CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-956

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-956 / S_000
Drug Name:	Toprol -XL®/HCT (metoprolol succinate and hydrochlorothiazide)
Indication(s):	Management of Hypertension
Applicant:	AstraZeneca
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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Study 324 (ATTACH) has demonstrated that at least 1 Toprol-XL/HCT combination exceeds the blood pressure (BP) lowering effects of its individual components with regard to placebo-corrected change from baseline to Week 8 in trough sitting diastolic blood pressure. The dose combination that performs better than its components was identified as Toprol-XL 100mg/HCT 12.5 mg. Support from Study S-902 is limited because of different study design, lacking consistent positive results and no multiplicity adjustment for multiple primary efficacy endpoints.

1.2 Brief Overview of Clinical Studies

This sNDA includes two studies to support the safety and efficacy of Toprol –XL/HCT in the treatment of patients with essential hypertension. One is a pivotal Phase III study (324, ATTACH) and the other is a supportive study (S-902).

The primary objective of Study 324 (ATTACH) 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 sitting diastolic blood pressure (SiDBP). The primary efficacy variable was the placebo-corrected change from baseline to Week 8 in trough sitting diastolic blood pressure (SiDBP).

The objectives of Study 902 were to evaluate the antihypertensive effect and tolerability of a new fixed combination formulation of metoprolol controlled release (succinate salt), 100 mg, and hydrochlorothiazide (HCT), 12.5 mg, in comparison with a conventional fixed combination of metoprolol (tartrate salt), 100 mg, and HCT, 12.5 mg. The primary efficacy variables were blood pressure and heart rate.

1.3 Statistical Issues and Findings

Study 324 (ATTACH) seems to suggest that Toprol- XL/HCT combination drug yields a BP lowering effect smaller than the sum of the effects of Toprol alone and HCT alone. Because of this potential negative drug by drug interaction, the validity of ANOVA using an additive model is questionable. TAVE test was used to test whether at least one of the dose combinations is effective than its components. Based on both TAVE test and traditional ANOVA along with an appropriate multiple comparisons adjustment, it can be concluded that there is at least one dose combination that is more effective than its components. The combination identified was Toprol-XL 100mg/HCT 12.5 mg.

In Study 902, over-parameterization in statistical model is a potential problem. When a simpler model is used, the analysis results are substantially different.

2. INTRODUCTION

2.1 Overview

Metoprolol is a beta-1-selective (cardio-selective) adrenoceptor blocking agent, long established as an antihypertensive agent. Metoprolol (Toprol-XL) has been available as a once daily, ER formulation of the succinate salt in the US since 1992. Hydrochlorothiazide (HCT) is a well-established diuretic and antihypertensive agent. A fixed-dose combination tablet of Toprol-XL/HCT 100/12.5 mg was developed and approved for in Europe in 1989. AstraZeneca is developing a new combination product of metoprolol succinate ER/HCT by establishing that both HCT and metoprolol succinate ER contribute to the antihypertensive activity of their combination. The pivotal study, a factorial clinical trial (324 ATTACH) was conducted to determine whether at least 1 metoprolol succinate ER/HCT combination (Toprol-XL/HCT) proved better than its individual components in lowering BP. The trial examined 3 dose levels of HCT, 4 dose levels of Toprol-XL, 9 of the Toprol-XL/HCT combinations, and placebo. In addition, another supportive study (S-902) conducted in Denmark and Sweden in 1987-88 evaluated the antihypertensive effect of 1 dose level of metoprolol succinate ER/HCT (100/12.5 mg) compared to that of the conventional fixed-dose combination of metoprolol tartrate IR/HCT in a population remaining hypertensive in spite of treatment with HCT 12.5 mg daily.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\Cdsesub1\N21956\N_000\2005-10-28 of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY A: 324 (ATTACH)

3.1.1.1 Study Objectives

The primary objective was to determine whether at least 1 Toprol-XL/HCT exceeds the blood pressure (BP) lowering effects of its individual components with regard to placebo-corrected change from baseline to Week 8 in trough sitting diastolic blood pressure (SiDBP).

3.1.1.2 Study Design

Study 324 (ATTACH) is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, unbalanced factorial study. 1571 subjects with essential hypertension

from the US were enrolled into the study. This study consisted of four sequential periods including 17 treatment groups as shown below in Table 1:

Table 1 Study Flow Chart

Screening	**Placebo run-in**		**Treatment**					**Follow-up** [a]
≤ 2 weeks	4 or 5 weeks		8 weeks					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)

[a] Includes study down titration.

(Source: Sponsor's figure 1)

3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary variable was the placebo-corrected change from baseline to Week 8 in trough sitting diastolic blood pressure (SiDBP).

(2) Secondary Efficacy Endpoints

- Changes from baseline to Week 8 in trough SiSBP, peak SiDBP, peak SiSBP, trough StDBP and trough StSBP
- Trough/peak ratio for SiDBP and SiSBP
- Categorical responses
- Subgroup analyses

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

Table 2 summarizes patient disposition, demographic and baseline characteristics.

Table 2 Demographic and Baseline Characteristics (All Randomized Patients)

		HCT	Toprol-XL dosage (mg)					
		dosage (mg)	0	25	50	100	200	
All randomized patients, N		0	152	89	94	96	52	N=1571
		6.25	86	147	137	45	NA	ITT=1559
		12.5	105	142	148	95	43	PP=1339
		25.0	48	NA	NA	42	50	
Sex, n (%)	Men	0	83 (55)	39 (44)	52 (55)	56 (58)	29 (56)	n =805 (51)
		6.25	45 (52)	73 (50)	65 (47)	25 (56)	NA	
		12.5	51 (49)	70 (49)	87 (59)	46 (48)	19 (44)	
		25.0	22 (46)	NA	NA	22 (52)	21 (42)	
	Women	0	69 (45)	50 (56)	42 (45)	40 (42)	23 (44)	n =766 (49)
		6.25	41 (48)	74 (50)	72 (53)	20 (44)	NA	
		12.5	54 (51)	72 (51)	61 (41)	49 (52)	24 (56)	
		25.0	26 (54)	NA	NA	20 (48)	29 (58)	
Age, (years) mean (SD)		0	53 (12)	52 (11)	52 (11)	55 (11)	54 (10)	53 (11)
		6.25	54 (12)	52 (11)	54 (11)	51 (11)	NA	
		12.5	54 (11)	53 (11)	54 (10)	55 (11)	56 (11)	
		25.0	53 (9)	NA	NA	51 (11)	50 (10)	
Race, n (%)	Caucasian	0	109 (72)	65 (73)	62 (66)	71 (74)	39 (75)	n=1122 (71)
		6.25	63 (73)	104 (71)	99 (72)	31 (69)	NA	
		12.5	78 (74)	91 (64)	110 (74)	71 (75)	27 (63)	
		25.0	35 (73)	NA	NA	32 (76)	35 (70)	
	Black	0	41 (27)	22 (25)	27 (29)	24 (25)	11 (21)	n=400 (26)
		6.25	21 (24)	39 (27)	34 (25)	12 (27)	NA	
		12.5	23 (22)	44 (31)	33 (22)	20 (21)	15 (35)	
		25.0	13 (27)	NA	NA	8 (19)	13 (26)	

Table 2 Demographic and Baseline Characteristics (All Randomized Patients) cont d'

	HCT dosage (mg)	Toprol-XL dosage (mg)					
		0	25	50	100	200	
Duration of hypertension (year), mean (SD)	0	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	8.4 (8.0)	8.3 (9.0)	9.6 (8.9)	8.5 (10.4)	NA	
	12.5	8.5 (8.8)	9.1 (8.4)	9.2 (9.1)	9.2 (8.9)	9.7 (11.6)	
	25.0	8.5 (7.9)	NA	NA	9.4 (7.2)	8.4 (8.2)	
Trough SiDBP, mmHg, mean (range) at study entry	0	94 (72-117)	92 (68-111)	93 (69-110)	92 (72-109)	94 (72-110)	93 (61-119)
	6.25	92 (65-112)	94 (61-111)	94 (71-115)	93 (61-110)	NA	
	12.5	93 (69-110)	93 (70-119)	93 (69-116)	92 (62-116)	92 (77-115)	
	25.0	92 (71-109)	NA	NA	95 (80-110)	93 (64-118)	
Trough SiSBP, mmHg, mean (range) at study entry	0	144 (113-188)	141 (112-183)	142 (109-172)	142 (112-181)	143 (109-180)	143 (91-211)
	6.25	142 (91-180)	145 (101-181)	145 (103-211)	143 (102-171)	NA	
	12.5	143 (114-185)	143 (109-178)	144 (101-176)	142 (109-188)	144 (115-170)	
	25.0	141 (115-173)	NA	NA	145 (121-172)	144 (115-201)	
Trough SiDBP, mmHg, mean (range) at randomization	0	100 (95-114)	100 (95-111)	100 (95-111)	100 (94-113)	100 (95-114)	100 (94-114)
	6.25	100 (95-113)	100 (95-111)	101 (95-113)	100 (95-113)	NA	
	12.5	100 (95-112)	100 (95-114)	101 (95-112)	100 (94-114)	98 (95-109)	
	25.0	100 (95-112)	NA	NA	101 (95-111)	101 (95-113)	
Trough SiSBP, mmHg, mean (range) at randomization	0	151 (119-179)	149 (124-179)	150 (126-178)	151 (125-177)	151 (130-177)	151 (119-179)
	6.25	152 (124-175)	151 (129-177)	151 (127-179)	151 (125-179)	NA	
	12.5	151 (122-176)	150 (119-179)	153 (128-179)	153 (133-179)	150 (130-176)	
	25.0	151 (130-178)	NA	NA	154 (121-179)	149 (120-177)	

(Source: Sponsor's Table 12)

3.1.1.5 Sponsor's Primary Efficacy Results

1. Primary analysis of TAVE test

The assessment of interaction based upon placebo-adjusted mean changes from baseline to Week 8/(last observation carry forward, LOCF) in trough SiDBP suggests that there is a systematic pattern of negative interaction existing across the cells. It implies the combination drug effect is less than its expecting effect if their component drugs work additively (See Table 3). A global α-level test, TAVE test proposed by Hung was used. A TAVE statistic equals to –1.33 which has an associated p-value of 0.0015. As this is a 1-sided hypothesis test, it is significant at an α level of 0.025 and concludes that at least 1 combination lowers trough SiDBP more effectively than both of its components. The result is shown in Table 4.

Table 3 Descriptive Assessment of Additivity (ITT)

	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

(Source: Sponsor's Table 29)

Table 4 TAVE Test Results: Changes from Baseline to Week 8/LOCF in Trough SiDBP (ITT)

	HCT dosage	Toprol-XL dosage			
		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
TAVE statistic		–1.3269			
p-value		0.0015			

(Source: Sponsor's Table 23)

2. Supportive ANCOVA analyses

Supportive ANCOVA analysis detected a statistically significant interaction between the two drugs, P=0.0951. It is significant at α-level of 0.10 (See Table 5). Pair-wise comparisons of the combination treatment groups versus their component treatment groups using the Hochberg procedure to adjust for multiplicity supported that at least 1 combination performs better than both of its components. The combination identified was Toprol-XL 100mg/HCT 12.5 mg, P_{adj} =0.0108 (See Table 6).

Table 5 Summary of ANCOVA Model with Interaction for Changes from Baseline to Week LOCF in Trough SiDBP (ITT)

	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

(Source: Sponsor's Table 24)

Table 6 Multiplicity-Adjusted Results for Pair-wise Comparisons of Combinations to Monotherapies for Mean Changes from Baseline to Week 8/LOCF for Trough DBP (ITT)

		Toprol-XL dosage			
	HCT dosage	25 mg	50 mg	100 mg	200 mg
P-values for pairwise comparisons of combinations to Toprol-XL monotherapy	6.25 mg	0.9858	0.2986	0.0163	NA
	12.5 mg	0.0516	0.0753	0.0003	0.8749
	25.0 mg	NA	NA	0.0043	0.0173
P-values for pairwise comparisons of combinations to HCT monotherapy	6.25 mg	0.6718	0.1046	0.0030	NA
	12.5 mg	0.8000	0.2613	0.0012	0.0409
	25.0 mg	NA	NA	0.0189	<0.0001
Maximum p-values	6.25 mg	0.9858	0.2986	0.0163	NA
	12.5 mg	0.8000	0.2613	0.0012	0.8749
	25.0 mg	NA	NA	0.0189	0.0173
Hochberg-adjusted p-values	6.25 mg	0.9858	0.9858	0.1134	NA
	12.5 mg	0.9858	0.9858	0.0108	0.9858
	25.0 mg	NA	NA	0.1134	0.1134

(Source: Sponsor's Table 27)

3.1.1.6 Sponsor's Secondary Efficacy Results

1. Dose response regression for change from baseline to Week 8/LOCFin trough SiDBP

A quadratic polynomial model was fitted to describe the dose response relationship. The estimated dose-response surface is

$$-5.35-0.35\,x_1-0.06\,x_2+0.007\,x_1^{\,2}+0.00015\,x_2^{\,2},$$

where x_1 presents HCT and x_2 presents Toprol-XL. The surface is shown graphically as Figure 1. This model is performed on the weighted cell means (the treatment group means weighted by the number of patients in each treatment group). The model is significant with a p-value <0.0001 and an R-square=0.90. Table 7 summaries the results.

Table 7 Final Polynomial Regression Model for Change from Baseline to Week 8/LOCF in Trough SiDBP (ITT)

Parameter	**DF**	**Estimate**	**Standard error**	**P-value**	**F-statistic for model**	**R-square**
Intercept	1	–5.34392	0.52584	<0.0001		
-Toprol-XL	1	–0.06023	0.01288	0.0005		
HCT	1	–0.34772	0.08818	0.0020		
Toprol-XL2	1	0.00015	0.00007	0.0442		
HCT2	1	0.00703	0.00384	0.0924		
Mean square error	12	90.07351				
F statistic for model					28.4217	
p-value					<0.0001	
R square						0.90

(Source: Sponsor's Table 30)

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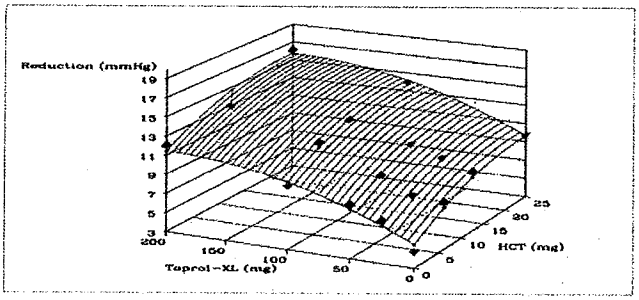
Figure 1 Dose Response Surface from Polynomial Regression of Changes from Baseline to Week 8/LOCF in Trough SIDBP (ITT)



Note: Pyramids represent the treatment group mean values. Upward pyramids are above the surface, and downward pyramids are below the surface. Lines connect the pyramids with the corresponding fitted value on the regression surface.

(Source: Sponsor's Figure 4)

2. Changes from baseline to Week 8/LOCF in trough SiSBP

1) TAVE test

The result of a TAVE statistic equals to –1.46 which has an associated p-value of 0.0006. As this is a 1-sided hypothesis test, it is significant at an α level of 0.025 and concludes that at least 1 combination lowers trough SiSBP more effectively than both of its components. Tables 8 and 9 summarize the results.

Table 8 Descriptive Assessment of Additivity Based upon Placebo-adjusted Mean Changes from Baseline to Week 8/LOCF in Trough SiSBP (ITT)

	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

(Source: Sponsor's Table 11.2.3.1.6, Section 11.2)

Table 9 TAVE Test Results: Changes from Baseline to Week 8/LOCF in Trough SiSBP (ITT)

	HCT dosage	Toprol-XL dosage			
		25 mg	50 mg	100 mg	200 mg
T statistics vs Toprol-XL monotherapy	6.25 mg	0.0903	–1.9845	–1.3050	NA
	12.5 mg	–1.8843	–2.1411	–4.2423	–1.2679
	25.0 mg	NA	NA	–3.3017	–1.5659
T statistics vs HCT monotherapy	6.25 mg	0.3781	–2.0173	–1.1303	NA
	12.5 mg	–1.1368	–1.7620	–3.6549	–2.6517
	25.0 mg	NA	NA	–1.2155	–1.3469
TAVEstatistic		–1.4579			
p-value		0.0006			

(Source: Sponsor's Table 11.2.3.1.5, Section 11.2)

2) ANOVA Analysis

ANCOVA analysis detected a statistically significant interaction between the two drugs, P=0.0771. It is significant at α-level of 0.10 (See Table 10). Pair-wise comparisons of the combination treatment groups versus their component treatment groups using the Hochberg procedure to adjust for multiplicity supported that at least 1 combination performs better than both of its components. The combination identified was Toprol-XL 100mg/HCT 12.5 mg, P_{adj} =0.0018 (See Table 11).

Table 10 Summary of ANCOVA Model with Interaction for Changes from Baseline to Week 8/LOCF in Trough SiSBP (ITT)

	DF	Mean square estimate	F-value	P-value
Parameter				
Toprol-XL	4	1669.42	9.13	<0.0001
HCT	3	2865.94	15.67	<0.0001
Toprol-XL·HCT	9	316.81	1.73	0.0771
Baseline SiSBP	1	27348.93	149.49	<0.0001
Model statistics				
Mean square error	1541	182.95		
F-statistic for model			16.84	
P-value for model				<0.0001

(Source: Sponsor's Table 11.2.3.1.7, Section 11.2)

Table 11 Multiplicity-Adjusted Results for Pair-wise Comparisons of Combinations Monotherapy for Mean Changes from Baseline to Week 8/LOCF for Trough SiSBP (ITT)

	HCT dosage	Toprol-XL dosage			
Trough SiSBP		25 mg	50 mg	100 mg	200 mg
P-values for pairwise comparisons of combinations to Toprol-XL monotherapy	6.25 mg	0.5149	0.0596	0.1580	NA
	12.5 mg	0.0803	0.0748	<0.0001	0.1257
	25.0 mg	NA	NA	0.0015	0.0387
P-values for pairwise comparisons of combinations to HCT monotherapy	6.25 mg	0.6670	0.0278	0.1786	NA
	12.5 mg	0.1567	0.1134	0.0002	0.0024
	25.0 mg	NA	NA	0.3131	0.0751
Maximum p-values	6.25 mg	0.6670	0.0596	0.1786	NA
	12.5 mg	0.1567	0.1134	0.0002	0.1257
	25.0 mg	NA	NA	0.3131	0.0751
Hochberg-adjusted p-values	6.25 mg	0.6670	0.4768	0.5358	NA
	12.5 mg	0.5358	0.5358	0.0018	0.5358
	25.0 mg	NA	NA	0.6262	0.5257

(Source: Sponsor's Table 11.2.3.1.11, Section 11.2)

3) Dose-response surface analysis

A quadratic polynomial model was fitted to describe the dose response relationship. The estimated dose-response surface is

$$-4.21-0.64\,x_1-0.09\,x_2+0.013\,x_1^{\,2}+0.00026\,x_2^{\,2},$$

where x_1 presents HCT and x_2 presents Toprol-XL. This model was performed on the weighted treatment group means and is significant with an p-value <0.0001 and an R-square=0.89.

3.1.1.7 Reviewer's Results

1) The reviewer attempted to confirm the sponsor's primary efficacy analysis of changes from baseline to Week 8/LOCF in trough SiDBP in ITT population using the FORTRAN program supplied by Dr. Hung. The p-value in this reviewer's analysis equals to 0.0056. It concurs with the sponsor's conclusion that at least 1 combination performs better than both of its components in lowering trough SiDBP. The reviewer also conducted pair-wise comparisons of the combination treatment groups versus their component treatment groups using Holm's procedure to adjust for multiplicity, the results were consistent with the sponsor's results using Hochberg procedure. The identified dose combination that performed better than both of its components is Toprol-XL 100 mg/HCT 12.5 mg (adjusted p-value P_{adj} =0.0108; see Table 12).

Table 12 Multiplicity-Adjusted Results for Pair-wise Comparisons of Combinations to Monotherapies for Mean Changes from Baseline to Week 8/LOCF for Trough SiDBP (ITT)

	HCT dosage	Toprol-XL dosage			
		25 mg	50 mg	100 mg	200 mg
Raw p-values	6.25 mg	0.9858	0.2986	0.0163	NA
	12.5 mg	0.8000	0.2613	0.0012	0.8749
	25.0 mg	NA	NA	0.0189	0.0173
Holm-adjusted p-values	6.25 mg	1.0000	1.0000	0.1304	NA
	12.5 mg	1.0000	1.0000	0.0108	1.0000
	25.0 mg	NA	NA	0.1304	0.1304

(Source: Reviewer's analysis)

2) The reviewer also verified sponsor's primary efficacy analysis of changes from baseline to Week 8 but not LOCF in trough SiDBP in both ITT and per-protocol population using the FORTRAN program by Dr. Hung. The p-value equals to 0.0309 for ITT population and is not statistically significant at the significance level of 0.025. For per-protocol population, the p-value equals to 0.0221 and is statistically significant at a significance level of 0.025.

3) The reviewer performed a test to check homogeneity of variances. The test suggested that there is no evidence that the variances for the treatment groups are heterogeneous (Levene's F test=1.08, p=0.3647). Thus it is not necessary to use weighted least squares in dose-response surface analysis. An un-weighted quadratic polynomial model was fitted to describe the dose response relationship. The estimated dose-response surface is

$$-5.72-0.30\,x_1-0.06\,x_2+0.006\,x_1^2+0.00015\,x_2^2,$$

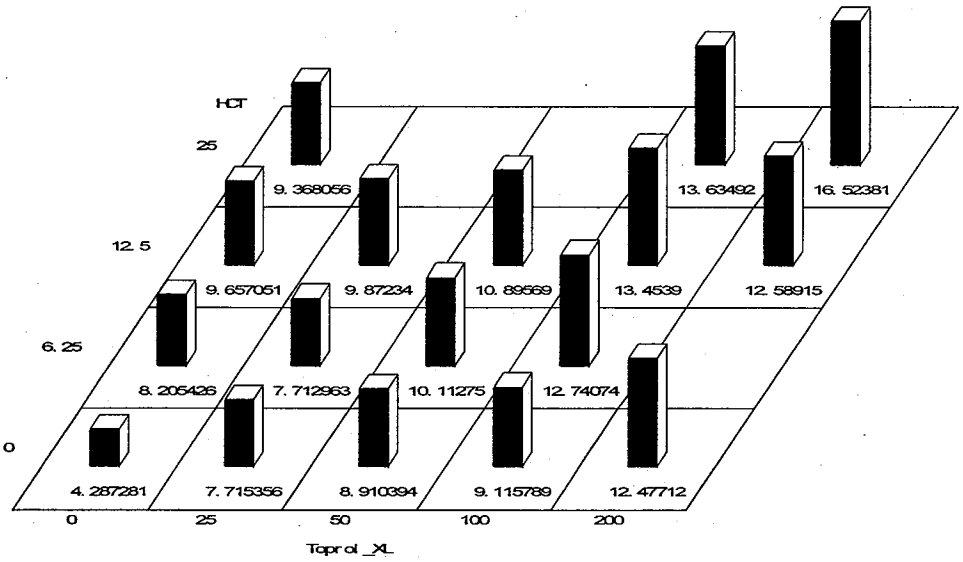
where x_1 presents HCT and x_2 presents Toprol-XL. The model is significant with a p-value <0.0001 and an R-square=0.90. The results are similar comparing the two models. Table 13 summaries the results. Figure 2 shows raw mean changes from baseline in strong SiDBP for all the dose combinations.

Table 13 Polynomial Regression Model for Change from Baseline to Week 8/LOCF in Trough SiDBP (ITT)

Parameter	DF	Estimate	Standard error	P-value	F-statistic for model	R-square
Intercept	1	–5.71525	0.59785	<0.0001		
Toprol-XL	1	–0.05933	0.01305	0.0007		
HCT	1	–0.29806	0.09443	0.0083		
Toprol-XL2	1	0.00015	0.00006	0.0345		
HCT2	1	0.00554	0.00370	0.1609		
Mean square error	12	1.12592				
F statistic for model					26.88	
p-value					<0.0001	
R square						0.8996

(Source: Reviewer's analysis)

Figure 2 Mean Changes from Baseline in Trough SiDBP



(Source: Reviewer's analysis)

3.1.1.8 Conclusions

The analysis of primary efficacy endpoint shows that at least 1 Toprol-XL/HCT exceeds the blood pressure lowering effects of its individual components with regard to placebo-corrected change from baseline to Week 8 in trough sitting diastolic blood pressure (P=0.0056). This result is consistent in both TAVE test and ANOVA along with a series of multiple comparisons adequately adjusting for overall type I error rate.

There was no evidence that the variances of treatment groups are heterogeneous. Using weighted least squares in dose-response surface analysis is not necessary. Comparing to the weighted model, the estimates of un-weighted model are very similar. Thus the concerns of modeling are ignorable.

3.1.2 STUDY B: S-902

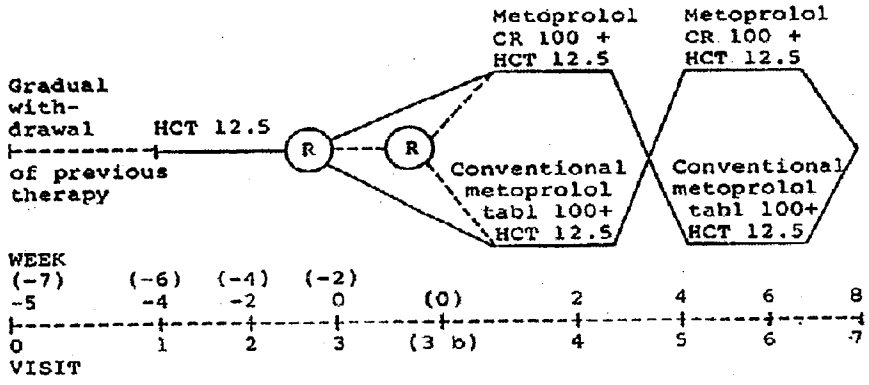
3.1.2.1 Study Objectives

The aim of this study was to evaluate the antihypertensive effect and tolerability of a new fixed combination product of metoprolol controlled release, 100 mg, and hydrochlorothiazide, 12.5 mg, in comparison with the conventional fixed combination of metoprolol tartrate, 100 mg, and hydrochlorothiazide, 12.5 mg.

3.1.2.2 Study Design

The study was a randomised, double-blind, cross-over design. The two double-blind periods comprised four weeks each and were preceded by a single-blind run-in period on HCT, 12.5 mg o.d., of four weeks' duration. There was no wash-out period between the two double-blind periods. The overall study design is shown in Figure 2.

Figure 3 Study Design Flow Chart



(Source: Sponsor's Figure 1, Section 4.1)

3.1.2.3 Efficacy Measures

(1) Primary Efficacy Endpoint

BP and HR were recorded at each visit to the clinic during the run-in period and during the double-blind periods in the supine and standing positions. The mean of two consecutive measurements performed with one minute's interval was recorded in the morning prior to dose intake.

(2) Secondary Efficacy Endpoints

- Descriptive statistics for BP and HR
- Responder rates

3.1.2.4 Patient Disposition, Demographic and Baseline Characteristics

Table 14 describes patient disposition, demographic and baseline characteristics.

Table 14 Summary of Demographics and Baseline Characteristics

S-902		Randomized to	
		CR/HCT-Tablet/HCT	Tablet/HCT-CR/HCT
Age (years)	N	22	25
	MEAN	56.32	55.88
	S.D.	10.02	12.81
	MINIMUM	37.00	23.00
	MAXIMUM	70.00	74.00
Weight (kg)	N	22	25
	MEAN	81.68	81.20
	S.D.	12.68	15.13
	MINIMUM	60.00	61.00
	MAXIMUM	115.00	120.00
Height (cm)	N	22	25
	MEAN	172.73	171.12
	S.D.	10.57	9.63
	MINIMUM	155.00	156.00
	MAXIMUM	192.00	190.00
Duration of hypertension history (years)	N	16	18
	MEAN	3.78	4.35
	S.D.	3.08	4.01
	MINIMUM	0.17	0.17
	MAXIMUM	9.58	11.17
Sex			
Male	N	16	18
Female	N	6	7

Table 14 Summary of Demographics and Baseline Characteristics

S-902		Randomized to	
		CR/HCT-Tablet/HCT	Tablet/HCT-CR/HCT
Age (years)	N	22	25
	MEAN	56.32	55.88
	S.D.	10.02	12.81
	MINIMUM	37.00	23.00
	MAXIMUM	70.00	74.00
Weight (kg)	N	22	25
	MEAN	81.68	81.20
	S.D.	12.68	15.13
	MINIMUM	60.00	61.00
	MAXIMUM	115.00	120.00
Height (cm)	N	22	25
	MEAN	172.73	171.12
	S.D.	10.57	9.63
	MINIMUM	155.00	156.00
	MAXIMUM	192.00	190.00
Duration of hypertension history (years)	N	16	18
	MEAN	3.78	4.35
	S.D.	3.08	4.01
	MINIMUM	0.17	0.17
	MAXIMUM	9.58	11.17
Sex			
Male	N	16	18
Female	N	6	7

Table 14 Summary of Demographics and Baseline Characteristics

S-902		Randomized to	
		CR/HCT-Tablet/HCT	Tablet/HCT-CR/HCT
Smoker			
No	N	17	23
Yes	N	5	2
Hypertension previously treated			
No	N	2	4
Yes	N	20	21
Hypertension treated last 6 months			
No	N	3	4
Metoprolol	N	7	8
Other Drug	N	12	13

(Source: Sponsor's analysis, Section 5, Table 3)

3.1.2.5 Sponsor's Primary Efficacy Results

There were no statistically significant differences in lowering blood pressure ($P>0.05$) between the new fixed combination and the old conventional fixed combination. Table 15 summarizes the results.

Table 15 Change in Supine and Standing Diastolic and Systolic BP and Heart Rate Following 4 Week Treatment (Per-Protocol Population) *

	Observed means (SD)					Least squares means				
Variable	meto CR/HCT		meto tablet/ HCT		Difference meto CR /HCT- tablet /HCT	meto CR /HCT	meto tablet/ HCT	Difference of least squares means		95% confidence limits
Supine										
DBP	90.3	(8.0)	92.2	(9.1)	-1.9	89.7	92.2	-2.5	(1.2)	(-5.0, 0.1)
SBP	146.5	(14.5)	149.2	(16.5)	-2.8	145.1	148.1	-3.0	(2.1)	(-7.3, 1.2)
HR	68.8	(15.4)	71.7	(14.8)	-2.9	67.9	71.0	-3.1	(1.6)	(6.5, 0.2)
Standing										
DBP	99.3	(8.7)	101.5	(9.0)	-2.2	98.8	101.5	-2.8	(1.4)	(-5.8,0.2)
SBP	147.7	(16.3)	150.6	(17.4)	-2.9	145.7	148.5	-2.9	(3.0)	(-8.9, 3.2)
HR	73.9	(13.7)	80.0	(16.1)	-6.1	72.8	78.5	-5.8	(2.3)	(-10.5, -1.0)

* Model includes fixed effects of centre, sequence, treatment, centre by sequence, sequence by treatment, centre by treatment, centre by sequence by treatment and patient within centre by sequence.
(Source: Sponsor's analysis, Table 21)

3.1.2.6 Sponsor's Secondary Efficacy Results

The results are presented in \\Cdsesub1\N21956\N_000\2005-10-28\clinstat \\ S-902, section 12, Tables 22, 23, 24, 25, 26, 27, respectively.

3.1.2.7 Reviewer's Results

To verify the sponsor's analysis, the reviewer conducted the efficacy analyses in both per-protocol and ITT population using a simpler model including sequence, period, centre, treatment, and treatment by centre as fixed effects and patient within sequence as a random effect. The results showed that there was a trend that the new fixed combination has numerically lower diastolic and systolic blood pressure and heart rate in both per-protocol and ITT population. However, statistically significant differences between the new fixed combination and the old conventional combination were only detected in supine diastolic blood pressure ($p=0.0287$) and standing heart rate ($p=0.0156$) in the per-protocol population; supine heart rate ($p=0.0004$), standing diastolic ($p=0.0045$) and systolic ($p=0.0372$) blood pressure and heart rate (<0.0001) in the ITT population. The results are summarized in Tables 16 and 17.

Table 16 Change in Supine and Standing Systolic and Diastolic Blood Pressure (SBP/DBP) and Heart Rate (HR) Following 4 Weeks Treatment in Per-Protocol Population

Variable	Means (SD)			
	Meto CR/HCT	Meto tablet/HCT	Difference	P-value
Supine				
DBP	90.3 (8.0)	92.2 (9.1)	-1.9	*0.0287
SBP	146.5 (14.5)	149.2 (16.5)	-2.8	0.1001
HR	68.8 (15.4)	71.7 (14.8)	-2.9	0.0872
Standing				
DBP	99.3 (8.7)	101.5 (9.0)	-2.2	0.0547
SBP	147.7 (16.3)	150.6 (17.4)	-2.9	0.2783
HR	73.9 (13.7)	80.0 (16.1)	-6.1	*0.0156

*Statistically significant at α=0.05, including sequence, period, centre, treatment and centre by treatment as fixed effects and patient within sequence as a random effect in the analysis
(Source: Reviewer's analysis)

Table 17 Change in Supine and Standing Systolic and Diastolic Blood Pressure (SBP/DBP)and Heart Rate (HR) Following 4 Weeks Treatment in ITT Population.

Variable	Means (SD)			
	Meto CR/HCT	Meto tablet/HCT	Difference	P-value
Supine				
DBP	90.9 (8.7)	91.2 (8.7)	-0.3	0.2644
SBP	148.1 (16.0)	150.7 (18.6)	-2.6	0.0924
HR	66.8 (13.5)	71.3 (14.0)	-4.5	*0.0004
Standing				
DBP	97.9 (9.1)	101.0 (10.0)	-3.1	*0.0045
SBP	146.4 (16.3)	151.1 (18.8)	-4.7	*0.0372
HR	72.5 (13.0)	80.5 (15.7)	-3.0	*< 0.0001

*Statistically significant at α=0.05, including sequence, period, centre, treatment and centre by treatment as fixed effects and patient within sequence as a random effect in the analysis
(Source: Reviewer's analysis)

3.1.2.8 Conclusions

The statistical model used by the sponsor may be over-parameterized. Based upon the reviewer's analyses using a simpler model in ITT population (instead of per-protocol population, proposed by the sponsor), the results showed that the new fixed combination is superior to the old conventional combination in lowering standing diastolic and systolic blood pressure and reducing both supine and standing heart rate. However, only limited

information of this study can be used to support the pivotal study because of different study design, lacking consistent positive results and no multiplicity adjustment for the multiple primary efficacy endpoints.

3.2 Evaluation of Safety

Please refer to Dr. Akinwole's review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Subgroup analysis of change from baseline to Week 8 in trough SiSDP by age, gender and race was conducted for study 324 (ATTCH), and blood pressure and heart rate by age and sex for study S-902. It is noticed that the drug shows better effect on non-black population compared to black population for all the dose combinations. Tables 18 and 19 summarize the results.

Table 18 Study 324 (ATTACH) Subgroup Analysis of Primary Endpoint (ITT)

		Toprol-XL Dosage (mg)					
Trough Sitting DBP	HCT Dosage (mg)	0	25	50	100	200	Total (N=1559)
Age (years) Mean (n)	0	-4.6 (124)	-7.5 (79)	-8.9 (80)	-9.6 (75)	-13.1 (45)	
	6.25	-7.9 (68)	-7.5 (127)	-10.1 (108)	-12.7 (40)		
<65	12.5	-9.7 (87)	-9.1 (121)	-10.6 (125)	-13.1 (71)	-11.8 (34)	-9.6 (1312)
	25	-9.0 (42)			-13.1 (40)	-17.2 (46)	
	0	-2.8 (28)	-9.4 (10)	-9.0 (13)	-7.5 (20)	-7.9 (6)	
	6.25	-9.4 (18)	-9.4 (17)	-10.3 (28)	-13.2 (5)		
>65	12.5	-9.5 (17)	-14.7 (20)	-12.3 (22)	-14.4 (23)	-15.7 (9)	-10.2 (247)
	25	-12.2 (6)			-24.3 (2)	-6.2 (3)	
Sex Mean (n)	0	-3.4 (83)	-8.8 (39)	-8.4 (51)	-8.5 (55)	-13.5 (28)	
	6.25	-8.0 (45)	-6.0 (72)	-9.5 (65)	-12.2 (25)		
Male	12.5	-8.8 (51)	-8.8 (70)	-11.3 (86)	-12.2 (46)	-11.5 (19)	-8.9 (799)
	25	-7.3 (22)			-12.6 (22)	-13.7 (20)	
	0	-5.4 (69)	-6.9 (50)	-9.5 (42)	-10.0 (40)	-11.2 (23)	
	6.25	-8.4(41)	-9.4 (72)	-10.7 (71)	-13.4 (20)		
Female	12.5	-10.5 (53)	-10.9 (71)	-10.3 (61)	-14.6 (48)	-13.4 (24)	-10.4 (760)
	25	-11.1 (26)			-14.8 (20)	-18.5 (29)	
Race Mean (n)	0	-3.1 (41)	-2.5 (22)	-7.4 (26)	-7.4 (23)	-10.1 (11)	
	6.25	-9.8 (21)	-5.6 (37)	-7.8 (33)	-10.2 (12)		
Black	12.5	-8.0 (23)	-10.0 (43)	-11.8 (33)	-13.2(19)	-11.0 (15)	-8.4 (392)
	25	-10.7 (13)			-8.3 (8)	-19.8 (12)	
	0	-4.7 (111)	-9.4 (67)	-9.5 (67)	-9.7 (72)	-13.1 (40)	
	6.25	-7.7 (65)	-8.5 (107)	-10.9 (103)	-13.7 (33)		-10.1 (1167)
Non-Black	12.5	-10.1 (81)	-9.8 (98)	-10.6 (114)	-13.5 (75)	-13.4 (28)	
	25	-8.9 (35)			-14.9 (34)	-15.5 (37)	

(Source: Sponsor's analysis, Table 11.2.8.1)

Table 19 Study S-902 Subgroup Analysis of Primary Endpoint by Age (ITT)

Age		Meto CR/HCT	Meto Tablet/HCT
<60 yrs N=28		Mean	Mean
	Supine DBP	92.1	91.7
	Supine SBP	145.4	148.1
	Supine HR	69.4	73.7
	Standing DBP	99.3	102.8
	Standing SBP	144.9	149.3
	Standing HR	75.8	83.4
≥ 60 yrs N=19	Supine DBP	88.3	90.5
	Supine SBP	152.0	154.5
	Supine HR	62.9	67.7
	Standing DBP	95.7	98.5
	Standing SBP	148.6	153.8
	Standing HR	67.7	76.2

(Source: Reviewer's analysis)

Table 20 Study S-902 Subgroup Analysis of Primary Endpoint by Sex (ITT)

Sex		Meto CR/HCT	Meto Tablet/HCT
Male N=34		Mean	Mean
	Supine DBP	91.5	92.1
	Supine SBP	147.9	152.3
	Supine HR	66.7	70.4
	Standing DBP	97.7	102.0
	Standing SBP	144.3	152.7
	Standing HR	72.3	80.2
Female N=13	Supine DBP	87.9	88.9
	Supine SBP	148.50	146.5
	Supine HR	66.9	73.5
	Standing DBP	98.4	98.5
	Standing SBP	151.9	146.8
	Standing HR	73.1	81.1

(Source: Reviewer's analysis)

4.2 Other Subgroup Populations

Other subgroup analyses such as body mass index, hypertension severity were performed for Study 324 (ATTACH), and hypertension treated within the last 6 months, hypertension treated with β-blocker for Study 902. The results were summarized in \\Cdsesub1\N21956\N_000\2005-10-28\clinstat\, Table 11.2.8.1 for Study 324 (ATTACH), and Tables 25, 26 for Study S-902.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Study 324 (ATTACH) seems to suggest that Toprol- XL/HCT combination drug yields a BP lowering effect smaller than the sum of the effects of Toprol alone and HCT alone. Because of this potential negative drug by drug interaction, the validity of ANOVA using an additive model is questionable. TAVE test was used to test whether at least one of the dose combinations is effective than its components. Based on both TAVE test and traditional ANOVA along with an appropriate multiple comparisons adjustment, it can be concluded that there is at least one dose combination that is more effective than its components. The dose combination identified was Toprol-XL 100mg/HCT 12.5 mg.

In Study 902, over-parameterization in statistical model is a potential problem. When a simpler model is used, the analysis results are substantially different. This inconsistence may suggest that the model used by the sponsor is not robust and the results may not be reliable.

5.2 Conclusions and Recommendations

Study 324 (ATTACH) has demonstrated that at least 1 Toprol-XL/HCT combination exceeds the blood pressure (BP) lowering effects of its individual components with regard to placebo-corrected change from baseline to Week 8 in trough sitting diastolic blood pressure. The dose combination that performs better than its components was identified as Toprol-XL 100mg/HCT 12.5 mg. Support from Study S-902 is limited because of different study design, lacking consistent positive results and no multiplicity adjustment for multiple primary efficacy endpoints.

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