg	HCT, 12.5 mg	–3.86	–6.19, –1.53	0.0012
Toprol-XL/HCT, 200/12.5 mg	HCT, 12.5 mg	–3.10	–6.07, –0.13	0.0409
Toprol-XL/HCT, 100/25 mg	HCT, 25 mg	–4.14	–7.60, –0.69	0.0189
Toprol-XL/HCT, 200/25 mg	HCT, 25 mg	–7.06	–10.39, –3.74	<0.0001

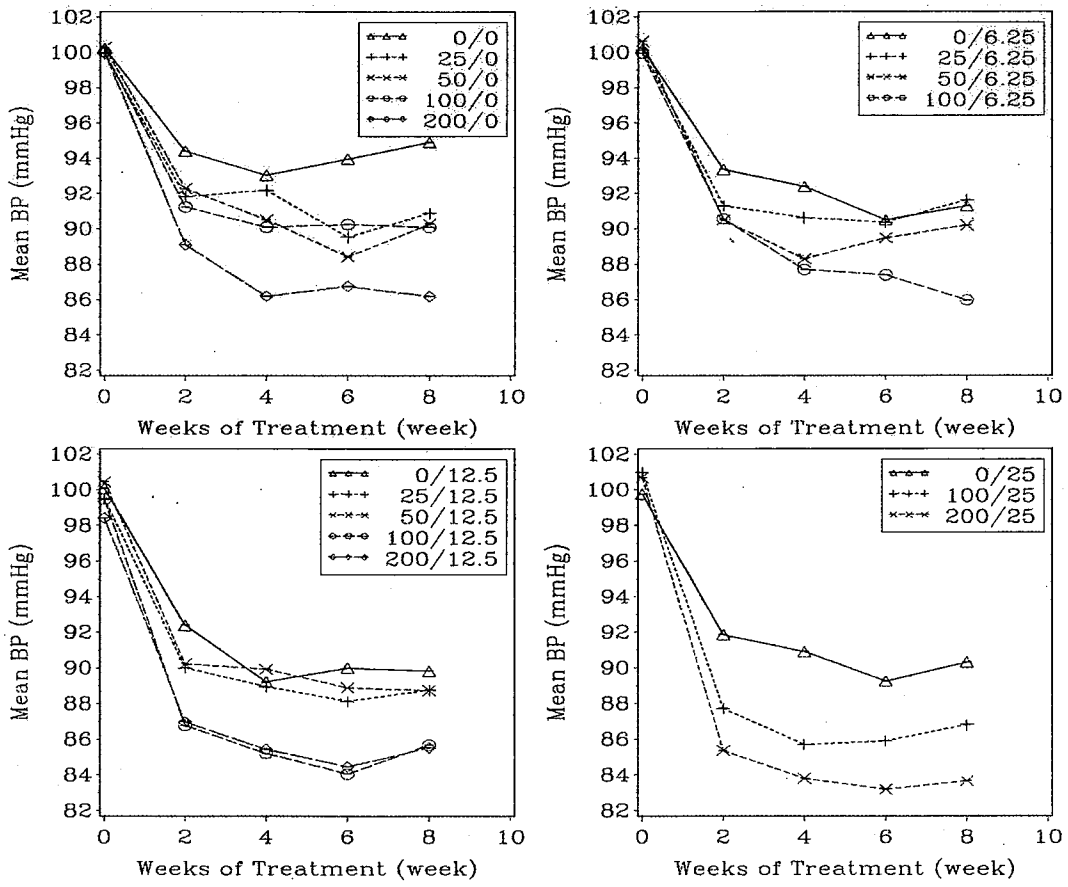
Blood Pressure response over time

Blood pressure declines were evident within 2 weeks of exposure and were maintained thereafter. The blood pressure lowering 24 hours post dosing retained approximately 96% of the peak (6 hours post dosing) effect. The antihypertensive effect was similar regardless of age or gender, and overall response to the metoprolol succinate extended release and hydrochlorothiazide combination was similar in black and non-black patients (Figures 6-9; Tables 5 and 22)

Diastolic Blood Pressure

As the figure 2 below illustrates, mean SiDBP declined within the first 2 weeks with all treatments. These reductions were generally maintained until the end of treatment at Week 8. The figure implies that mean SiDBP values less than 90 mmHg were attainable with several of the active treatments including the Toprol-XL/HCT 50/6.25 mg, Toprol-XL/HCT 100/6.25 mg and all the Toprol-XL combinations with HCT 12.5 mg and with HCT 25 mg.

Figure 4: Trough SiDBP over time from baseline to week 8 - ITT- Study 324



Systolic Blood Pressure

As the figure 3 illustrates, mean SiSBP declined within the first 2 weeks with all treatments. These reductions were generally maintained until the end of treatment at Week 8. The figure implies that mean SiSBP values less than 140 mmHg were attainable with several of the active treatments including the Toprol-XL/HCT 50/6.25 mg, Toprol-XL/HCT 100/6.25 mg and all the Toprol-XL combinations with HCT 12.5 mg and with HCT 25 mg.

Figure 5: Trough SiSBP over time - from baseline to week 8 - ITT

Figure 6 Trough SiSBP over time (intention-to-treat population)

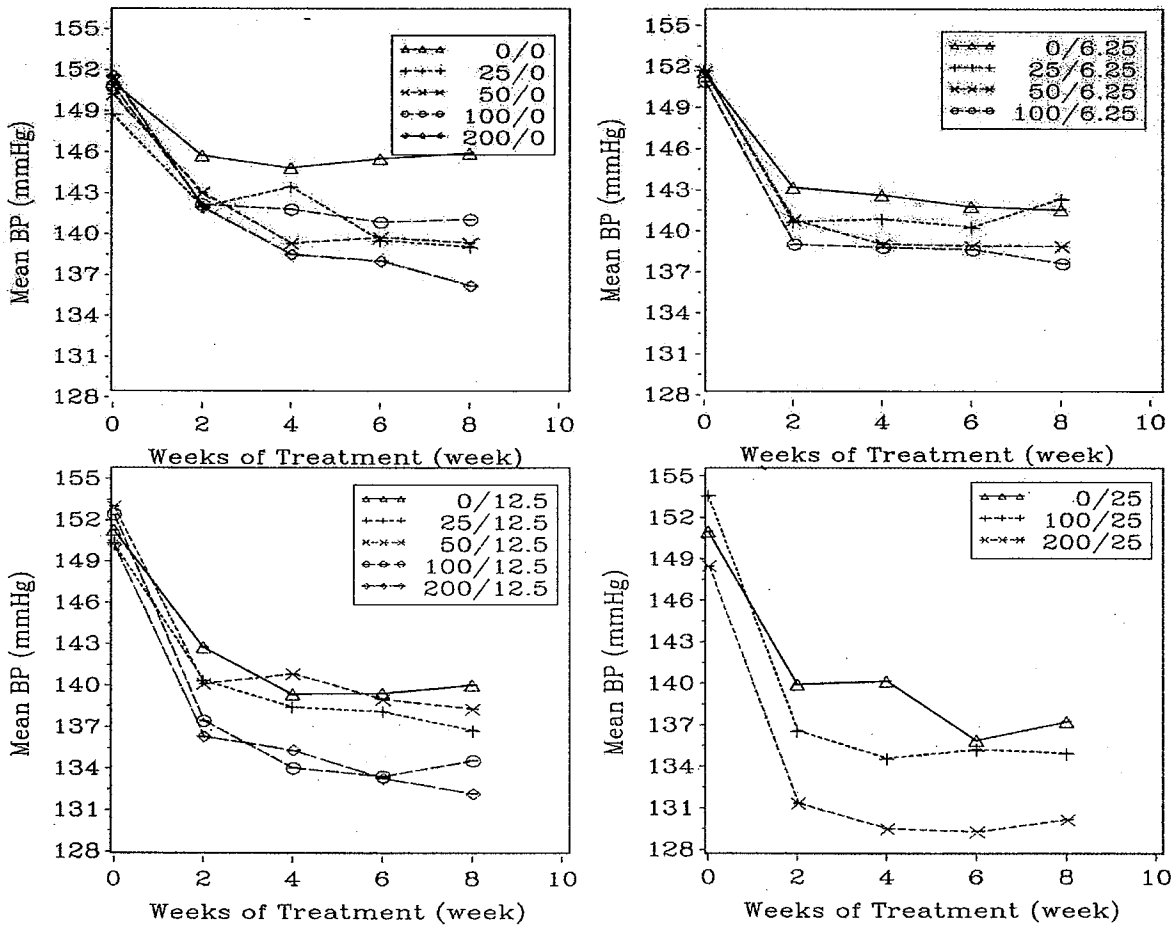


Table 20: Descriptive assessment of additivity for SiDBP from baseline to week 8 - ITT- Study 324

Table 29 Descriptive assessment of additivity based upon placebo-adjusted mean changes from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)

	HCT dosage	Toprol-XL dosage			
Trough SiDBP		**25 mg**	**50 mg**	**100 mg**	**200 mg**
Sum of mean changes for monotherapies (expected change if treatments are additive)	6.25 mg	–7.35	–8.54	–8.75	–12.11
	12.5 mg	–8.80	–9.99	–10.2	–13.56
	25.0 mg	–8.51	–9.70	–9.91	–13.27
Observed mean change for combinations	6.25 mg	–3.43	–5.83	–8.45	NA
	12.5 mg	–5.59	–6.61	–9.17	–8.30
	25.0 mg	NA	NA	–9.35	–12.24
Difference (observed minus expected)	6.25 mg	3.92	2.71	0.30	NA
	12.5 mg	3.21	3.38	1.03	5.26
	25.0 mg	NA	NA	0.56	1.03

Note: Values are placebo-adjusted. If the difference is negative, then the combination had a greater than additive effect; if the difference is positive, then the combination had a less than additive effect.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure.
Data derived from Table 11.2.2.1.6, Section 11.2.

The point estimates for the combination examined in this study are provided below. All confidence limits are negative, indicating that all studied treatments were desirable according to the regression model. As an example, the Toprol-XL/HCT 25/6.25 mg treatment yielded, with 95% confidence, at least –0.56 mmHg more in the change from baseline to Week 8/LOCF in trough SiDBP than Toprol-XL 25 mg alone, HCT 6.25 mg alone, and placebo. Similarly, the Toprol-XL/HCT 100/25 mg treatment provided, with 95% confidence, at a minimum, an additional –1.53 mmHg over Toprol-XL 100 mg alone, HCT 25 mg alone, and placebo.

Table 21: Point estimates for trough SiDBP ITT-Study 324

Table 32 Point estimates for the upper 95% confidence surface based upon the final polynomial regression for changes from baseline to Week 8/LOCF for trough SiDBP (intent-to-treat population)

	HCT dosage	Toprol-XL dosage			
Trough SiDBP		**25 mg**	**50 mg**	**100 mg**	**200 mg**
Upper 95% confidence surface	6.25 mg	–0.56	–0.64	–0.64	NA
	12.5 mg	–0.56	–1.15	–1.45	–1.45
	25.0 mg	NA	NA	–1.53	–1.53

Note: The upper confidence surface represents the maximum of the confidence points for comparisons of combination to each monotherapy and to placebo, based upon the final weighted least squares polynomial regression model.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure
Data derived from Table 11.2.2.1.16, Section 11.2.

The 95% confidence surface for this analysis was constructed for the entire dose region, even those combinations not specifically examined in this study. Figure 5 provides a contour plot representing the 95% confidence surface over the dosage area. As can be seen in the figure, the contours are all negative, indicating that all combinations in these dose ranges performed better than both monotherapies and placebo.

The response surface model predicts placebo-corrected reductions in SiSBP/SiDBP ranging from 5.5/3.3 mmHg for the Toprol-XL/HCT 25/6.25 mg combination to 14.7/10.4 mmHg for the 200/25 mg combination. It also implies that all combinations induce numerically greater SiDBP reductions than either of the components.

Changes in trough standing and peak sitting blood pressures were generally consistent with the results for trough SiDBP and SiSBP. The peak to trough ratios at Week 8/LOCF across all treatment groups indicated that approximately 96% to 99% of the BP lowering effect at peak was still apparent at trough.

In accordance with federal regulations (US Code of Federal Regulations CFR 300.50), this study was designed to test the hypothesis that the antihypertensive effect of at least 1 Toprol- XL/HCT combination was greater than both of its monotherapy components. It was also constructed to examine the independent antihypertensive effects of each monotherapy and their combinations over a broad range of doses.

By using the T_{AVE} statistic as the primary analysis, it was shown that at least 1 combination treatment exceeded the reductions of both monotherapy components of Toprol-XL and HCT for both trough SiDBP and SiSBP. The results of this analysis were confirmed by the pairwise comparisons based upon the ANCOVA model, when even after adjustment for multiplicity, the Toprol-XL/HCT 100/12.5 mg treatment remained significantly better in reducing trough SiDBP and SiSBP than both the Toprol-XL 100 mg treatment and the HCT 12.5 mg treatment.

In addition, the ANCOVA analysis demonstrated that all combination treatments were significantly better than placebo in reducing trough SiDBP and SiSBP from baseline to Week 8/LOCF. It further showed that 3 Toprol-XL/HCT low-dose combination groups (25/12.5 mg, 50/6.25 mg, and 50/12.5 mg) had comparable effectiveness for both trough SiDBP and SiSBP versus the high-dose HCT group (HCT 25 mg). Although the 2 drugs were not fully additive at the extreme ends of the dosage range, particularly for the Toprol-XL/HCT 25/6.25 mg group and the 200/12.5 mg group, the combinations with Toprol-XL 100 mg (Toprol-XL/HCT 100/6.25 mg, 100/12.5 mg, 100/25 mg) were almost fully additive.

The second regulatory guidance suggests to characterize dose response and Study 324 did so by fitting response surface models.

According to a regression model that contained both linear and quadratic terms for the dosage strengths of the 2 drugs, reductions in trough SiDBP and SiSBP increased with increasing doses of each drug. There was no significant interaction between the drugs and the model predicted

greater BP lowering with the combination than the components across the entire range of doses studied (Figures 3 and 21)

Changes from baseline to Week 8/LOCF in trough StDBP and StSBP and peak SiDBP and SiSBP were also examined. Although the results of analyses on these variables were not exactly the same, they were generally consistent with the results for trough SiDBP and SiSBP.

Trough to peak ratios for SiDBP and SiSBP had values very close to 1 and changed little from baseline to Week 8/LOCF for all treatment groups, implying that treatment effects applied almost equally to both trough and peak BPs.

Subgroup Analyses: Age, Gender and Race
According to subgroup analyses of both trough SiDBP and SiSBP, there was some evidence that females had greater reductions than males. Additionally, Black patients appeared to have smaller reductions than non-Black patients; however, increasing HCT dosage strengths appeared to cancel out this difference; Black patients responded somewhat better to HCT.

ANCOVA analyses demonstrated that all combinations were significantly better than placebo in reducing trough SiDBP and SiSBP. In pairwise comparisons of combinations versus their components, the decline in SiDBP was numerically greater for all combinations except for Toprol-XL/HCT 25/6.25 mg. Four treatment combinations (Toprol-XL/HCT 100/6.25 mg, 100/12.5 mg, 100/25 mg, and 200/25 mg) had significantly greater reductions than both of their respective components, at a nominal 0.05 significance level.

Pairwise comparisons also indicated that 4 low dose Toprol-XL/HCT combinations (25/6.25 mg, 25/12.5 mg, 50/6.25 mg, and 50/12.5 mg) were approximately as effective as at least 1 of the high dose monotherapies.

Subgroup analyses of trough SiDBP and SiSBP suggested greater blood pressure reductions for women than men but the difference was small. Black patients appeared to be slightly more responsive to HCT alone and non-Black patients were more responsive to Toprol-XL alone, which was reflected in the combination treatments.

	Trough Sitting DBP		Trough Sitting SBP	
	Black	Non-black	Black	Non-black
P-value	0.2085	0.0217*	0.1779	0.0178*

*Statistically significant at an α=0.025

Table 22: Distribution of randomized patients by age sex and race- ITT-Study 324

		Toprol-XL dosage					
Trough SiDBP	**HCT mg**	**0 mg**	**25 mg**	**50 mg**	**100 mg**	**200 mg**	**Total**
ITT, N	0	152	89	93	95	51	1559
	6.25	86	144	136	45	NA	
	12.5	104	141	147	94	43	
	25	48	NA	NA	42	49	
Age (yrs) n, Mean (SD)							
<65	0	124, –5 (9)	79, –8 (9)	80, –9 (8)	75, –10 (8)	45, –13 (9)	1312, –10 (9)
	6.25	68, –8 (8)	127, –8 (8)	108, –10 (8)	40, –13 (10)	NA	
	12.5	87, –10 (9)	121, –9 (8)	125, –11 (9)	71, –13 (7)	34, –12 (9)	
	25	42, –9 (7)	NA	NA	40, –13 (10)	46, –17 (9)	
≥65	0	28, –3 (8)	10, –9 (7)	13, –9 (5)	20, –8 (10)	6, –8 (13)	247, –10 (9)
	6.25	18, –9 (8)	17, –9 (9)	28, –10 (8)	5, –13 (8)	NA	
	12.5	17, –10 (10)	20, –15 (7)	22, –12 (8)	23, –14 (6)	9, –16 (8)	
	25	6, –12 (12)	NA	NA	2, –24 (16)	3, –6 (6)	
Sex n, Mean (SD)							
Male	0	83, –3 (9)	39, –9 (8)	51, –8 (8)	55, –9 (9)	28, –14 (9)	799, –9 (9)
	6.25	45, –8 (8)	72, –6 (8)	65, –10 (8)	25, –12 (10)	NA	
	12.5	51, –9 (7)	70, –9 (8)	86, –11 (9)	46, –12 (8)	19, –12 (11)	
	25	22, –7 (7)	NA	NA	22, –13 (11)	20, –14 (9)	
Female	0	69, –5 (8)	50, –7 (10)	42, –10 (7)	40, –10 (7)	23, –11 (11)	760, –10 (9)
	6.25	41, –8 (8)	72, –9 (8)	71, –11 (7)	20, –13 (9)	NA	
	12.5	53, –11 (10)	71, –11 (8)	61, –10 (8)	48, –15 (6)	24, –13 (7)	
	25	26, –11 (8)	NA	NA	20, –15 (9)	29, –19 (10)	
Race, n, Mean (SD)							
Black	0	41, –3 (10)	22, –3 (8)	26, –7 (8)	23, –7 (8)	11, –10 (9)	392, –8 (9)
	6.25	21, –10 (9)	37, –6 (9)	33, –8 (8)	12, –10 (12)	NA	
	12.5	23, –8 (6)	43, –10 (8)	33, –12 (9)	19, –13 (8)	15, –11 (6)	
	25	13, –11 (10)	NA	NA	8, –8 (10)	12, –20 (11)	
Non-Black	0	111, –5 (8)	67, –9 (9)	67, –10 (7)	72, –10 (8)	40, –13 (10)	1167, –10 (9)
	6.25	65, –8 (8)	107, –9 (8)	103, –11 (8)	33, –14 (8)	NA	
	12.5	81, –10 (9)	98, –10 (8)	114, –11 (8)	75, –14 (7)	28, –13 (10)	
	25	35, –9 (7)	NA	NA	34, –15 (10)	37, –16 (9)	

Data derived from Table 11.2.8.1, Section 11.2.

Figure 6: Pairwise comparison between racial groups-Trough SiDBP-Study 324

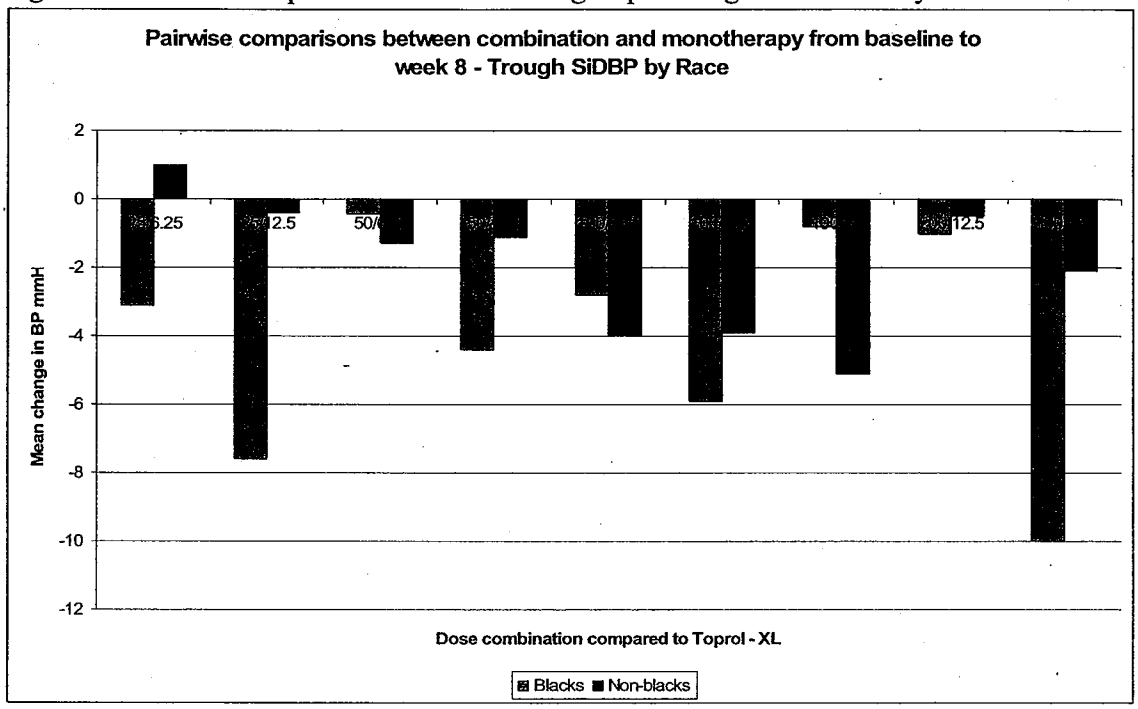


Figure 7:Pairwise comparison between racial groups- Trough SiDBP-Study 324

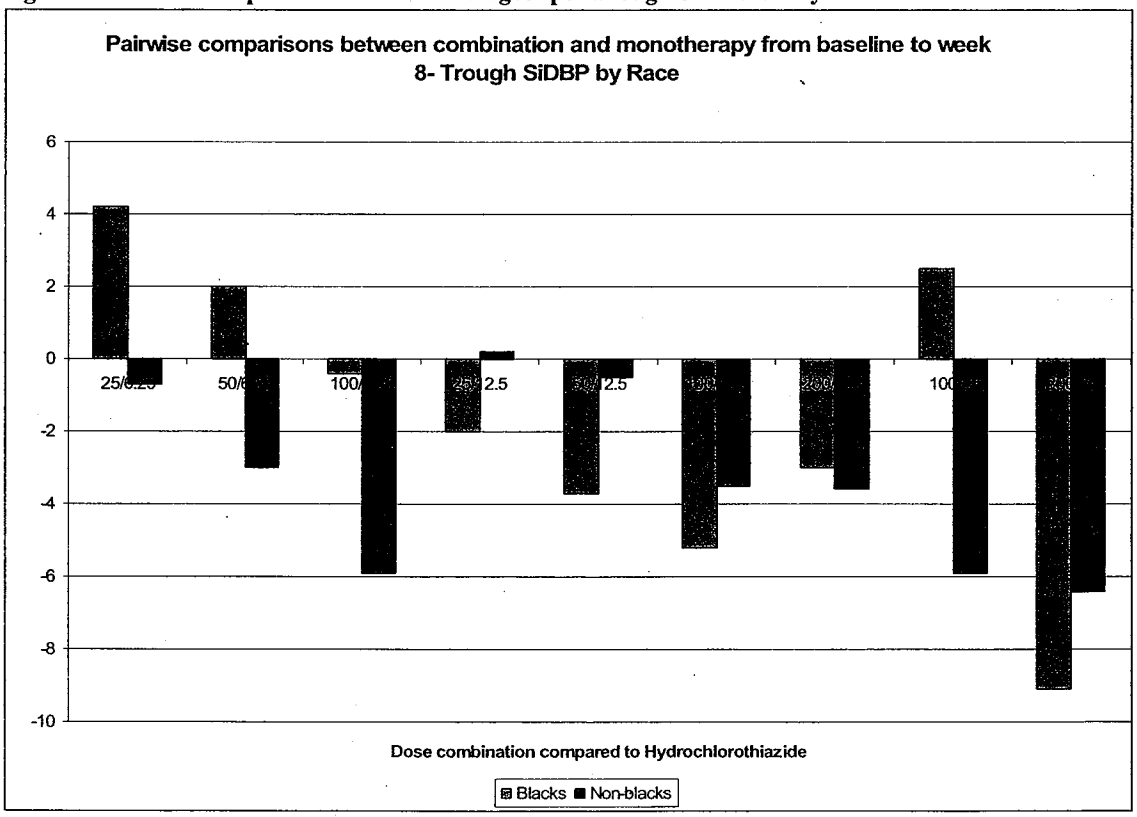


Figure 8:Pairwise comparisons between racial groups - Trough SiSBP-Study 324

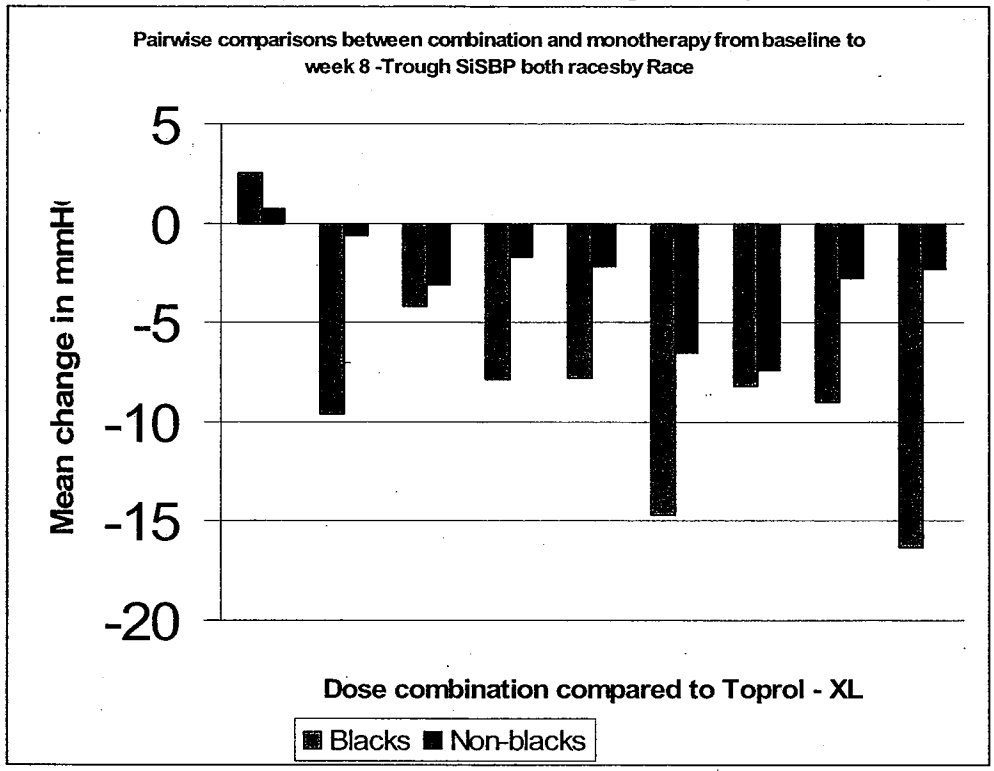
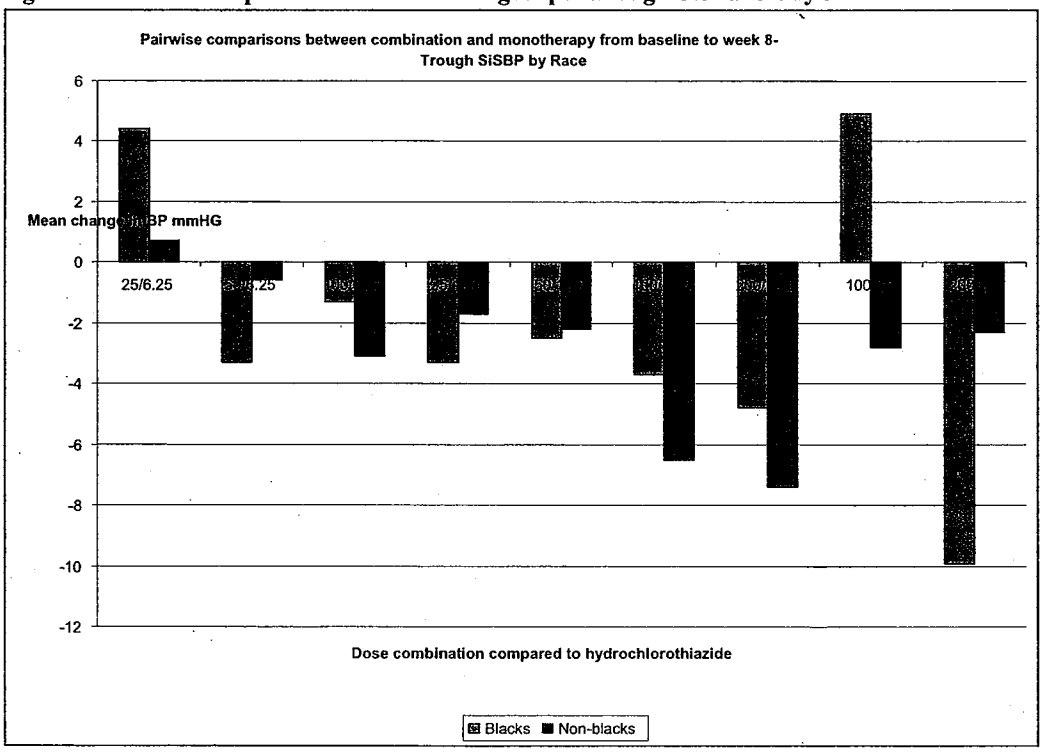


Figure 9:Pairwise comparison between racial groups- Trough SiSBP-Study 324



Responder analyses

Table 23: Number (%) of controlled patients at week 8 - ITT- Study 324

Table 52 Number (%) of controlled patients at Week 8 (intent-to-treat population)

Treatment group	N	Number and % of controlled patients	95% CI	Percentage difference from placebo	95% CI	P-value
Toprol-XL/HCT, 100/25.0 mg	42	20 (47.6)	25.73, 69.51	33.8	17.73, 49.87	<0.0001
Toprol-XL/HCT, 200/12.5 mg	43	26 (60.5)	41.67, 79.26	46.6	31.04, 62.26	<0.0001
Toprol-X/HCT, 200/25.0 mg	49	32 (65.3)	48.81, 81.80	51.5	37.08, 65.90	<0.0001

Note: A patient was controlled if SiDBP was less than 90 mmHg and SiSBP was less than 140 mmHg at Week 8. No DBP values were carried forward. A patient with no value at Week 8 was analyzed as not controlled.
Data derived from Table 11.2.9.2, Section 11.2.

Table 24: Number (%) of responders at week 8 - ITT- Study 324

Table 51 Number (%) of responders at Week 8 (intent-to-treat population)

Treatment group	N	Number and % of responders	95% CI	Percentage difference from placebo	95% CI	P-value
Toprol-XL, HCT 0/0 mg	152	43 (28.3)	14.83, 41.75			
Toprol-XL, 25 mg	89	45 (50.6)	35.95, 65.17	22.3	9.66, 34.89	0.0005
Toprol-XL, 50 mg	93	51 (54.8)	41.18, 68.50	26.5	14.16, 38.94	<0.0001
Toprol-XL, 100 mg	95	44 (46.3)	31.58, 61.05	18.0	5.70, 30.35	0.0041
Toprol-XL, 200mg	51	33 (64.7)	48.40, 81.01	36.4	21.47, 51.36	<0.0001
HCT, 6.25 mg	86	43 (50.0)	35.06, 64.94	21.7	8.95, 34.48	0.0009
HCT, 12.5 mg	104	52 (50.0)	36.41, 63.59	21.7	9.73, 33.69	0.0004
HCT, 25.0 mg	48	23 (47.9)	27.50, 68.33	19.6	3.78, 35.47	0.0152
Toprol-XL/HCT, 25/6.25 mg	144	67 (46.5)	34.58, 58.47	18.2	7.39, 29.08	0.0010
Toprol-XL/HCT, 25/12.5 mg	141	82 (58.2)	47.48, 68.83	29.9	19.02, 40.71	<0.0001
Toprol-XL/HCT, 50/6.25 mg	136	72 (52.9)	41.41, 64.47	24.7	13.62, 35.68	<0.0001
Toprol-XL/HCT, 50/12.5 mg	147	89 (60.5)	50.39, 70.70	32.3	21.59, 42.92	<0.0001
Toprol-XL/HCT, 100/6.25 mg	45	35 (77.8)	64.00, 91.55	49.5	35.39, 63.59	<0.0001
Toprol-XL/HCT, 100/12.5 mg	94	63 (67.0)	55.41, 78.63	38.7	26.83, 50.63	<0.0001
Toprol-XL/HCT, 100/25.0 mg	42	27 (64.3)	46.21, 82.36	36.0	19.83, 52.16	<0.0001
Toprol-XL/HCT, 200/12.5 mg	43	32 (74.4)	59.30, 89.54	46.1	31.25, 61.01	<0.0001
Toprol-X/HCT, 200/25.0 mg	49	36 (73.5)	59.05, 87.89	45.2	30.89, 59.47	<0.0001

Secondary Objectives

Reduction of Systolic Blood Pressure

Table 25: Mean changes in trough SiSBP baseline to week 8 by age sex and race- ITT- Study 324

Table 55 Mean (SD) for changes from baseline to Week 8/LOCF in trough SiSBP for selected subgroups: age, sex, and race (intent-to-treat population)

		Toprol-XL dosage					
Trough SiSBP	**HCT**	**0 mg**	**25 mg**	**50 mg**	**100 mg**	**200 mg**	**Total**
ITT group, N	0	152	89	93	95	51	1559
	6.25	86	144	136	45	NA	
	12.5	104	141	147	94	43	
	25	48	NA	NA	42	49	
Age (yrs), n, Mean (SD)							
<65	0	124, –4 (14)	79, –8 (14)	80, –10 (16)	75, –9 (14)	45, –14 (14)	1312, –11 (14)
	6.25	68, –9 (11)	127, –8 (13)	108, –13 (13)	40, –12 (14)	NA	
	12.5	87, –10 (13)	121, –11 (13)	125, –13 (14)	71, –18 (14)	34, –17 (14)	
	25	42, –13 (12)	NA	NA	40, –17 (15)	46, –19 (15)	
≥65	0	28, –2 (15)	10, –8 (27)	13, –4 (16)	20, –8 (18)	6, –4 (20)	247, –10 (17)
	6.25	18, –9 (12)	17, –12 (18)	28, –12 (12)	5, –13 (21)	NA	
	12.5	17, –8 (21)	20, –17 (15)	22, –16 (13)	23, –15 (17)	9, –17 (10)	
	25	6, –18 (20)	NA	NA	2, –30 (34)	3, –<1 (2)	
Sex, n, Mean (SD)							
Male	0	83, –2 (15)	39, –6 (17)	51, –9 (17)	55, –8 (15)	28, –15 (15)	799, -10 (15)
	6.25	45, –9 (12)	72, –6 (13)	65, –13 (13)	25, –12 (12)	NA	
	12.5	51, –8 (15)	70, –10 (11)	86, –13 (15)	46, –15 (14)	19, –19 (14)	
	25	22, –10 (14)	NA	NA	22, –14 (14)	20, –16 (17)	
Female	0	69, –4 (14)	50, –10 (15)	42, –9 (15)	40, –10 (13)	23, –11 (15)	760, -12 (15)

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Table 26: Mean differences in SiDBP between combination and comparator - ITT - Study 324

Combination treatment group	Comparator monotherapy	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Toprol-XL, 25 mg	0.02	-2.19, 2.23	0.9858
Toprol-XL/HCT, 25/12.5 mg	Toprol-XL, 25 mg	-2.20	-4.42, 0.01	0.0516
Toprol-XL/HCT, 50/6.25 mg	Toprol-XL, 50 mg	-1.17	-3.37, 1.03	0.2986
Toprol-XL/HCT, 50/12.5 mg	Toprol-XL, 50 mg	-1.97	-4.14, 0.20	0.0753
TOPROL-X/HCTL, 100/6.25 mg	Toprol-XL, 100 mg	-3.63	-6.59, -0.67	0.0163
TOPROL-X/HCT, 100/12.5 mg	Toprol-XL, 100 mg	-4.39	-6.77, -2.01	0.0003
Toprol-XL/HCT, 100/25 mg	Toprol-XL, 100 mg	-4.42	-7.45, -1.39	0.0043
Toprol-XL/HCT, 200/12.5 mg	Toprol-XL, 200 mg	-0.27	-3.66, 3.12	0.8749
Toprol-XL/HCT, 200/25 mg	Toprol-XL, 200 mg	-3.98	-7.25, -0.71	0.0173
Toprol-XL/HCT, 25/6.25 mg	HCT, 6.25 mg	0.48	-1.75, 2.71	0.6718
Toprol-XL/HCT, 50/6.25 mg	HCT, 6.25 mg	-1.87	-4.12, 0.39	0.1046
Toprol-XL/HCT, 100/6.25 mg	HCT, 6.25 mg	-4.56	-7.57, -1.55	0.0030
Toprol-XL/HCT, 25/12.5 mg	HCT, 12.5 mg	-0.27	-2.39, 1.84	0.8000
Toprol-XL/HCT, 50/12.5 mg	HCT, 12.5 mg	-1.20	-3.30, 0.89	0.2613
Toprol-XL/HCT, 100/12.5 mg	HCT, 12.5 mg	-3.86	-6.19, -1.53	0.0012
Toprol-XL/HCT, 200/12.5 mg	HCT, 12.5 mg	-3.10	-6.07, -0.13	0.0409
Toprol-XL/HCT, 100/25 mg	HCT, 25 mg	-4.14	-7.60, -0.69	0.0189
Toprol-XL/HCT, 200/25 mg	HCT, 25 mg	-7.06	-10.39, -3.74	<0.0001

Note: Based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction of Toprol-XL and

1.3.5 Safety

Safety measures included Adverse events (AEs), AEs leading to discontinuation, serious adverse events (SAEs), laboratory measures, heart rate, physical examinations, and electrocardiographic findings.

The safety population consisted of all patients (N= 1564) who received at least 1 dose of the investigational product and for whom post-dose data are available.

- Exposure data show that, on average, placebo run-in lasted 30 days, double-blind treatment 55 days, and down titration/follow-up lasted 15 days.

- Safety data show that no deaths occurred during the study.

- An analysis of AEs found that 42% of patients had at least 1 treatment-emergent adverse event (TEAE); the most common of these were as follows: headache (6.2%), upper respiratory tract infection (3.9%), and nasopharyngitis (2.6%).

- An analysis of treatment emergent SAEs and discontinuations due to AEs show that the rates were low: 1.5% and 2.9%, respectively.

- Two SAEs occurred in more than 1 patient during the study: coronary artery disease (3 patients) and myocardial infarction (3 patients) (1 patient had both events). The coronary artery disease and MIs were not temporally related to abrupt cessation of beta-blocker treatment (1 MI occurred during down titration, and 2 MIs and 3 coronary artery diseases occurred either the last day of treatment or the day after treatment was stopped).

- The most common AEs leading to treatment discontinuation were headache (5 patients, 0.3%), with erectile dysfunction, fatigue, and hypertension each occurring in 0.2% of patients.

- Analyses also show that there were no notable clustering of AEs in any 1 treatment group. Headache occurred at comparable frequencies across all treatment groups including placebo. There were no appreciable 'additive' safety findings with the possible exception of fatigue, which occurred at high dose HCT in combination with Toprol-XL, most notably in combination with high dose (200 mg) Toprol-XL.

- An analysis of laboratory data found that serum potassium declined, while serum uric acid and blood urea nitrogen increased with increasing doses of HCT, largely independent of the Toprol-XL dose; there was a small dose-related decline in HDL-cholesterol with Toprol-XL; triglyceride levels increased slightly with both HCT and Toprol-XL and the combinations tended to reflect the effects of both agents. Neither Toprol-XL, HCT, nor their combinations were associated with consistent changes in blood glucose whether for the whole population or for patients with diabetes. Also,

neither Toprol-XL, HCT, nor their combinations were associated with consistent changes in serum sodium.

- Analyses of ECG and physical examinations data show the expected slowing of heart rate at higher doses of Toprol-XL but no patient was discontinued due to bradycardia. Otherwise, the findings indicate no clinically meaningful changes with any of the treatments.

- A total of 24 patients (1.5%) had least 1 SAE during the trial. A total of 5 patients had a manifestation of coronary artery disease (3 had myocardial infarction). None of these events appeared to be temporally related to abrupt cessation of beta-blocking treatment.

1.3.6 Dosing Regimen and Administration

Investigational product and comparator(s): dosage and mode of administration: HCT tablet strengths were 6.25 mg, 12.5 mg, and 25 mg. Toprol-XL tablet strengths were 25 mg and 100 mg. The drug was packaged in a 'double-dummy' fashion that required all patients to take 5 tablets once daily.

Investigational product and comparator(s): dosage and mode of administration: HCT tablet strengths were 6.25 mg, 12.5 mg, and 25 mg. Toprol-XL tablet strengths were 25 mg and 100 mg. The drug was packaged in a 'double-dummy' fashion that required all patients to take 5 tablets once daily. Placebo tablets identical in appearance to each of the investigational product strengths served as a comparator.

Table 27: Investigational products including batch numbers, dosage and strengths

Active treatments (investigational product or other treatment)	Dosage form and strength	Batch number for active treatments	Batch number for matching placebo[a]	Manufacturer for active treatments and placebo
Toprol-XL	25 mg	H 0960-10-01-02	H 1014-03-01-01 H 1014-03-01-02 H 1014-03-01-03	AstraZeneca, Sweden
Toprol-XL	100 mg	H 0585-25-03-07	H 0737-04-01-05 H 0737-04-01-06	AstraZeneca, Sweden
Hydrochlorothiazide, USP	6.25 mg	H 1651-01-01-03	H 1654-01-01-01	AstraZeneca, Sweden
Hydrochlorothiazide, USP	12.5 mg	H 1652-01-01-02	H 1654-01-01-01	AstraZeneca, Sweden
Hydrochlorothiazide, USP	25.0 mg	H 1653-01-01-02	H 1654-01-01-01	AstraZeneca, Sweden

[a] Placebo tablets that were identical in appearance to each investigational product strength in the study served as the comparator.

1.3.7 Drug-Drug Interactions

Drug Interactions

Metoprolol

Catecholamine-depleting drugs (eg, reserpine, mono-amine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Patients treated with

TOPROL-XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.37 Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive metabolizer phenotype, coadministration of quinidine 100 mg and immediate release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.
Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

Hydrochlorothiazide
When administered concurrently the following drugs may interact with thiazide diuretics:
Alcohol, barbiturates, or narcotics – Potentiation of orthostatic hypotension may occur.
See Biopharm review.

1.3.8 Special Populations

The following are special populations studied in this submission.

- The Elderly (age)..... See Table 22
- Diabetes ..... See Table 28
- Populations with SiDBP <100 and >100 mm Hg SiDBP and SiSBP <145 and > 145 mm Hg. See table 28

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Table 28: Mean changes in blood pressure from baseline to week 8 by diabetes and level of blood pressure - ITT- Study 324

Table 56 Mean (SD) for changes from baseline to Week 8/LOCF in trough SiSBP for selected subgroups: SiDBP, SiSBP, and diabetes mellitus (intent-to-treat population)

Trough SiSBP	HCT dose	Toprol-XL dosage					Total
		0 mg	25 mg	50 mg	100 mg	200 mg	
Baseline trough SiDBP, mmHg, n, Mean (SD)							
<100	0 mg	86, –2 (15)	53, –9 (17)	50, –8 (15)	51, –9 (13)	29, –11 (15)	904, –10 (15)
	6.25 mg	49, –8 (12)	82, –8 (14)	71, –11 (14)	29, –12 (13)	NA	
	12.5 mg	60, –9 (14)	89, –13 (14)	79, –13 (17)	61, –17 (13)	34, –14 (12)	
	25 mg	33, –12 (11)	NA	NA	23, –15 (16)	25, –21 (14)	
≥100	0 mg	66, –4 (14)	36, –8 (15)	43, –11 (17)	44, –8 (16)	22, –16 (15)	655, –12 (15)
	6.25 mg	37, –10 (10)	62, –9 (14)	65, –15 (11)	16, –12 (17)	NA	
	12.5 mg	44, –11 (16)	52, –10 (13)	68, –14 (11)	33, –19 (18)	9, –26 (11)	
	25 mg	15, –17 (17)	NA	NA	19, –21 (15)	24, –14 (17)	
Baseline trough SiSBP, mmHg, n, Mean (SD)							
<145	0 mg	58, <1 (11)	37, –5 (17)	29, –3 (12)	31, –3 (12)	21, –6 (9)	531, –6 (12)
	6.25 mg	27, –2 (8)	46, –2 (12)	47, –7 (12)	15, –12 (8)	NA	
	12.5 mg	33, –3 (12)	51, –8 (8)	39, –8 (13)	31, –11 (12)	16, –12 (10)	
	25 mg	18, –7 (8)	NA	NA	10, –7 (16)	22, –14 (17)	
≥145	0 mg	94, –5 (16)	52, –10 (15)	64, –12 (17)	64, –11 (15)	30, –18 (17)	1028, –14 (15)
	6.25 mg	59, –12 (11)	98, –11 (14)	89, –16 (12)	30, –12 (17)	-NA	
	12.5 mg	71, –13 (15)	90, –15 (15)	108, –15 (14)	63, –21 (15)	27, –20 (14)	
	25 mg	30, –18 (14)	NA	NA	32, –21 (14)	27, –21 (14)	
Diabetes mellitus, n, Mean (SD)							
Yes	0 mg	10, –5 (12)	6, –15 (21)	9, –13 (16)	9, –7 (14)	3, –23 (14)	152, –13 (16)
	6.25 mg	9, –8 (10)	12, –9 (14)	18, –13 (15)	6, 1 (16)	NA	
	12.5 mg	14, –17 (15)	13, –19 (14)	12, –9 (22)	8, –23 (16)	9, –17 (16)	
	25 mg	7, –17 (15)	NA	NA	4, –19 (17)	3, –<1 (36)	
No	0 mg	142, –3 (15)	83, –8 (16)	84, –9 (16)	86, –9 (15)	48, –13 (15)	1407, –11 (15)
	6.25 mg	77, –9 (11)	132, –8 (14)	118, –13 (12)	39, –14 (13)	NA	
	12.5 mg	90, –9 (14)	128, –11 (13)	135, –14 (13)	86, –17 (15)	34, –17 (12)	
	25 mg	41, –13 (13)	NA	NA	38, –17 (16)	46, –19 (13)	

NA Not applicable.

2 INTRODUCTION AND BACKGROUND

Lowering blood pressure (BP) with drug therapy dramatically reduces the risk for catastrophic fatal and nonfatal cardiovascular events such as stroke and myocardial infarction (Dahlof et al 1991; Herbert et al 1993; SHEP 1991; Medical Research Council 1992; Collins and MacMahon 1994). Improved control of BP accounts for a substantial portion of the reduction in cardiovascular morbidity and mortality rates that occurred in the US between the years 1976 and 1994 (JNC 7 report 2003).

Numerous drugs from many classes are now available for treating hypertension. There is, however, no universally effective and tolerable antihypertensive drug or combination of drugs. In part, this is related to the heterogeneity of hypertension as a disease but, primarily, it is due to the marked variability in individual patient's BP response and to their side effect experiences. Nonetheless, expert groups such as the Joint National Committee (JNC) recommend antihypertensive regimens likely to prove effective and safe and to prevent the cardiovascular consequences of hypertensive disease. In this regard, JNC 7 includes diuretics and beta-blockers as therapies for patients with hypertension given the extensive clinical trial outcome data supporting the benefits of these agents (JNC 7 report 2003).

Expert groups also acknowledge the value of treating hypertensive patients with more than 1 agent, usually of different classes, as the antihypertensive effects of such regimens tend to be additive. This allows low-dose multi-drug regimes as an alternative to high-dose monotherapy, thereby, avoiding dose-related side effects of the individual agents. Furthermore, there are some patients for whom combinations of agents may be justified as initial treatment (JNC 7 report 2003, Stanton et al 2002).

2.1 PRODUCT INFORMATION

Toprol-XL

Metoprolol succinate extended-release tablet (Toprol-XL) is a beta-1-selective (cardio-selective) adrenoceptor blocking agent formulated to provide controlled and predictable release of metoprolol for once daily administration. It does not have intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at plasma concentrations much higher than required for beta-blocking activity. Toprol-XL is an approved drug in over 55 countries. In the US, approved indications include: treatment of hypertension, either alone or in combination with other products, the long-term treatment of angina pectoris, and the treatment of stable, symptomatic (New York Heart Association [NYHA] Class II to III) heart failure. For hypertension, dosing recommendations suggest a starting dose of 25 mg to 100 mg once daily. Recommendations allow for dose increases to 400 mg once daily but doses above 200 mg daily are rarely used clinically.

Toprol-XL shares the same potential side effects as all other cardio-selective beta-blockers such as bradycardia, aggravation of bronchospastic disease, and fatigue. Abrupt cessation of therapy with certain beta-blocking agents is associated with exacerbations of angina pectoris

and, in some cases, myocardial infarctions have occurred. Due to the release formulation, Toprol-XL tablets cannot be crushed or chewed.

Hydrochlorothiazide

Hydrochlorothiazide (HCT) is a well-established diuretic and antihypertensive agent, which promotes natruresis by acting on the distal renal tubule. This is accompanied by some potassium and bicarbonate loss. Although the antihypertensive mechanism of HCT is not well understood, clinical trials clearly confirm its BP lowering effect when used alone or in combination with other drugs and large clinical trials have established the clinical benefit in terms of preventing hypertensive cardiovascular consequences. The traditional HCT antihypertensive dosage recommendation was 25 mg or 50 mg HCT is a long-recognized effective thiazide diuretic and antihypertensive agent. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing sodium and chloride excretion. There is a consequent reduction in intravascular volume and this is accompanied by an increase in plasma renin activity and an increase in aldosterone secretion (HydroDiuril® Product Insert 1998). Early on, recommended HCT doses for lowering BP ranged from 50 to 100 mg once daily, but more recent information indicates that doses of 12.5 mg and 25 mg and even 6.25 mg are effective (Frishman 1994) and carry a lesser risk for high-dose related metabolic/electrolyte abnormalities. Furthermore, low-dose diuretic regimens are the most beneficial in terms of clinical outcomes (Psaty et al 2003).

Metoprolol is a beta1-selective (cardio-selective) adrenoceptor-blocking agent, long established as an antihypertensive agent. It has been available as a once daily, extended release formulation of the succinate salt in the US since 1992. Agents that block the beta-adrenergic receptor slow heart rate and reduce cardiac output. Blood pressure also declines although the actual causal mechanism is not clearly established. Peripheral resistance tends to Metoprolol succinate ER reduces BP over the range of doses of 25 mg to 400 mg; however, high plasma levels correlate with less selectivity in beta1 blockade. Metoprolol succinate ER can be used in combination with other agents for additive antihypertensive activity.

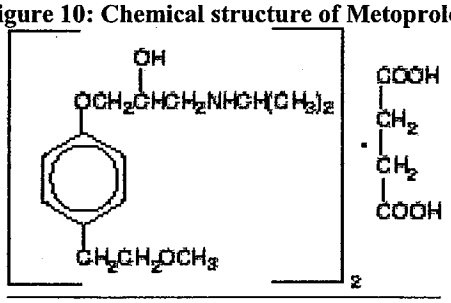
Combining antihypertensive agents into a single drug product is an additional approach geared to improving drug therapy compliance by increasing dosing convenience. Such combination products, when they are available in a variety of dosage strengths, provide the clinician with considerable flexibility in individualizing a patient's treatment.

Taken together, the advantages of combination agents, including diuretics with beta-blockers, may contribute to improved control of hypertension (Moser and Sitar 2004). From a population perspective, even small incremental improvements in BP control may translate into substantially fewer cardiovascular events such as stroke (Cook et al 1995; MacMahon et al 1990).

Product Information

Metoprolol succinate is chemically described as (±) 1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate (2:1) (salt). Its structural formula is]:[1]

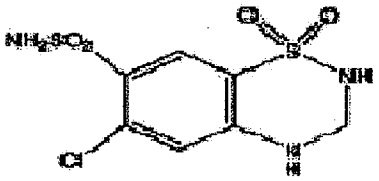
Figure 10: Chemical structure of Metoprolol



Metoprolol succinate is a white crystalline powder with a molecular weight of 652.8. It is freely soluble in water; soluble - in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl-acetate, acetone, diethylether and heptane.[2]

Hydrochlorothiazide is 6-chloro-3, 4-dihydro-2H-1, 2, 4-benzothiadiazine-7-sulfonamide 1, 1-dioxide. Its empirical formula is $C_7H_8ClN_3O_4S_2$ and its structural formula is: [3]

Figure 11: Chemical structure of Hydrochlorothiazide



[3]HydroDIURIL, approved labeling (PI#7897450)

2.2 Currently Available Treatment for Indication - Hypertension

Two trials specifically allowed for the inclusion of the beta-blocker metoprolol succinate ER. The Swedish Trial in Old People with Hypertension (STOP-Hypertension) determined that a treatment regimen of a thiazide diuretic or a beta-blocker (100 mg metoprolol extended release, 50 mg atenolol, or 5 mg pindolol) or their combination reduced blood pressure (BP) and the corresponding risk for the composite endpoint, myocardial infarction, stroke or other cardiovascular death (Dahlof et al 1991). The second Swedish Trial in Old People (STOP- Hypertension 2) indicated that a similar thiazide, beta-blocker, or combination regimen was effective in reducing cardiovascular death and was as beneficial as newer treatment regimens based on angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers (Hansson et al 1999). A number of other trials have also evaluated clinical outcomes in hypertensive patients treated with diuretics plus beta-blockers including the North American ALLHAT trial. This 33,357 patient trial found that a regimen based upon the thiazide diuretic chlorthalidone, and which allowed for the addition of a

beta-blocker as well as other agents, was as effective as antihypertensive regimens based on ACE inhibitors or calcium channel blockers in reducing the risk for fatal/nonfatal myocardial infarction (ALLHAT Officers and Coordinators 2002).

2.3 Availability of Proposed Active Ingredient in the United States

All ingredients for this product are available in the United States.

2.4 Important Issues with Pharmacologically Related Products

Not applicable. There are no important issues with pharmacologically related products known to this reviewer. Two trials have specifically allowed the inclusion of the beta-blocker metoprolol succinate ER. The Swedish Trial in Old People with Hypertension (STOP-Hypertension) determined that a treatment regimen of a thiazide diuretic or a beta-blocker (100 mg metoprolol extended release, 50 mg atenolol, or 5 mg pindolol) or their combination reduced blood pressure (BP) and the corresponding risk for the composite endpoint, myocardial infarction, stroke or other cardiovascular death (Dahlof et al 1991). The second Swedish Trial in Old People (STOP-Hypertension 2) indicated that a similar thiazide, beta-blocker, or combination regimen was effective in reducing cardiovascular death and was as beneficial as newer treatment regimens based on angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers (Hansson et al 1999). A number of other trials have also evaluated clinical outcomes in hypertensive patients treated with diuretics plus beta-blockers including the North American ALLHAT trial.

2.5 Pre-submission Regulatory Activity

AstraZeneca LP (AstraZeneca) has developed a combination product containing metoprolol succinate extended release (trade name is Toprol-XL ®) and hydrochlorothiazide (HCT), for the management of hypertension in adults. AstraZeneca intends to provide a proposed trade name and supportive information for the Division's consideration as an amendment to this NDA in December 2005 to address the Division's comments that were provided on August 19, 2005. NDA 19-962 for Toprol-XL® (metoprolol succinate) ER Tablets was approved on January 10, 1992 for the treatment of hypertension and angina in adults and approval was granted for NDA 19-962/S-013 on February 5, 2001 for the treatment of stable, symptomatic (NYHA Class II or III) heart failure of ischemic, hypertensive, or cardiomyopathic origin. Hydrochlorothiazide is commonly used for the treatment of hypertension and there are several approved combination products with this drug as a component for the treatment of hypertension.

AstraZeneca is pursuing approval for commercial marketing of the tablet strengths of 25/12.5 mg, 50/12.5 mg, and 100/12.5 mg extended release tablets (metoprolol succinate and hydrochlorothiazide, respectively). AstraZeneca does not intend to pursue approval of the 25/6.25 mg extended release tablet of metoprolol succinate and hydrochlorothiazide, respectively, for commercial marketing. The Chemistry, Manufacturing and Controls and Clinical information available for the formulated tablet of 25/6.25 mg and at this dosage is contained in this NDA as supportive information for the intended commercial extended release

tablet strengths of 25/12.5 mg, 50/12.5 mg, and 100/12.5 mg of metoprolol succinate and hydrochlorothiazide, respectively.

Investigational New Drug Application

An End of Phase 2 Briefing Document was submitted to the Division (IND 40,602, Serial No 0235)1 on December 19, 2002. followed by an end of Phase 2 meeting (Type B) on January 24, 2003. At this End of Phase 2 meeting, AstraZeneca provided a detailed plan for a Phase 3 development program, including our proposal for a bioequivalence program, the proposed design of a double-blind controlled factorial clinical study, as well as preliminary pharmaceutical development plans. The Division provided minutes from this End of Phase 2 meeting on February 12, 2003. AstraZeneca also prepared meeting minutes and submitted these minutes to the Division under IND 40,602 for Toprol-XL® (AstraZeneca correspondence dated January 31, 2003; Serial No. 0239) for the End of Phase 2 meeting and subsequently submitted additional reference information for Dr. James Hung regarding 2-D Emax models on March 19, 2003 (IND 40,602; Serial No. 0242).

AstraZeneca submitted an Investigational New Drug application for metoprolol succinate extended release and hydrochlorothiazide tablets on March 17, 2003 (IND 67,095; Serial No. 000).

Interactions between AstraZeneca and the Division during the Development of the Combination Product occurred during the development of metoprolol succinate extended release and hydrochlorothiazide tablets. These include the following:

• April 21, 2004, IND 67,095 - Serial No. 00133; Information Amendment, Clinical - Draft Statistical Analysis Plan for Study Protocol 324 (ATTACH; double-blind placebo-controlled, factorial clinical study) was submitted for the Division's review.

- On December 8, 2004, IND 67,095 = Serial No. 00284; Information Amendment, Clinical – Statistical Analysis Plan for Study Protocol 324 (ATTACH; double-blind, placebo-controlled, factorial clinical study) was submitted to the IND.
- The Division provided comments to AstraZeneca for this Statistical Analysis Plan in correspondence dated January 26, 2005.5 AstraZeneca took these comments into consideration for the analysis of this study.
- On July 8, 2005, IND 67,095 – Serial No. 0033; Information Amendment, Clinical – Clinical Study Report for ATTACH (double-blind placebo-controlled, factorial clinical study) was submitted for the Division's review in order to facilitate the review of the NDA submission and allow for the possibility of the Division completing the NDA review prior to the 10-month PDUFA clock.

Other Relevant Background Information

In addition to the factorial study a supportive study conducted in Denmark and Sweden in 1987-88 (Study S-902, 47 ITT patients – Module 5) evaluated the antihypertensive effect of

metoprolol succinate ER/HCT (100/12.5 mg) in comparison to a conventional metoprolol tartrate/HCT combination in a population remaining hypertensive in spite of treatment with HCT 12.5 mg daily.

Both metoprolol succinate ER and HCT as individual entities, are well-established antihypertensive agents; there is an extensive post-marketing experience in other countries with metoprolol/HCT combination products (commercially available as metoprolol tartrate/HCT and metoprolol succinate ER/HCT), which have been available for over 25 years and 16 years, respectively. Contemporary treatment guidelines increasingly stress the necessity of combination antihypertensive therapy (JNC 7 Report 2003).

Large clinical outcome trials clearly established that diuretic/beta-blocker treatment regimens reduce the risk for the severely debilitating cardiovascular morbidity and mortality associated with hypertension, most notably, the risk for stroke and cardiovascular mortality (Turnbull 2003). Two trials have specifically allowed the inclusion of the beta-blocker metoprolol succinate ER. The Swedish Trial in Old People with Hypertension (STOP-Hypertension) determined that a treatment regimen of a thiazide diuretic or a beta-blocker (100 mg metoprolol extended release, 50 mg atenolol, or 5 mg pindolol) or their combination reduced blood pressure (BP) and the corresponding risk for the composite endpoint, myocardial infarction, stroke or other cardiovascular death (Dahlof et al 1991). The second Swedish Trial in Old People (STOP-Hypertension 2) indicated that a similar thiazide, beta-blocker, or combination regimen was effective in reducing cardiovascular death and was as beneficial as newer treatment regimens based on angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers (Hansson et al 1999).

A number of other trials have also evaluated clinical outcomes in hypertensive patients treated with diuretics plus beta-blockers including the North American ALLHAT trial. This 33,357 patient trial found that a regimen based upon the thiazide diuretic chlorthalidone, and which allowed for the addition of a beta-blocker as well as other agents, was as effective as antihypertensive regimens based on ACE inhibitors or calcium channel blockers in reducing the risk for fatal/nonfatal myocardial infarction (ALLHAT Officers and Coordinators 2002).

Expert groups have called attention to the necessity to combine antihypertensive agents and that usually a thiazide diuretic should be included. Such recommendations are based on the established effectiveness and safety of the agents and their predictable behavior in combination regimens. Furthermore, fixed-dose combination products may lead to better compliance (JNC 7 Report 2003).

Metoprolol is a beta1-selective (cardio-selective) adrenoceptor-blocking agent, long established as an antihypertensive agent. It has been available as a once daily, extended release formulation of the succinate salt in the US since 1992. Agents that block the beta-adrenergic receptor slow heart rate and reduce cardiac output. Blood pressure also declines although the actual causal mechanism is not clearly established. Peripheral resistance tends to Metoprolol succinate ER reduces BP over the range of doses of 25 mg to 400 mg; however, high plasma levels correlate

with less selectivity in beta1 blockade. Metoprolol succinate ER can be used in combination with other agents for additive antihypertensive activity.

Fixed-dose combination tablets of metoprolol tartrate, an immediate release (IR) formulation, with HCT have been available since 1978 and a combination, specifically, of the ER succinate salt of metoprolol and HCT (100/12.5 mg) became available in 1989 and is an approved antihypertensive agent in 11 countries.

Given the above background, and after discussion with the Division of Cardio-Renal Drug Products (End of Phase 2 Meeting, 24 January 2003), AstraZeneca sought to directly address the FDA guidance for combination products by establishing that both HCT and metoprolol succinate ER contribute to the antihypertensive activity of their combination and to describe the corresponding dose response behavior. This goal was addressed with a single factorial clinical trial (the ATTACH study, Assessment of Toprol-XL Taken in Combination with Hydrochlorothiazide, Study 324 with 1,559 patients).

In addition to the factorial study a supportive study conducted in Denmark and Sweden in 1987-88 (Study S-902, 47 ITT patients – Module 5) evaluated the antihypertensive effect of metoprolol succinate ER/HCT (100/12.5 mg) in comparison to a conventional metoprolol tartrate/HCT combination in a population remaining hypertensive in spite of treatment with HCT 12.5 mg daily.

[redacted] fixed combination tablets planned for clinical use in the US include 3 tablet strengths: 25/12.5 mg, 50/12.5 mg, and 100/12.5 mg. The 100/12.5 mg tablet is scored and is divisible to 50/6.25 mg. In addition, a lower dose tablet of metoprolol succinate ER/HCT 25/6.25 mg was developed and investigated in a clinical study but is not planned for marketing.

Pediatric waiver request

On July 28, 2005, AstraZeneca LP submitted a formal request for full pediatric waiver from assessing the safety and effectiveness of [redacted] (metoprolol succinate and hydrochlorothiazide) Extended Release Tablets for hypertension in pediatric patients. Attached is the justification submitted to the FDA.

FDA response of August 16, 2005, granted a waiver for pediatric studies in [redacted] (metoprolol succinate and hydrochlorothiazide) Extended Release Tablets for hypertension under section 2 of the Pediatric Research Equity Act.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Not applicable.

3.2 Animal Pharmacology/Toxicology

Not applicable.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical data

The sources of data are from IND 40,602, 67,095, NDA 19,962 and NDA 21,956 from the EDR. Integrity of data is very good (See Tables 27 to below).

Table 29: List of INDs including indication and dosage regimen

Table 1 List of IND's and NDA's

Application No.	Established Name (Proper name, USP/USAN name)	Proprietary Name (Trade name)	Strength/Dosage Form	Route	Indication	Submission Date	Approval Date
40,602	Metoprolol succinate	TOPROL - XL®	25, 50, 100 and 200 mg ER Tablets	Oral	Oral Treatment of hypertention, long term treatment of angina pectoris and for the treatment of stable symptomatic (NYHA Class II or III) heart failure of ischemic hypertensive, or cardiomyopathic origin.	09/18/92	N/A
67,095	Metoprolol succinate and hydrochlorothiazide, in combination	[redacted]	25, 50, 100 mg ER Tablets	Oral	For the treatment of hypertension	03/17/2003	N/A

Table 30: List of INDs / NDA including indication and dosage regimen

Application No.	Established Name (Proper name, USP/USAN name)	Proprietary Name (Trade name)	Strength/Dosage Form	Route	Indication	Submission Date	Approval Date
19-962	Metoprolol succinate	TOPROL - XL®	25, 50, 100 and 200 mg ER Tablets	Oral	Oral Treatment of hypertention, long term treatment of angina pectoris and for the treatment of stable symptomatic (NYHA Class II or III) heart failure of ischemic hypertensive, or cardiomyopathic origin.	12/22/89	01/10/92

4.2: Tables of Clinical Studies

Table 31: List of clinical studies including objectives and dosage regimen

1. LISTING OF CLINICAL STUDIES

Table 1 Listing of clinical studies									
Type of Study	Study Identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
PK	S-895		To determine (1) the relative oral bioavailability of metoprolol given as a fixed combination of metoprolol CR 100 mg plus HCT 12.5 mg and as metoprolol CR 100 mg alone; and (2) the relative oral bioavailability of HCT given as a fixed combination of metoprolol CR 100 mg plus HCT 12.5 mg, as a HCT 12.5 mg tablet and as Esidrex® 25 mg tablet.	A 4-way, randomized, open, crossover bioavailability study.	Each subject received 4 treatments (>5-day washout in-between): Metoprolol succinate ER 100 mg alone; HCT 12.5 mg (IR) alone, HCT 25 mg [Esidrex®] alone; Fixed-dose combination tablet of metoprolol-succinate ER/HCT 100/12.5 mg Once-daily oral doses for 5 days, for each of 4 treatment periods.	12	Healthy men	20 days	Complete, Full

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ON ORIGINAL

Table 32: List of clinical studies including objectives and dosage regimen

1. LISTING OF CLINICAL STUDIES

Table 1 Listing of clinical studies									
Type of Study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
PK	S-895		To determine (1) the relative oral bioavailability of metoprolol given as a fixed combination of metoprolol CR 100 mg plus HCT 12.5 mg and as metoprolol CR 100 mg alone; and (2) the relative oral bioavailability of HCT given as a fixed combination of metoprolol CR 100 mg plus HCT 12.5 mg, as a HCT 12.5 mg tablet and as Esidrex® 25 mg tablet.	A 4-way, randomized, open, crossover bioavailability study.	Each subject received 4 treatments (>5-day washout in-between): Metoprolol succinate ER 100 mg alone; HCT 12.5 mg (IR) alone, HCT 25 mg [Esidrex®] alone; Fixed-dose combination tablet of metoprolol-succinate ER/HCT 100/12.5 mg Once-daily oral doses for 5 days, for each of 4 treatment periods.	12	Healthy men	20 days	Complete, Full

Table 33: List of clinical studies including objectives and dosage regimen

1. LISTING OF CLINICAL STUDIES

Table 1 Listing of clinical studies									
Type of Study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
PK	S-895		To determine (1) the relative oral bioavailability of metoprolol given as a fixed combination of metoprolol CR 100 mg plus HCT 12.5 mg and as metoprolol CR 100 mg alone; and (2) the relative oral bioavailability of HCT given as a fixed combination of metoprolol CR 100 mg plus HCT 12.5 mg, as a HCT 12.5 mg tablet and as Esidrex® 25 mg tablet.	A 4-way, randomized, open, crossover bioavailability study.	Each subject received 4 treatments (>5-day washout in-between): Metoprolol succinate ER 100 mg alone; HCT 12.5 mg (IR) alone, HCT 25 mg [Esidrex®] alone; Fixed-dose combination tablet of metoprolol-succinate ER/HCT 100/12.5 mg Once-daily oral doses for 5 days, for each of 4 treatment periods.	12	Healthy men	20 days	Complete, Full

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Table 34: List of clinical studies including objectives and dosage regimen

Table 1 Listing of clinical studies									
Type of Study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
PK PD	S-896		To evaluate (1) the relative oral availability of metoprolol and HCT given in the new CR combination compared with the conventional combination, and (2) the effect on exercise tachycardia in relation to placebo after administration of the 2 different combination tablets.	A double-blind, randomized, 3-way, open, crossover study.	Each subject received 3 treatments (>5-day washout in-between): Placebo Fixed-dose combination tablet of metoprolol (tartrate) IR/HCT 100/12.5 mg; Fixed-dose combination tablet of metoprolol-(succinate)-ER/HCT 100/12.5 mg Once-daily oral doses for 5 days, for each of 3 treatment periods.	12	Healthy men	15 days	Complete, Full
PK	S-897		To evaluate (1) the extent and rate of bioavailability of metoprolol given in a fixed combination of metoprolol-CR/HCT 50/12.5 mg and as metoprolol-CR 50 mg alone, and (2) the extent and rate of bioavailability of HCT given in a fixed combination of metoprolol-CR/HCT 50/12.5 mg and as 12.5 mg HCT alone	An open, randomized, 3-way, crossover study.	Each subjects received 3 treatments (>5-day washout in-between): Reference: metoprolol-succinate-ER 50 mg alone, HCT 12.5 mg alone, Test: Fixed-dose combination tablet metoprolol-ER/HCT 50/12.5 mg Once-daily oral doses for 5 days, for each of 3 treatment periods.	12	Healthy men	15 days	Complete, Full

Table 35: List of clinical studies including objectives and dosage regimen

Table 1 Listing of clinical studies									
Type of Study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
PK	S-998		To show, at steady state, bioequivalence between a modified formulation of a fixed combination of metoprolol CR 100 mg + HCT 12.5 mg (investigational/ test) and the marketed formulation of metoprolol CR 100 mg + HCT 12.5 mg (reference).	An open, randomized, 2-way crossover study at steady state conditions.	Each subject received 2 treatments (≥7 days washout in-between): A modified fixed-dose combination tablet of metoprolol succinate CR 100 mg + HCT 12.5 mg Reference: The marketed fixed-dose combination tablet of metoprolol succinate CR 100 mg + HCT 12.5 mg Once-daily oral doses for 7 days, for each of 2 treatment periods.	30	Healthy men	14 days	Complete, Full

Table 36: List of clinical studies including objectives and dosage regimen

Table 1 Listing of clinical studies									
Type of Study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
PK	D4026C00005		To determine whether the fixed combination tablet (test) was bioequivalent to the free combination (reference) of metoprolol succinate ER (1 x 100 mg) and HCT (1 x 12.5 mg).	An open, single-dose, randomized, 4-way crossover study.	Each subject received 4 single dose treatments (≥7 days washout in-between) Metoprolol succinate ER 1 x 100 mg and HCT 1 x 12.5 mg in fed and fasted states and in free and fixed combinations. Treatment A – Fasting, oral, free combination Treatment B – Fasting, oral fixed combination Treatment C – Fed, oral, free combination Treatment D – Fed, oral fixed combination A single dose in the morning followed by 48-hour PK sampling, for each treatment period.	48 (27 men and 21women)	Healthy male (M) and female (F) subjects with a resting heart rate above 50 beats/min.	4 days	Complete, Full

Table 37: List of clinical studies including objectives and dosage regimen

Table 1 Listing of clinical studies									
Type of Study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
PK	D4026C00006		To determine whether the fixed combination tablet (2 test tablets) was bioequivalent to the free combination (reference) of metoprolol succinate ER (2 x 25 mg) and HCT (2 x 6.25 mg).	An open, single-dose, randomized, 2-way crossover study.	Each subject received 2 treatments (≥7 days washout in-between) (one treatment with 2 fixed-dose combination tablets and another with free combinations of: Metoprolol succinate ER 2 x 25 mg and HCT 2 x 6.25 mg Treatment A – Fasting, oral fixed combination Treatment B – Fasting, oral free combination A single dose in the morning followed by 48-hour PK sampling, for each treatment period.	44 (26 men and 18 women)	Healthy male (M) and female (F) subjects with a resting heart rate above 50 beats/min.	2 days	Complete, Full

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Table 38: List of clinical studies including objectives and dosage regimen

Table 1 Listing of clinical studies									
Type of Study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy	S-902		To compare the effect on blood pressure and heart rate 24 hours after administration of the new combination product metoprolol CR,100 mg, and HCT, 12.5 mg, with that of the conventional combination of metoprolol , 100 mg, and HCT, 12.5 mg, in patients with essential hypertension. A secondary aim was to investigate the tolerability of the 2 fixed combinations of metoprolol and HCT.	This was a 2-way crossover, double-blind study comparing 2 fixed-dose combination tablets of metoprolol/HCT. The double-blind period was preceded by a single-blind, run-in period with HCT 12.5 mg, which lasted for 4 weeks.	Each patient received 2 combination treatments, for 4 weeks each: Metoprolol succinate ER/HCT 100/12.5 mg Conventional metoprolol tartrate/HCT 100/12.5 mg	48 randomized patients 47 ITT population	Patients with essential hypertension and who remained hypertensive after the 4-week run-in period (treatment with HCT 12.5 mg).	Patients were exposed to combination treatment for a total of 8 weeks (4 weeks each treatment period).	Complete. Full

Table 39: List of clinical studies including objectives and dosage regimen

Table 1 Listing of clinical studies									
Type of Study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
Efficacy	D4026C00001 Study 324 (ATTACH)		Determine if at least 1 Toprol-XL/HCT combination exceeds the blood pressure (BP) lowering effects of its individual components with regard to the placebo-corrected change from baseline to Week 8 in trough sitting diastolic blood pressure (SiDBP) in hypertensive adults. Also, determine if at least 1 combination exceeds the contribution of each component for SiSBP, describe dose response, compare each combination to its components, compare combinations to placebo, examine the same objectives for standing BPs, and describe dose response across subgroups	This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, unbalanced factorial study that examined the BP lowering effects of 3 dose levels of HCT, 4 dose levels of Toprol-XL, and 9 Toprol-XL/HCT combinations.	Placebo; 3 dose levels of HCT (6.25 mg, 12.5 mg, and 25 mg). 4 dose levels of Toprol-XL (25 mg, 50 mg, 100 mg, and 200 mg). 9 Toprol-XL/HCT combinations: 25/6.25 mg, 25/12.5 mg, 50/6.25 mg, 50/12.5 mg, 100/6.25 mg, 100/12.5 mg, 100/25 mg, 200/12.5 mg, 200/25 mg	1571 randomized patients 1559 ITT population	Patients with essential hypertension; patients with DBP between 95 and 114 mmHg at Week -1 and Study Day 0, and SBP <180 mmHg at Day 0.	Patients were exposed to 1 of 17 treatments for a total of 8-weeks.	Complete. Full

CR Controlled release. Note: CR and extended release (ER) are used interchangeably.
IR Immediate release.
HCT Hydrochlorothiazide.
PK Pharmacokinetics.
PD Pharmacodynamic.
ITT Intent-to-treat population
SiDBP Sitting diastolic blood pressure. SI SBP Sitting systolic blood pressure. St DBP Standing diastolic blood pressure. StSBP Standing systolic blood pressure.

Table 40: List of clinical studies including objectives and dosage regimen

Table 1 Listing of clinical studies									
Type of Study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control	Test product(s); Dosage regimen; Route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status; Type of report
PK	D4026C00006		To determine whether the fixed combination tablet (2 test tablets) was bioequivalent to the free combination (reference) of metoprolol succinate ER (2 x 25 mg) and HCT (2 x 6.25 mg).	An open, single-dose, randomized, 2-way crossover study.	Each subject received 2 treatments (≥7 days washout in-between) (one treatment with 2 fixed-dose combination tablets and another with free combinations of: Metoprolol succinate ER 2 x 25 mg and HCT 2 x 6.25 mg Treatment A – Fasting, oral fixed combination Treatment B – Fasting, oral free combination A single dose in the morning followed by 48-hour PK sampling, for each treatment period.	44 (26 men and 18 women)	Healthy male (M) and female (F) subjects with a resting heart rate above 50 beats/min.	2 days	Complete, Full

4.3 Review Strategy

The purpose of this review is to focus on the single large factorial study by evaluating the data and checking their accuracy and quality. The cells of interest have been adequately populated for the dose ranging study. The reviewer has ascertained that the treatment effect of the combination product at most of the doses, not all, exceeded those of its component. This is a *sine qua non* for approval of a combination product. Furthermore the reviewer has ascertained that there is no interaction between the two components. Although the two components are approved drugs the reviewer has ascertained that there are no notable adverse or serious adverse events that occurred due to the combined product. Most of the FDA guidelines for approval of combined product were reviewed carefully. The small study on a similar product carried out in Sweden was helpful in the safety database. Since this has been used in Europe since 1994, there has been no significant post marketing adverse events or unfavorable incidents reported.

4.4 Data Quality and Integrity

The data quality was found to be very good and of high integrity.

The study incorporated the following key clinical design features to generate high quality data:

• Randomized allocation of subjects to treatment groups assured that treatment comparisons were based on subjects sampled from the same population and that statistics were valid.

• Double-blind study conduct minimized the risk for study endpoint ascertainment bias and differential clinical patient management. This was important given the known risk for observer bias in recording BP readings.

• A placebo control group allowed quantification of treatment-related BP reductions after adjusting for placebo effect.

• The factorial parallel group design determined the effects of each individual drug across several dose levels as well as possible combinations. The unbalanced design placed more subjects in cells of pre-specified interest to provide greater precision for these key comparisons. All cells, however, contributed to the overall response surface analyses.

• A placebo run-in period minimized variability in baseline BP determination and also assured washout of potentially confounding antihypertensive medication.

4.5 Compliance with Good Clinical Practices

There was compliance and good clinical practice based on the data and the case report forms. In spite of the several treatment arms during the double blind treatment phase, mean compliance with study drug was at least 97% for each treatment group.

4.6 Financial Disclosures

Certificates of financial disclosure were submitted. See example below.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.
Toprol-XL
D4026C00006

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	SEE ATTACHED REPORT(S)	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Anthony F. Rogers	Vice President, Regulatory Affairs
FIRM / ORGANIZATION: AstraZeneca LP	
SIGNATURE: [signature]	DATE: 7/26/05

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

For all pharmacokinetic and pharmacodynamic variables mean and standard deviations (SD) were calculated.

The plasma concentrations of metoprolol and HCT at the end of the dosing intervals (24 hours after dose) on days 4, 5 and 6 were evaluated by repeated measures analysis of variance (ANOVA) in order to ascertain that steady state conditions had been reached.

The significance level of observed differences between the formulations were tested by two-tailed t-tests for C°°y, C°°„ (only metoprolol), log transformed AUC values, C°ppf E°°„ and AUEC considering $p < 0.05$ as statistically significant. Bioequivalence regarding these variables was concluded at the a=0.05 level of significance if a 90X confidence interval for the mean difference between test and reference formulation vas within +20X of reference mean (4,5). The standard deviations used in the calculations of the confidence intervals were given by repeated measures ANOVA. The statistical significance of differences of t°°° vas esrabli°h°4 l>v rhe .signed raiil, r P C1 for matched pairs according en Wi 1co ::<.°ii.

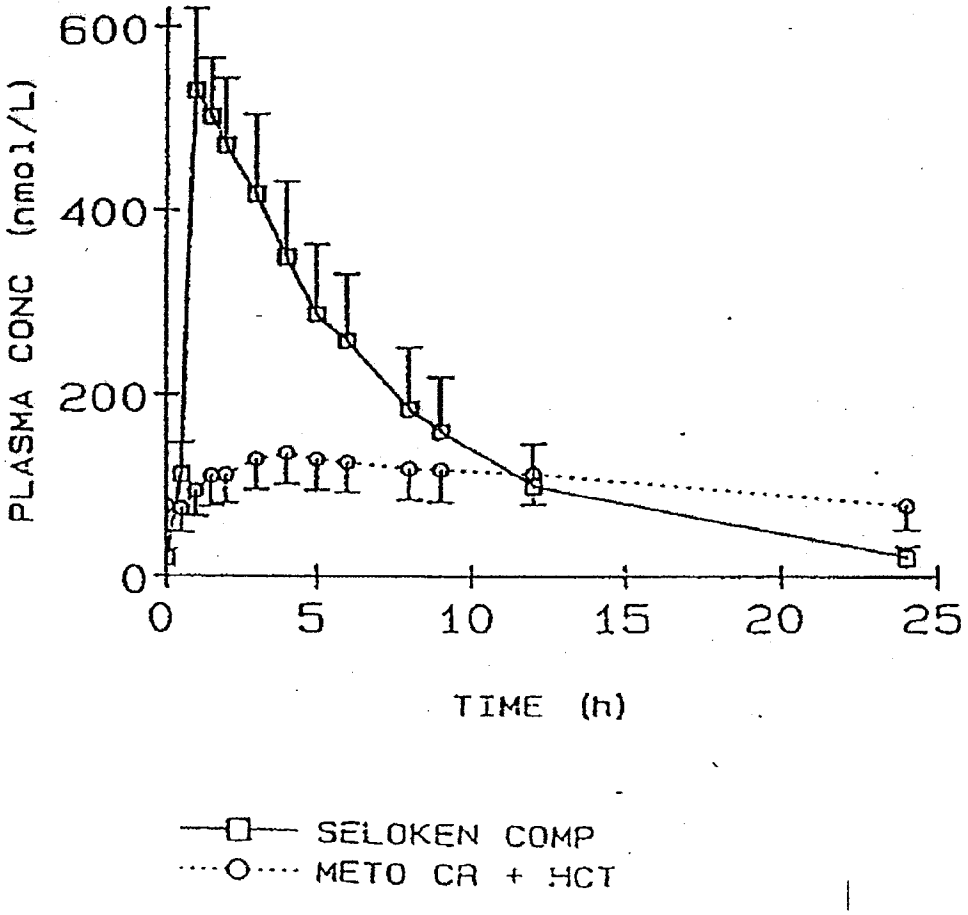
Plasma concentrations: Investigation of steady-state conditions

Individual plasma concentrations of metoprolol and HCT at the end of the dosing intervals (24 hours after dose) on days 4, 5 and 6 and the corresponding ANOVA tables are given in Appendix VII. The 24 hour plasma concentrations were not significantly different far any drug, indicating that the subjects were at steady state.

Metoprolol

Individual plasma concentration data, including concentration vs time curves and pharmacokinetic variables are in an Appendix submitted by the sponsor. ANOVA tables are also given in another Appendix submitted by the sponsor. Mean pharmacokinetic variables together with significance levels from the statistical tests and the 90% confidence intervals are presented in table 2. Mean plasma concentration profiles are given below in figure 8.

Figure 12: Mean (n=12) and SEM plasma concentration (nmol/L) profiles of metoprolol after 5 days dosing.



The mean plasma concentration values of metoprolol obtained after the CR formulation created a more even 24 hours profile than those of the conventional tablet. This difference in profiles could be quantified by the degree of fluctuation in the plasma concentration during a dosage interval (FI). The FI was considerably lower for meto CR + HCT (range 32-144X) than for Seloken° Comp (range 180-1070X) for all subjects.

After administration of Seloken° Comp, the mean maximal plasma concentration (C°°y), 629 nmol/L, was reached after a mean time of 1.4 h. The minimal plasma concentration was below the minimum determinable concentration (10 nmol/L) in 9 subjects (mean value 20 nmol/L). The more extended absorption process for the CR formulation resulted in a significantly lower mean C°°° (138 nmol/L) and a significantly higher mean t°°° (5.1 h). Further, measurable Cy°„ values were obtained in 11 subjects for meto CR + HCT resulting in a significantly higher mean C°°„

(74 nmol/L) compared with Seloken° Comp. Expressed as the 90X confidence intervals, the reduction of C°°° was 368-615 nmol/L, and the increase of C°°„ 28-79 nmollL for meto CR + HCT compared with the conventional combination tablet.

The mean elimination half-life (tyg), obtained from the rapidly dissolving Seloken° Comp tablet, was 3.5 hours which is consistent with corresponding data for plain metoprolol tablets.

The mean AUC values, 2564 nmol h/L and 3656 nmol h/L, for meto CR + HCT and Seloken° Comp respectively, resulted in a mean relative bioavailability (F,°y) of 68%. The difference of AUC was statistically significant and the 90X confidence interval for the new combination was 62-74%, expressed as percentage of the reference mean.

Hydrochlorothiazide

Individual plasma concentration data of HCT after administration of meto CR + HCT and Seloken° Comp are given as tables and graphs in Appendix IX. Individual data of pharmacokinetic variables are also included in Appendix IX. ANOVA tables are given in Appendix XII.

The mean plasma profiles can be seen in figure 9. Mean pharmacokinetic variables together with significance levels from the statistical tests and the 90X confidence intervals are given in table 3.

Figure 3 Mean (n=12) and SEH concentration of HCT in plasma (nrnol/L) after 5 days dosing.

Figure 13: Mean (n=12) and SEM concentration of HCT in plasma (nrnol/L) after 5 days dosing.

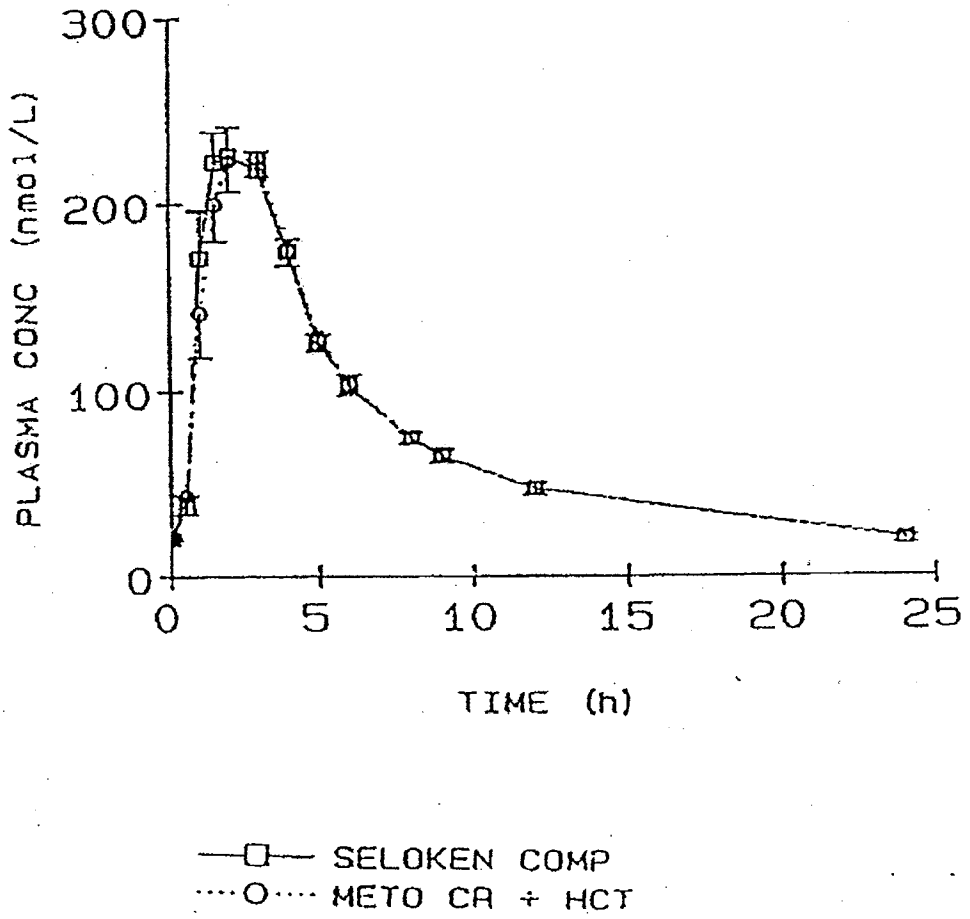


Table 41: PK data for Hydrochlorothiazide

HYDROCHLOROTHIAZIDE

		Dosage	
Variables		**Seloken® Comp**	**meto CR+HCT**
C_{max} (nmol/L)	Mean	256	239
	SD	44	52
	Range	166-306	176-361
	t-test	p > 0.05	
	90% CI	(-33)-6 [87-102%][1]	
C_{min} (nmol/L)	Mean	20	20
	SD	6.2	8.0
	Range	11-30	8-40
t_{max} (h)	Mean	1.9	2.1
	SD	0.7	0.7
	Range	1.0-3.0	1.0-3.0
	Wilcoxon	p > 0.05	
$t_{½\beta}$ (h)	Mean	9.0	9.0
	SD	1.2	1.8
	Range	6.9-11.6	6.9-13.9
AUC (nmol·h/L)	Mean	1771	1765
	SD	303	367
	Range	1393-2174	1280-2285
	t-test[2]	p > 0.05	
	CI[2]	(-89)-53 [95-103%][1]	
F_{rel} (%)	Mean	100	99
	SD	-	8.2
	Range	-	86-111

[1] CI for the mean difference between test and reference (Seloken® Comp) also expressed within [] as per cent of the test formulation in relation to the reference
[2] performed on log transformed values

The plasma profiles, after. administration of the two formulations, were almost super imposable in most of the subjects. HCT was rapidly absorbed from both tablets as indicated by the mean C°y° and t°°° values, 239 nmol/L after a mean time of 2.1 hours for meto CR + HCT and 256

nmol/L after 1.9 hours for Seloken° Comp. In the comparisons between the formulations the mean C°°° and t°„ were not significantly different. According to the 90 K confidence interval of the mean difference for C°°°, (-33)-6 nmol/L, the treatments were also bioequivalent.

The mean C°°„ was 20 nmol/L for both formulations, the mean elimination half life (t°), also equal after administration of both treatments, was 9.0 h.

The mean AUC values for meto CR + HCT and Seloken° Comp were 1765 and 1771 nmol h/L, respectively, and the mean F„°y was 99X. The formulations were bioequivalent regarding the extent of bioavailability since the 90% confidence interval 95-103X, was within the stated bioequivalence interval, 80-120X

5.2 Pharmacodynamics

Effect on exercise heart rate:

The mean absolute values of exercise heart rate after Seloken@ Comp, meto CR + HCT and placebo are shown in figure 4. All individual data are given in Appendix X.

The effect, i.e degree of Ry-blockade expressed as per cent change in exercise heart rate in relation to placebo, is shown in figure S. The individual effect data are given in Appendix X.

Mean, SD and range for the pharmacodynamic variables are shown in table 4 and individual data in Appendix X. Results from the statistical analysis of differences between the formulations ace included in table 4. ANOVA tables ace given in Appendix XII.

Figure 4 Mean (n=12) and SEH exercise heart rate (beats/min)

Figure 14: Mean (n=12) and SEM exercise heart rate (beats/min)

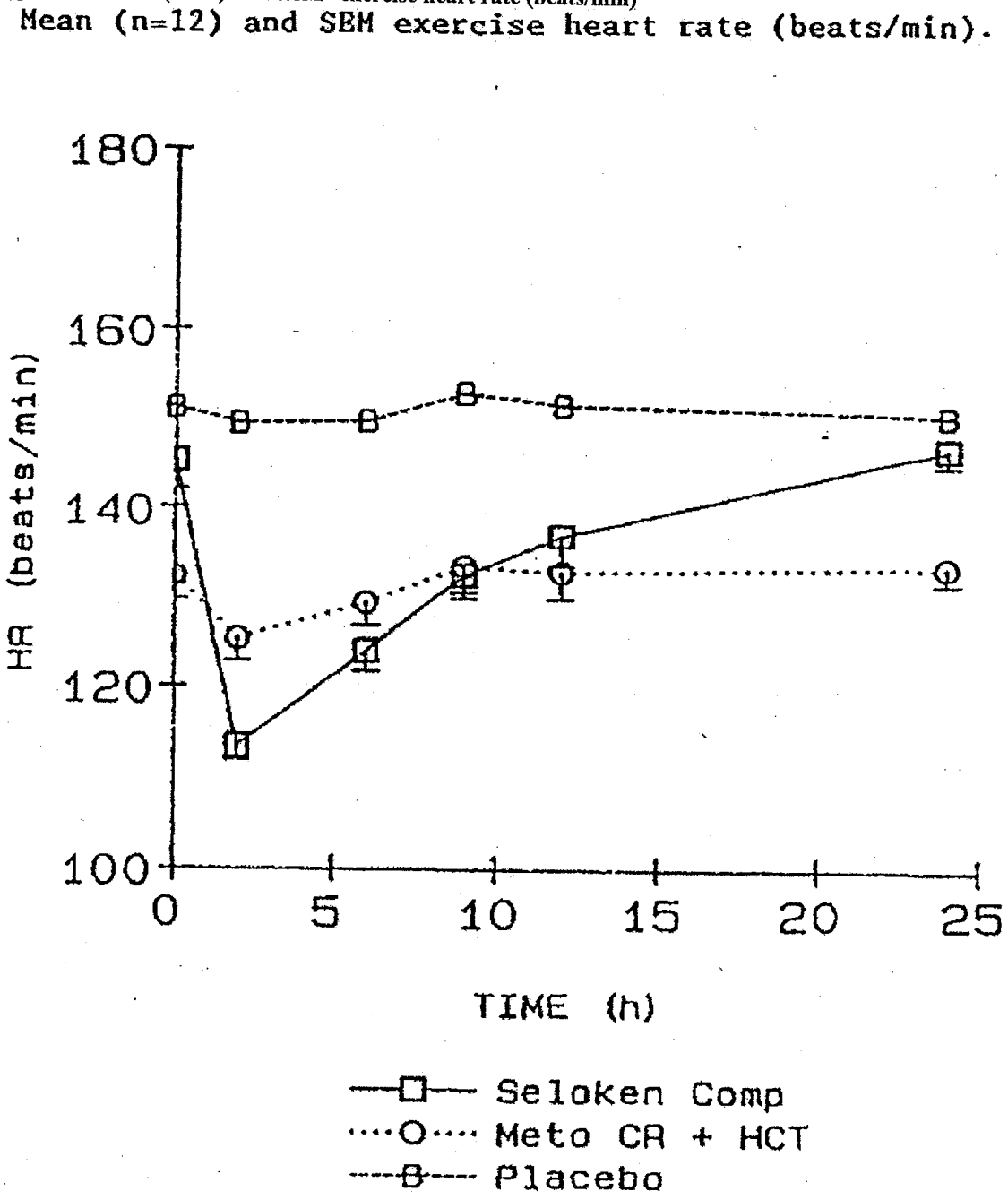
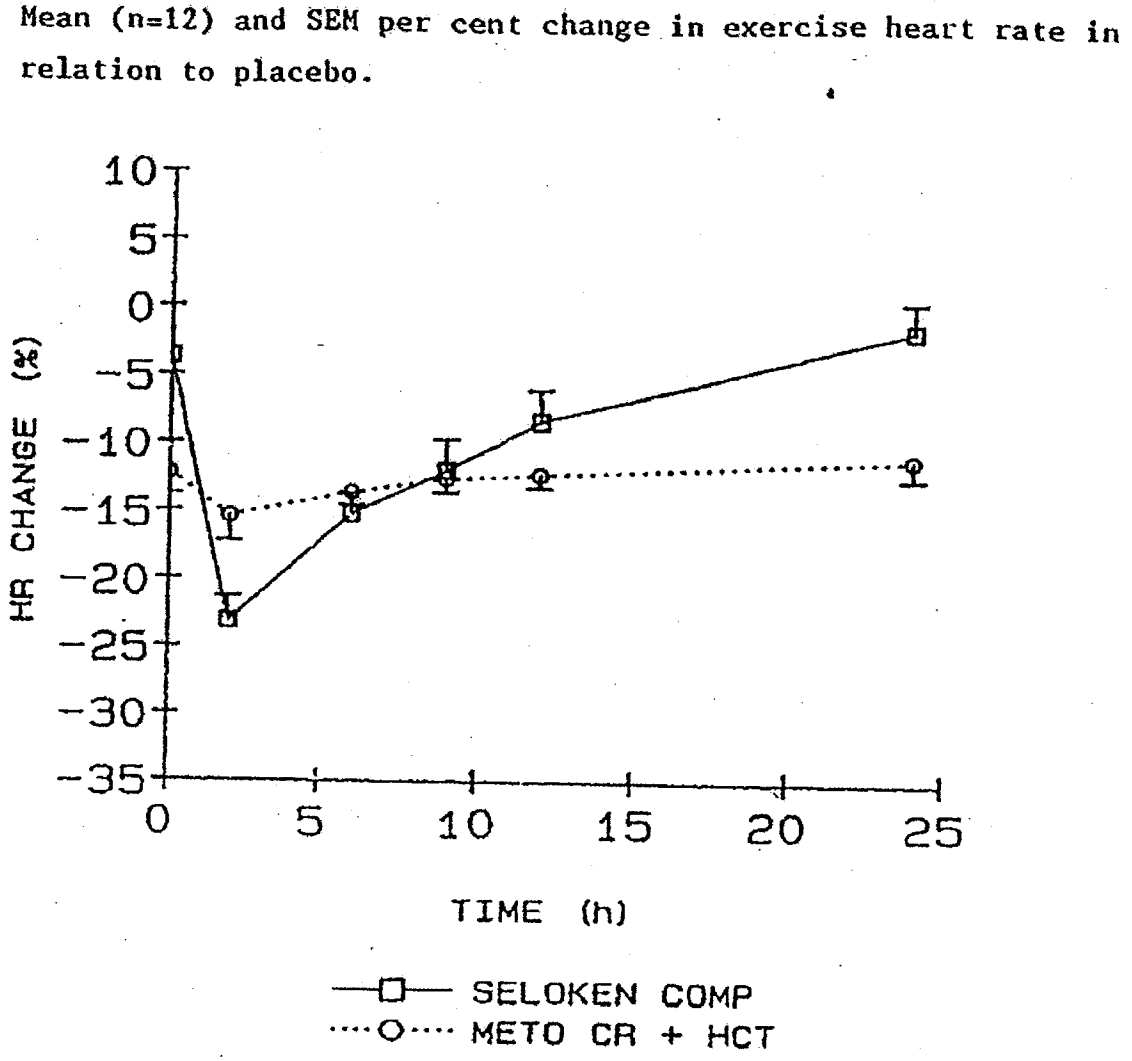


Figure 15: Mean (n=12) and SEM per cent change in exercise heart rate (beats/min) compared to placebo



In agreement with the more even plasma concentration profiles of metoprolol obtained after administration of the meto CR + HCT tablet compared with Seloken° Comp the effect vs time profile over 24 hours was also much more even. The difference between the treatments of the effect vs time profiles vas also shown by the considerably lower values of the fluctuation of the effect over a dosage interval (FIE) in all subjects for the CR formulation (mean 56%) compared with the conventional formulation (mean 280X)

The mean E°°° for meto CR + HCT. (15.8/) were significantly reduced compared with the corresponding value for Seloken° Comp (23.0X). In the comparison of mean E°; „ a significantly higher effect was obtained Eor the nev combination (9 9K) compared with the conventional tablet (2.3K).

The mean area under the effect curve (AUEC), representing a quantitative measurement of the total effect during the 24-houc dosage interval, vas significantly higher for, meto CR + HCT (303K h) compared with Seloken° Comp (259X h). The confidence interval regarding the total effect (AUEC) was 105-129% for the new tablet in relation to the conventional combination.

Mean (n=l2), SD and range of pharmacodynamic variables • Statistical significance levels and 90% confidence intervals (CI) for differences between the formulations.
Table 40

Table 42: PK data for metoprolol ER and Hydrochlorothiazide

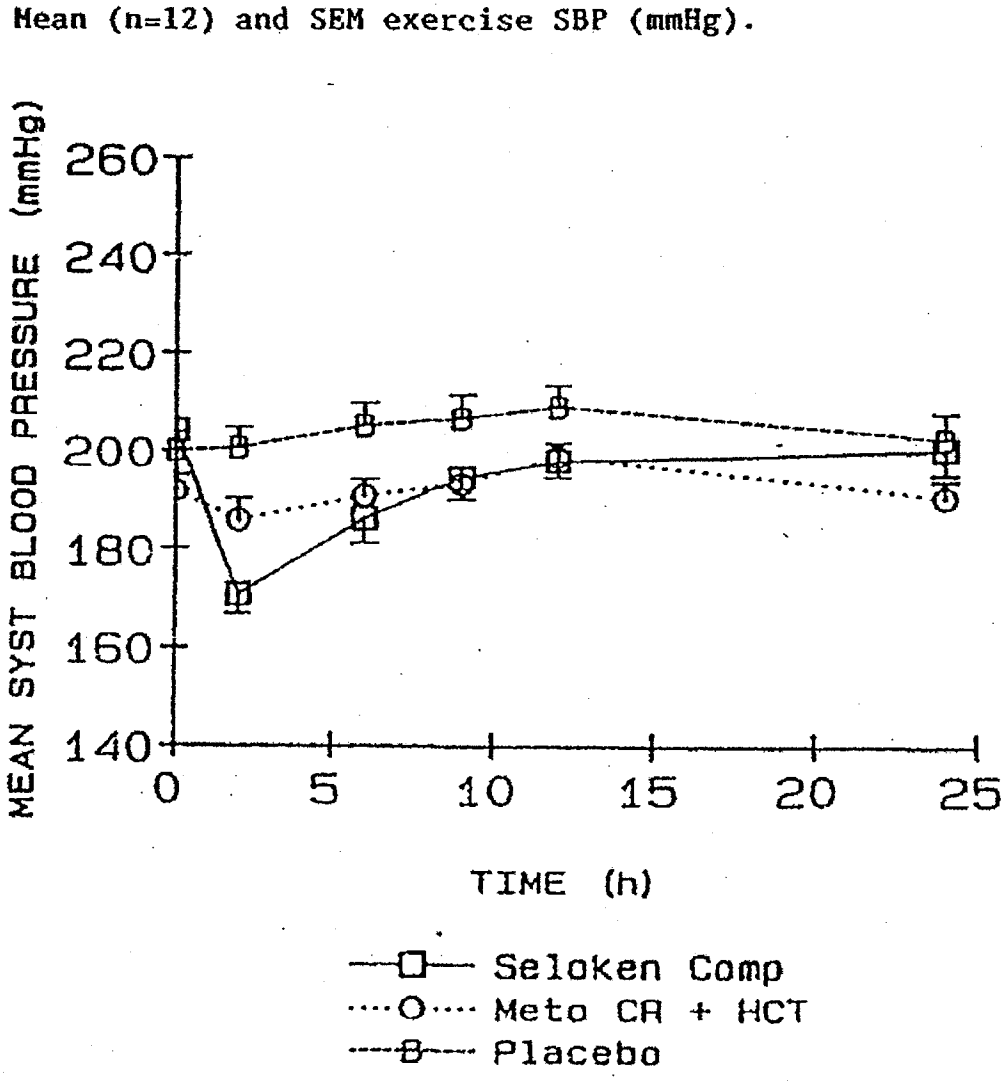
		Dosage	
		Seloken® Comp	meto CR+HCT
E_{max} (%)	Mean	23.0	15.8
	SD	6.2	7.0
	Range	12.0-32.0	3.3-26.4
	t-test	p < 0.001	
	90% CI	(-10.0)-(-4.4) [57-74%][1]	
E_{min} (%)	Mean	2.3	9.9
	SD	6.4	5.7
	Range	(-6.2)-17.9	0.7-23.5
	t-test	p < 0.001	
	90% CI	5.9-9.3 [360-500%][1]	
FI_E (%)	Mean	280	56
	SD	260	36
	Range	53-1040	11-142
AUEC (%·h)	Mean	259	303
	SD	145	147
	Range	61-599	44-604
	t-test	p < 0.05	
	90% CI	13-75 [105-129%][1]	

[1] CI for the mean difference between test and reference (Seloken® Comp) also expressed within [] as per cent of the test formulation in relation to the reference

Effect on exercise blood pressure

The mean values (SEM) of exercise Sl3P are shown in figure 6 and individual data are given in Appendix X. The effect of the two treatments on exercise SBP generally corresponded well with the effect on EHR, described in 5.3.1. Meto CR + HCT yielded a more even SBP vs time profile than the conventional combination tablet.

Figure 16: Mean (n=12) and SEM exercise in Systolic Blood Pressure



DISCUSSION AND CONCLUSIONS for pharmacodynamics (PD)

The controlled delivery of metoprolol from the meto CR + HCT tablet resulted in smoother metoprolol plasma concentration profiles without pronounced plasma peaks and with considerably higher trough values, as compared with Seloken° Comp. Also the effect-time profile for meto CR + HCT was flatter with a reduction of the peak effect and a considerably higher minimal effect compared with Seloken° Comp. This could be expected from the obtained plasma concentration profiles for metoprolol. These comparisons, regarding both plasma and effect profile characteristics, were in accordance with the results obtained in a previous study on metoprolol CR and conventional metoprolol tablets (1).

The amount of metoprolol reaching the systemic circulation was significantly reduced for the CR combination compared with the conventional tablet. The mean F°yy was 68X and the 90X confidence interval 62-74X. However, in contrast to this reduction of AUC, the total effect during a dosing interval, calculated as AVEC, vas significantly higher for the CR combination giving 105-129X (90X Cl) of the effect measured for the conventional tablet. The higher total Ry-blockade during a dosage interval after administration of the CR tablet can be explained by the plasma profile having a longer period of "effective" metoprolol concentrations during the dosage interval. Similar results have been found in an earlier study comparing metoprolol CR and plain tablets (1).

The relationship between plasma metoprolol levels and reduction in exercise heart rate is independent of the pharmaceutical formulation. Using an E_{max} model, the maximum effect is a 30% reduction in exercise heart rate, which is attributed to $beta_1$-blockade. $Beta_1$-blocking effects in the range of 30–80% of the maximal effect (approximately 8–23% reduction in exercise heart rate) correspond to metoprolol plasma concentrations from 30-540 nmol/L. The relative $beta_1$-selectivity of metoprolol diminishes and blockade of $beta_2$-adrenoceptors increases at higher plasma concentrations above 300 nmol/L.

Table 43: PK data for metoprolol and Hydrochlorothiazide continued

METOPROLOL

Variable		Dosage: Seloken® Comp	Dosage: meto CR+HCT
C_{max} (nmol/L)	Mean	629	138
	SD	326	121
	Range	235-1260	20-459
	t-test	p < 0.001	
	90% CI	(-615)-(-368) [2-41%][1]	
C_{min} (nmol/L)	Mean	20	74
	SD	47	92
	Range	0-162	0-328
	t-test	p < 0.01	
	90% CI	28-79 [240-495%][1]	
t_{max} (h)	Mean	1.4	5.1
	SD	0.6	2.7
	Range	1-3	3-12
	Wilcoxon	p < 0.01	
$t^{1/2}_{\beta}$ (h)	Mean	3.5	-
	SD	1.2	-
	Range	2.3-6.9	-
FI (%)	Mean	550	79
	SD	260	29
	Range	180-1070	32-144
AUC (nmol·h/L)	Mean	3656	2564
	SD	3717	2636
	Range	562-14350	334-9837
	t-test[2]	p < 0.001	
	90% CI[2]	(-1389)-(-951) [62-74%][1]	
F_{rel} (%)	Mean	100	68
	SD	-	11
	Range	-	50-83

[1] CI for the mean difference between test and reference (Seloken® Comp) also expressed within [] as per cent of the test formulation in relation to the reference
[2] performed on log transformed values

EFFICACY AND PHARMACOKINETIC RESULTS
Summary of efficacy and pharmacokinetic results

The primary objective of this study was to determine whether at least 1 Toprol-XL/HCT combination exceeded the BP lowering effects of its individual components with regard to the placebo-corrected change from baseline to Week 8 in trough SiDBP; a secondary variable, SiSBP, was analyzed in a similar manner.

The following outcomes are as follows:

(i) The T_{AVE} test shows that at least 1 combination treatment group exceeded the reductions of both monotherapy components of Toprol-XL and HCT for both trough SiDBP and SiSBP.

(ii) An ANCOVA analysis shows that both drugs had significant effects on changes in trough SiDBP from baseline to Week 8/LOCF and that all 9 combination treatment groups had significantly greater reductions compared to placebo. Pairwise comparisons of combination treatment groups versus their component treatment groups showed numerically greater reductions with combinations (except for Toprol-XL/HCT 25/6.25 mg) and that 4 Toprol-XL/HCT treatment groups (100/6.25 mg, 100/12.5 mg, 100/25 mg, and 200/25 mg) all had significantly greater reductions from baseline in trough SiDBP when compared to their respective monotherapy treatment groups.

(iii) Multiplicity-adjusted results for the pairwise comparisons support the conclusions of the primary analysis that at least 1 combination performed better than both components.

(iv) Several low-dose combinations were approximately as effective in lowering SiDBP and SiSBP as at least 1 of the high-dose monotherapies.

(v) An assessment of additivity shows that the 2 drugs were less than fully additive at the extreme ends of the dosage range (particularly for the Toprol-XL/HCT 25/6.25 mg group and the 200/12.5 mg group) but the combinations with Toprol- XL 100 mg (Toprol-XL/HCT 100/6.25 mg, 100/12.5 mg, 100/25 mg) were almost fully additive.

(vi) Dose response surface analyses demonstrate that the data were well-described by a quadratic model and that the model predicts additive contributions of the components after accounting for the placebo effect over the range of doses studied.

(vii) An analysis that considered, jointly, combinations vs their components and combinations vs placebo found that all combinations were 'desirable', ie, all combinations performed better than both their components and placebo.

5.2 Pharmacodynamics

Similar analyses of other secondary objectives show trough StDBP and StSBP and peak SiDBP and SiSBP changes from baseline to Week 8/LOCF and that results were generally consistent

with the results for trough SiDBP and SiSBP. The ratio of trough to peak BP illustrates that most all of the BP lowering effect at peak drug effect was retained at trough.

Treatment effects expressed as categorical variables illustrate significantly greater proportions of patients responding to and controlled by active treatments than patients given placebo.

Subgroup analyses suggest that females had greater reductions than males for trough SiDBP and SiSBP. Also, analyses show that Black patients appeared to have smaller overall BP reductions than non-Black patients, largely reflecting a lesser response to Toprol-XL. However, the response of Black patients to HCT tended to be greater than for non-Black patients.
Heart rate

Individual clinically important abnormalities in ECG

There was a reduction in heart rate noted with Toprol-XL, which is consistent with its beta-blocking pharmacological effects. There were no other clinically important changes in ECGs except for those noted for Patients 023/4772 and 055/4200 described in Table 83.

Electrocardiograms
The data from electrocardiograms at study entry and week 8 are in Tables 44 and 45 below. There was a reduction in heart rate noted with Toprol-XL, which is consistent with its beta-blocking pharmacological effects. There were no other clinically important changes in ECGs except for those noted for Patients 023/4772 and 055/4200 described in Table 83. The QT interval was within normal limits.

The relatively small dose-related slowing of heart rate with Toprol-XL is consistent with its known beta-blocking pharmacological effects and this effect was not modified by concomitant treatment with HCT. No other relevant electrocardiographic findings were apparent. There were no clinically relevant changes noted by physical examination. Tables 44 and 45 summarize the ECG findings in the study.

Table 44: Data from electrocardiograms at study entry and week 8 - ITT-324

Table 66 Mean (SD) ECG heart rate, PR interval, QRS duration, and QTc duration at study entry and Week 8 and change between visits (safety population)

	6.25 mg	82, –2 (17)	138, –1 (25)	131, 0 (17)	44, 1 (12)	NA
	12.5 mg	101, –2 (13)	136, –1 (26)	141, –3 (24)	91, 0 (18)	42, 5 (13)
	25.0 mg	48, 4 (14)	NA	NA	41, –1 (21)	49, 1 (15)
QRS duration (ms)						
Visit 1 (study entry)	0 mg	153, 88 (15)	89, 88 (17)	93, 87 (14)	94, 90 (18)	51, 87 (11)
	6.25 mg	86, 89 (14)	144, 87 (13)	136, 87 (14)	45, 86 (15)	NA
	12.5 mg	105, 88 (13)	141, 90 (18)	147, 88 (16)	95, 89 (19)	43, 86 (11)
	25.0 mg	48, 86 (12)	NA	NA	42, 87 (12)	49, 90 (9)
Change from Visit 1 to Visit 8	0 mg	146, 1 (10)	89, 0 (11)	90, 0 (6)	92, –1 (10)	50, 2 (25)
	6.25 mg	82, 1 (6)	139, 3 (13)	132, 1 (10)	44, –1 (9)	NA
	12.5 mg	102, 1 (7)	136, 0 (9)	142, 1 (9)	92, 0 (9)	43, 0 (7)
	25.0 mg	48, 1 (10)	NA	NA	41, 1 (6)	49, 1 (7)
QTc interval (ms)						
Visit 1 (study entry)	0 mg	153, 408 (45)	89, 413 (31)	92, 406 (38)	94, 410 (36)	51, 404 (46)
	6.25 mg	86, 413 (36)	143, 414 (28)	135, 411 (42)	44, 407 (43)	NA
	12.5 mg	105, 417 (25)	140, 408 (37)	147, 412 (25)	95, 408 (39)	43, 414 (28)
	25.0 mg	47, 416 (24)	NA	NA	41, 408 (27)	48, 413 (23)
Change from Visit 1 to Visit 8	0 mg	146, 2 (27)	89, 0 (21)	89, 3 (22)	92, –2 (27)	50, 2 (29)
	6.25 mg	82, –1 (21)	138, 1 (26)	131, 0 (25)	43, 2 (21)	NA
	12.5 mg	102, –1 (21)	135, 6 (28)	142, 3 (28)	92, 4 (25)	43, 2 (22)
	25.0 mg	47, 2 (28)	NA	NA	40, 0 (25)	48, 4 (22)

Note: Includes all patients in the safety population with data available at baseline and post-baseline.
Data derived from Table 11.3.8.1.6, Section 11.3

Table 45: Data from electrocardiograms at study entry and week 8 - ITT- Study 324

Table 66 Mean (SD) ECG heart rate, PR interval, QRS duration, and QTc duration at study entry and Week 8 and change between visits (safety population)

ECG parameter	HCT dose	Toprol-XL dosage				
		0 mg n , Mean (SD)	25 mg n , Mean (SD)	50 mg n , Mean (SD)	100 mg n , Mean (SD)	200 mg n , Mean (SD)
Heart rate (bpm)						
Visit 1 (study entry)	0 mg	153, 68 (11)	89, 69 (10)	94, 70 (11)	95, 68 (10)	51, 68 (12)
	6.25 mg	86, 70 (12)	145, 70 (11)	136, 69 (12)	45, 70 (12)	NA
	12.5 mg	105, 69 (11)	141, 69 (12)	147, 68 (10)	95, 68 (10)	43, 69 (9)
	25.0 mg	48, 69 (11)	NA	NA	42, 70 (11)	49, 68 (11)
Change from Visit 1 to Visit 8	0 mg	146, 2 (9)	89, 1 (10)	91, –2 (10)	92, –4 (9)	50, –9 (10)
	6.25 mg	82, 3 (13)	140, –2 (9)	132, –2 (10)	44, –4 (9)	NA
	12.5 mg	102, 3 (10)	136, 0 (10)	142, –2 (9)	92, –4 (9)	43, –8 (9)
	25.0 mg	48, 3 (10)	NA	NA	41, –3 (11)	49, –7 (10)
PR interval (ms)						
Visit 1 (study entry)	0 mg	153, 162 (23)	89, 165 (27)	93, 165 (26)	94, 167 (24)	51, 162 (24)
	6.25 mg	86, 163 (26)	144, 160 (26)	135, 168 (23)	45, 168 (27)	NA
	12.5 mg	105, 168 (21)	141, 167 (26)	147, 165 (30)	94, 168 (26)	42, 165 (20)
	25.0 mg	48, 162 (25)	NA	NA	42, 161 (24)	49, 164 (27)
Change from Visit 1 to Visit 8	0 mg	146, –2 (20)	89, –1 (19)	90, 2 (17)	92, 2 (14)	49, 1 (20)

5.3 Exposure-Response Relationships

Duration of treatment:

The mean duration of each treatment period was: run-in period 30 days, double-blind treatment period 55 days, and the down-titration/follow-up period 15 days. Study patients entered a single-blind placebo 4 or 5 week run-in period prior to randomization into an 8-week double-blind treatment period that was followed by a 2-week down-titration/follow-up period.

6 INTEGRATED Review of Efficacy

6.1 Indication: For the treatment of essential hypertension.

6.1.1 Methods

Methods of assessment

All blood pressure measurements required a mercury sphygmomanometer with an appropriate size cuff positioned on the right arm, approximately at the level of the heart. Patients remained sitting for at least 5 minutes before the sitting BP measurements.

SiDBP was determined as the mean of 3 consecutive readings taken at least 1 minute apart and with no more than a 5 mmHg difference between the highest and lowest reading. If fewer than 3 measurements were collected, the mean was based upon the available measurements.

(b) Calculation or derivation of outcome variable

The measure of antihypertensive effect, change from baseline to Week 8 in trough SiDBP, was calculated as the BP value at Week 8 minus the baseline value. The Week 8 measures were to be collected at the end of Week 8 of double-blind treatment. If the patient discontinued prior to Week 8 then the last observation was carried forward (LOCF).

Trough BP was defined as 24 hours (± 2 hours) after receiving the last dose of study medication at double-blind Week 8.

Table 46: Population of pre-specified treatment cells for unbalanced factorial design -Study 324

Hydrochlorothiazide	Metoprolol succinate extended-release				
	0 mg	25 mg	50 mg	100 mg	200 mg[a]
0 mg	135	90	90	90	45
6.25 mg	90	135	135	45	0
12.5 mg	90	135	135	90	45
25.0 mg	45	0	0	45	45

Total number of patients=1485

[a] Patients assigned 200 mg metoprolol succinate received 100 mg once daily for 1 week before escalation to 200 mg.

Methods for assigning patients to treatment groups

Patients were assigned to treatment groups by a central randomization office that employed an interactive voice response system (IVRS). The randomization office randomly assigned the patient to 1 of the 17 treatment groups, allocated according to 1 predefined, blocked, randomization schedule created for the study by AstraZeneca Biostatistics and Statistical

Patient eligibility was established before treatment randomization. Patients were randomized strictly sequentially at each site as patients became eligible for randomization. If a patient discontinued from the study, the patient number was not be reused, and the patient could not re-enter the study.

Patients that were incorrectly randomized were allowed to remain in the study, if agreed to by the Sponsor, unless the Investigator determined that there was a potential safety issue.

6.1.2 General Discussion of Endpoints

Measurement of Primary variable

SiDBP determined at trough (24±2 hrs, Visit 8) served as the primary efficacy measure. The primary measure of effect was the placebo-corrected change from baseline to Week 8 in trough SiDBP. Change to Week 8 in trough SiDBP without placebo adjustment served as the measure of effect for other analyses. Each blood pressure determination represented the mean of 3 readings with less than 5 mmHg between the highest and lowest value.

Efficacy measurements and variables
The primary efficacy measurement was SiDBP determined at trough. The primary measure of effect was the placebo-corrected change from baseline to Week 8 in trough SiDBP (where baseline was the last determination prior to dosing at randomization). Each BP determination represents the mean of 3 readings with less than 5 mmHg between the highest and lowest value.

Secondary BP measures of effect included change from baseline in trough SiSBP, peak sitting BPs, and trough StSBP and StDBP.

Statistics for endpoints- See Statistical review and Table 47 below.

Table 47: Endpoints and statistical analyses plans

Objective	Endpoints	Summary statistic for analysis (including population and timepoint)	Planned analysis	Significance of results
Primary				
Determine if at least one combination exceeds the contribution of each component for SiDBP	Trough SiDBP	Placebo-corrected change from baseline to Week 8 (ITT/LOCF)	H_0:$\mu ij \geq \mu io$ or $\mu ij \geq \mu oj$ for all i and j H_1:$\mu ij < \mu io$ and $\mu ij < \mu oj$ for some i and j Global test (Hung 2000	Reject H_0: At least one combination exceeds the contribution of both components
Secondary				
Determine if at least one combination exceeds the contribution of each component for SiSBP	Trough SiSBP	Placebo-corrected change from baseline to Week 8 (ITT/LOCF)	H_0:$\mu ij \geq \mu io$ or $\mu ij \geq \mu oj$ for all i and j H_1:$\mu ij < \mu io$ and $\mu ij < \mu oj$ for some i and j Global test (Hung 2000)	Reject H_0: At least one combination exceeds the contribution of both components
Describe dose response	Trough SiDBP Trough SiSBP	Change from baseline to Week 8 (ITT/LOCF)	Response surface analysis	Describes dose response by surface analysis
Compare each combination to its components	Trough SiDBP Trough SiSBP	Change from baseline to Week 8 (ITT/LOCF)	For each i & j test: H_0: $\mu ij = \mu io$ H_1: $\mu ij \neq \mu io$ And H_0: $\mu ij = \mu oj$ H_1: $\mu ij \neq \mu oj$ ANCOVA	Examines each combination individually for benefit over components
Compare combinations to placebo	Trough SiDBP Trough SiSBP	Change from baseline to week 8 (ITT/LOCF)	For each i & j test: H_0: $\mu ij = \mu oo$ H_1: $\mu ij \neq \mu oo$ ANCOVA	Reject H_0: the combination(s) differs from placebo
Determine if at least one combination exceeds the contribution of each component for other BP measures	Trough StDBP and StSBP Peak SiDBP and SiSBP	Placebo-corrected change from baseline to Week 8 (ITT/LOCF)	H_0: $\mu ij \geq \mu io$ or $\mu ij \geq \mu oj$ for all ij H_1:$\mu ij < \mu io$ and $\mu ij < \mu oj$ for some ij Global test (Hung 2000)	Reject H_0: at least one combination exceeds the contribution of both components
Describe dose response for other measures	Peak SiDBP and SiSBP Trough StDBP and StSBP	Change from baseline to Week 8 (ITT/LOCF)	Response surface analysis	Describes dose response by surface analysis for peak and standing measures
Describe dose response across subgroups	Trough SiDBP and SiSBP	Change from baseline to Week 8 (ITT/LOCF)	Response surface analysis	Describes dose response across subgroups

SiDBP Sitting diastolic blood pressure. DBP Diastolic blood pressure. ITT Intention to treat. LOCF Last observation carried forward. SiSBP Sitting systolic blood pressure. StDBP Standing diastolic blood pressure. StSBP Standing systolic blood pressure. BP Blood pressure.

6.1.3 Study Design for "ATTACH" – showing sequence of treatment - Study 324

Screening ≤2 weeks	Placebo run-in 4 or 5 weeks		Treatment 8 weeks					Follow-up[a] 2 weeks
Visit 1 Enrollment (Week –7 to –5)	Visit 2 (Week –5 or –4)	Visit 3 (Week –1)	Visit 4 (Day 0) Randomization	Visit 5 (Week 2)	Visit 6 (Week 4)	Visit 7 (Week 6)	Visit 8 (Week 8) End of treatment	Visit 9 (Week 10)
Patients with hypertension	Placebo run-in		Treatment group (see Table 2 for treatment groups)					

[a] Includes study down titration.

Screening ≤2 weeks	Placebo run-in 4 or 5 weeks		Treatment 8 weeks					Follow-up[a] 2 weeks
Visit 1 Enrollment (Week –7 to –5)	Visit 2 (Week –5 or –4)	Visit 3 (Week –1)	Visit 4 (Day 0) Randomization	Visit 5 (Week 2)	Visit 6 (Week 4)	Visit 7 (Week 6)	Visit 8 (Week 8) End of treatment	Visit 9 (Week 10)

Table 48: Schedule of activities and sequence of treatment periods -Study 324

	Screen	Placebo run-in		Treatment					Follow-up[a,b]
Duration	Up to 2 weeks	4 or 5 weeks[c]		8 weeks					2 weeks
Time point		Week –5/-4	Week -1[c]	Day 0	Week 2	Week 4	Week 6	Week 8[b] E-O-T	Week 10
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Informed consent	√								
Medical history	√								
Physical examination	√							√	
Weight	√							√	
Height	√								
Prior & concurrent medications	√	√	√	√	√	√	√	√	√
Blood pressure trough, sitting and/or standing	Sit	Sit	Sit[d]	Sit[d,e] Stand[e]	Sit[f]	Sit[f]	Sit[f]	Sit[f] Stand	Sit
Blood pressure peak[g]			Sit					Sit	
Heart rate	√			√[e]	√	√	√	√	
Electrocardiogram	√							√	
Hematology	√			√[e]	√			√	
Chemistry[h]	√			√[e]	√			√	
Lipids[h]				√[e]				√	
Urinalysis	√							√	
Pregnancy[i]	√							√	
Single-blind study drug		√	√						
Single-blind drug accountability			√	√					
Study drug distribution				√	√	√	√	√[j]	
Drug accountability					√	√	√	√	√[j]
Adverse events	√	√	√	√	√	√	√	√	√

[a] Included study drug down-titration.
[b] Also required for patients prematurely discontinuing.
[c] An extra week was permitted for patients to meet randomization blood pressure criteria.
[d] Week –1 and Day 0 blood pressure must meet eligibility criteria.
[e] Prior to first dose of study drug.
[f] 24 ± 4 hrs since last dose (except Week 8. ± 2 hrs).
[g] Peak was 6 ± 1 hr post dosing at Visit 8. Peak was between 1600 and 2000 hrs at Visit 3.
[h] Required collection in fasting state.
[i] Females.
[j] Down titration medication.

Table 49: Inclusion and Exclusion criteria - Study 324

5.3 Selection of study population

5.3.1 Inclusion criteria

To be eligible for randomization, the protocol required that patients fulfill all of the following criteria:

1. Provision of a signed written or informed consent.
2. Male or female, 18 years (or legal age of consent) to 80 years of age.
3. DBP between 95 and 114 mmHg at Week –1 and Study Day 0.

5.3.2 Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

1. Significant clinical, laboratory or electrocardiographic abnormalities that placed the patient at undue risk (in the Investigator's opinion) including:
   a. Significant renal impairment (serum creatinine >2.0 mg/dl)
   b. Acute or chronic hepatitis or cirrhosis (clinical diagnosis)
   c. Uncontrolled hyperthyroidism (clinical diagnosis)

3. SBP ≥180 mmHg at Day 0

4. Hypersensitivity to or history of severe adverse reaction to beta-blockers or to hydrochlorothiazide

5. Asthma or chronic obstructive pulmonary disease with bronchospastic component.

6. Symptomatic bradycardia, heart rate <50 bpm, or sick sinus syndrome (unless managed by a pacemaker)

7. Heart block greater than first degree (unless managed by a pacemaker)

8. Poorly controlled diabetes mellitus (in Investigator's opinion; eg, poorly controlled diabetes mellitus resulting in hospitalization or symptomatic hypoglycemia within the past 3 months)

9. Moderately severe or severe symptomatic peripheral arterial disease, eg, claudication with walking less than 1 block

10. Other medical conditions that contraindicated use of diuretics or beta-blockers, eg, poorly controlled gout

11. Any medical condition that required treatment with a beta-blocker or diuretic, eg, recent myocardial infarction, chronic symptomatic angina pectoris, rapid atrial fibrillation, NYHA Class II to IV congestive heart failure, nephrolithiasis

12. Use of a medication contraindicated for use with a diuretic or beta-blocker, eg, lithium

13. Inability to be off antihypertensive medication for up to 16 weeks including calcium- channel blockers and beta-blockers used for other indications (Note: topical beta-blocking agents, eg, eye drops, were allowed)

14. Inability to discontinue medications that may contribute to increased BP, eg, corticosteroids exceeding the equivalent of prednisone 5 mg/day

15. Significant laboratory abnormalities including:

    a. Serum creatinine >2.0 mg/dl

    b. Serum alanine aminotransferase (ALT) or serum aspartate aminotransferase (AST) >2.5 x upper limit of reference range

    c. Serum potassium <3.0 mEq/L

    d. Serum sodium ≤130 mEq/L

Voluntary discontinuation by a patient
Patients were free to discontinue their participation in the study at any time, without prejudice to further treatment. Patients who discontinued were asked about the reason(s) for their discontinuation and about the presence of any AEs. If possible, they were seen and assessed by an investigator. Adverse events were followed up, and any investigational products and study materials were to be returned by the patient.

Specific reasons for discontinuing a patient from this study were as follows:

1. Voluntary discontinuation by the patient who was free to discontinue participation in the study at any time, without prejudice to further treatment

2. Safety reasons as judged by the investigator and/or AstraZeneca

3. Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca

4. Incorrect enrollment or randomization of the patient (Subject to discussion with the Sponsor).

5. Adverse event that, in the opinion of the investigator, precluded further study drug administration

6. Insufficient therapeutic response. The decision to discontinue a patient for elevated BP levels was based on the clinical judgment of the investigator. Examples included: sitting SBP exceeding 180 mmHg and/or DBP exceeding 110 mmHg on 2 consecutive occasions over a 3 to 4 day period despite a minimum of 2 weeks persisting for more than 6 weeks after starting double-blind study drug; or, BP levels of eminent safety risk in the opinion of the investigator.

7. Patient lost to follow-up

8. Development of an exclusion criterion, eg, pregnancy or requirement for a contraindicated medication (subject to discussion with the Sponsor).

Procedures for discontinuation

Procedures for discontinuation study drug included these instructions:

Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred.

When discontinuing chronically administered Toprol-XL, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 2 weeks and the patients should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, Toprol-XL administration may be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be

taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue Toprol-XL therapy abruptly even in patients treated only for hypertension.

Blinded study drug discontinuation medication kits were available for patients requiring study drug discontinuation to provide an opportunity for each patient to undergo gradual discontinuation of study drug.

Blinding
All study drug kits had an identical appearance. Study drug was prepared and packaged to be visually indistinguishable across treatment assignments. All study patients received the same dosing instructions. Specifically, study drug was packaged on blister cards with tablets of active drug or placebo configured to correspond to the assigned treatment. Study drug discontinuation blister cards were also prepared so as to maintain the study blind.

Blinding of investigators, staff, Sponsor, Contract Research Organization (CRO), and randomization center was assured through procedures for data management, monitoring of sites, clinical supplies, etc. in accordance with Sponsor SOPs.

Compliance

Investigators were advised that it was essential that all medication was accounted for by the investigator or institution, and that any discrepancies were explained and documented.

Patients were required to return all unused medication and empty containers to the investigator. The number of tablets dispensed and returned, dates when dispensed and returned, and dates of first and last dose were recorded, and this information was used to determine patient compliance and study drug accountability.

The investigator retained the returned medication until AstraZeneca authorized personnel collected it, along with any study treatments not dispensed. At the termination of the study or at the request of the Sponsor, the investigator returned any unused supplies to AstraZeneca.
At the end of the study, study drug delivery records and records of usage and returned stock were reconciled with full accountability for any discrepancies. Certificates of delivery and return were signed.

6.1.4 Efficacy Findings

Patient population: The trial investigators randomized 1571 patients; 89% (n=1395) completed the study and 11% (n=176) discontinued for a variety of reasons; 2.9% (n=46) discontinued because of adverse events.

The efficacy analyses were all based upon the ITT population using Week 8/LOCF. This means that if a patient dropped from the study early and did not have a Week 8 measurement, the last

available observation was used instead. Overall, 91% of ITT patients had Week 8 values. The placebo group had the fewest patients with Week 8 values, 84%. The active treatment groups had, at a minimum, 88% of patients with Week 8 values, and the Week 8 retention rate did not appear to be dose-related.

All analyses were repeated for the ITT population using only Week 8 values and for the PP population. Overall, the results were very consistent with the ITT, Week 8/LOCF analyses. It should be noted that 85% of randomized patients were included in the PP population indicating good compliance with the protocol procedures.

ANCOVA analyses demonstrated that all combinations were significantly better than placebo in reducing trough SiDBP and SiSBP. In pairwise comparisons of combinations versus their components, the decline in SiDBP was numerically greater for all combinations except for Toprol-XL/HCT 25/6.25 mg. Four treatment combinations (Toprol-XL/HCT 100/6.25 mg, 100/12.5 mg, 100/25 mg, and 200/25 mg) had significantly greater reductions than both of their respective components, at a nominal 0.05 significance level. Pairwise comparisons also indicated that 4 low dose Toprol-XL/HCT combinations (25/6.25 mg, 25/12.5 mg, 50/6.25 mg, and 50/12.5 mg) were approximately as effective as at least 1 of the high dose monotherapies.

Subgroup analyses of trough SiDBP and SiSBP suggested greater blood pressure reductions for women than men but the difference was small. Black patients appeared to be slightly more responsive to HCT alone and non-Black patients were more responsive to Toprol-XL alone, which was reflected in the combination treatments.

Efficacy: Primary variable: Change from baseline to Week 8 in trough SiDBP.

Secondary outcome variables: Secondary measures of effect included the change from baseline to Week 8 in trough SiSBP, trough StSBP and StDBP, and peak SiSBP and SiDBP.

Secondary objectives were as follows:

- To determine whether at least 1 Toprol-XL/HCT combination exceeded the BP lowering effects of its individual components with regard to the placebo-corrected mean change from baseline to Week 8 in trough sitting systolic blood pressure (SiSBP).

- To describe the dose effects of the individual drugs (Toprol-XL and HCT) and their combinations by response surface analysis in terms of the change from baseline to Week 8 in trough SiDBP and SiSBP.

- To compare each Toprol-XL/HCT combination to its components with regard to the change from baseline to Week 8 in trough SiDBP and SiSBP.

- To compare each combination to placebo with regard to the change from baseline to Week 8 in SiDBP and SiSBP.

- To determine whether at least 1 treatment combination was superior to the individual components with regard to the change from baseline to Week 8 in peak SiDBP and SiSBP and in trough standing diastolic blood pressure and systolic blood pressure (StDBP and StSBP).

Table 50: Descriptive statistics for trough SiDBP at study entry and randomization- Study 324

7.2.1.1 Descriptive summary of trough SiDBP

Table 21 presents descriptive statistics for trough SiDBP at study entry and at randomization. The mean SiDBP values at study entry were similar across the 17 treatment groups with mean values ranging from 91.6 to 94.5 mmHg. Patients then proceeded into a 4- to 5-week placebo run-in period in which they were not allowed to take any other antihypertensive medications. At the time of randomization, trough SiDBP mean values had risen to a mean value of 100.1 mmHg overall, with mean values ranging from 98.4 to 101.0 mmHg across the treatment groups.

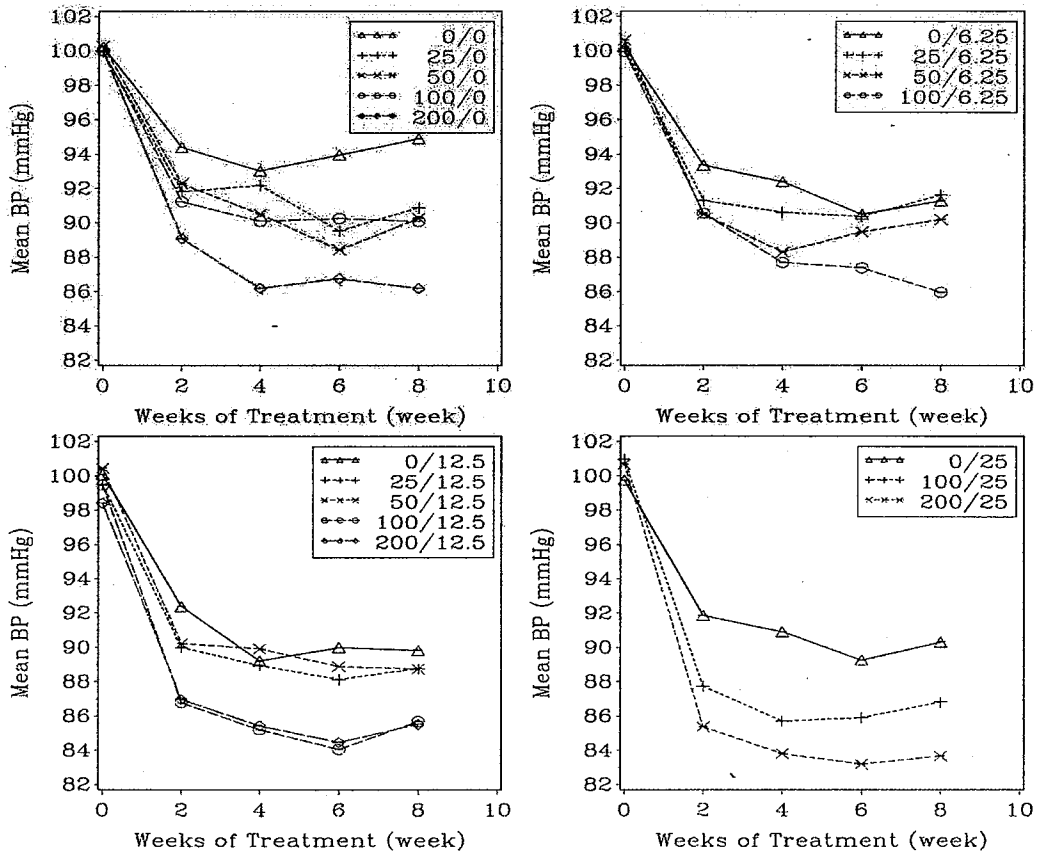
Table 21 Descriptive statistics for trough SiDBP at study entry and randomization (all randomized patients)

		Toprol-XL dosage					
	HCT dosage	0 mg	25 mg	50 mg	100 mg	200 mg	Total
All randomized patients, N	0 mg	152	89	94	96	52	1571
	6.25 mg	86	147	137	45	NA	
	12.5 mg	105	142	148	95	43	
	25.0 mg	48	NA	NA	42	50	
Trough SiDBP							
-At study entry (Visit 1):							
Mean (SD)	0 mg	93.7 (8.6)	91.9 (8.7)	92.9 (9.0)	92.0 (7.8)	93.9 (8.7)	93.0 (8.9)
	6.25 mg	92.2 (8.5)	93.7 (9.3)	94.3 (9.6)	92.9 (10.1)	NA	
	12.5 mg	92.9 (9.1)	93.4 (8.9)	92.6 (8.9)	91.6 (9.3)	92.2 (8.2)	
	25.0 mg	91.7 (9.0)	NA	NA	94.5 (7.7)	92.5 (9.0)	
-At baseline, randomization							
Mean (SD)	0 mg	100.2 (4.4)	100.0 (4.1)	100.3 (4.1)	100.0 (3.9)	100.0 (4.7)	100.1 (4.2)
	6.25 mg	100.2 (4.5)	100.1 (3.8)	100.6 (4.7)	100.0 (4.6)	NA	
	12.5 mg	100.1 (4.1)	99.6 (3.8)	100.5 (4.4)	99.6 (4.0)	98.4 (3.4)	
	25.0 mg	99.8 (4.2)	NA	NA	101.0 (5.0)	100.7 (4.4)	

N Total number of patients in treatment group.
SiDBP Sitting diastolic blood pressure.

As figures 17 and 19 illustrate, mean SiDBP and SiSBP, at trough, declined within the first 2 weeks with all treatments. These reductions were generally maintained until the end of treatment at Week 8. The figure implies that mean SiDBP values less than 90 mmHg were attainable with several of the active treatments including the Toprol-XL/HCT 50/6.25 mg, Toprol-XL/HCT 100/6.25 mg and all the Toprol-XL combinations with HCT 12.5 mg and with HCT 25 mg. Figure 18 shows the raw mean reductions in trough SiDBP from baseline to week 8/LOCF.

Figure 17: Trough SiDBP from baseline to week 8/LOCF

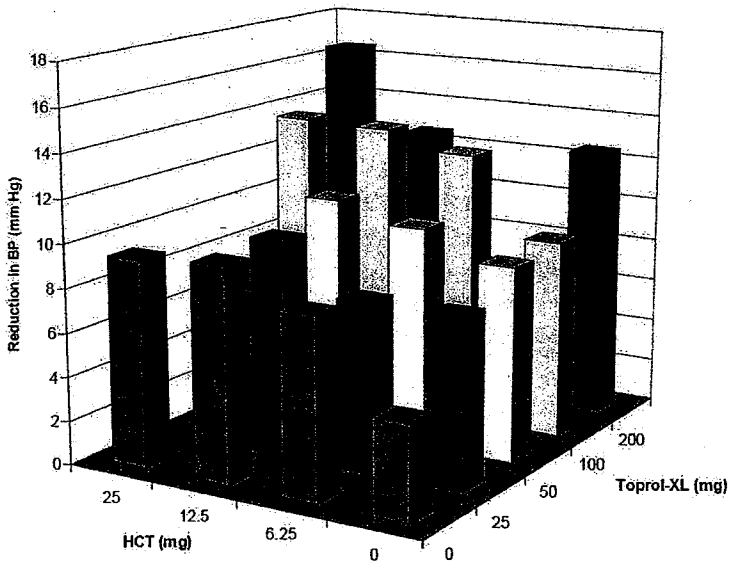


The placebo group in this study had a raw mean change from baseline of –4.3 mmHg. With Toprol-XL monotherapy, SiDBP declined in an approximately dose-related manner (from –7.7 mmHg with Toprol-XL 25 mg to –12.5 mmHg with Toprol-XL 200 mg). The declines with HCT monotherapy were similar in magnitude to those of Toprol-XL monotherapy but the reductions did not appear to be as dose related (–8.2 with HCT 6.25 mg, –9.7 with HCT 12.5 mg and –9.4 with HCT 25 mg).

Otherwise, mean changes from baseline for the combination treatment groups tended to demonstrate dose-related SiDBP changes that ranged from –7.7 mmHg for the Toprol- XL/HCT 25/6.25 mg group to –16.5 mmHg for the Toprol-XL/HCT 200/25 mg group. The magnitude of the reductions with the Toprol-XL 100 mg combinations with HCT (–12.7 to –13.6 mmHg) were about the same as those attained by the highest dose (200 mg) of Toprol- XL either alone (–12.5 mmHg) or in combination with HCT 12.5 mg (–12.6 mmHg). The mean changes from baseline in SiDBP are further illustrated in Figure 3.

Figure 18: Raw mean reductions from baseline to week 8/LOCF in trough SiDBP-ITT

Figure 3 Raw mean reductions from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)



Primary analysis of changes from baseline in trough SiDBP

Table 51 presents the results of the T_{AVE} test. The primary objective of the study was to determine whether at least 1 Toprol-XL/HCT combination exceeds the effects of both individual components with respect to changes from baseline to Week 8/LOCF in trough SiDBP. The T statistics versus Toprol-XL and versus HCT, presented in the table, are the actual 2-sample T statistic values comparing a combination versus the corresponding monotherapy treatment group. For example, under T statistics versus Toprol-XL monotherapy, the Toprol-XL/HCT 100/12.5 mg cell has a value of –3.4133, which is the T-statistic value for comparing this combination treatment group versus the Toprol-XL 100 mg treatment group. These T-statistics are a basis for the TAVE calculation.

The result was a T_{AVE} statistic equal to –1.33 which has an associated p-value of 0.0015. As this is a 1-sided hypothesis test, it is a significant finding when compared to a significance level of 0.025 and confirms that at least 1 combination lowers trough SiDBP more effectively than both of its components.

Table 51: Tave statistics for changes from baseline to week 8/LOCF-ITT-Study 324

Table 23 T_{AVE} test results: changes from baseline to Week 8/LOCF in trough SiDBP (mmHg) (intent-to-treat population)

	HCT dosage	Toprol-XL dosage			
Trough SiDBP		**25 mg**	**50 mg**	**100 mg**	**200 mg**
T statistics vs Toprol-XL monotherapy	6.25 mg	0.0020	–1.0228	–2.2929	NA
	12.5 mg	–1.8238	–1.7151	–3.4133	–0.0619
	25.0 mg	NA	NA	–2.7916	–2.3156
T statistics vs HCT monotherapy	6.25 mg	0.4136	–1.5847	–2.8217	NA
	12.5 mg	–0.1907	–1.1065	–3.0539	–1.8512
	25.0 mg	NA	NA	–2.3116	–4.0334
T_{AVE} statistic		–1.3269			
p-value		0.0015			

LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure.
Data derived from Table 11.2.2.1.5, Section 11.2.

ANCOVA analyses for changes from baseline in trough SiDBP

Supportive ANCOVA analyses were performed to further describe the treatment effects.

Table 52 summarizes the ANCOVA model noting terms for Toprol-XL, HCT, the interaction between Toprol-XL and HCT, and baseline trough SiDBP. According to the model, both drugs significantly reduced trough SiDBP from baseline to Week 8/LOCF ($p<0.050$). (The baseline covariate was also significant.) The interaction between the 2 drugs was also considered significant, at a 0.10 level.

In an ANCOVA model without the interaction term, the treatment effects remained significant, as did the baseline covariate. Prior to Study 324, there was no existing evidence to suggest a biological basis for a treatment interaction between the 2 drugs. However, there was no interaction between the components ($p=0.73$).

Table 52: ANCOVA model with interaction for changes from baseline to week 8/LOCF in trough SiDBP-ITT

Table 24 Summary of ANCOVA model with interaction for changes from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)

	DF	Mean square estimate	F-value	P-value
Parameter				
Toprol-XL	4	1211.50	17.40	<0.0001
HCT	3	851.72	12.23	<0.0001
Toprol-XL*HCT	9	115.21	1.65	0.0951
Baseline SiDBP	1	281.10	4.04	0.0447
Model statistics				
Mean square error	1541	69.63		
F-statistic for model			9.80	
P-value for model				<0.0001

DF Degrees of freedom; SiDBP Sitting diastolic blood pressure.
Data derived from Table 11.2.2.1.7, Section 11.2.

The ANCOVA model, with the interaction term included, was used to perform 3 sets of pairwise comparisons: the combinations versus placebo, the combinations versus their components, and low-dose combinations versus high-dose monotherapies. The tests were 2- sided and the level used in assessing significance for the pairwise comparisons was 0.050. P-values are not adjusted for multiplicity unless otherwise specified.

Table 53 shows the results of the pairwise comparisons of each of the 9 combination treatment groups versus the placebo group. The mean differences ranged from –3.4 for the lowest strength combination group (Toprol-XL/HCT 25/6.25 mg) to –12.2 for the highest-strength combination group (Toprol-XL/HCT 200/25 mg). All 9 combination treatment groups had highly significantly reductions from baseline to Week 8/LOCF in trough SiDBP when compared to the placebo group (all p-values =0.0004).

Tables 54 and 59 present pairwise comparisons for the low-dose combination to high-dose monotherapies in changes from baseline to the LOCF in trough SiDBP for the ITT population. Positive mean differences indicate that the combination treatment group observed less BP lowering effect than the high-dose monotherapy. Negative differences indicate that the combination treatment group had greater BP lowering than the monotherapy.

Table 53: Pairwise comparisons for each combination to placebo change from baseline to week 8/LOCF in trough SiDBP

Table 25 Pairwise comparisons for each combination to placebo, change from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)

Combination treatment group	Comparator treatment	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Placebo	–3.44	–5.34, –1.53	0.0004
Toprol-XL/HCT, 25/12.5 mg	Placebo	–5.66	–7.57, –3.74	<0.0001
Toprol-XL/HCT, 50/6.25 mg	Placebo	–5.79	–7.72, –3.86	<0.0001
Toprol-XL/HCT, 50/12.5 mg	Placebo	–6.59	–8.48, –4.69	<0.0001
Toprol-XL/HCT, 100/6.25 mg	Placebo	–8.48	–11.26, –5.71	<0.0001
Toprol-XL/HCT, 100/12.5 mg	Placebo	–9.25	–11.39, –7.10	<0.0001
Toprol-XL/HCT, 100/25 mg	Placebo	–9.27	–12.13, –6.42	<0.0001
Toprol-XL/HCT, 200/12.5 mg	Placebo	–8.49	–11.32, –5.66	<0.0001
Toprol-XL/HCT, 200/25.0 mg	Placebo	–12.19	–14.88, –9.50	<0.0001

Note: Based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction between Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure; CI Confidence interval; LL Lower limit; UL Upper limit.
Data derived from Table 11.2.2.1.12, Section 11.2.

Table 53 presents pairwise comparisons of the combination treatment groups versus their component treatment groups. Numerically, all combinations induced greater trough SiDBP reductions from baseline to Week 8 than their components with the exception of the TXL/HCT 25/6.25 mg combination.

Table 54 below summarizes pairwise comparisons between combination and monotherapy for mean change from baseline to week 8 /LOCF in trough SiDBP (intent to treat patients)

Table 54: Combination versus comparator monotherapy

Combination treatment group	Comparator monotherapy	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Toprol-XL, 25 mg	0.02	–2.19, 2.23	0.9858
Toprol-XL/HCT, 25/12.5 mg	Toprol-XL, 25 mg	–2.20	–4.42, 0.01	0.0516
Toprol-XL/HCT, 50/6.25 mg	Toprol-XL, 50 mg	–1.17	–3.37, 1.03	0.2986
Toprol-XL/HCT, 50/12.5 mg	Toprol-XL, 50 mg	–1.97	–4.14, 0.20	0.0753
TOPROL-X/HCTL, 100/6.25 mg	Toprol-XL, 100 mg	–3.63	–6.59, –0.67	0.0163
TOPROL-X/HCT, 100/12.5 mg	Toprol-XL, 100 mg	–4.39	–6.77, –2.01	0.0003
Toprol-XL/HCT, 100/25 mg	Toprol-XL, 100 mg	–4.42	–7.45, –1.39	0.0043
Toprol-XL/HCT, 200/12.5 mg	Toprol-XL, 200 mg	–0.27	–3.66, 3.12	0.8749
Toprol-XL/HCT, 200/25 mg	Toprol-XL, 200 mg	–3.98	–7.25, –0.71	0.0173
Toprol-XL/HCT, 25/6.25 mg	HCT, 6.25 mg	0.48	–1.75, 2.71	0.6718
Toprol-XL/HCT, 50/6.25 mg	HCT, 6.25 mg	–1.87	–4.12, 0.39	0.1046
Toprol-XL/HCT, 100/6.25 mg	HCT, 6.25 mg	–4.56	–7.57, –1.55	0.0030
Toprol-XL/HCT, 25/12.5 mg	HCT, 12.5 mg	–0.27	–2.39, 1.84	0.8000
Toprol-XL/HCT, 50/12.5 mg	HCT, 12.5 mg	–1.20	–3.30, 0.89	0.2613
Toprol-XL/HCT, 100/12.5 mg	HCT, 12.5 mg	–3.86	–6.19, –1.53	0.0012
Toprol-XL/HCT, 200/12.5 mg	HCT, 12.5 mg	–3.10	–6.07, –0.13	0.0409
Toprol-XL/HCT, 100/25 mg	HCT, 25 mg	–4.14	–7.60, –0.69	0.0189
Toprol-XL/HCT, 200/25 mg	HCT, 25 mg	–7.06	–10.39, –3.74	<0.0001

Note: Based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction of Toprol-XL and

In comparison to Toprol-XL 200 mg, the low-dose combinations Toprol-XL/HCT 25/6.25 mg, 25/12.5 mg, and 50/6.25 mg were generally not as effective. However, the Toprol-XL/HCT 50/12.5 mg group was not significantly different from Toprol-XL 200 mg. The mean difference was 1.63 mmHg (95% confidence interval: –1.03 to 4.29 mmHg).(Table 55).

While statistical interpretation of these comparisons must take into account that sample sizes (and power) differed for some contrasts, 4 combination treatment groups of Toprol-XL/HCT (100/6.25 mg, 100/12.5 mg, 100/25 mg, and 200/25 mg) all had significantly ($p<0.050$) greater reductions from baseline in trough SiDBP compared to their respective monotherapy treatment groups. ***In a 5th combination treatment group, Toprol-XL/HCT 200/12.5 mg, SiDBP change was not significantly different from the Toprol-XL 200 mg group, but it was significantly greater than the HCT 12.5 mg group.***

Examining the comparisons to HCT 25 mg, the 4 low-dose combination treatment groups were not significantly different from this high-dose monotherapy (p-values ranging from

0.2239 to 0.7045). The mean differences between the combinations and HCT 25 mg were small, all less than 2 mmHg, and the 95% confidence intervals for the mean differences were all within a 5 mmHg limit.

According to these comparisons, the Toprol-XL/HCT combination groups with Toprol-XL 25 or 50 mg and HCT 6.25 or 12.5 mg provided similar effectiveness to HCT 25 mg in lowering trough SiDBP from baseline to Week 8/LOCF. Three low-dose combinations induced numerically greater reductions than HCT 25 mg (Toprol-XL/HCT 25/12.5 mg, 50/6.25 mg, 50/12.5 mg). On the other hand, the 25/6.25 mg group did not perform as well as the Toprol-XL 200 mg treatment group, and only the 50/12.5 mg group yielded results that approached the effectiveness of this high-dose (200 mg) Toprol-XL group.

To further characterize the additivity properties of the 2 drugs, additional analyses were considered (Table 29). As no drug-drug interaction was anticipated, it was possible that the 2 drugs would act independently and with fully additive effects. The table considers the mean changes from baseline to Week 8/LOCF in trough SiDBP, after subtraction of the placebo effect. The top set of numbers are the sum of the monotherapy effects. For example, the –7.35 mmHg in the Toprol-XL/HCT 25/6.25 mg group represents the sum of the –3.43 net change after placebo from the Toprol-XL 25 mg group and the –3.92 net change after placebo from the HCT 6.25 mg group. These numbers provide an estimate of the potentially additive effects of the 2 drugs given their independently observed effects. The mean changes actually observed from the combination treatment groups are provided in the second set of numbers. The bottom set of numbers in the table provides the difference between the observed effects from the combination treatment groups and the expected, potential effects under the condition of full additivity and with the observed effects from the 2 drugs when given separately (Table 56).

Positive values for the differences indicate that the combination treatment groups did not perform to full additivity. The largest difference, 5.26, was observed with the Toprol- XL/HCT 200/12.5 mg treatment group. This treatment group had a mean change from baseline in SiDBP of –8.30 mmHg, whereas the 2 corresponding monotherapies when added together had a potential effect of –13.56 mmHg. The second largest difference between the observed and expected values was in the Toprol-XL/HCT 25/6.25 mg group, 3.92 mmHg. The other Toprol-XL/HCT low-dose combination treatment groups (25/12.5 mg, 50/6.25 mg, and 50/12.5 mg) had differences ranging from 2.71 to 3.38 mmHg. However, the 3 combination treatment groups with Toprol-XL 100 mg and the Toprol-XL/HCT 200/25 mg group had differences that were small, 0.30 to 1.03 mmHg, which indicated that for these 4 treatment groups the effects of the 2 drugs were almost fully additive.

It was this trend (less than full additivity at the extremes of the dose ranges), particularly for the Toprol-XL/HCT 200/12.5 mg and 25/6.25 mg treatment groups, that accounts for the significant interaction term for Toprol-XL and HCT in the ANCOVA model (Table 56).

Table 55: Pairwise comparisons for low dose combinations to high-dose monotherapies, change from baseline to week 8 /LOCF in trough SiDBP-

Table 28 Pairwise comparisons for low-dose combinations to high-dose monotherapies, change from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)

Combination treatment group	Comparator monotherapy treatment	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Toprol-XL, 200 mg	4.78	2.11, 7.44	0.0005
Toprol-XL/HCT, 25/6.25 mg	HCT, 25 mg	1.69	–1.03, 4.42	0.2239
Toprol-XL/HCT, 25/12.5 mg	Toprol-XL, 200 mg	2.56	–0.12, 5.23	0.0611
Toprol-XL/HCT, 25/12.5 mg	HCT, 25 mg	–0.53	–3.26, 2.20	0.7045
Toprol-XL/HCT, 50/6.25 mg	Toprol-XL, 200 mg	2.43	–0.26, 5.11	0.0767
Toprol-XL/HCT, 50/6.25 mg	HCT, 25 mg	–0.66	–3.40, 2.09	0.6393
Toprol-XL/HCT, 50/12.5 mg	Toprol-XL, 200 mg	1.63	–1.03, 4.29	0.2304
Toprol-XL/HCT, 50/12.5 mg	HCT, 25 mg	–1.46	–4.18, 1.26	0.2938

Note: Based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction of Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure; CI Confidence Interval; LL Lower limit; UL Upper Limit.

Table 56: Descriptive assessment of additivity from baseline to week 8/LOCF in trough SiDBP

Table 29 Descriptive assessment of additivity based upon placebo-adjusted mean changes from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)

	HCT dosage	Toprol-XL dosage			
Trough SiDBP		**25 mg**	**50 mg**	**100 mg**	**200 mg**
Sum of mean changes for monotherapies (expected change if treatments are additive)	6.25 mg	–7.35	–8.54	–8.75	–12.11
	12.5 mg	–8.80	–9.99	–10.2	–13.56
	25.0 mg	–8.51	–9.70	–9.91	–13.27
Observed mean change for combinations	6.25 mg	–3.43	–5.83	–8.45	NA
	12.5 mg	–5.59	–6.61	–9.17	–8.30
	25.0 mg	NA	NA	–9.35	–12.24
Difference (observed minus expected)	6.25 mg	3.92	2.71	0.30	NA
	12.5 mg	3.21	3.38	1.03	5.26
	25.0 mg	NA	NA	0.56	1.03

Note: Values are placebo-adjusted. If the difference is negative, then the combination had a greater than additive effect; if the difference is positive, then the combination had a less than additive effect.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure.
Data derived from Table 11.2.2.1.6, Section 11.2.

Table 57: Mean differences between Combination product and monotherapies. ITT- Study 324

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Combination treatment group	Comparator monotherapy	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Toprol-XL, 25 mg	0.02	–2.19, 2.23	0.9858
Toprol-XL/HCT, 25/12.5 mg	Toprol-XL, 25 mg	–2.20	–4.42, 0.01	0.0516
Toprol-XL/HCT, 50/6.25 mg	Toprol-XL, 50 mg	–1.17	–3.37, 1.03	0.2986
Toprol-XL/HCT, 50/12.5 mg	Toprol-XL, 50 mg	–1.97	–4.14, 0.20	0.0753
TOPROL-X/HCTL, 100/6.25 mg	Toprol-XL, 100 mg	–3.63	–6.59, –0.67	0.0163
TOPROL-X/HCT, 100/12.5 mg	Toprol-XL, 100 mg	–4.39	–6.77, –2.01	0.0003
Toprol-XL/HCT, 100/25 mg	Toprol-XL, 100 mg	–4.42	–7.45, –1.39	0.0043
Toprol-XL/HCT, 200/12.5 mg	Toprol-XL, 200 mg	–0.27	–3.66, 3.12	0.8749
Toprol-XL/HCT, 200/25 mg	Toprol-XL, 200 mg	–3.98	–7.25, –0.71	0.0173
Toprol-XL/HCT, 25/6.25 mg	HCT, 6.25 mg	0.48	–1.75, 2.71	0.6718
Toprol-XL/HCT, 50/6.25 mg	HCT, 6.25 mg	–1.87	–4.12, 0.39	0.1046
Toprol-XL/HCT, 100/6.25 mg	HCT, 6.25 mg	–4.56	–7.57, –1.55	0.0030
Toprol-XL/HCT, 25/12.5 mg	HCT, 12.5 mg	–0.27	–2.39, 1.84	0.8000
Toprol-XL/HCT, 50/12.5 mg	HCT, 12.5 mg	–1.20	–3.30, 0.89	0.2613
Toprol-XL/HCT, 100/12.5 mg	HCT, 12.5 mg	–3.86	–6.19, –1.53	0.0012
Toprol-XL/HCT, 200/12.5 mg	HCT, 12.5 mg	–3.10	–6.07, –0.13	0.0409
Toprol-XL/HCT, 100/25 mg	HCT, 25 mg	–4.14	–7.60, –0.69	0.0189
Toprol-XL/HCT, 200/25 mg	HCT, 25 mg	–7.06	–10.39, –3.74	<0.0001

Tables 54 and 59 present pairwise comparisons for the low-dose combination to high-dose monotherapies in changes from baseline to the LOCF in trough SiDBP for the ITT population. Positive mean differences indicate that the combination treatment group observed less BP lowering effect than the high-dose monotherapy. Negative differences indicate that the combination treatment group had greater BP lowering than the monotherapy.

Table 58: Pairwise comparisons for low-dose combinations to high-dose monotherapies

Table 28 Pairwise comparisons for low-dose combinations to high-dose monotherapies, change from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)

Combination treatment group	Comparator monotherapy treatment	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Toprol-XL, 200 mg	4.78	2.11, 7.44	0.0005
Toprol-XL/HCT, 25/6.25 mg	HCT, 25 mg	1.69	–1.03, 4.42	0.2239
Toprol-XL/HCT, 25/12.5 mg	Toprol-XL, 200 mg	2.56	–0.12, 5.23	0.0611
Toprol-XL/HCT, 25/12.5 mg	HCT, 25 mg	–0.53	–3.26, 2.20	0.7045
Toprol-XL/HCT, 50/6.25 mg	Toprol-XL, 200 mg	2.43	–0.26, 5.11	0.0767
Toprol-XL/HCT, 50/6.25 mg	HCT, 25 mg	–0.66	–3.40, 2.09	0.6393
Toprol-XL/HCT, 50/12.5 mg	Toprol-XL, 200 mg	1.63	–1.03, 4.29	0.2304
Toprol-XL/HCT, 50/12.5 mg	HCT, 25 mg	–1.46	–4.18, 1.26	0.2938

Note: Based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction of Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure; CI Confidence Interval; LL Lower limit; UL Upper Limit.
Data derived from Table 11.2.2.1.13, Section 11.2

Table 59: Descriptive assessment of additivity from baseline to week 8/LOCF in trough SiDBP

Table 29 Descriptive assessment of additivity based upon placebo-adjusted mean changes from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)

	HCT dosage	Toprol-XL dosage			
Trough SiDBP		25 mg	50 mg	100 mg	200 mg
Sum of mean changes for monotherapies (expected change if treatments are additive)	6.25 mg	–7.35	–8.54	–8.75	–12.11
	12.5 mg	–8.80	–9.99	–10.2	–13.56
	25.0 mg	–8.51	–9.70	–9.91	–13.27
Observed mean change for combinations	6.25 mg	–3.43	–5.83	–8.45	NA
	12.5 mg	–5.59	–6.61	–9.17	–8.30
	25.0 mg	NA	NA	–9.35	–12.24
Difference (observed minus expected)	6.25 mg	3.92	2.71	0.30	NA
	12.5 mg	3.21	3.38	1.03	5.26
	25.0 mg	NA	NA	0.56	1.03

Note: Values are placebo-adjusted. If the difference is negative, then the combination had a greater than additive effect; if the difference is positive, then the combination had a less than additive effect.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure.
Data derived from Table 11.2.2.1.6, Section 11.2.

Table 60: Regression model for change from baseline to week 8/LOCF in trough SiDBP- ITT-Study 324

regression model, for change from baseline to Week 8/LOCF in trough SiDBP (intent-to-treat population)

Treatment group	Predicted change	Placebo-corrected change	95% CI for placebo-corrected change LL, UL
Toprol-XL/HCT, 0/0 mg	–5.34	0.00	–1.15, 1.15
Toprol-XL, 25 mg	–6.76	–1.41	–2.36, –0.46
Toprol-XL, 50 mg	–7.98	–2.64	–3.66, –1.62
Toprol-XL, 100 mg	–9.88	–4.53	–5.77, –3.30
Toprol-XL, 200 mg	–11.43	–6.09	–8.03, –4.15
HCT, 6.25 mg	–7.24	–1.90	–2.87, –0.92
HCT, 12.5 mg	–8.59	–3.25	–4.34, –2.16
HCT, 25.0 mg	–9.64	–4.30	–6.30, –2.30
Toprol-XL/HCT, 25/6.25 mg	–8.66	–3.31	–3.97, –2.66
Toprol-XL/HCT, 25/12.5 mg	–10.00	–4.66	–5.46, –3.86
Toprol-XL/HCT, 50/6.25 mg	–9.88	–4.54	–5.25, –3.82
Toprol-XL/HCT, 50/12.5 mg	–11.23	–5.89	–6.73, –5.04
Toprol-XL/HCT, 100/6.25 mg	–11.78	–6.43	–7.44, –5.43
Toprol-XL/HCT, 100/12.5 mg	–13.13	–7.78	–8.86, –6.70
Toprol-XL/HCT, 100/25.0 mg	–14.18	–8.83	–10.84, –6.83
Toprol-XL/HCT, 200/12.5 mg	–14.68	–9.34	–11.30, –7.37
Toprol-XL/HCT, 200/25.0 mg	–15.73	–10.39	–12.46, –8.32

LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure.
Derived from Table 11.2.2.1.28.

In Figure 4, changes from baseline are shown in a positive scale (ie, reductions in BP). The response surface shows greater BP reductions with increasing doses of Toprol-XL and HCT, independently and in combination. The pyramid symbols in the figure represent the treatment group means. Generally, the response surface fits the treatment group means well, with the possible exceptions at the Toprol-XL/HCT 200/12.5 mg combination and the placebo group.

Figure 4 in text immediately above is Figure 21 on page 116 below in this review.

Table 61: Descriptive statistics for trough SiSBP at study entry and randomization

Table 33 Descriptive statistics for trough SiSBP at study entry and randomization (all randomized patients)

		TOPROL XL dosage					
	HCT dosage	0 mg	25 mg	50 mg	100 mg	200 mg	Total
All randomized patients, N	0 mg	152	89	94	96	52	1571
	6.25 mg	86	147	137	45	NA	
	12.5 mg	105	142	148	95	43	
	25.0 mg	48	NA	NA	42	50	
Trough SiSBP							
At study entry (Visit 1)							
Mean (SD)	0 mg	144.0 (14.5)	141.2 (13.7)	142.3 (13.6)	141.5 (14.4)	142.6 (16.0)	143.2 (14.7)
	6.25 mg	142.2 (14.7)	145.1 (15.5)	144.5 (15.8)	142.7 (16.3)	NA	
	12.5 mg	142.6 (14.4)	143.2 (14.7)	144.1 (14.6)	141.9 (14.8)	143.5 (13.8)	
	25.0 mg	141.4 (13.7)	NA	NA	145.2 (14.2)	143.8 (16.5)	
At baseline, randomization							
Mean (SD)	0 mg	151.1 (13.2)	148.7 (11.2)	150.0 (11.7)	150.5 (12.4)	151.3 (11.6)	151.1 (12.4)
	6.25 mg	151.6 (12.6)	151.4 (12.1)	151.4 (12.4)	150.7 (13.2)	NA	
	12.5 mg	151.2 (13.2)	150.3 (12.6)	153.0 (12.2)	152.5 (12.3)	150.0 (12.0)	
	25.0 mg	151.0 (12.6)	NA	NA	153.5 (12.4)	148.9 (12.9)	

N Total number of patients in treatment group

Figure 19: Trough SiSBP over time- ITT- Study 324

Figure 6 Trough SiSBP over time (intention-to-treat population)

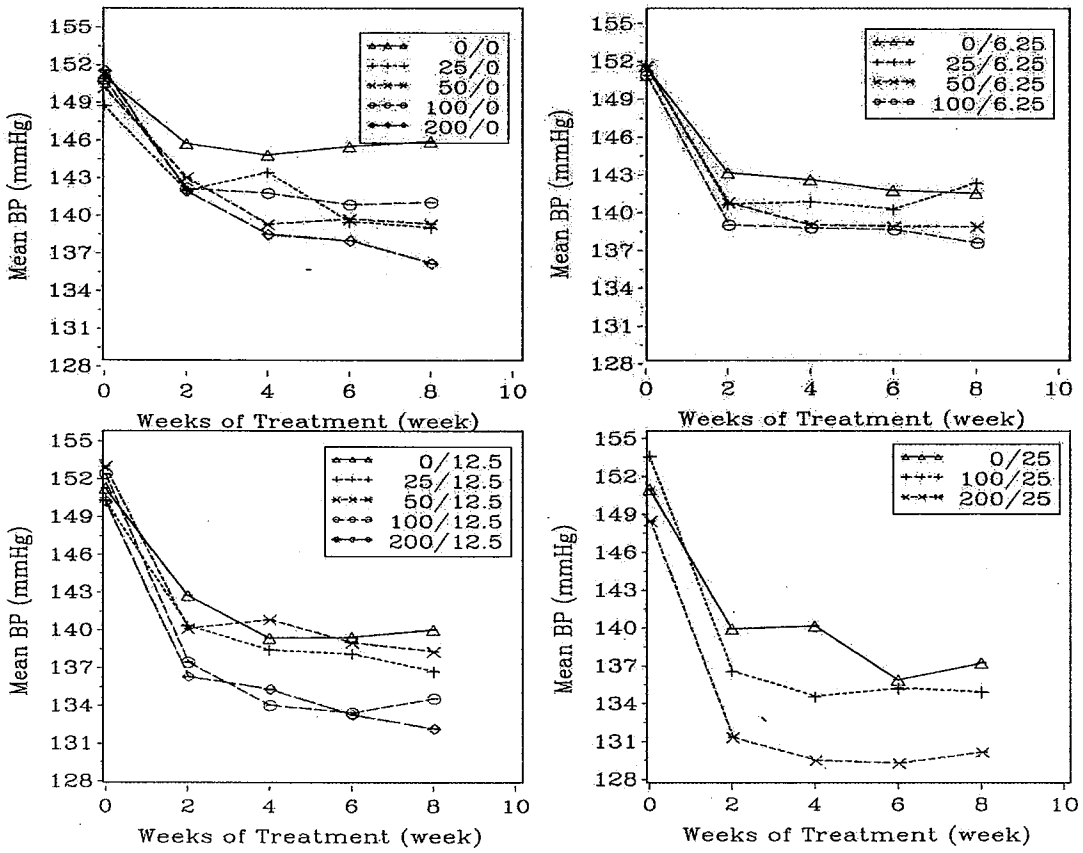

Figure 20: Trough SiSBP -ITT-Study 324

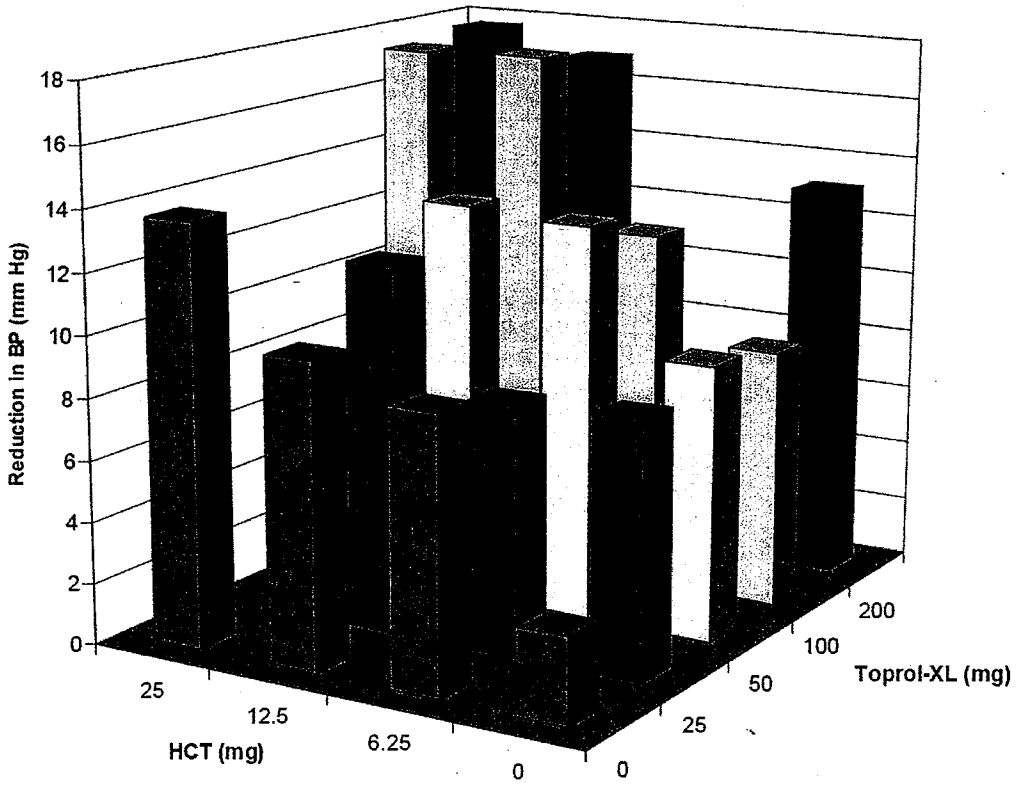

Table 62: Pairwise comparisons for each combination to placebo from baseline to week 8/LOCF

Table 37 Pairwise comparisons for each combination to placebo, change from baseline to Week 8/LOCF in trough SiSBP (intent-to-treat population)

Combination treatment group	Comparator treatment	Mean difference	CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Placebo	–5.16	–8.24, –2.08	0.0011
Toprol-XL/HCT, 25/12.5 mg	Placebo	–9.56	–12.66, –6.46	<0.0001
Toprol-XL/HCT, 50/6.25 mg	Placebo	–10.06	–13.19, –6.93	<0.0001
Toprol-XL/HCT, 50/12.5 mg	Placebo	–9.82	–12.89, –6.76	<0.0001
Toprol-XL/HCT, 100/6.25 mg	Placebo	–9.30	–13.80, –4.80	0.0001
Toprol-XL/HCT, 100/12.5 mg	Placebo	–14.36	–17.84, –10.88	<0.0001
Toprol-XL/HCT, 100/25.0 mg	Placebo	–13.84	–18.46, –9.21	<0.0001
Toprol-XL/HCT, 200/12.5 mg	Placebo	–14.54	–19.12, –9.96	<0.0001
Toprol-XL/HCT, 200/25.0 mg	Placebo	–15.85	–20.20, –11.49	<0.0001

Note: Based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction of Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiSBP Sitting systolic blood pressure; CI Confidence interval; LL Lower limit; UL Upper Limit.
Data derived from Table 11.2.3.1.12, Section 11.2.

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Table 63: Mean change from baseline to week 8/LOCF in trough SiSBP - ITT- Study 324

mean change from baseline to Week 8/LOCF in trough SiSBP (intent-to-treat population)

Combination treatment group	Comparator monotherapy	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Toprol-XL, 25 mg	1.19	–2.39, 4.77	0.5149
Toprol-XL/HCT, 25/12.5 mg	Toprol-XL, 25 mg	–3.21	–6.80, 0.38	0.0803
Toprol-XL/HCT, 50/6.25 mg	Toprol-XL, 50 mg	–3.43	–7.00, 0.14	0.0596
Toprol-XL/HCT, 50/12.5 mg	Toprol-XL, 50 mg	–3.20	–6.71, 0.32	0.0748
Toprol-XL/HCT, 100/6.25 mg	Toprol-XL, 100 mg	–3.46	–8.25, 1.34	0.1580
Toprol-XL/HCT, 100/12.5 mg	Toprol-XL, 100 mg	–8.51	–12.37, –4.65	<0.0001
Toprol-XL/HCT, 100/25.0 mg	Toprol-XL, 100 mg	–7.99	–12.91, –3.08	0.0015
Toprol-XL/HCT, 200/12.5 mg	Toprol-XL, 200 mg	–4.29	–9.78, 1.20	0.1257
Toprol-XL/HCT, 200/25.0 mg	Toprol-XL, 200 mg	–5.60	–10.91, –0.30	0.0387
Toprol-XL/HCT, 25/6.25 mg	HCT, 6.25 mg	0.79	–2.82, 4.41	0.6670
Toprol-XL/HCT, 50/6.25 mg	HCT, 6.25 mg	–4.10	–7.76, –0.45	0.0278
Toprol-XL/HCT, 100/6.25 mg	HCT, 6.25 mg	–3.35	–8.23, 1.53	0.1786
Toprol-XL/HCT, 25/12.5 mg	HCT, 12.5 mg	–2.48	–5.90, 0.95	0.1567
Toprol-XL/HCT, 50/12.5 mg	HCT, 12.5 mg	–2.75	–6.14, 0.65	0.1134
Toprol-XL/HCT, 100/12.5 mg	HCT, 12.5 mg	–7.28	–11.05, –3.50	0.0002
Toprol-XL/HCT, 200/12.5 mg	HCT, 12.5 mg	–7.46	–12.27, –2.65	0.0024
Toprol-XL/HCT, 100/25.0 mg	HCT, 25.0 mg	–2.88	–8.49, 2.72	0.3131
Toprol-XL/HCT, 200/25.0 mg	HCT, 25.0 mg	–4.89	–10.28, 0.49	0.0751

Note: Based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction between Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiSBP Sitting systolic blood pressure; CI Confidence interval; LL Lower limit; UL Upper Limit.
Data derived from Table 11.2.3.1.10, Section 11.2.

Table 64: Pairwise comparisons for low dose combinations to high dose monotherapy change from baseline to week 8/LOCF in trough SiSBP -ITT-Study 324

Table 40 Pairwise comparisons for low-dose combination to high-dose monotherapy, change from baseline to Week 8/LOCF in trough SiSBP (intent-to-treat population)

Trough SiSBP Combination treatment group	Comparator monotherapy treatment	Mean difference	95% CI LL, UL	p-value
Toprol-XL/HCT, 25/6.25 mg	Toprol-XL, 200 mg	5.08	0.76, 9.40	0.0212
Toprol-XL/HCT, 25/6.25 mg	HCT, 25 mg	5.79	1.37, 10.21	0.0103
Toprol-XL/HCT, 25/12.5 mg	Toprol-XL, 200 mg	0.69	–3.64, 5.02	0.7550
Toprol-XL/HCT, 25/12.5 mg	HCT, 25 mg	1.40	–3.03, 5.83	0.5367
Toprol-XL/HCT, 50/6.25 mg	Toprol-XL, 200 mg	0.19	–4.16, 4.54	0.9324
Toprol-XL/HCT, 50/6.25 mg	HCT, 25 mg	0.90	–3.56, 5.35	0.6934
Toprol-XL/HCT, 50/12.5 mg	Toprol-XL, 200 mg	0.42	–3.89, 4.73	0.8481
Toprol-XL/HCT, 50/12.5 mg	HCT 25	1.13	–3.28, 5.54	0.6160

Note: ANCOVA model with parameters for Toprol-XL, HCT, the interaction between Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiSBP Sitting systolic blood pressure; CI Confidence interval; LL Lower limit; UL Upper limit.
Data derived from Table 11.2.3.1.13, Section 11.2.

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Table 65: Descriptive assessment of additivity from baseline to week 8/LOCF in trough SiSBP-ITT-Study 324

Table 41 Descriptive assessment of additivity based upon placebo-adjusted mean changes from baseline to Week 8/LOCF in trough SiSBP (intent-to-treat population)

Trough SiSBP	HCT dosage	Toprol-XL dosage			
		25 mg	50 mg	100 mg	200 mg
Sum of mean changes for monotherapies (expected change if treatments are additive)	6.25 mg	–11.67	–12.41	–11.83	–16.45
	12.5 mg	–12.68	–13.41	–12.84	–17.46
	25 mg	–16.46	–17.19	–16.62	–21.24
Observed mean change for combinations	6.25 mg	–5.37	–10.19	–9.17	NA
	12.5 mg	–9.28	–10.44	–14.75	–14.17
	25 mg	NA	NA	–14.67	–14.92
Difference (observed minus expected)	6.25 mg	6.30	2.22	2.66	NA
	12.5 mg	3.40	2.97	–1.91	3.29
	25 mg	NA	NA	1.95	6.32

Note: Values are placebo-adjusted. If the difference is negative, then the combination had a greater than additive effect; if the difference is positive, then the combination had a less than additive effect.

Table 66: Predicted and placebo-corrected values for change from baseline to week 8/LOCF in trough SiSBP - ITT- Study 324

Table 43 Predicted and placebo-corrected values from final polynomial regression model, for change from baseline to Week 8/LOCF in trough SiSBP (intent-to-treat population)

Treatment group	Predicted change	Placebo-corrected change	95% CI for placebo-corrected change LL, UL
Toprol-XL/HCT, 0/0 mg	–4.21	0.00	–1.83, 1.83
Toprol-XL, 25 mg	–6.21	–2.00	–3.52, –0.49
Toprol-XL, 50 mg	–7.89	–3.68	–5.32, –2.05
Toprol-XL, 100 mg	–10.28	–6.08	–8.05, –4.10
Toprol-XL, 200 mg	–11.23	–7.02	–10.12, –3.93
HCT, 6.25 mg	–7.68	–3.47	–5.03, –1.92
HCT, 12.5 mg	–10.12	–5.91	–7.65, –4.17
HCT, 25.0 mg	–11.89	–7.69	–10.88, –4.49

Figure 21: Dose response surface from baseline to week 8/LOCF in trough SiSBP - ITT- Study 324

Figure 8 **Dose response surface from final polynomial regression of changes from baseline to Week 8/LOCF in trough SiSBP (intention-to-treat population)**

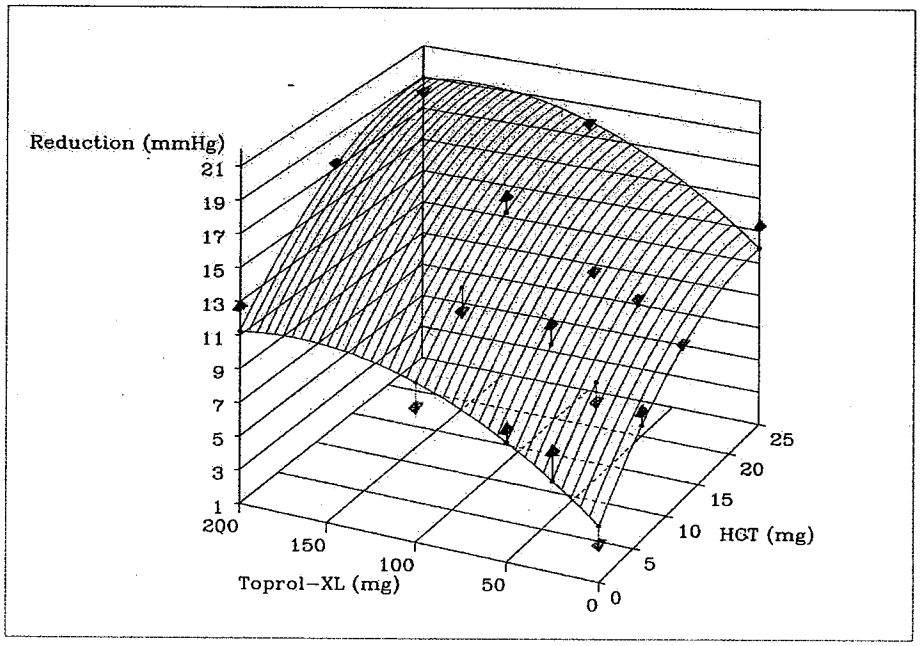

Table 67: Point estimates for the upper 95% confidence surface response for changes from baseline to week 8/LOCF for trough SiSBP - ITT- Study 324

Table 44 Point estimates for the upper 95% confidence surface base upon the final polynomial regression for changes from baseline to Week 8/LOCF for trough SiSBP (intent-to-treat population)

Trough SiSBP	HCT dosage	Toprol-XL dosage			
		25 mg	50 mg	100 mg	200 mg
Upper 95% confidence surface	6.25 mg	–0.63	–1.31	–1.46	NA
	12.5 mg	–0.63	–1.31	–2.69	–2.65
	25 mg	NA	NA	–2.69	–2.65

Note: The upper confidence surface represents the maximum of the confidence points for comparisons of combination to each monotherapy and to placebo, based upon the final weighted least-squares polynomial regression model.
LOCF Last observation carried forward.
SiSBP Sitting systolic blood pressure.

Table 68: Raw and adjusted means for changes from baseline to week 8/LOCF in trough StDBP - ITT- Study 324

Table 45 Raw and adjusted means for changes from baseline to Week 8/LOCF in trough StDBP (mmHg) (intent-to-treat population)

Treatment group	N	Observed raw change		Adjusted change		
		Mean change	Standard error	Mean change	Standard error	95% CI LL, UL
TOPROL-X/HCTL, 100/6.25 mg	43	–11.05	1.37	–11.23	1.28	–13.73, –8.73
TOPROL-X/HCT, 100/12.5 mg	91	–12.54	0.81	–12.74	0.88	–14.46, –11.02
Toprol-XL/HCT, 100/25 mg	42	–12.78	1.25	–12.65	1.29	–15.18, –10.12
Toprol-XL/HCT, 200/12.5 mg	43	–9.60	1.33	–9.97	1.28	–12.47, –7.47
Toprol-XL/HCT, 200/25 mg	47	–15.68	1.40	–15.53	1.22	–17.93, –13.14

Note: Adjusted numbers were based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction of Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure; N Total number of patients in treatment group; CI Confidence interval; LL Lower limit; UL Upper limit

Figure 22: Raw mean reductions from baseline to week 8/LOCF in trough StDBP - ITT

Figure 10 **Raw mean reductions from baseline to Week 8/LOCF in trough StDBP (intention-to-treat population)**

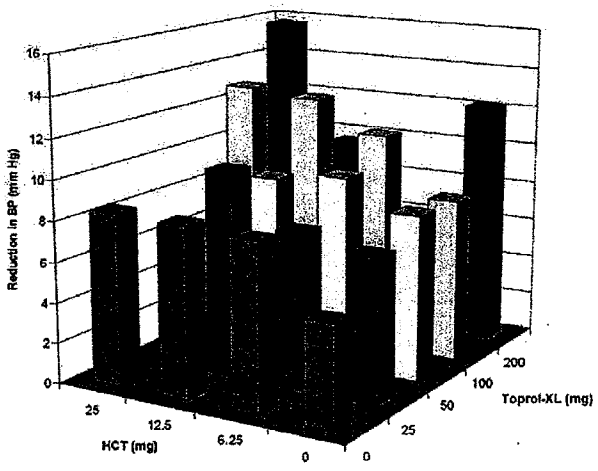

Table 69: Raw and adjusted means for changes from baseline to week 8/LOCF in trough StSBP - ITT- Study 324

Table 46 **Raw and adjusted means for changes from baseline to Week 8/LOCF in trough StSBP (mmHg) (intent-to-treat population)**

Treatment group	N	Observed raw change		Adjusted change		
		Mean change	Standard error	Mean change	Standard error	95% CI LL, UL
Toprol-XL/HCT, 0/0 mg	145	–3.91	1.07	–4.00	1.13	–6.21, –1.79
Toprol-XL, 25 mg	87	–6.52	1.71	–7.89	1.46	–10.76, –5.03
Toprol-XL, 50 mg	92	–7.73	1.77	–8.07	1.42	–10.84, –5.29
Toprol-XL, 100 mg	90	–7.40	1.51	–7.39	1.43	–10.19, –4.58
Toprol-XL, 200mg	50	–14.59	1.84	–13.67	1.92	–17.44, –9.90
HCT, 6.25 mg	82	–9.14	1.42	–9.01	1.50	–11.94, –6.07
HCT, 12.5 mg	101	–8.71	1.46	–8.94	1.35	–11.58, –6.29
HCT, 25.mg	48	–12.90	2.01	–13.13	1.96	–16.97, –9.28
Toprol-XL/HCT, 25/6.25 mg	142	–9.08	1.19	–8.81	1.14	–11.04, –6.57
Toprol-XL/HCT, 25/12.5 mg	136	–12.85	1.13	–12.95	1.16	–15.23, –10.67
Toprol-XL/HCT, 50/6.25 mg	131	–11.33	1.20	–11.30	1.19	–13.63, –8.98

Table 70: Raw and adjusted means for changes from baseline to week 8/LOCF in trough StSBP- ITT-Study 324

Table 46 Raw and adjusted means for changes from baseline to Week 8/LOCF in trough StSBP (mmHg) (intent-to-treat population)

Treatment group	N	Observed raw change		Adjusted change		
		Mean change	Standard error	Mean change	Standard error	95% CI LL, UL
Toprol-XL/HCT, 50/12.5 mg	143	–10.70	1.28	–10.24	1.14	–12.47 –8.01
TOPROL-X/HCTL, 100/6.25 mg	43	–12.02	2.25	–12.51	2.07	–16.57, –8.45
TOPROL-X/HCT, 100/12.5 mg	91	–16.81	1.52	–16.36	1.42	–19.15, –13.57
Toprol-XL/HCT, 100/25 mg	42	–18.27	2.22	–17.17	2.10	–21.28, –13.06
Toprol-XL/HCT, 200/12.5 mg	43	–15.81	1.86	–15.83	2.07	–19.89, –11.77
Toprol-XL/HCT, 200/25 mg	47	–17.90	2.19	–18.36	1.98	–22.24, –14.47

Note: Adjusted numbers were based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction between Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure; N Total number of patients in treatment group; CI Confidence interval; LL Lower limit; UL Upper limit
Data derived from Table 11.2.5.1.9, Section 11.2.

Table 71: Raw and adjusted means for changes from baseline to week 8/LOCF in peak SiDBP - ITT- Study 324

Table 47 Raw and adjusted means for changes from baseline to Week 8/LOCF in peak SiDBP (mmHg) (intent-to-treat population)

Treatment group	N	Observed raw change		Adjusted change		
		Mean change	Standard error	Mean change	Standard error	95% CI LL, UL
TOPROL-X/HCTL, 100/6.25 mg	41	–14.87	1.25	–14.60	1.32	–17.18, –12.01
TOPROL-X/HCT, 100/12.5 mg	84	–15.69	0.97	–15.80	0.92	–17.60, –13.99
Toprol-XL/HCT, 100/25 mg	38	–14.66	1.39	–14.65	1.37	–17.33, –11.96
Toprol-XL/HCT, 200/12.5 mg	39	–13.11	1.34	–13.41	1.35	–16.06, –10.76
Toprol-XL/HCT, 200/25 mg	42	–14.23	1.35	–14.05	1.30	–16.60, –11.49

Note: Adjusted numbers were based upon an ANCOVA model with parameters for Toprol-XL, HCT, the interaction between Toprol-XL and HCT, and baseline blood pressure.
LOCF Last observation carried forward; SiDBP Sitting diastolic blood pressure; N Total number of patients in treatment group; CI Confidence interval; LL Lower limit; UL Upper limit
Data derived from Table 11.2.6.1.9, Section 11.2.

Figure 23: Raw mean reductions from baseline to week 8 / LOCF in peak SiDBP - ITT-Study 324

Figure 12 Raw mean reductions from baseline to Week 8/LOCF in peak SiDBP (intention-to-treat population)

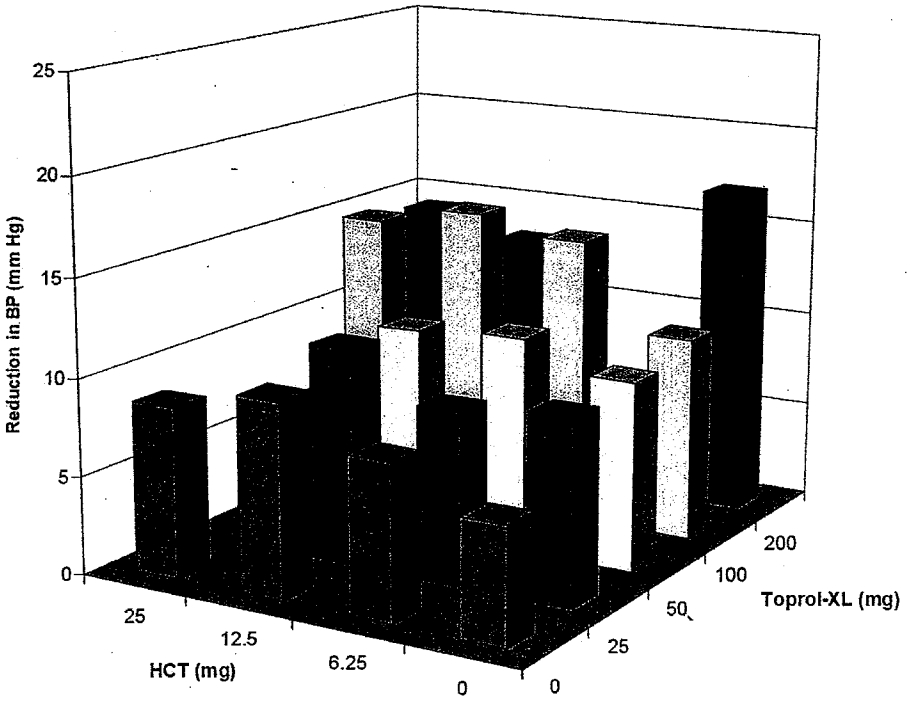

Table 72: Trough to Peak ratio of SiSBP at baseline and week 8/LOCF - ITT- Study 324
Table 50 Trough to peak ratio of SiSBP at baseline and Week 8/LOCF (intent-to-treat population)

	Baseline (Visit 3)				Week 8 (LOCF)			
Treatment group	**N**	**Mean**	**SD**	**95% CI**	**N**	**Mean**	**SD**	**95%CI**
Toprol-XL, HCT 0/0 mg	150	1.002	0.056	0.993, 1.010	129	1.011	0.085	0.996, 1.025
Toprol-XL, 25 mg	88	1.011	0.059	0.999, 1.023	77	1.002	0.062	0.988, 1.016
Toprol-XL, 50 mg	92	1.009	0.070	0.995, 1.023	79	1.014	0.079	0.997, 1.031
Toprol-XL, 100 mg	92	1.004	0.049	0.994, 1.014	84	1.027	0.072	1.012, 1.043
Toprol-XL, 200mg	50	1.013	0.065	0.995, 1.031	45	1.027	0.072	1.006, 1.048
HCT, 6.25 mg	84	1.003	0.056	0.991, 1.015	73	1.007	0.074	0.990, 1.024
HCT, 12.5 mg	104	1.010	0.056	0.999, 1.021	91	1.013	0.070	0.999, 1.028
HCT, 25.0 mg	48	1.004	0.054	0.989, 1.019	46	0.998	0.073	0.977, 1.019
Toprol-XL/HCT, 25/6.25 mg	142	0.997	0.046	0.989, 1.004	127	1.021	0.069	1.009, 1.033
Toprol-XL/HCT, 25/12.5 mg	140	1.002	0.047	0.994, 1.010	127	1.009	0.071	0.996, 1.021
Toprol-XL/HCT, 50/6.25 mg	135	1.008	0.059	0.998, 1.018	129	1.017	0.088	1.002, 1.032
Toprol-XL/HCT, 50/12.5 mg	146	1.009	0.057	1.000, 1.018	130	1.019	0.070	1.007, 1.031
Toprol-XL/HCT, 100/6.25 mg	45	0.991	0.064	0.972, 1.009	41	1.013	0.068	0.992, 1.034
Toprol-XL/HCT, 100/12.5 mg	94	0.997	0.056	0.986, 1.009	85	1.019	0.075	1.003, 1.035
Toprol-XL/HCT,100/25.0 mg	41	1.015	0.061	0.996, 1.034	38	1.041	0.055	1.024, 1.059
Toprol-XL/HCT,200/ 12.5 mg	43	1.015	0.072	0.994, 1.037	38	1.003	0.072	0.980, 1.026
Toprol-XL/HCT, 200/25.0 mg	49	1.016	0.065	0.997, 1.034	42	1.021	0.070	1.000, 1.042
Total	1543	1.005	0.057	1.002, 1.008	1381	1.015	0.074	1.011, 1.019

Data derived from Table 11.2.10.7, Section 11.2.

Table 73: Number (%) responders at week 8 - ITT- Study 324

Table 51 Number (%) of responders at Week 8 (intent-to-treat population)

Treatment group	N	Number and % of responders	95% CI	Percentage difference from placebo	95% CI	P-value
Toprol-XL, HCT 0/0 mg	152	43 (28.3)	14.83, 41.75			
Toprol-XL, 25 mg	89	45 (50.6)	35.95, 65.17	22.3	9.66, 34.89	0.0005
Toprol-XL, 50 mg	93	51 (54.8)	41.18, 68.50	26.5	14.16, 38.94	<0.0001
Toprol-XL, 100 mg	95	44 (46.3)	31.58, 61.05	18.0	5.70, 30.35	0.0041
Toprol-XL, 200mg	51	33 (64.7)	48.40, 81.01	36.4	21.47, 51.36	<0.0001
HCT, 6.25 mg	86	43 (50.0)	35.06, 64.94	21.7	8.95, 34.48	0.0009
HCT, 12.5 mg	104	52 (50.0)	36.41, 63.59	21.7	9.73, 33.69	0.0004
HCT, 25.0 mg	48	23 (47.9)	27.50, 68.33	19.6	3.78, 35.47	0.0152
Toprol-XL/HCT, 25/6.25 mg	144	67 (46.5)	34.58, 58.47	18.2	7.39, 29.08	0.0010
Toprol-XL/HCT, 25/12.5 mg	141	82 (58.2)	47.48, 68.83	29.9	19.02, 40.71	<0.0001
Toprol-XL/HCT, 50/6.25 mg	136	72 (52.9)	41.41, 64.47	24.7	13.62, 35.68	<0.0001
Toprol-XL/HCT, 50/12.5 mg	147	89 (60.5)	50.39, 70.70	32.3	21.59, 42.92	<0.0001
Toprol-XL/HCT, 100/6.25 mg	45	35 (77.8)	64.00, 91.55	49.5	35.39, 63.59	<0.0001
Toprol-XL/HCT, 100/12.5 mg	94	63 (67.0)	55.41, 78.63	38.7	26.83, 50.63	<0.0001
Toprol-XL/HCT, 100/25.0 mg	42	27 (64.3)	46.21, 82.36	36.0	19.83, 52.16	<0.0001
Toprol-XL/HCT, 200/12.5 mg	43	32 (74.4)	59.30, 89.54	46.1	31.25, 61.01	<0.0001
Toprol-X/HCT, 200/25.0 mg	49	36 (73.5)	59.05, 87.89	45.2	30.89, 59.47	<0.0001

Table 74: Number (%) of controlled patients at week 8 - ITT-Study 324

Table 52 Number (%) of controlled patients at Week 8 (intent-to-treat population)

Treatment group	N	Number and % of controlled patients	95% CI	Percentage difference from placebo	95% CI	P-value
Toprol-XL, HCT 0/0 mg	152	21 (13.8)	–0.94, 28.57			
Toprol-XL, 25 mg	89	31 (34.8)	18.06, 51.60	21.0	9.70, 32.33	0.0003
Toprol-XL, 50 mg	93	29 (31.2)	14.32, 48.04	17.4	6.47, 28.26	0.0018
Toprol-XL, 100 mg	95	28 (29.5)	12.59, 46.36	15.7	4.97, 26.34	0.0041
Toprol-XL, 200mg	51	24 (47.1)	27.09, 67.03	33.2	18.49, 48.00	<0.0001
HCT, 6.25 mg	86	25 (29.1)	11.27, 46.87	15.3	4.20, 26.31	0.0068
HCT, 12.5 mg	104	38 (36.5)	21.23, 51.85	22.7	11.96, 33.48	<0.0001
HCT, 25.0 mg	48	18 (37.5)	15.13, 59.87	23.7	8.93, 38.44	0.0017
Toprol-XL/HCT, 25/6.25 mg	144	45 (31.3)	17.71, 44.79	17.4	8.08, 26.78	0.0003
Toprol-XL/HCT, 25/12.5 mg	141	52 (36.9)	23.77, 49.99	23.1	13.39, 32.73	<0.0001
Toprol-XL/HCT, 50/6.25 mg	136	42 (30.9)	16.91, 44.86	17.1	7.56, 26.57	0.0004
Toprol-XL/HCT, 50/12.5 mg	147	54 (36.7)	23.88, 49.59	22.9	13.39, 32.45	<0.0001
Toprol-XL/HCT, 100/6.25 mg	45	22 (48.9)	28.00, 69.78	35.1	19.47, 50.67	<0.0001
Toprol-XL/HCT, 100/12.5 mg	94	49 (52.1)	38.14, 66.11	38.3	26.82, 49.80	<0.0001

Table 75: Number (%) of controlled patients at week 8 - ITT-Study 324

Table 52 Number (%) of controlled patients at Week 8 (intent-to-treat population)

Treatment group	N	Number and % of controlled patients	95% CI	Percentage difference from placebo	95% CI	P-value
Toprol-XL/HCT, 100/25.0 mg	42	20 (47.6)	25.73, 69.51	33.8	17.73, 49.87	<0.0001
Toprol-XL/HCT, 200/12.5 mg	43	26 (60.5)	41.67, 79.26	46.6	31.04, 62.26	<0.0001
Toprol-X/HCT, 200/25.0 mg	49	32 (65.3)	48.81, 81.80	51.5	37.08, 65.90	<0.0001

Note: A patient was controlled if SiDBP was less than 90 mmHg and SiSBP was less than 140 mmHg at Week 8. No DBP values were carried forward. A patient with no value at Week 8 was analyzed as not controlled.
Data derived from Table 11.2.9.2, Section 11.2.

Analysis by race shows some significant differences when the data are looked at in a generic and non-discriminatory manner. This suggests that the black population do not respond as well to the drugs as the non-black population (See Table 76 below)

	Trough Sitting DBP		Trough Sitting SBP	
	Black	Non-black	Black	Non-black
P-value	0.2085	0.0217*	0.1779	0.0178*

*Statistically significant at an α=0.025

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Table 76: Number (%) of selected patients with mean changes from baseline to week 8 by age, and sex and race - ITT-Study 324

		Toprol-XL dosage					
Trough SIDBP	HCT mg	0 mg	25 mg	50 mg	100 mg	200 mg	Total
ITT, N	0	152	89	93	95	51	1559
	6.25	86	144	136	45	NA	
	12.5	104	141	147	94	43	
	25	48	NA	NA	42	49	
Age (yrs) n, Mean (SD)							
<65	0	124, -5 (9)	79, -8 (9)	80, -9 (8)	75, -10 (8)	45, -13 (9)	1312, -10 (9)
	6.25	68, -8 (8)	127, -8 (8)	108, -10 (8)	40, -13 (10)	NA	
	12.5	87, -10 (9)	121, -9 (8)	125, -11 (9)	71, -13 (7)	34, -12 (9)	
	25	42, -9 (7)	NA	NA	40, -13 (10)	46, -17 (9)	
≥65	0	28, -3 (8)	10, -9 (7)	13, -9 (5)	20, -8 (10)	6, -8 (13)	247, -10 (9)
	6.25	18, -9 (8)	17, -9 (9)	28, -10 (8)	5, -13 (8)	NA	
	12.5	17, -10 (10)	20, -15 (7)	22, -12 (8)	23, -14 (6)	9, -16 (8)	
	25	6, -12 (12)	NA	NA	2, -24 (16)	3, -6 (6)	
Sex n, Mean (SD)							
Male	0	83, -3 (9)	39, -9 (8)	51, -8 (8)	55, -9 (9)	28, -14 (9)	799, -9 (9)
	6.25	45, -8 (8)	72, -6 (8)	65, -10 (8)	25, -12 (10)	NA	
	12.5	51, -9 (7)	70, -9 (8)	86, -11 (9)	46, -12 (8)	19, -12 (11)	
	25	22, -7 (7)	NA	NA	22, -13 (11)	20, -14 (9)	
Female	0	69, -5 (8)	50, -7 (10)	42, -10 (7)	40, -10 (7)	23, -11 (11)	760, -10 (9)
	6.25	41, -8 (8)	72, -9 (8)	71, -11 (7)	20, -13 (9)	NA	
	12.5	53, -11 (10)	71, -11 (8)	61, -10 (8)	48, -15 (6)	24, -13 (7)	
	25	26, -11 (8)	NA	NA	20, -15 (9)	29, -19 (10)	
Race, n, Mean (SD)							
Black	0	41, -3 (10)	22, -3 (8)	26, -7 (8)	23, -7 (8)	11, -10 (9)	392, -8 (9)
	6.25	21, -10 (9)	37, -6 (9)	33, -8 (8)	12, -10 (12)	NA	
	12.5	23, -8 (6)	43, -10 (8)	33, -12 (9)	19, -13 (8)	15, -11 (6)	
	25	13, -11 (10)	NA	NA	8, -8 (10)	12, -20 (11)	
Non-Black	0	111, -5 (8)	67, -9 (9)	67, -10 (7)	72, -10 (8)	40, -13 (10)	1167, -10 (9)
	6.25	65, -8 (8)	107, -9 (8)	103, -11 (8)	33, -14 (8)	NA	
	12.5	81, -10 (9)	98, -10 (8)	114, -11 (8)	75, -14 (7)	28, -13 (10)	
	25	35, -9 (7)	NA	NA	34, -15 (10)	37, -16 (9)	

Data derived from Table 11.2.8.1, Section 11.2.

Table 77: Number (%) of selected patients with mean changes from baseline to week 8 by age, and sex - ITT-Study 324

Table 55 Mean (SD) for changes from baseline to Week 8/LOCF in trough SiSBP for selected subgroups: age, sex, and race (intent-to-treat population)

		Toprol-XL dosage					
Trough SiSBP	**HCT**	**0 mg**	**25 mg**	**50 mg**	**100 mg**	**200 mg**	**Total**
ITT group, N	0	152	89	93	95	51	1559
	6.25	86	144	136	45	NA	
	12.5	104	141	147	94	43	
	25	48	NA	NA	42	49	
Age (yrs), n, Mean (SD)							
<65	0	124, –4 (14)	79, –8 (14)	80, –10 (16)	75, –9 (14)	45, –14 (14)	1312, –11 (14)
	6.25	68, –9 (11)	127, –8 (13)	108, –13 (13)	40, –12 (14)	NA	
	12.5	87, –10 (13)	121, –11 (13)	125, –13 (14)	71, –18 (14)	34, –17 (14)	
	25	42, –13 (12)	NA	NA	40, –17 (15)	46, –19 (15)	
≥65	0	28, –2 (15)	10, –8 (27)	13, –4 (16)	20, –8 (18)	6, –4 (20)	247, –10 (17)
	6.25	18, –9 (12)	17, –12 (18)	28, –12 (12)	5, –13 (21)	NA	
	12.5	17, –8 (21)	20, –17 (15)	22, –16 (13)	23, –15 (17)	9, –17 (10)	
	25	6, –18 (20)	NA	NA	2, –30 (34)	3, –<1 (2)	
Sex, n, Mean (SD)							
Male	0	83, –2 (15)	39, –6 (17)	51, –9 (17)	55, –8 (15)	28, –15 (15)	799, -10 (15)
	6.25	45, –9 (12)	72, –6 (13)	65, –13 (13)	25, –12 (12)	NA	
	12.5	51, –8 (15)	70, –10 (11)	86, –13 (15)	46, –15 (14)	19, –19 (14)	
	25	22, –10 (14)	NA	NA	22, –14 (14)	20, –16 (17)	
Female	0	69, –4 (14)	50, –10 (15)	42, –9 (15)	40, –10 (13)	23, –11 (15)	760, -12 (15)

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Table 78: Mean changes from baseline to week 8/LOCF in trough SiSBP by age, and sex and race - ITT-Study 324T

Table 55 Mean (SD) for changes from baseline to Week 8/LOCF in trough SiSBP for selected subgroups: age, sex, and race (intent-to-treat population)

		Toprol-XL dosage					
Trough SiSBP	**HCT**	**0 mg**	**25 mg**	**50 mg**	**100 mg**	**200 mg**	**Total**
	6.25	41, –9 (11)	72, –10 (15)	71, –13 (12)	20, –12 (17)	NA	
	12.5	53, –12 (15)	71, –14 (15)	61, –14 (13)	48, –20 (16)	24, –16 (12)	
	25	26, –17 (12)	NA	NA	20, –21 (17)	29, –19 (15)	
Race, n, Mean (SD)							
Black	0	41, –<1 (17)	22, –7 (12)	26, –8 (12)	23, –3 (13)	11, –10 (19)	392, –11 (15)
	6.25	21, –9 (12)	37, –5 (13)	33, –12 (14)	12, –12 (14)	NA	
	12.5	23, –13 (12)	43, –16 (14)	33, –17 (14)	19, –17 (15)	15, –18 (12)	
	25	13, –15 (12)	NA	NA	8, –13 (19)	12, –23 (14)	
Non-Black	0	111, –4 (13)	67, –9 (17)	67, –10 (17)	72, –10 (15)	40, –14 (14)	1167, –11 (15)
	6.25	65, –9 (11)	107, –9 (14)	103, –13 (12)	33, –12 (15)	NA	
	12.5	81, –9 (15)	98, –10 (13)	114, –12 (14)	75, –18 (15)	28, –17 (13)	
	25	35, –13 (14)	NA	NA	34, –19 (15)	37, –16 (16)	

NA Not applicable.
Data derived from Table 11.2.8.2. Section 11.2.

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Table 79: Mean changes from baseline to week 8/LOCF in trough SiSBP for selected subgroups: SiDBP SiSBP and Diabetes Mellitus - ITT-Study 324

Table 56 Mean (SD) for changes from baseline to Week 8/LOCF in trough SiSBP for selected subgroups: SiDBP, SiSBP, and diabetes mellitus (intent-to-treat population)

Trough SiSBP	HCT dose	Toprol-XL dosage 0 mg	25 mg	50 mg	100 mg	200 mg	Total
Baseline trough SiDBP, mmHg, n, Mean (SD)							
<100	0 mg	86, –2 (15)	53, –9 (17)	50, –8 (15)	51, –9 (13)	29, –11 (15)	904, –10 (15)
	6.25 mg	49, –8 (12)	82, –8 (14)	71, –11 (14)	29, –12 (13)	NA	
	12.5 mg	60, –9 (14)	89, –13 (14)	79, –13 (17)	61, –17 (13)	34, –14 (12)	
	25 mg	33, –12 (11)	NA	NA	23, –15 (16)	25, –21 (14)	
≥100	0 mg	66, –4 (14)	36, –8 (15)	43, –11 (17)	44, –8 (16)	22, –16 (15)	655, –12 (15)
	6.25 mg	37, –10 (10)	62, –9 (14)	65, –15 (11)	16, –12 (17)	NA	
	12.5 mg	44, –11 (16)	52, –10 (13)	68, –14 (11)	33, –19 (18)	9, –26 (11)	
	25 mg	15, –17 (17)	NA	NA	19, –21 (15)	24, –14 (17)	
Baseline trough SiSBP, mmHg, n, Mean (SD)							
<145	0 mg	58, <1 (11)	37, –5 (17)	29, –3 (12)	31, –3 (12)	21, –6 (9)	531, –6 (12)
	6.25 mg	27, –2 (8)	46, –2 (12)	47, –7 (12)	15, –12 (8)	NA	
	12.5 mg	33, –3 (12)	51, –8 (8)	39, –8 (13)	31, –11 (12)	16, –12 (10)	
	25 mg	18, –7 (8)	NA	NA	10, –7 (16)	22, –14 (17)	
≥145	0 mg	94, –5 (16)	52, –10 (15)	64, –12 (17)	64, –11 (15)	30, –18 (17)	1028, –14 (15)
	6.25 mg	59, –12 (11)	98, –11 (14)	89, –16 (12)	30, –12 (17)	-NA	
	12.5 mg	71, –13 (15)	90, –15 (15)	108, –15 (14)	63, –21 (15)	27, –20 (14)	
	25 mg	30, –18 (14)	NA	NA	32, –21 (14)	27, –21 (14)	
Diabetes mellitus, n, Mean (SD)							
Yes	0 mg	10, –5 (12)	6, –15 (21)	9, –13 (16)	9, –7 (14)	3, –23 (14)	152, –13 (16)
	6.25 mg	9, –8 (10)	12, –9 (14)	18, –13 (15)	6, 1 (16)	NA	
	12.5 mg	14, –17 (15)	13, –19 (14)	12, –9 (22)	8, –23 (16)	9, –17 (16)	
	25 mg	7, –17 (15)	NA	NA	4, –19 (17)	3, –<1 (36)	
No	0 mg	142, –3 (15)	83, –8 (16)	84, –9 (16)	86, –9 (15)	48, –13 (15)	1407, –11 (15)
	6.25 mg	77, –9 (11)	132, –8 (14)	118, –13 (12)	39, –14 (13)	NA	
	12.5 mg	90, –9 (14)	128, –11 (13)	135, –14 (13)	86, –17 (15)	34, –17 (12)	
	25 mg	41, –13 (13)	NA	NA	38, –17 (16)	46, –19 (13)	

NA Not applicable.

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

6.7 Conclusions on study patients

Of the 1571 patients randomized into the double-blind treatment period, 1559 (99.2%) were included in the ITT population, 1564 (99.6%) in the safety population, and 1339 (85.2%) in the PP population. Of all randomized patients, 89% completed the study and 11% discontinued for any reason.

The study population was typical of a US hypertensive population: about half were men, most (71%) were Caucasian but Blacks were also well-represented (26%), and many patients were overweight (57%). Mean pretreatment BP was 151/100 mm/Hg. Most patients were taking antihypertensive medication prior to study enrollment.

In spite of the many treatment groups, the randomization procedure produced treatment groups balanced on key baseline characteristics. During double-blind treatment, mean compliance with study drug was at least 97% for each treatment group.

In addition to the factorial study a small clinical study conducted in Denmark and Sweden in 1987-88 (Study S-902, 47 ITT patients) evaluated the antihypertensive effect of metoprolol succinate ER/HCT (100/12.5 mg) in comparison to a conventional metoprolol tartrate/HCT combination in a population remaining hypertensive in spite of treatment with HCT 12.5 mg daily. There was no dose ranging evaluation but the safety data contributes to the database for the combined product.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety results: The mean duration of each period was: run-in period 30 days, double-blind treatment period 55 days, and the down-titration/follow-up period 15 days.

The safety population was composed of 1564 patients: 42% had at least 1 AE, 1.5% had SAEs and 2.9% discontinued treatment due to an AE. There were no deaths during the study. SAEs were reported for 24 patients (1.5%); 5 had coronary artery disease manifestation (3 of which had a myocardial infarction). The events were not temporally related to abrupt cessation of beta-blocker treatment. Headache was the most common AE (6.2% overall, and 9.3% in the HCT 6.25 mg monotherapy group and 9.2% in the placebo group). There was no

apparent additive effect of the 2 agents with regard to AEs with the possible exception of fatigue (1.2% to 6.3% with HCT monotherapy and 10.2% with Toprol-XL/HCT 200/25 mg). The AE treatment discontinuation rate was low (2.9%); the most common reason for discontinuation overall was headache (0.3%).
With HCT treatment, serum potassium declined (max. mean change –0.32 mEq/L for HCT 25 mg), uric acid increased (max. mean change 0.94 mg/dl for HCT 25 mg) and BUN increased (max. mean change 2.2 mg/dl with HCT 12.5 mg); these changes were largely independent of Toprol-XL treatment. No consistent pattern of changes was observed for mean blood glucose results in the overall population or for the diabetic subgroup nor was there a consistent pattern of changes for serum sodium. There were small increases in serum triglycerides with both monotherapies and a small reduction in HDL cholesterol with Toprol-XL.
Treatment with Toprol-XL and its combinations was associated with a dose-related slowing of the heart rate, which is consistent with its known pharmacologic action.
Conclusion(s): Toprol-XL/HCT is an effective antihypertensive combination product which reflects the additive blood pressure lowering contributions of its individual components. Toprol-XL 50 mg/HCT 6.25 and 12.5 mg combinations lower blood pressure to levels close to those attainable with at least 1 of the high dose monotherapies (200 mg Toprol-XL or 25 mg HCT) and carry a lower risk for side effects such as fatigue and metabolic abnormalities.

Adverse events from label
The metoprolol succinate extended release and hydrochlorothiazide combination was evaluated for safety in 891 patients treated for hypertension in clinical trials. In the placebo-controlled trial, 843 patients were treated with various combinations of metoprolol succinate (doses of 25 to 200 mg) and hydrochlorothiazide (doses of 6.25 to 25 mg). Overall, the frequencies of adverse experiences reported with the combination was comparable to placebo.

Adverse events, whether or not attributed to treatment, occurring in greater than 1% of patients treated with Metoprolol succinate/HCT and at a rate equal to or greater than with placebo were: nasopharyngitis (3.4% vs 1.3%), fatigue (2.6% vs 0.7%), dizziness (2.6% vs 2.6%), back pain (1.7% vs 1.3%), and nausea (1.4% vs 0.7%). Adverse experiences were usually mild and transient in nature and infrequently required discontinuation of therapy (2.7% vs 2.6% with placebo).

Metoprolol Tartrate Immediate release
Most adverse effects were mild and transient. The following adverse reactions have been reported for immediate release metoprolol tartrate.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, somnolence, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations;

congestive heart failure; peripheral edema; syncope; chest pain; and hypotension have been reported in about 1 of 100 patients (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, digestive tract disorders, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash has occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, decreased libido, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with metoprolol.

Potential Adverse Reactions
In addition, there are a variety of adverse reactions not listed above, which have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to Metoprolol succinate / HCT. These include:

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see CONTRAINDICATIONS).

Hematologic: Agranulocytosis, non-thrombocytopenic purport, thrombocytopenic purpura.

Summary of safety.
The safety population consisted of all patients who received at least 1 dose of the investigational product and for whom post-dose data is available. In this safety section the following results will be shown for the 1564 patients in the safety population:

- Exposure data show that, on average, placebo run-in lasted 30 days, double-blind treatment 55 days, and down titration/follow-up 15 days.

- Safety data show that no deaths occurred during the study.

- An analysis of AEs found that 42% of patients had at least 1 treatment-emergent adverse event (TEAE); the most common of these were headache (6.2%), upper respiratory tract infection (3.9%), and nasopharyngitis (2.6%).

- An analysis of treatment emergent SAEs and discontinuations due to AEs show that rates were low: 1.5% and 2.9%, respectively. Two SAEs occurred in more than1 patient during the study: coronary artery disease (3 patients) and myocardial infarction (3 patients) (1 patient had both events). The coronary artery disease and MIs were not temporally related to abrupt cessation of beta-blocker treatment (1 MI occurred during down titration, and 2 MIs and 3 coronary artery diseases occurred either the last day of treatment or the day after treatment was stopped). The most common AEs leading to treatment discontinuation were headache (5 patients, 0.3%), with erectile dysfunction, fatigue, and hypertension each occurring in 0.2% of patients.

- Analyses also show that there were no notable clustering of AEs in any 1 treatment group. Headache occurred at comparable frequencies across all treatment groups including placebo. There were no appreciable 'additive' safety findings with the possible exception of fatigue, which occurred at high dose HCT in combination with Toprol-XL, most notably in combination with high dose (200 mg) Toprol-XL.

- An analysis of laboratory data found that serum potassium declined, while serum uric acid and blood urea nitrogen increased with increasing doses of HCT, largely independent of the Toprol-XL dose; there was a small dose-related decline in HDL-cholesterol with Toprol-XL; triglyceride levels increased slightly with both HCT and Toprol-XL and the combinations tended to reflect the effects of both agents. Neither Toprol-XL, HCT, nor their combinations were associated with consistent changes in blood glucose whether for the whole population or for patients with diabetes. Also, neither Toprol-XL, HCT, nor their combinations were associated with consistent changes in serum sodium. There was no notable shift with any treatment in the distribution of patients in the National Cholesterol Education Program (NCEP) lipid categories. Very few patients had AEs associated with theses laboratory assessments and none were SAEs.

- Analyses of ECG and physical examinations data show the expected slowing of heart rate at higher doses of Toprol-XL but no patient was discontinued due to bradycardia. Otherwise, the findings indicate no clinically meaningful changes with any of the treatments.

- Safety measures included AEs, AEs leading to discontinuation, SAEs, laboratory measures, heart rate, physical examinations, and electrocardiographic findings.

7.1.1 Deaths - Nil

7.1.2 Other Serious Adverse Events

Of the 1564 safety population patients 1.5% had serious adverse events. There were no deaths during the study. SAEs were reported for 24 patients (1.5%); 5 had coronary artery disease manifestation (3 of which had a myocardial infarction). The events were not temporally related to abrupt cessation of beta-blocker treatment.
With HCT treatment, serum potassium declined (max. mean change –0.32 mEq/L for HCT 25 mg), uric acid increased (max. mean change 0.94 mg/dl for HCT 25 mg) and BUN increased (max. mean change 2.2 mg/dl with HCT 12.5 mg); these changes were largely independent of Toprol-XL treatment. No consistent pattern of changes was observed for mean blood glucose results in the overall population or for the diabetic subgroup nor was there a consistent pattern of changes for serum sodium. There were small increases in serum triglycerides with both monotherapies and a small reduction in HDL cholesterol with Toprol-XL. Treatment with Toprol-XL and its combinations was associated with a dose-related slowing of the heart rate, which is consistent with its known pharmacologic action.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The discontinuation rate was low (2.9%); the most common discontinuation AE was headache (5 patients overall). Other common AEs leading to discontinuation included erectile dysfunction (3 patients), fatigue (3 patients), and hypertension (3 patients).

7.1.3.2 Adverse events associated with dropouts

The discontinuation rate was low (2.9%); the most common discontinuation AE was headache (5 patients overall). Other common AEs leading to discontinuation included erectile dysfunction (3 patients), fatigue (3 patients), and hypertension (3 patients).

7.1.3.3 Other significant adverse events

Metabolic events of special interest were cited as AEs in only a few cases (hypokalemia (6 patients), hyponatremia (no patients), dyslipidemia (1 patient), hypergylcemia (8 patients), and hyperuricemia (1 patient).

7.1.4 Other Search Strategies

7.1.5 Common Adverse Events
Headache was the most common reason (5 patients total) for treatment discontinuation. Other reasons occurred in 0.2% of patients or less, with most occurring in only 1 or 2 patients. Headache was the most common AE (6.2% overall, and 9.3% in the HCT 6.25 mg monotherapy group and 9.2% in the placebo group). There was no apparent additive effect of the 2 agents with

regard to AEs with the possible exception of fatigue (1.2% to 6.3% with HCT monotherapy and 10.2% with Toprol-XL/HCT 200/25 mg). The AE treatment discontinuation rate was low (2.9%); the most common reason for discontinuation overall was headache (0.3%).

7.1.5.1 Eliciting adverse events data in the development program

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

7.1.5.3 Incidence of common adverse events

Headache was the most common AE (6.2% overall, and 9.3% in the HCT 6.25 mg monotherapy group and 9.2% in the placebo group).

7.1.5.4 Common adverse event tables

7.1.5.5 Identifying common and drug-related adverse events

7.1.5.6 Additional analyses and explorations

7.1.6 Less Common Adverse Events
Headache was the most common reason (5 patients total) for treatment discontinuation. Other reasons occurred in 0.2% of patients or less, with most occurring in only 1 or 2 patients.

7.1.7 Laboratory Findings

Laboratory Test Findings In controlled clinical trials, clinically important changes in standard laboratory parameters were infrequently associated with the administration of TRADE NAME. The laboratory test findings with metoprolol or hydrochlorothiazide or their combination may include:

Creatinine, Blood Urea Nitrogen—There were minor increases in blood urea nitrogen (BUN).

Serum Electrolytes—There were declines in serum potassium, sodium, chloride, magnesium. Increases in serum calcium and uric acid.

Glucose—There was Increase in serum or blood glucose.

Lipids—Increase in serum total cholesterol, triglycerides. Decreases in high density lipoprotein (HDL).

Liver Function Tests—Increases in liver enzymes and/or serum bilirubin.

7.1.7.1 Overview of laboratory testing in the development program

Not applicable

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

Not applicable

7.1.7.3 Standard analyses and explorations of laboratory data

Not applicable

7.1.7.3.1 Analyses focused on measures of central tendency
Not applicable

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal
Changes in values over time for selected hematology variables

Mean changes from baseline to Visit 8 in hematology test results (hematocrit, hemoglobin, platelet counts, and white blood cell counts) were small with no consistent treatment group associations (except for platelet counts) and were without apparent clinical significance.

The proportions of patients with shifts in hematology test results from baseline below, within, and above the reference ranges were small across the treatment groups, without consistent treatment group association and without apparent clinical significance. Scatterplots of baseline versus Visit 5 and versus Visit 8 laboratory values illustrate an absence of directional trends for selected hematology parameters.

Mean changes from baseline to Visit 8 in chemistry test results (liver enzymes, electrolytes, renal function, lipids, and total protein, albumin, glucose, uric acid, calcium, and phosphorus) except as noted below..

Shifts for selected chemistry and liver enzyme results were consistent with the findings described for mean changes, ie, no consistent treatment-associated changes except as noted below

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities
See lab abnormalities in the safety section of review.

7. 1.7.4 Additional analyses and explorations

Not applicable and not indicated.

7.1.7.5 Special assessments

Not applicable and not indicated.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Not applicable

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

Not applicable

7.1.8.3 Standard analyses and explorations of vital signs data

Not applicable

7.1.8.3.1 Analyses focused on measures of central tendencies
Not applicable

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal
Not applicable

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities
Not applicable

7.1.8.4 Additional analyses and explorations

Not applicable

7.1.9 Electrocardiograms (ECGs)

See Section 5 - Pharmacodynamics.
There was a reduction in heart rate noted with Toprol-XL, which is consistent with its beta-blocking pharmacological effects. There were no other clinically important changes in ECGs except for those noted for Patients 023/4772 and 055/4200 described in Table 83.

The relatively small dose-related slowing of heart rate with Toprol-XL is consistent with its known beta-blocking pharmacological effects and this effect was not modified by concomitant treatment with HCT. No other relevant electrocardiographic findings were apparent. There were no clinically relevant changes noted by physical examination. Tables 44 and 45 summarize the ECG findings in the study.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Not applicable

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

Not applicable

7.1.9.3 Standard analyses and explorations of ECG data

Not applicable

7.1.9.3.1 Analyses focused on measures of central tendency
Not applicable

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal
Not applicable

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities
Not applicable

Adverse events
Eleven of the 24 patients with SAEs had the serious events begin during the follow-up period (ie, after the last full dose of double-blind medication). Narratives for these patients are presented in Tables 82-86. Each event occurred only once and none led to death.

Six of the 11 patients were not dispensed down-titration medications and 5 of these 6 patients had AEs that started on the day after the last double-blind dose.

None of the 11 patients were given open-label beta-blockers, except 1 patient who had an MI and was given Coreg (this patient completed down-titration medication).

Discontinuations due to adverse events

During study

Tables 87 and 88 present a summary of TEAEs that led to treatment discontinuation, by preferred term. Of the 45 patients (2.9%) who had treatment discontinued, 44 were also discontinued from the study (1 patient who received 6.25 mg HCT was reported as having an AE of headache and nervousness that led to treatment discontinuation but this patient was not discontinued from the study).

Headache was the most common reason (5 patients total) for treatment discontinuation. Other reasons occurred in 0.2% of patients or less, with most occurring in only 1 or 2 patients.

Among the 5 patients with some manifestation of coronary artery or ischemic heart disease, 2 patients had SAEs that occurred in the post treatment follow-up period. None of the 5 patients had known unstable coronary artery disease or MI's at study entry. None of the episodes were temporally related to abrupt cessation of beta-blocker treatment, either as a pre-study medication or as study drug. One patient (055/4202; treatment Toprol-XL/HCT 50/6.25 mg) experienced a myocardial infarction 10 days after stopping study drug. The patient was receiving blinded down-titration medication (Toprol XL 25 mg for 4 days and then placebo), ie, the patient was not on beta-blocker therapy at the time of the event; after the MI, the patient was given Coreg. The second patient (101/6116; treatment HCT 12.5 mg monotherapy) experienced coronary artery disease the day after stopping study drug.

The discontinuation rate was low (2.9%); the most common discontinuation AE was headache (5 patients overall). Other common AEs leading to discontinuation included erectile dysfunction (3 patients), fatigue (3 patients), and hypertension (3 patients).

Metabolic events of special interest were cited as AEs in only a few cases (hypokalemia (6 patients), hyponatremia (no patients), dyslipidemia (1 patient), hypergylcemia (8 patients), and hyperuricemia (1 patient).

8.5.2 Clinical chemistry

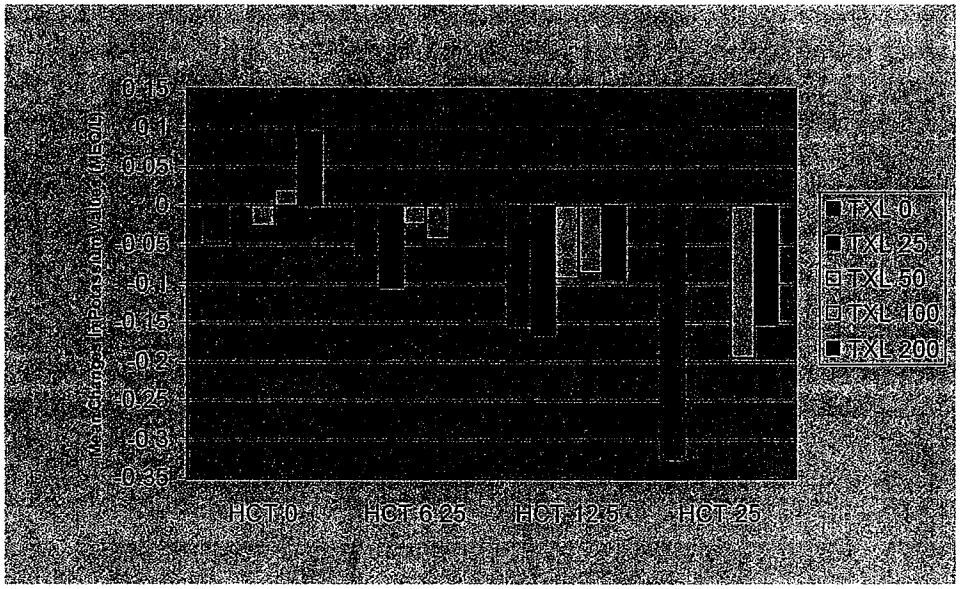
8.5.2.1 Changes in mean values over time in clinical chemistry

Mean changes from baseline to Visit 8 in chemistry test results (liver enzymes, electrolytes, renal function, lipids, and total protein, albumin, glucose, uric acid, calcium, and phosphorus) were observed.

Shifts for selected chemistry and liver enzyme results were consistent with the findings described for mean changes, ie, no consistent treatment-associated changes except as noted below

Serum potassium
Mean serum potassium level declined with increasing dose of HCT (maximum mean change of –0.32 mEq/L; HCT 25 mg), a trend that was largely independent of Toprol-XL dose. Figure 14 presents mean change from baseline to Visit 8 for potassium values. In total, 1.3% (19 of 1520) of patients with normal baseline potassium values shifted to 'below' the reference range of 3.5 meq/L at Visit 8 and all but 2 of these patients (1 on placebo and 1 on Toprol-XL 25 mg) were in a HCT or HCT/Toprol-XL group A total of 12 patients were below the reference range at baseline, and all but 2 of these patients (both on placebo) shifted to within normal range by Visit 8. No patient had a potassium result below 2.5 mEq/L.

Figure 9
Figure 24: Serum potassium values: mean change from baseline to visit 8 (safety population) - Study 324

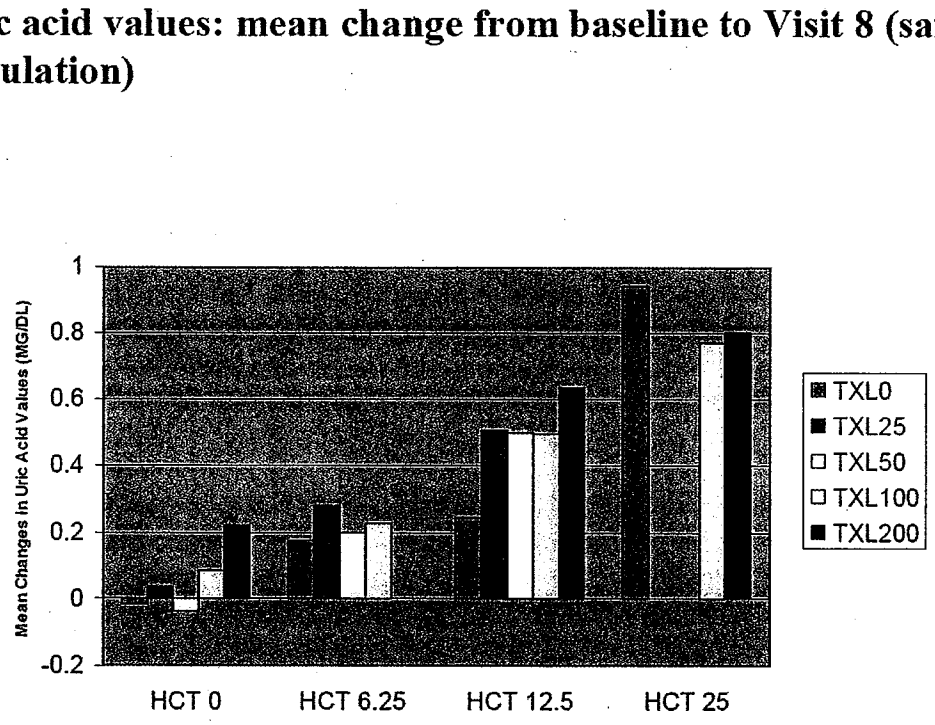


Serum sodium

Overall there was a decline in mean serum sodium with no consistent pattern of change over any of the treatment groups. Shift analyses identified very few (total of 10) patients with a Week 8 sodium value below the reference range. This is evidence of hyponatremia in the treated group compared to placebo.

Uric acid
Mean uric acid increased with increasing HCT dose (maximum change = 0.94 mg/dl; HCT 25 mg) and did so, largely, independent of Toprol-XL dose (Figure 10).

Figure 25: Uric acid values: mean change from baseline to visit 8 (safety population) Study 324



A total of 92 patients had a Week 8 uric acid level above the reference range of 8.5 mg/dl: 9 of 478 (1.8%) not on HCT (placebo or Toprol-XL monotherapy); and 83 of 1071 (7.7%) on a HCT treatment 11.3.7.1.6

Blood urea nitrogen and creatinine

Mean BUN increased with higher doses of HCT (12.5 and 25 mg), largely independent of Toprol-XL dose. The maximum mean change was 2.16 mg /dl (HCT 12.5mg/TXL 100 mg). There was no apparent parallel change in mean serum creatinine.

Most patients were within the BUN reference range (7 to 25 mg/dl) both at baseline and at Week 8. At Week 8, the proportion of patients with shifts from normal at baseline to above the reference range was 1.3%, (20 of 1527 patients).

For creatinine results, few patients had shifts from 'normal' at baseline to 'above' normal at Week 8 (1.1%, 16 of 1511 patients).

There were no consistent changes in mean blood glucose levels across any of the treatment groups. Mean changes for serum glucose values are displayed in and for diabetic patients

Glucose
Of 1316 patients entering the trial with a blood glucose in the reference range (70 to 125 mg/dl), 79 (6.0%) had a Week 8 glucose above the reference range and 142 of 223 entering the trial with an elevated glucose had an elevated level at Week 8 (64%). For both these subpopulations (normal at baseline or elevated at baseline) the proportions with elevated glucose at Week 8 were approximately the same over all treatment groups.

A listing of patients with blood glucose values greater than 180 mg/dl is shown in Table 11.3.7.2.7. Seventy patients had glucose values greater than 180 mg/dl and more than half of these patients had values greater than 180 mg/dl at baseline or run-in. There was no apparent clustering of these patients in any 1 treatment group.

Serum lipids

There was a suggestion of a decline in total cholesterol with Toprol-XL and an increase with HCT as monotherapies; the combination treatments tended to reflect the influence of the effects of the individual agents, ie, no consistent change.

There was a small decline in mean HDL cholesterol with Toprol XL (maximum change = -3.7 mg/dl; Toprol-XL/HCT 100/6.25 mg and 200/12.5 mg), and this was largely independent of HCT treatment.

There was no consistent pattern of change in mean LDL cholesterol across the treatment groups.

There was a suggestion of an increase in triglyceride level with both Toprol-XL and with the higher doses of HCT and both appeared to contribute to an increase with the combinations.

There was no noticeable shift in the distributions of patients by NCEP II category.

Metabolic events

Metabolic AEs of special interest included: hypokalemia, hyponatremia, dyslipidemia, hyperglycemia, and hyperuricemia.

Hypokalemia was reported for 6 (0.4%) patients overall and no treatment-related trends were apparent. Four of the 6 patients were on combination treatments and 2 patients were on monotherapy (HCT 12.5 mg; Toprol-XL 50 mg).

The term dyslipidemia was reported for 1 patient (combination treatment = Toprol-XL/HCT 25/6.25 mg).

Hyperglycemia was reported for 8 (0.5%) patients overall: 3 patients in the Toprol-XL/HCT combination 50/12.5 mg group and 0 to 1 patient in any of the other treatment groups. Four of these patients had a history of hyperglycemia or borderline hyperglycemia.

Hyperuricemia was reported for 1 patient (combination treatment = Toprol-XL/HCT 50/6.25 mg).

There were no clinical reports of hyponatremia but there was lab. evidence of hypopnatremia.

There were 4 reports of gout, of which 3 occurred in patients receiving monotherapy (2 patients receiving HCT 12.5 mg and 1 receiving Toprol-XL 200 mg).

There were 4 cases of nephrolithiasis (2 patients were on monotherapies [Toprol-XL 25 mg and HCT 12.65 mg, and 2 patients were on combination treatments [Toprol-XL/HCT at 25/6.25 mg and at 25/12.5 mg]).

From urinalyses, there were occasional (generally no more than 1 patient per treatment group) reports of glycosuria (=2+) at Week 8 but there were no apparent dose or treatment-related trends.

There were occasional reports of positive urine occult blood at Week 8 but the distribution of these reports was similar to that recorded at baseline. (Follow-up of these findings was at the discretion of the investigator, eg, concurrent menses, etc.)

There were occasional reports of proteinuria (=2+) at Week 8 but the distribution was similar to that reported at baseline and there were no apparent treatment associated trends.

Table 80: Electrocardiograms at study entry and week 8 and changes between visits- Safety population- Study 324.

Table 66 Mean (SD) ECG heart rate, PR interval, QRS duration, and QTc duration at study entry and Week 8 and change between visits (safety population)

ECG parameter	HCT dose	Toprol-XL dosage				
		0 mg n , Mean (SD)	25 mg n , Mean (SD)	50 mg n , Mean (SD)	100 mg n , Mean (SD)	200 mg n , Mean (SD)
Heart rate (bpm)						
Visit 1 (study entry)	0 mg	153, 68 (11)	89, 69 (10)	94, 70 (11)	95, 68 (10)	51, 68 (12)
	6.25 mg	86, 70 (12)	145, 70 (11)	136, 69 (12)	45, 70 (12)	NA
	12.5 mg	105, 69 (11)	141, 69 (12)	147, 68 (10)	95, 68 (10)	43, 69 (9)
	25.0 mg	48, 69 (11)	NA	NA	42, 70 (11)	49, 68 (11)
Change from Visit 1 to Visit 8	0 mg	146, 2 (9)	89, 1 (10)	91, –2 (10)	92, –4 (9)	50, –9 (10)
	6.25 mg	82, 3 (13)	140, –2 (9)	132, –2 (10)	44, –4 (9)	NA
	12.5 mg	102, 3 (10)	136, 0 (10)	142, –2 (9)	92, –4 (9)	43, –8 (9)
	25.0 mg	48, 3 (10)	NA	NA	41, –3 (11)	49, –7 (10)
PR interval (ms)						
Visit 1 (study entry)	0 mg	153, 162 (23)	89, 165 (27)	93, 165 (26)	94, 167 (24)	51, 162 (24)
	6.25 mg	86, 163 (26)	144, 160 (26)	135, 168 (23)	45, 168 (27)	NA
	12.5 mg	105, 168 (21)	141, 167 (26)	147, 165 (30)	94, 168 (26)	42, 165 (20)
	25.0 mg	48, 162 (25)	NA	NA	42, 161 (24)	49, 164 (27)
Change from Visit 1 to Visit 8	0 mg	146, –2 (20)	89, –1 (19)	90, 2 (17)	92, 2 (14)	49, 1 (20)

Table 81: Narratives of serious adverse events - Study 324

8.1 Narratives of serious adverse events

Table 27 Narratives of serious adverse events during the run-in period (Study 324 safety population)

Center/ patient number	Actual treatment group	Sex/age/ race	Verbatim term	Start/Stop Day	Causal	Max intensity	Day of last DB dose	Details/action taken
092/6074	T25/H12.5	M/47/C	Cellulitis of anterior abdominal wall	-1/unk	No	Severe	2	Hospitalized for abdominal wall cellulites. Treated by surgical incision and drainage and antibiotics. Recovered/ Discontinued treatment on Day 2.
099/6099	T50/H6.25	M/64/C	Gastrointestinal bleeding/colon polyps	-32/-30	No	Severe	57	Hospitalized for rectal bleeding. Colonoscopy: colon polyps. Completed study
131/6423	T100/H12.5	M/44/C	Crohn's disease	-43/unk	No	Mild	56	Hospitalized for suspect acute appendicitis. Underwent partial colectomy for Crohn's Disease. Completed study

Note: Start/stop day refers to the timing of the event in relation to the first day of treatment in the double-blind period.
Unk Unknown.
Derived from Table 62 in Study 324 clinical report.

Table 82: Narratives of serious adverse events - Study 324

Table 28 Narratives of serious adverse events (Study 324 safety population)

Center/ patient number	Actual treatment group	Sex/age/race	Verbatim term	Start/Stop Day	Causal	Max intensity	Day of last DB dose*	Details/Action Taken
Placebo treated patients								
055/4200	T-0/H-0	F/68/C	Right Bundle Branch Block	12/Unk	Yes	Severe	11	Patient developed chest pain. EKG determined new Right Bundle Branch Block. Hospitalized Diagnosis: Cholecystitis. Underwent endoscopic cholecystectomy Treatment was unblinded to the ER physician. / Discontinued.
			Cholecystitis	12/17	No	Severe	11	See above
061/5377	T-0/H-0	F/31/B	Migraine	23/24	Yes	Severe	26	Patient seen in emergency room for migraine and back muscle cramps. A CK value was elevated but was normal on repeat exam. All Symptoms resolved. / Discontinued.
089/5179	T-0/H-0	M/75/C	Myocardial Infarction	38/43	No	Severe	38	Patient experienced acute myocardial infarction and underwent bypass surgery. Uneventful recovery. / Discontinued.
Double-blind treatment - Toprol-XL, HCT, or combination treatment								
020/5001	T50/H12.5	M/52/C	Uncontrolled Hypertension	29/32	Yes	Severe	29	Patient complained of headache and blurred vision. Blood Pressure 212/126. Norvasc administered. Symptoms resolved. Withdrawn from study. Important medical event. / Discontinued
023/4772	T25/H6.25	M/63/C	Ischemic Heart Disease w/ 3 vessel Coronary Occlusion; Coronary Artery Disease; Myocardial Infarction	56/64	No	Moderate	56	End of study EKG showed ST-T changes. Echocardiogram: inferior hypokinesis. Angiography: 3 vessel coronary artery disease. Patient underwent coronary artery bypass graft surgery with uneventful recovery. / Discontinued

Table 83: Narratives of serious adverse events - Study 324

Table 28 Narratives of serious adverse events (Study 324 safety population)

Center/ patient number	Actual treatment group	Sex/age/race	Verbatim term	Start/Stop Day	Causal	Max intensity	Day of last DB dose[a]	Details/Action Taken
035/5650	T50/H12.5	M/72/C	Cervical vertebral fracture C5-6, C7-T1 spine fracture	4/38	No	Severe	5	Patient slipped and fell, sustaining a cervical spine fracture. Underwent surgery and had residual extremity weakness. / Discontinued.
062/5066	T50/H6.25	M/67/C	Acute Gastroenterocolitis	28/39	No	Moderate	30	Hospitalized for nausea, vomiting, and diarrhea. Diagnosis: acute gastroenterocolitis. / Discontinued.
065/4050	T25/H6.25	M/55/C	Diverticulitis	43/Unk	No	Severe	55	Patient underwent sigmoid resection for perforated sigmoid diverticulitis. Required repeat laparotomy because of leukocytosis. Discharged with colostomy. Recovering. / Discontinued.
068/4091	T100/H6.25	F/45/C	Pleomorphic adenoma of right parotid	43/45	No	Moderate	57	Underwent surgical resection of long-standing parotid mass. Pleomorphic adenoma. Uneventful recovery. / Completed.
077/4295	T50/H12.5	M/67/A	Pulmonary Embolism/ Deep vein Thrombosis	9/20	No	Severe	9	Patient seen in emergency room for chest pain 2 weeks following leg injury. Deep Vein Thrombosis with Pulmonary Embolism diagnosed and treated. Uneventful recovery. / Discontinued.
099/5756	T25/H-0	M/71/C	Acute Coronary Syndrome	13/43	No	Moderate	27	Patient complained of shortness of breath. Acute EKG changes. Underwent cardiac catheterization and coronary bypass graft surgery. Uneventful recovery. / Discontinued.
101/5900	T200/H-0	M/63/C	Mitral Insufficiency/Coronary Artery Disease	56/137	No	Severe	56	Heart murmur noted. ECHO: mitral regurgitation. Cardiac catheterization: mitral regurgitation and coronary artery disease. Coronary artery bypass graft surgery with mitral valve replacement. Uneventful recovery. / Completed.
109/5503	T50/H12.5	M/62/B	Atrial Flutter	28/30	No	Moderate	56	Patient presented with shortness of

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Table 84: Narratives of serious adverse events - Study 324

Table 28 Narratives of serious adverse events (Study 324 safety population)

Center/ patient number	Actual treatment group	Sex/age/race	Verbatim term	Start/Stop Day	Causal	Max intensity	Day of last DB dose[a]	Details/Action Taken
								breath, palpitations and atrial flutter. Hospitalized and underwent cardioversion. / Completed.
134/5457	T200/H-0	F/74/C	Congestive Heart Failure	12/17	Yes	Moderate	16	Developed shortness of breath. Congestive heart failure diagnosed. Improved with diuretic therapy. / Discontinued.
Events during follow-up/down titration period								
003/5970	T50/H-0	M/46/C	Supraventricular tachycardia; hypotension	72/73	No	Moderate	54	Hospitalized for hypotension and tachycardia which followed administration of Avapro at study conclusion. / Completed
034/6159	T100/H12.5	F/66/C	Depression	27/Unk	Yes	Severe	26	Patient hospitalized 12 days for depression. Treated with anti-depressants. / Discontinued
053/5493	T50/6.25	F/64/C	Ruptured Cerebral Aneurysm	70/70	No	Severe	60	Patient complained of neck pain and headache and was hospitalized with ruptured cerebral aneurysm. Antecedent BP was controlled. Underwent surgery. Some residual hemiparesis; began rehabilitation. / Discontinued.
055/4200	See narrative under placebo treatment							
055/4202	T50/H6.25	M/56/C	Myocardial Infarction	70/73	No	Severe	60	Patient hospitalized during down titration period with myocardial infarction. Underwent angioplasty with stent placement. Uneventful recovery. / Completed.
055/4208	T50/H12.5	M/60/C	Right Foot Fracture	22/57	No	Moderate	21	Hospitalized with foot fracture suffered in auto accident. / Discontinued.
092/6074	T25/H12.5	M/47/C	Rash over anterior abdominal wall	9/13	No	Severe	2	Hospitalized for abdominal wall cellulitis on day of last double-blind dose (Day 2). Treated by surgical incision and drainage

Table 85: Narratives of serious adverse events - Study 324

Table 28 Narratives of serious adverse events (Study 324 safety population)

Center/ patient number	Actual treatment group	Sex/age/race	Verbatim term	Start/Stop Day	Causal	Max intensity	Day of last DB dose*	Details/Action Taken
								and antibiotics. Recovered /Discontinued
			Methicillin-resistant Staphylococcus aureus	3/13	No	Severe	2	See above
			Rash on upper extremities and medial thighs	10/13	No	Severe	2	See above
101/6116	T0/H12.5	M/55/C	Severe coronary artery disease	17/90	No	Severe	16	Developed nausea with EKG changes. Cardiac catheterization: severe coronary artery disease. Underwent coronary artery bypass surgery. Uneventful recovery. / Discontinued.
			Hyperthermia malignant	27/29	No	Severe	16	Patient had malignant hyperthermia while in hospital; attributed to anesthetic agent./ Discontinued
123/4488	T50/H12.5	F/47/C	Malignant mass/colon	69/90	No	Mild	64	Patient underwent partial colectomy for colon mass.
			Vomiting	111/112	No	Severe	64	Patient was readmitted for vomiting and hypokalemia, treated with IV fluids. / Completed.
124/4931	T25/H12.5	M/40/C	Hepatitis C	42/Unk	No	Severe	29	Hepatic enzymes increased to >2.5 times upper limit of normal. Diagnosis: Hepatitis C. Referred for treatment. / Early discontinuation.
135/4832	T50/H6.25	M/41/C	Cellulitis of left leg	76/92	No	Severe	56	Hospitalized and treated for leg cellulitis consequent to a leg injury. / Completed.

* Day of last double-blind dose refers to the double-blind period and not the follow-up/down titration period.
Note: Start/stop day refers to the timing of the event in relation to the first day of treatment in the double-blind period.
Unk Unknown.
Data derived from Table 64 in Study 324.

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Table 86: Number (%) of patients with treatment emergent adverse events leading to treatment discontinuation - Study 324

Table 65 Number (%) of patients with treatment-emergent adverse events leading to treatment discontinuation (that occurred in more than 2 patients overall), sorted by decreasing order of frequency (safety population)

Preferred term[a]	HCT dosage	Toprol-XL dosage					Total
		0 mg	25 mg	50 mg	100 mg	200 mg	
Safety population	0 mg	153	89	94	95	51	1564
	6.25 mg	86	145	136	45	NA	
	12.5 mg	105	141	147	95	43	
	25.0 mg	48	NA	NA	42	49	
Number (%) of patients with at least 1 DAE	0 mg	4 (2.6)	3 (3.4)	1 (1.1)	3 (3.2)	4 (7.8)	45 (2.9)
	6.25 mg	1 (1.2)	3 (2.1)	3 (2.2)	1 (2.2)	NA	
	12.5 mg	6 (5.7)	4 (2.8)	7 (4.8)	4 (4.2)	0	
	25.0 mg	0	NA	NA	1 (2.4)	0	
Headache	0 mg	0	0	1 (1.1)	0	2 (3.9)	5 (0.3)
	6.25 mg	1 (1.2)	0	0	0	NA	

Table 87: Number (%) of patients with treatment-emergent adverse events leading to treatment discontinuation - Study 324

Table 65 Number (%) of patients with treatment-emergent adverse events leading to treatment discontinuation (that occurred in more than 2 patients overall), sorted by decreasing order of frequency (safety population)

Preferred term[a]	HCT dosage	Toprol-XL dosage					Total
		0 mg	25 mg	50 mg	100 mg	200 mg	
	12.5 mg	0	0	1 (0.7)	0	0	
	25.0 mg	0	NA	NA	0	0	
Erectile dysfunction	0 mg	0	0	0	0	0	3 (0.2)
	6.25 mg	0	0	0	0	NA	
	12.5 mg	0	0	1 (0.7)	1 (1.1)	0	
	25.0 mg	0	NA	NA	1 (2.4)	0	
Fatigue	0 mg	0	0	0	2 (2.1)	0	3 (0.2)
	6.25 mg	0	0	0	0	NA	
	12.5 mg	0	0	0	0	0	
	25.0 mg	0	NA	NA	1 (2.4)	0	
Hypertension	0 mg	0	0	0	1 (1.1)	0	3 (0.2)
	6.25 mg	0	0	0	0	NA	
	12.5 mg	0	1 (0.7)	1 (0.7)	0	0	
	25.0 mg	0	NA	NA	0	0	

[a] A patient is counted only once for a preferred term if he or she had 1 or more treatment-emergent adverse events leading to discontinuations within that term.

Note: Treatment-emergent adverse events include AEs reported during follow-up and any AEs that occurred during interruption of double-blind treatment.

DAE Adverse event leading to discontinuation; NA Not applicable.

Data derived from Table 11.3.5.1.3, Section 11.3.

7.1.9 Electrocardiograms

Evaluation of electrocardiograms are presented in tables 44 and 45. There was a reduction in heart rate noted with Toprol-XL, which is consistent with its beta-blocking pharmacological effects. There were no other clinically important changes in ECGs except for those noted for Patients 023/4772 and 055/4200 described in Table 83. The QT interval was within normal limits.

The small dose-related slowing of heart rate with Toprol-XL is consistent with its known beta-blocking pharmacological effects and this effect was not modified by concomitant treatment with hydrochlorothiazide. No other relevant electrocardiographic findings were apparent. There were no clinically relevant changes noted on physical examination. Tables 44 and 45 summarize the ECG findings in the study.

7.1.10 Immunogenicity

Not applicable

7.1.11 Human Carcinogenicity

Not applicable because both products have been approved.

7.1.12 Special Safety Studies

Not applicable.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable. There is information in the label for each component but there is no information on the combined product.

7.1.14 Human Reproduction and Pregnancy Data

Not applicable

7.1.15 Assessment of Effect on Growth

Not applicable

7.1.16 Overdose Experience

The most frequently observed signs expected with overdosage of a beta-blocker are bradycardia and hypotension. Lethargy is also common, and with severe overdoses, delirium, coma, convulsions, and respiratory arrest have been reported to occur. Congestive heart failure, bronchospasm, and hypoglycemia may occur, particularly in patients with underlying conditions. With thiazide diuretics, acute intoxication is rare. The most prominent feature of overdose is acute loss of fluid and electrolytes. Signs and symptoms include cardiovascular (tachycardia, hypotension, shock), neuromuscular (weakness, confusion, dizziness, cramps of the calf muscles, paresthesia, fatigue, impairment of consciousness), gastrointestinal (nausea, vomiting, thirst) renal (polyuria, oliguria, or anuria [due to hemoconcentration]), and laboratory findings (hypokalemia, hyponatremia, hypochloremia, alkalosis, increased BUN [especially in patients with renal insufficiency]).[67]
If overdosage of metoprolol and hydrochlorothiazide is

suspected, the patient should be observed closely. Treatment is symptomatic and supportive; there is no specific antidote. Limited data suggest metoprolol is not dialyzable; similarly, there is no indication that hydrochlorothiazide is dialyzable. Suggested general measures include induction of emesis and/or gastric lavage, administration of activated charcoal, respiratory support, correction of fluid and electrolyte imbalance, and treatment of convulsions. Based on the expected pharmacologic actions and recommendations for other beta blockers and hydrochlorothiazide, the following measures should be considered when clinically warranted.[68] Bradycardia: Administer IV atropine. If the response is inadequate, isoproterenol or another agent with positive chronotropic properties may be given cautiously. Under some circumstances, transvenous pacemaker insertion may be necessary.

7.1.17 Postmarketing Experience

Both metoprolol succinate ER and HCT as individual entities, are well-established antihypertensive agents; there is an extensive post-marketing experience in other countries with metoprolol/HCT combination products (commercially available as metoprolol tartrate/HCT and metoprolol succinate ER/HCT), which have been available for over 25 years and 16 years, respectively. Further experience will be generated when product after approval and marketing.

7.2 Adequacy of Patient Exposure and Safety Assessments

This is considered adequate.

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

For description see overview of clinical program on pages 14 – 52 of this review and also lists of clinical tables (Tables 30 to 40). These studies are considered adequate to evaluate clinical safety by this reviewer.

7.2.1.1 Study type and design/patient enumeration

See Section 1.3

7.2.1.2 Demographics

See Section 1.3 Tables 5-7

7.2.1.3 Extent of exposure (dose/duration)

See Section 1.3

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

See Section 1.3 Tables 31- 40

7.2.2 Other studies

S-902 – ITT Swedish studies

7.2. Postmarketing experience

Not applicable as combination product is not yet on the market.

7.2. Literature

See references

7.2.3 Adequacy of Overall Clinical Experience

The mean duration of each treatment period was: run-in period 30 days, double-blind treatment period 55 days, and the down-titration/follow-up period 15 days. Study patients entered a single-blind placebo 4 or 5 week run-in period prior to randomization into an 8-week double-blind treatment period that was followed by a 2-week down-titration/follow-up period. See section 1.3 for adequacy of clinical experience.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Both components of the combination have been approved. Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

Not applicable

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Not applicable

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

This is not a new drug as both components have been approved.

7.2.8 Assessment of Quality and Completeness of Data

This is adequate and acceptable

7.2.9 Additional Submissions, Including Safety Update

Not required as all studies have been completed.

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

See Tables 82 to 88. A significant number of diabetics were enrolled in the study. The presence of erectile dysfunction and glycosuria as adverse events need to be evaluated further.

7.4 General Methodology

This was acceptable.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

There was only one factorial study therefore there were no data to be pooled.

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

This model is performed on the weighted cell means (ie, the treatment group means weighted by the number of patients in each treatment group). The model is significant with an F p-value <0.0001 and an R-square=0.90. According to the model, the intercept estimates the placebo effect on the change from baseline to Week 8/LOCF to be –5.34 mmHg. The estimated add-on effects of Toprol-XL range from –1.4 mmHg for the 25 mg dose to –6.1 mmHg for the 200 mg dose. Similarly, the add-on effects of HCT range from –1.9 mmHg for the 6.25 mg dose to –4.3 mmHg for the 25 mg dose. When combined, this range of effects translates into reductions of –3.3 mmHg for the Toprol-XL/HCT 25/6.25 mg combination to –10.4 mmHg for the Toprol-XL/HCT 200/25 mg combination, after accounting for the placebo effect (Table 18).Reproduced below for ease of reference.
Table 18

Table 1. Placebo-corrected Predicted Values for Change from Baseline in SBP/DBP

	TOPROL-XL Dosage				
HCT Dosage	**0 mg SBP/DBP**	**25 mg SBP/DBP**	**50 mg SBP/DBP**	**100 mg SBP/DBP**	**200 mg SBP/DBP**
0 mg	0/0	-2.0/-1.4	-3.7/-2.6	-6.1/-4.5	-7.0/-6.1
6.25 mg	-3.5/-1.9	-5.5/-3.3	-7.2/-4.5	-9.6/-6.4	10.5/-8.0
12.5 mg	-5.9/-3.3	-7.9/-4.7	-9.6/-5.9	-12.0/-7.8	-12.9/-9.3
25 mg	-7.7/-4.3	-9.7/-5.7	-11.4/-6.9	-13.8/-8.8	-14.7/-10.4

[a] Predicted values from a least-squares quadratic regression model.

7.4.2.1 Explorations for dose dependency for adverse findings

Not applicable

7.4.2.2 Explorations for time dependency for adverse findings

Not applicable

7.4.2.3 Explorations for drug-demographic interactions

Not applicable

7.4.2.4 Explorations for drug-disease interactions

Not applicable

7.4.2.5 Explorations for drug-drug interactions

See Sections 1.3.7 and 8.2

7.4.3 Causality Determination

Shown on ECG pharmacologically driven for beta blockers on page 84.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Doses and treatment regimes
Study patients first received 5 placebo tablets once daily during the 4- or 5-week run-in period. Randomized eligible patients began dosing in the 8-week double-blind treatment period with 1 of 4 dose levels of Toprol-XL, 1 of 3 dose levels of HCT, 1 of the 9 combinations, or placebo. Patients assigned 200 mg metoprolol succinate received 100 mg for the 1st week of the double-blind period before the dose was escalated. Dosing was once daily. Dosing instructions included the admonition that tablets should not be crushed or chewed. Dosing at Day 0 was in the morning.

The double-dummy study drug packaging design required that patients take 5 tablets at each dosing.

Blinded study drug discontinuation medication was available for patients who required study drug discontinuation during the study as well as for all patients at the end of the 8-week double-blind period. The discontinuation medication provided for down-titration of patients receiving Toprol-XL, either alone or as a combination.

8.2 Drug-Drug Interactions

Drug Interactions
Metoprolol
Catecholamine-depleting drugs (eg, reserpine, mono amine oxidase (MAO) inhibitors) may have an additive effect when given with beta-blocking agents. Patients treated with TOPROL-XL plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.37
Drugs that inhibit CYP2D6 such as quinidine, fluoxetine, paroxetine, and propafenone are likely to increase metoprolol concentration. In healthy subjects with CYP2D6 extensive

metabolizer phenotype, coadministration of quinidine 100 mg and immediate release metoprolol 200 mg tripled the concentration of S-metoprolol and doubled the metoprolol elimination half-life. In four patients with cardiovascular disease, coadministration of propafenone 150 mg t.i.d. with immediate release metoprolol 50 mg t.i.d. resulted in two- to five-fold increases in the steady-state concentration of metoprolol. These increases in plasma concentration would decrease the cardioselectivity of metoprolol.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two drugs are coadministered, the beta blocker should be withdrawn several days before the gradual withdrawal of clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.
For HCTZ see label section 9 below.

8.3 Special Populations

See Section 1.3.8

8.4 Pediatrics

Waiver requested.

8.5 Advisory Committee Meeting

Not required

8.6 Literature Review

See page 188

8.7 Postmarketing Risk Management Plan

Post-Marketing Experience In addition, the following adverse reactions have been reported with metoprolol succinate in worldwide post-marketing use, regardless of causality:

Cardiovascular: 2nd and 3rd degree heart block. Gastrointestinal: hepatitis, vomiting. Hematologic: thrombocytopenia. Musculoskeletal: arthralgia. Nervous System/Psychiatric: anxiety/nervousness, hallucinations, paresthesia. Reproductive, male: impotence. Skin: increased sweating, photosensitivity, urticaria. Special Sense Organs: taste disturbances.

8.8 Other Relevant Materials

Not applicable

9 OVERALL ASSESSMENT

9.1 Conclusions

Study 324 met its primary objective, establishing that at least 1 Toprol-XL/HCT combination was superior to its components in lowering SiDBP. The conclusion is supported by a statistically significant T_{AVE} test. Importantly, however, several study observations support the validity and generalizability of Toprol -XL/HCT combination therapy. First, the study investigators enrolled a population typical of a US hypertensive population - one which included a sufficient representation of Blacks and women so as to adequately allow for evaluations of treatment responses for these key subpopulations. Average pre-treatment BP was 151/100 mm/Hg, indicating a population with moderately severe hypertension – a group for which aggressive treatment is justified. In spite of the many treatment groups, the randomization process was successful in producing treatment groups that were generally well-balanced with regard to key patient and potentially confounding characteristics.

Study drug compliance (97% per treatment group) was based on counting the patient's medication (pill counts) and compliance was very good. Protocol violations were minimal and not disruptive to the conduct of the study. The discontinuation rate from the study was low and reasonable for this type of study (11%); the discontinuation rate for AEs was 2.9% which is also low and the reasons are not unexpected. In addition, most randomized patients completed the entire 8- week treatment period. In relatively few cases was it necessary to impute a Week 8 BP value by carrying forward the last observation.

Furthermore, the study met the secondary study objectives based on SiSBP and standing BPs (statistically significant TAVE tests). Subsidiary analyses based on ANOVA methods also supported the statistical conclusions based on the TAVE test statistic. Even more to the point, a response surface analysis which considers, jointly, a combination therapy's BP reduction relative to placebo and to its components indicated that all combinations are 'desirable'.

The magnitude of the BP reductions with the study treatments, including the combinations, was in keeping with results of other studies in which these agents were evaluated (Moser and Setaro 2004), and the reductions were clinically meaningful. To that end, the clinical response rates ranging from 46.3% to 77.8% and control rates 29.1% to 65.3% compare favorably with those attainable with most effective antihypertensive treatments (JNC 7 report 2003).

One argument in favor of combination antihypertensive treatment asserts that the BP lowering effects of antihypertensive agents tend to be additive. This, then, allows the prescribing physician to employ lower doses in combination to achieve BP responses ordinarily attainable only with

large doses of single agent treatment and can do so avoiding dose-related AEs. In general, Study 324 confirms this argument - the 2 agents were additive in their effects. However, additivity was less apparent at the extremes of the dose ranges. At the high dose range, this is of less interest - the individual agents are probably already near the top of their individual dose response curves. In addition, the magnitude of the BP reductions in the high combination groups was substantial so there is less clinical demand for additivity at this end of the dose range.

In the lower ranges of doses, additivity is desirable but such additivity was not evident in Study 324. This is largely attributable to the greater-than-expected BP reduction with the HCT 6.25 mg dose. Based on the literature that was available when Study 324 was designed, HCT 6.25 mg was expected to lower SiDBP by 1.1 to 2.5 mmHg. In fact, it lowered DBP by 3.9 mmHg (after subtracting the placebo effect). This could be considered an atypical finding. If, in fact, the HCT 6.25 mg group had performed more as expected, additivity at these low doses would likely be more strongly supported. It is important to note, however, that all the Toprol-XL/HCT combinations, including those of lower doses, were very effective at lowering BP, ie, highly statistically significant reductions compared to placebo.

Study 324 employed a factorial design. One feature of this design is that it allowed summary estimates of the treatment effects - ones that are less vulnerable to atypical responses in a treatment group (cell). We used this design feature to address a second regulatory guidance to characterize dose response relationships by constructing response surface models. In these dose response surface analyses, the Study 324 data was well described by a quadratic model. The better fit with a quadratic than a linear model suggests that the trial included a clinically meaningful wide range of doses that approached the top of the dose response curves. The model predicts BP reductions of 5.5/3.3 for the lowest (Toprol-XL/HCT 25/6.25 mg) after accounting for the placebo effect. Hence, the dose response supports the conclusion that not only are all combinations effective, but that there is a contribution from both components. This also implies that a low dose combination may be a better alternative treatment than the individual agents, as the combination is predicted to yield a greater BP reduction. For example, the model predicts a placebo-corrected SiSBP/SiDBP decline of 2.0/1.4 mmHg if one treats with Toprol-XL 25 mg as monotherapy; 3.5/1.9 mmHg with HCT 6.25 mg as monotherapy, but 5.5/3.3 mmHg if one selects the Toprol-XL/HCT 25/6.25 mg combination.

A recommendation to employ antihypertensive treatment with combinations and then proceed with combination dose adjustment, if necessary can also be supported by the study findings. In simple pairwise comparisons, some low dose Toprol-XL (25 or 50 mg)/low dose HCT (6.25 mg but particularly 12.5 mg) combinations were about as effective as high dose monotherapy. This was particularly true for comparisons to high dose (25 mg) HCT. Importantly, these lower dose combinations avoided some of the high HCT dose-attendant metabolic abnormalities (hypokalemia and hyperuricemia). Although lower dose combinations were not quite as effective as high dose Toprol-XL (200 mg) in lowering BP, high Toprol-XL dose carries a higher risk for fatigue, particularly when it is used with high dose HCT. In this context, it is important to note that fatigue is a common treatment-limiting adverse effect of beta-blocker treatment (Moser and Setaro 2004, JNC 7 report 2003).

Study 324 also provides information as to the expected treatment responses by important sub-populations. Women tended to respond somewhat better than men but these treatments by gender differences were small. Blacks tended to respond less well than non-Blacks but this largely reflected Blacks' lesser response to Toprol-XL. Blacks tended to respond well to HCT, which is in keeping with prior accounts of racial differences in response to antihypertensive treatment (JNC 7 2003). In addition, the findings of almost identical BPs at trough (24 hours post dosing) and peak (6 hours post dosing) across all treatment groups are consistent with current recommendations for once daily dosing with HCT and Toprol-XL.

The safety findings in Study 324 are also highly consistent with the well-described historical reports of these 2 well-established individual agents. The only finding suggestive of an additive risk was for the complaint of fatigue among patients receiving high dose HCT in combination with Toprol-XL. The dose-related metabolic consequences of diuretic treatment were also apparent (hypokalemia and hyperuricemia) but, as noted above, these can be partly avoided by combining lower HCT doses with Toprol-XL.

9.2 Recommendations on Regulatory Action

Toprol-XL/HCT is an effective antihypertensive combination product which reflects the additive BP lowering contributions of its individual components.

Toprol-XL 50 mg/HCT 6.25 and 12.5 mg combinations lower blood pressure to levels close to those attainable with at least 1 of the high dose monotherapies (200 mg Toprol-XL or 25 mg HCT). The risk for side effects such as fatigue and metabolic abnormalities, albeit on the low side should be carefully monitored during Postmarketing period.

9.3 Recommendation on Postmarketing Actions

Post-Marketing Experience with individual components are well known and characterized. The adverse reactions which have been reported with metoprolol succinate in worldwide post-marketing use, regardless of causality include the following:

Cardiovascular: 2nd and 3rd degree heart block. Gastrointestinal: hepatitis, vomiting. Hematologic: thrombocytopenia. Musculoskeletal: arthralgia. Nervous System/Psychiatric: anxiety/nervousness, hallucinations, paresthesia. Reproductive, male: impotence. Skin: increased sweating, photosensitivity, urticaria. Special Sense Organs: taste disturbances.

9.3.1 Risk Management Activity should be as recommended in Section 1.2.1 of Executive summary.

9.3.2 Required Phase 4 Commitments: Not required

9.3.3 Other Phase 4 Requests: Not applicable

9.4 Labeling Review –TO BE CARRIED OUT WITH OTHER DISCIPLINES

Rx only

21 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

10 APPENDICES

10.1 Review of Individual Study Reports

In addition to the factorial study submitted by the sponsor, a small study conducted in Denmark and Sweden in 1987-88 (Study S-902, 47 ITT patients –) evaluated the antihypertensive effect of metoprolol succinate ER/HCT (100/12.5 mg) in comparison to a conventional metoprolol tartrate/HCT combination in a population remaining hypertensive in spite of treatment with HCT 12.5 mg daily. There was no dose ranging response study and the results are therefore of limited value. The disposition of the study and the study design are in Figures 22 and 23 below.

Figure 26: Disposition of patients in Swedish study of Met ER and HCT in 1987-N=47 ITT

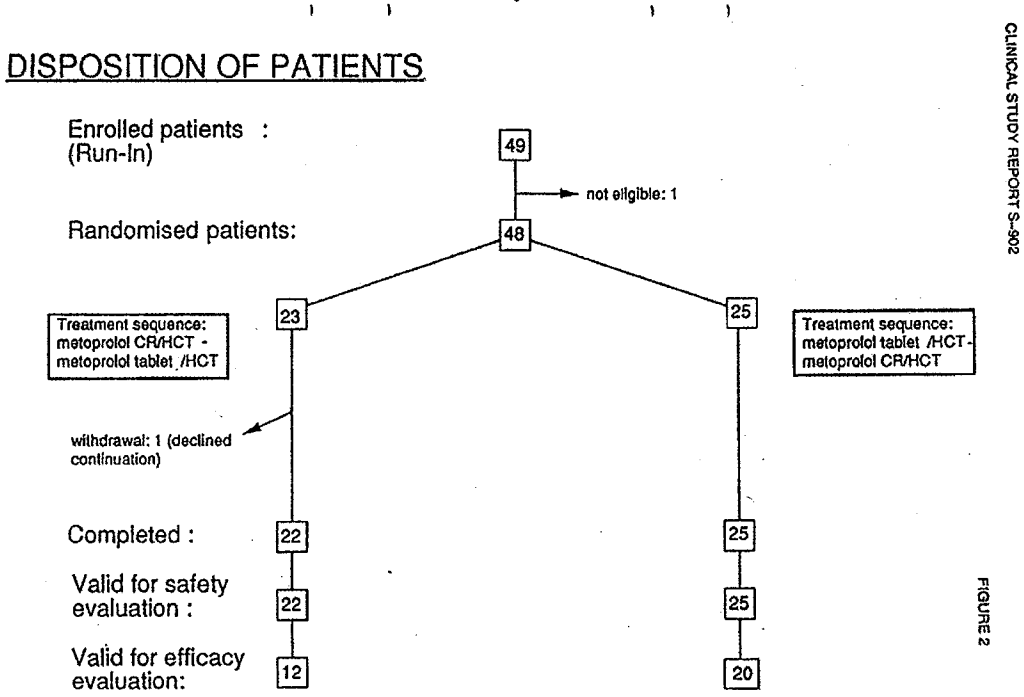
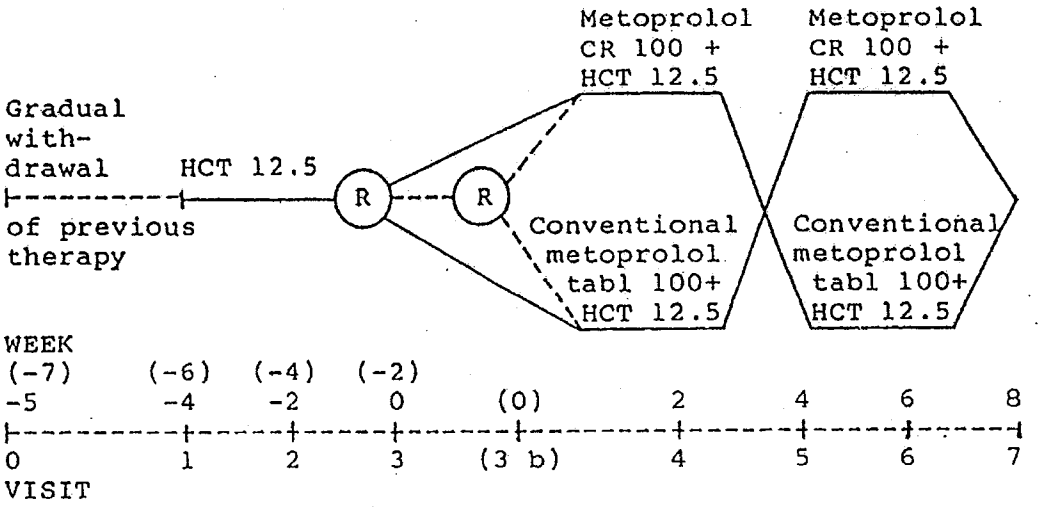


Figure 27: Study design in Swedish Study 1987 - 47 ITT patients



APPEARS THIS WAY
ON ORIGINAL

Line-by-Line Labeling Review

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Appendix See Figures 6-9

Pairwise Comparisons between Combination and Monotherapy for mean change from Baseline to Week 8/LOCF in Trough SiDBP among Black			
Combination Treatment Group (n)	Comparator Monotherapy (n)	Mean Difference*	96% CI LL, UL
Toprol-XL/HCT, 25/6.25 mg (37)	Toprol-XL, 25 mg (22)	-3.1	-7.7, 1.5
Toprol-XL/HCT, 25/12.5 mg (43)	Toprol-XL, 25 mg	-7.6	-12.1, -3.1
Toprol-XL/HCT, 50/6.25 mg (33)	Toprol-XL, 50 mg (26)	-0.42	-4.9, 4.1
Toprol-XL/HCT, 50/12.5 mg (33)	Toprol-XL, 50 mg	-4.4	-8.9, 0.1
Toprol-XL/HCT, 100/6.25 mg (12)	Toprol-XL, 100 mg (23)	-2.8	-9.0 , 3.3
Toprol-XL/HCT, 100/12.5 mg (19)	Toprol-XL, 100 mg	-5.9	-11.2, -0.6
Toprol-XL/HCT, 100/25 mg (8)	Toprol-XL, 100 mg	-0.8	-7.9, 6.2
Toprol-XL/HCT, 200/12.5 mg (15)	Toprol-XL, 200 mg (11)	-1.0	-7.9, 5.8
Toprol-XL/HCT, 200/25 mg (12)	Toprol-XL, 200 mg	-10.0	-17.0, -2.6
Toprol-XL/HCT, 25/6.25 mg (37)	HCT, 6.25 mg (21)	4.2	-0.5, 8.9
Toprol-XL/HCT, 50/6.25 mg (33)	HCT, 6.25 mg	2.0	-2.8, 6.8
Toprol-XL/HCT, 100/6.25 mg (12)	HCT, 6.25 mg	-0.4	-6.7, 5.8
Toprol-XL/HCT, 25/12.5 mg	HCT, 12.5 mg (23)	-2.0	-6.4, 2.4

(43)			
Toprol-XL/HCT, 50/12.5 mg (33)	HCT, 12.5 mg	-3.7	-8.4, 0.9
Toprol-XL/HCT, 100/12.5 mg (19)	HCT, 12.5 mg	-5.2	-10.6, 0.1
Toprol-XL/HCT, 200/12.5 mg (15)	HCT, 12.5 mg	-3.0	-8.8, 2.7
Toprol-XL/HCT, 100/25 mg (8)	HCT, 25 mg (13)	2.5	-5.2, 10.2
Toprol-XL/HCT, 200/25 mg (12)	HCT, 25 mg	-9.1	-16.0, -2.3
N=392			

* Difference=Week 8-baseline

Pairwise Comparisons between Combination and Monotherapy for mean change from Baseline to Week 8/LOCF in Trough SiDBP among Non-Black			
Combination Treatment Group (n)	Comparator Monotherapy (n)	Mean Difference*	96% CI LL, UL
Toprol-XL/HCT, 25/6.25 mg (107)	Toprol-XL, 25 mg (67)	1.0	-1.5, 3.5
Toprol-XL/HCT, 25/12.5 mg (98)	Toprol-XL, 25 mg	-0.4	-2.9, 2.2
Toprol-XL/HCT, 50/6.25 mg (103)	Toprol-XL, 50 mg (67)	--1.3	-3.8, 1.2
Toprol-XL/HCT, 50/12.5 mg (114)	Toprol-XL, 50 mg	-1.1	-3.6, 1.3
Toprol-XL/HCT, 100/6.25 mg (33)	Toprol-XL, 100 mg (72)	-4.0	-7.3, -0.6
Toprol-XL/HCT, 100/12.5 mg (75)	Toprol-XL, 100 mg	-3.9	-6.5, -1.2
Toprol-XL/HCT, 100/25 mg (34)	Toprol-XL, 100 mg	-5.1	-8.4, -1.7
Toprol-XL/HCT, 200/12.5 mg (28)	Toprol-XL, 200 mg (40)	-0.5	-4.4, 3.5
Toprol-XL/HCT, 200/25 mg (37)	Toprol-XL, 200 mg	-2.1	-5.8, 1.5
Toprol-XL/HCT, 25/6.25 mg (107)	HCT, 6.25 mg (65)	-0.7	-3.2, 1.8
Toprol-XL/HCT, 50/6.25 mg	HCT, 6.25 mg	-3.0	-5.6, -0.5

(103)			
Toprol-XL/HCT, 100/6.25 mg (33)	HCT, 6.25 mg	-5.9	-9.3, -2.5
Toprol-XL/HCT, 25/12.5 mg (98)	HCT, 12.5 mg (81)	0.2	-2.2, 2.6
Toprol-XL/HCT, 50/12.5 mg (114)	HCT, 12.5 mg	-0.5	-2.8, 1.8
Toprol-XL/HCT, 100/12.5 mg (75)	HCT, 12.5 mg	-3.5	-6.1, -0.9
Toprol-XL/HCT, 200/12.5 mg (28)	HCT, 12.5 mg	-3.6	-7.1, -0.1
Toprol-XL/HCT, 100/25 mg (34)	HCT, 25 mg (35)	-5.9	-9.7, -2.0
Toprol-XL/HCT, 200/25 mg (37)	HCT, 25 mg	-6.4	-10.2, -2.7
N=1167			

* Difference=Week 8-baseline

Pairwise Comparisons between Combination and Monotherapy for mean change from Baseline to Week 8/LOCF in Trough SiSBP among Black			
Combination Treatment Group (n)	Comparator Monotherapy (n)	Mean Difference*	96% CI LL, UL
Toprol-XL/HCT, 25/6.25 mg (37)	Toprol-XL, 25 mg (22)	2.5	-4.6, 9.6
Toprol-XL/HCT, 25/12.5 mg (43)	Toprol-XL, 25 mg	-9.6	-16.6, -2.7
Toprol-XL/HCT, 50/6.25 mg (33)	Toprol-XL, 50 mg (26)	-4.2	-11.1, 2.7
Toprol-XL/HCT, 50/12.5 mg (33)	Toprol-XL, 50 mg	-7.9	-14.8, -0.9
Toprol-XL/HCT, 100/6.25 mg (12)	Toprol-XL, 100 mg (23)	-7.8	-17.2, 1.6
Toprol-XL/HCT, 100/12.5 mg (19)	Toprol-XL, 100 mg	-14.7	-22.8, -6.5
Toprol-XL/HCT, 100/25 mg (8)	Toprol-XL, 100 mg	-8.2	-19.1, 2.6
Toprol-XL/HCT, 200/12.5 mg (15)	Toprol-XL, 200 mg (11)	-9.0	-19.5, 1.4
Toprol-XL/HCT, 200/25 mg (12)	Toprol-XL, 200 mg	-16.3	-27.3, -5.2

Toprol-XL/HCT, 25/6.25 mg (37)	HCT, 6.25 mg (21)	4.4	-2.8, 11.6
Toprol-XL/HCT, 50/6.25 mg (33)	HCT, 6.25 mg	-3.3	-10.6, 4.1
Toprol-XL/HCT, 100/6.25 mg (12)	HCT, 6.25 mg	-1.3	-10.8, 8.3
Toprol-XL/HCT, 25/12.5 mg (43)	HCT, 12.5 mg (23)	-3.3	-10.1, 3.5
Toprol-XL/HCT, 50/12.5 mg (33)	HCT, 12.5 mg	-2.5	-9.7, 4.7
Toprol-XL/HCT, 100/12.5 mg (19)	HCT, 12.5 mg	-3.7	-11.8, 4.5
Toprol-XL/HCT, 200/12.5 mg (15)	HCT, 12.5 mg	-4.8	-13.6, 3.9
Toprol-XL/HCT, 100/25 mg (8)	HCT, 25 mg (13)	4.9	-6.9, 16.8
Toprol-XL/HCT, 200/25 mg (12)	HCT, 25 mg	-9.9	-20.4, 0.7
N=392			

* Difference=Week 8-baseline

Pairwise Comparisons between Combination and Monotherapy for mean change from Baseline to Week 8/LOCF in Trough SiSBP among Non-Black			
Combination Treatment Group (n)	Comparator Monotherapy (n)	Mean Difference*	96% CI LL, UL
Toprol-XL/HCT, 25/6.25 mg (107)	Toprol-XL, 25 mg (67)	0.7	-3.4, 4.9
Toprol-XL/HCT, 25/12.5 mg (98)	Toprol-XL, 25 mg	-0.6	-4.8, 3.6
Toprol-XL/HCT, 50/6.25 mg (103)	Toprol-XL, 50 mg (67)	-3.1	-7.2, 1.1
Toprol-XL/HCT, 50/12.5 mg (114)	Toprol-XL, 50 mg	-1.7	-5.8, 2.4
Toprol-XL/HCT, 100/6.25 mg (33)	Toprol-XL, 100 mg (72)	-2.2	-7.7, 3.4
Toprol-XL/HCT, 100/12.5 mg (75)	Toprol-XL, 100 mg	-6.5	-10.9, -2.1
Toprol-XL/HCT, 100/25 mg (34)	Toprol-XL, 100 mg	-7.4	-12.9, -1.9
Toprol-XL/HCT, 200/12.5 mg (28)	Toprol-XL, 200 mg (40)	-2.8	-9.3, 3.7
Toprol-XL/HCT, 200/25 mg (37)	Toprol-XL, 200 mg	-2.3	-8.4, 3.7
Toprol-XL/HCT, 25/6.25 mg (107)	HCT, 6.25 mg (65)	-0.5	-4.6, 3.7
Toprol-XL/HCT, 50/6.25 mg (103)	HCT, 6.25 mg	-4.3	-8.5, -0.2
Toprol-XL/HCT, 100/6.25 mg (33)	HCT, 6.25 mg	-4.2	-9.8, 1.5

Toprol-XL/HCT, 25/12.5 mg (98)	HCT, 12.5 mg (81)	-1.6	-5.6, 2.4
Toprol-XL/HCT, 50/12.5 mg (114)	HCT, 12.5 mg	-2.8	-6.6, 1.0
Toprol-XL/HCT, 100/12.5 mg (75)	HCT, 12.5 mg	-8.3	-12.5, -4.1
Toprol-XL/HCT, 200/12.5 mg (28)	HCT, 12.5 mg	-8.1	-13.8, -2.3
Toprol-XL/HCT, 100/25 mg (34)	HCT, 25 mg (35)	-4.9	-11.3, 1.4
Toprol-XL/HCT, 200/25 mg (37)	HCT, 25 mg	-3.4	-9.6, 2.9
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* Difference=Week 8-baseline

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/s/

Akinwole Williams
7/16/2006 06:12:55 PM
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