

STATISTICAL
REV

NDA 19546

STATISTICAL REVIEW AND EVALUATION

NDA #: 19,546 **Drug Class:** 1C

Date: JAN 24 1989

Applicant: Sandoz Pharmaceuticals Corporation

Name of Drug: Dynacirc (isradipine) capsules, 2.5, 5.0, 7.5, and 10.0 mg bid.

Indication: Management of Hypertension

Documents Reviewed: Volumes 1-2, 113-114, and 117-118, of the New Drug Application dated December 27, 1985. Also volumes 69-84 and 121-122 of the NDA amendments of April 24, 1986 and May 30, 1986 which contained final reports on the Phase III placebo-controlled studies. Also reviewed were volumes 1, 24-48, and 60-61 of the NDA amendment dated November 26, 1986, which contained the final reports on the Phase III active-controlled studies.

Medical Officer: This review has been discussed with the medical officer, Dr. Robert W. Kimball, and he is in agreement with its findings.

Relevant Issues discussed in this Review:

1. Efficacy results are all based on blood pressure data at peak.
2. Failure to establish a proper dosing range.
3. Dose-response relationship not evident in larger doses.
4. An interim analysis was performed.
5. Time to titration was too short in all titration studies.
6. No advantage to use of drug in combination with HCTZ.
7. Adverse experiences in cardiovascular and respiratory systems that are dose related in combination with HCTZ.

I. INTRODUCTION

Dynacirc (isradipine) is a calcium-channel blocking agent of the dihydropyridine class which has potent vasodilating properties. It has been developed by Sandoz Pharmaceuticals for use in the management of hypertension. Calcium entry blocking agents modify a number of calcium dependent processes including that of excitation-contraction coupling in both cardiac and vascular smooth muscle by decreasing or inhibiting the entry of calcium to the interior of the cell. While the qualitative actions of calcium blockers are similar, they differ quantitatively in the

Key Words: Peak effect, Dosing range, Interim analysis, Titration period.

relative depression of cardiac contractility and in the relative dilation of peripheral vascular smooth muscle. Laboratory tests show that Dynacirc exhibits a high affinity and specificity for smooth muscle as opposed to cardiac muscle. Dynacirc can be used as monotherapy or in combination with a thiazide type diuretic.

The sponsor submitted the results of nine distinct double-blind studies on patients with benign essential hypertension which were carried out to determine the efficacy and safety of Dynacirc. Three of these, Studies 7, 9, and 11, were placebo-controlled phase II studies and were relatively small, with only 16-24 patients each. The six Phase III studies consisted of two placebo-controlled studies (Studies 301 and 302), three active-controlled studies comparing Dynacirc with hydrochlorothiazide (HCTZ), propranolol, and prazosin, respectively (Studies 303, 304 and 305), and a combination study (Study 307) where Dynacirc in combination with HCTZ was compared with propranolol in combination with HCTZ. In all of these studies a patient was evaluated at the same time each evaluation day. The time was usually not specified, however in at least one study the protocol required the evaluation to be done 2-3 hours post-dose. The morning dose was to be taken before evaluation, hence these are generally peak observations. The only trough result was contained in Study 9.

II. PHASE II STUDIES

Three Phase II placebo-controlled studies were carried out to establish the safety and efficacy of Dynacirc for use in patients with mild to moderate essential hypertension. Subjects entered into these studies were required to be at least 18 years old and to exhibit a supine diastolic blood pressure of at least 95 mmHg on at least two visits during the washout period, including the final visit (baseline). Females capable of becoming pregnant were required to practice an appropriate method of birth control other than oral contraceptives. Reasons for exclusion from the study included: any form of hypertension other than benign essential hypertension; supine diastolic blood pressure exceeding 110 on two consecutive visits during the washout period, a history of alcoholism, drug abuse, or cerebral insufficiency; pregnancy or lactation; active angina pectoris; congestive heart failure; myocardial infarction within six months; cardiac arrhythmias; bradycardia; known serious adverse reaction to similar drugs; any disease or abnormal conditions of the GI tract, kidney or liver; use or any other investigational new drug within four weeks prior to the study; and concurrent use of medications that are known to be particularly toxic to a major organ system within three months prior to entry into the study.

II.A. STUDY 7

1. Study Description

Study 7 was a randomized, double-blind, parallel group, placebo-controlled trial design. It was a single center study with 23 patients entered. An initial three week

single-blind placebo washout period was followed by a four week double-blind treatment period. Twelve patients were randomized to receive Dynacirc and eleven patients to receive a placebo. The groups were comparable with respect to age, size, race, and various laboratory values. All patients began with one 2.5 mg dose of Dynacirc or a matching placebo given twice a day, before breakfast and after supper. The dose was doubled at the beginning of weeks 2 and 3 if the supine diastolic blood pressure was still greater than 90 mmHg. Therefore the dose levels during the plateau period (weeks 3 and 4) ranged from 2.5 mg to 10 mg, bid. This seven week period was followed by an additional two-week treatment phase for some of the patients to determine the possibility of once daily administration of Dynacirc. The entire daily dose was given before breakfast with patients receiving the same dosage formulation as used during the plateau weeks of the bid dosage period.

Patients were monitored weekly throughout the study, with visits at approximately the same time each evaluation day. The efficacy variables were supine diastolic blood pressure, supine systolic blood pressure, supine pulse, standing diastolic blood pressure, standing systolic blood pressure, and standing pulse. These readings were taken after the patient had rested in the prescribed position for at least 3 minutes. The same arm and the same size blood pressure cuff were used throughout the study, and the same individual performed the evaluation as often as possible. Safety was monitored by a physical examination, vital signs recordings, clinical laboratory analysis, electrocardiogram, cardiopulmonary evaluation and recording of the concomitant medications, compliance and adverse reactions.

Nine Dynacirc patients and six placebo patients were considered "completely valid" or valid throughout the study period. Three Dynacirc patients were considered "partially valid", or valid for part of the study period. One discontinued due to adverse reaction and one due to continued need for a disallowed concomitant medication after week 1. One completed the study but did not take the morning dose at week 4 visit. Two placebo patients were considered partially valid. One discontinued after week 2 because of ineffectiveness and the other completed the study but did not take the morning dose at week 4 visit. Three placebo patients were considered totally invalid. One had a nonqualifying blood pressure at baseline (94 mmHg), one did not take the morning dose on the day of the baseline visit, and one was noncompliant.

2. Sponsor's Analysis

A repeated measures analysis of variance was used to evaluate the changes from baseline for blood pressure and pulse for all valid patients. A per time point analysis of variance for each study week was performed on the patients who were valid for that week and an endpoint analysis was performed for all patients entered into the study. The results of the different analyses were quite similar. Table 1 gives the results of the analysis for the plateau period and the endpoint analysis. Significant differences from baseline were found for many of the efficacy variables. Significant differences between treatments were found for supine diastolic blood pressure for

the plateau period (p=.0051) and in the endpoint analysis (p=.0016). The difference between treatments for the other blood pressure variables were not significant, although Dynacirc tended to produce greater reduction in all of the blood pressure variables than did placebo.

Eleven patients entered the once daily dosing period, seven taking Dynacirc and four taking placebo. The reduction in both supine and standing blood pressure continued during week 5, but were not maintained during week 6. Descriptive statistics only were given for this period because of the small number of patients involved. The once daily dosing schedule was not adequate for these patients.

Five of the twelve patients in the Dynacirc group and three of the eleven patients in the placebo group reported at least one newly-occurring adverse reaction during the double-blind portion of this study. The most frequently reported adverse reactions in the Dynacirc group were palpitations and headaches, which accounted for 5 of the 11 occurrences. Other adverse reactions for this group included edema, tachycardia, dizziness, tinnitus, flushing, and tingling. The Placebo group experienced burning of the eyes, edema, diarrhea, and visual disturbances.

3. Reviewer's Comments

Even though the number of patients involved in this study was relatively small, it demonstrated that Dynacirc when given on a twice daily dosing schedule, tended to lower both diastolic and systolic blood pressure. The once daily dosing schedule was clearly not effective, at least for this group of patients. Since the supine diastolic blood pressure reading was used to determine eligibility for the study, the titration schedule, and the categories involved in the categorical analysis, it would appear that it was considered the most important efficacy variable, although the sponsor did not say so. The Dynacirc group demonstrated significantly greater reduction in this variable in both the analysis of the plateau period and the endpoint analysis.

The table below gives the number of valid patients in each group for each week of the study, along with the percentage of patients completing the plateau period. Figure 1 gives a comparison of the mean change from baseline for both Dynacirc and placebo for all valid patients during weeks 1-6 of the active treatment period. This gives a clear indication of the reduction in diastolic blood pressure during the twice daily dosing period, and of the lack of effectiveness of the once daily dosing after two weeks.

Number of Valid Patients for each Week							
Week	0	1	2	3	4	5	6
Dynacirc	12	12	10	10	9(75%)	7	5
Placebo	11	8	8	7	6(54%)	4	3
{-PLATEAU PERIOD-}							

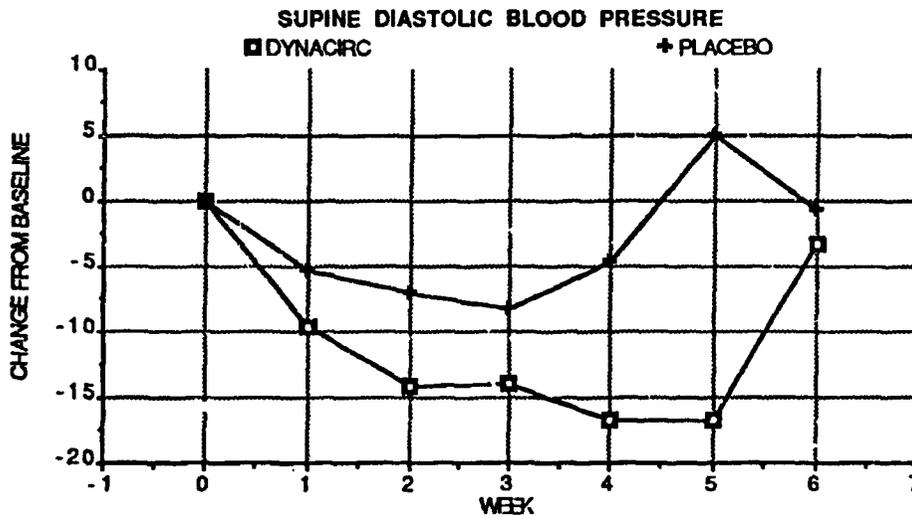


Figure 1

II.B. STUDY 9

1. Study Description

Study 9 was a randomized, double-blind, 4x4 Latin Square, placebo-controlled study designed to find the dose-response curve of Dynacirc in patients with benign essential hypertension. It involved sixteen patients at one center and all patients were able to complete the study. The inclusion and exclusion parameters were the same as those of Study 7. Study 9 began with a two week single-blind outpatient washout period followed by a three day single-blind inpatient washout period. The nine day double-blind inpatient study period consisted of single doses of Dynacirc on each of four days separated by one day of placebo administration. The doses of Dynacirc were 2.5 mg, 5 mg, 10 mg, and 20 mg which were given in a random order. The patients were randomized into four groups and the order of administration for each group was different. On any day of the double-blind treatment period, half of the patients received Dynacirc and half of the patients received a placebo. All doses were given before breakfast, after the pre-dose evaluation for that day.

On each day of the double-blind treatment phase, supine and standing blood pressure, pulse, and respiratory rate were recorded pre-dose and then every 30 minutes for the next three hours. They were then measured every hour until 12 hours post-dose, and at 15, 21, and 24 hours post-dose. This final reading also served as the pre-dose reading for the subsequent day of the study. The variables of most interest from the 18 timepoints was the total area under the change from baseline curve (calculated using the sum of trapezoids) which was used to calculate the

average change in the parameters for different timepoints.

2. Sponsor's Analysis

Analysis of variance was performed initially on the placebo days to justify using a Latin Square analysis on the Dynacirc treatment days. There were no statistically significant differences for the vital signs variables on any of the placebo days. Analysis of variance of the pre-dose values on each of the active treatment days was also performed to verify the validity of the Latin Square analysis. None of the variables showed statistically significant differences between the pre-dose values of the four active treatment days.

Table 2A gives the average change in the supine diastolic and systolic blood pressure measurements over nine hours, 12 hours, and 21 hours. The 10 mg and 20 mg doses all showed statistically significant differences in both blood pressure measurements from the 2.5 mg dose and the 5 mg dose over 9 and 12 hours. The differences between the 10 mg and 20 mg dose was not significant in any cases. The changes in pulse and respiratory rate were not significant in any cases. The results for the standing variables were similar to those for the supine variables.

Eleven of the sixteen patients in this study reported at least one newly-occurring adverse reaction during the double-blind treatment portion of the study. The most frequently reported adverse reactions were headache, abdominal discomfort, and dizziness.

3. Reviewer's Comments

This study demonstrated a dose response relationship for Dynacirc between the two lower doses, 2.5 mg, 5.0 mg, and the higher doses, 10 mg and 20 mg, with each higher dose giving a greater reduction in blood pressure over 9, 12, and 21 hours than did the lower doses. This study involved multiple comparisons (six) for each category. In many cases the p-value for the comparison was small enough that it would remain significant even using the conservative Bonferroni approach and multiplying each p-value by 6.

Table 2B gives the mean change from baseline for each dose level at each measured timepoint. These results are shown graphically in Figure 2. The dose response relationship is very obvious in the graph, as is the time effect of the drug. The two lower doses produce a peak response in under two hours and a fairly consistent decrease in diastolic blood pressure of from 5 to 10 mmHg which continues for at least 12 hours. This indicates that a twice daily dosing schedule is probably sufficient for those dose levels. The two higher dose levels reach peak response in under three hours, but the reduction decreases steadily and is less than half of the peak value after 12 hours. A twice daily dosing schedule might not be frequent enough to give consistent control of blood pressure at these dose levels.

**COMPARISON OF DIASTOLIC BLOOD PRESSURE
FOR 24 HOURS AFTER A SINGLE DOSE**

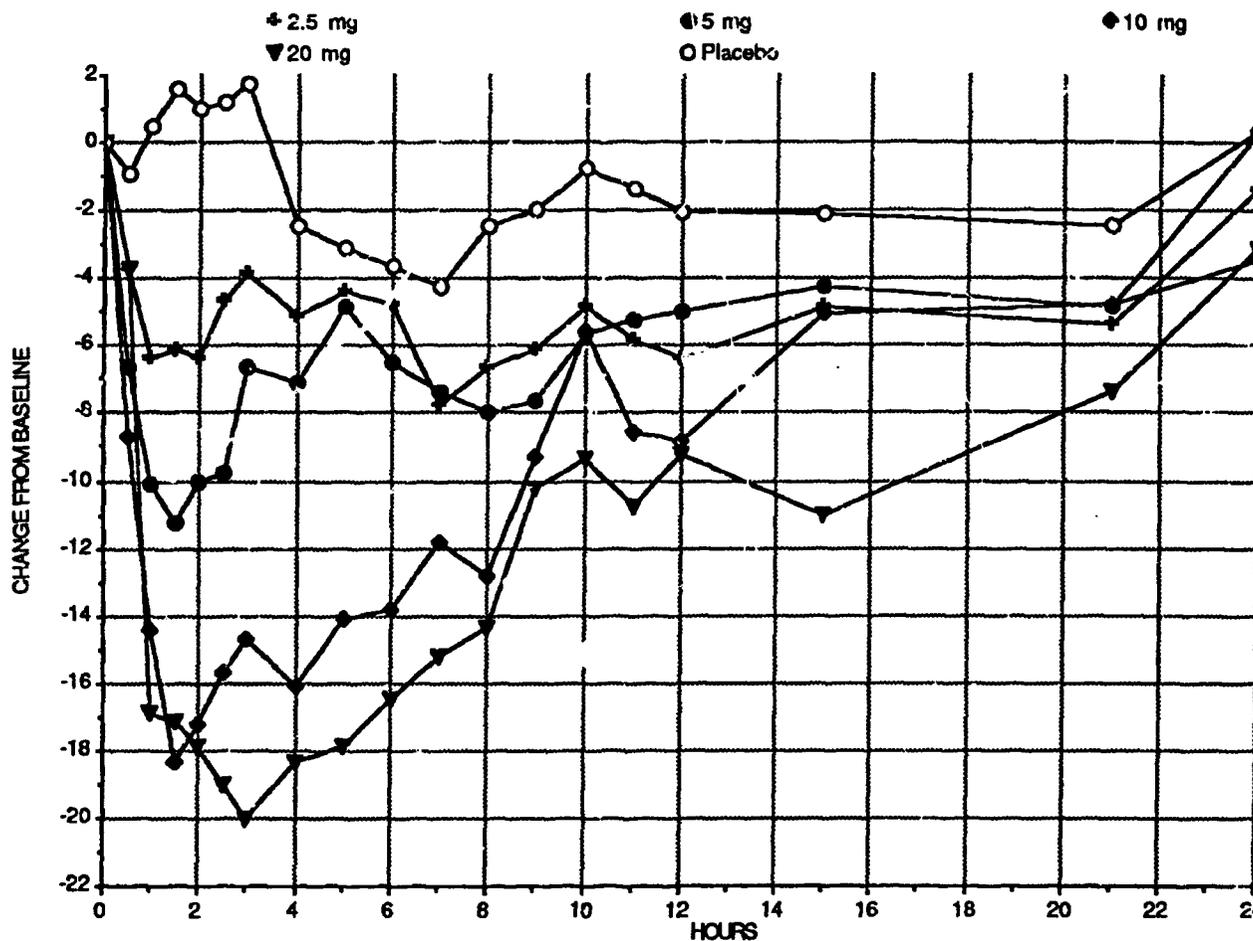


Figure 2

II.C. STUDY 11

1. Study Description

Study 11 was a double-blind, randomized, parallel group study similar to Study 7 except that all patients were on a fixed titration schedule. 24 patients with benign essential hypertension were enrolled in the study at one center. The study involved a single-blind three week placebo washout period, a three week double-blind placebo-controlled bid study period, and a 2 week double blind placebo-controlled study of once daily administration of Dynacirc for some of the patients. On the bid schedule,

the dose was taken before breakfast and supper. All patients were evaluated weekly and they were required to take their morning dose for each visit day 2-3 hours before the evaluation. During the once daily administration the patients were instructed to take the dose before breakfast, but not to take their morning dose on the evaluation days, hence the qd blood pressure values are trough results.

All patients were randomized to either the placebo group or to a fixed titration of Dynacirc, with all patients in this group receiving 2.5 mg bid the first week, 5 mg bid the second week, and 10 mg bid the third week. The placebo was also titrated. The inclusion and exclusion parameters were the same as for Study 7. Two of the patients in the placebo group were not considered valid because they did not take the morning dose on one of the evaluation days.

2 Sponsor's Analysis

Analysis of variance was performed on the data for the valid patients for each of the three weeks of the bid study and for the average change over the three weeks. Analysis of variance was also performed on the "all treated" population for the three weeks, with the results for week 3 given in Table 3. The Dynacirc group had a significantly greater reduction in both supine and standing diastolic and systolic blood pressure than did the placebo group. Although the supine and sitting pulse rate increased, it was not enough to be statistically significant.

Only seven patients, three taking Dynacirc and four taking placebo, were entered into the once daily dosing portion of the study. The results were similar to those of Study 7, with the decreases in blood pressure for the dynacirc patients being maintained during the first week of the extension but the blood pressure returning to near the baseline values for the second week.

Seven of the twelve patients in the Dynacirc group and five of the twelve patients in the placebo group reported at least one newly-occurring adverse reaction during the double-blind portion of this study. Non of these were serious or of concern to the investigators. The majority (5 of 7) of the adverse reactions occurring in the Dynacirc group occurred during the third week when the dose was highest. The most frequently reported adverse reactions in the Dynacirc group were dizziness and fatigue.

3. Reviewer's Comments

This study, although small, gives a clear indication of the efficacy of Dynacirc in the treatment of benign essential hypertension. The reduction in blood pressure was greater during each successive week during this study. The sponsor indicates that this is due to the fact that the dose was titrated upward each week. They did not consider the fact that there could be a cumulative effect, or a time-response effect involved in this continual decline in blood pressure. The fact that the blood pressure remained deflated during the first week of the once daily dosing schedule before returning to near baseline values during the second week indicates that there is some

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sort of time-effect being experienced with the drug. This will be discussed in more detail in the discussion of Study 301.

During the twice daily portion of this study the patients were specifically instructed to take their morning dose two to three hours before arriving at the clinic for evaluation. The results are therefore peak measurements of the reduction in blood pressure. The evaluations during the once daily portion of the study were done at least 24 hours after the last dose and were therefore are trough measurements. A valid comparison of the two dosing schedules cannot be made without consistent measurements.

III. PHASE III PLACEBO-CONTROLLED STUDIES

Two Phase III multi-center placebo-controlled studies were submitted by the sponsor to substantiate their claim of the efficacy and safety of Dynacirc when used in the treatment of benign essential hypertension. Both of these studies had a randomized double-blind parallel group design. Each study was preceded by a three week single-blind placebo washout period. Patients were admitted to the study who had an average supine diastolic blood pressure of at least 100 mmHg, at the end of the washout period. In addition, a decreasing trend in the diastolic blood pressure during the washout period could not be present.

Reasons for exclusion from the study included: malignant, accelerated, or severe hypertension; angina pectoris; history of myocardial infarction; cardiac arrhythmias; patients who had received any other investigational drugs within 4 weeks prior to entering this study; congestive heart failure; bradycardia; history of alcohol or drug abuse; cerebral vascular insufficiency; known adverse reaction or hypersensitivity to any calcium channel blocking agent; required use of disallowed concurrent medication; patients with creatinine >2.0 mg%; and pregnant or lactating females. Medications which were disallowed included: All agents used for the treatment of hypertension except the study drugs; adrenergic augmenting drugs; adrenolytic drugs; antiarrhythmic drugs; psychotropic drugs; oral contraceptives; and antacids with high sodium content.

Evaluations were done weekly during both the single-blind and double-blind portions of the trials. The efficacy variables were supine diastolic blood pressure, supine systolic blood pressure, supine pulse, standing diastolic blood pressure, standing systolic blood pressure, and standing pulse. Each value is the average of two readings taken three minutes apart, after the patient had been resting in the required position for at least three minutes. The same size blood pressure cuff and the same arm were used each time, and readings were taken by the same person and at the same time of day each week if possible. The time of day at which the evaluation occurred was not specified in any of the studies. The morning dose was to be taken before breakfast on each evaluation day.

III.A. STUDY 301

1. Study Description

Study 301 was a double-blind, parallel group, randomized six-center trial to determine the efficacy and safety of four different doses of Dynacirc administered in a fixed manner in patients with mild to moderate essential hypertension. The four doses which were studied were 2.5 mg, 5 mg, 7.5 mg, and 10 mg administered twice daily. The double-blind portion of the study lasted five weeks.

A total of 203 patients were enrolled in this study, 15.8% from Center A, 14.8% from Center B, 21.7% from Center C, 20.7% from Center D, 11.8% from Center E, and 15.3% from Center F. The patients were randomized to the five parallel groups based on a stratified schedule. Patients with supine diastolic blood pressure between 100 and 105 mmHg were randomized separately from those with a supine diastolic blood pressure over 105. 40 patients were randomized to Dynacirc 2.5 mg bid, 40 patients to Dynacirc 5 mg bid, 41 patients to Dynacirc 7.5 mg bid, 41 patients to Dynacirc 10 mg bid, and 41 patients to the placebo group. Each of the six centers had at least one patient in each of the five treatment groups. The five groups were comparable in terms of age, sex, race, and various laboratory values.

The patients assigned to the Dynacirc 2.5 mg, 5 mg, and 7.5 mg groups initially received 2.5 mg bid. The 10 mg group began with 5 mg the first week. These doses were titrated upward in increments of 2.5 mg on a weekly basis until the assigned dose of the drug was reached. The placebo group received placebo during the entire study. All patients were to take their medication before breakfast and supper each day. Weeks 3 - 5, when all patients were receiving their assigned dose, were known as the plateau period.

187 patients were considered valid for efficacy, as shown below. 11 patients were considered partially valid, because of adverse reactions, treatment failures, or lack of cooperation. Five patients were considered invalid because of lack of compliance, non-qualifying baseline value, and loss to follow-up.

Status	2.5 mg bid	5 mg bid	7.5 mg bid	10 mg bid	Placebo
Valid	35	34	38	41	39
Partially Valid	4	4	1	0	2
Invalid	1	2	2	0	0

2. Sponsor's Analysis

A two-way analysis of variance/covariance model with repeated measurements was used to justify the pooling of the data from the six centers. None of the interactions for the blood pressure or pulse variables were statistically significant in examining

the treatment x investigator and treatment x investigator x time interactions during the plateau period.

A one-way analysis of variance/covariance with repeated measures was performed for the valid patients at the plateau period and for the valid and partially valid patients for weeks 1 and 2, the plateau period, and the endpoint. An "all patient" analysis of variance/covariance was done on the endpoint values. In addition to evaluating weeks 1 and 2 based on the assigned groups, an analysis of variance was performed based on the actual dose taken during this period of titration (i.e. during the first week all patients assigned to the 2.5 mg, 5mg, and 7.5 mg groups received 2.5 mg bid and those assigned to the 10 mg group received 5 mg).

Table 4a gives the results for the valid patients over the plateau period, and table 4b gives the results of the "all patient" endpoint analysis. In both analyses, all the Dynacirc groups demonstrated changes from baseline that were highly statistically significant ($p=.0001$). The comparisons with placebo were also highly statistically significant ($p\leq.0001$). The changes in pulse rate, although sometimes statistically significant, were never large enough to be considered clinically significant (all < 5 beats/minute).

The comparisons between the different dose levels of Dynacirc demonstrated that the three higher dose levels gave a somewhat greater reduction in both of the blood pressure measures than did the 2.5 mg bid dose. A similar pattern was demonstrated by the increases in the pulse rate. There were no statistically significant differences among the three higher dose levels in any of the efficacy variables. The sponsor claimed that the results demonstrated an ordering of a dose-response relationship up to the 7.5 mg bid dose.

Approximately 41% of the Dynacirc patients experienced newly occurring adverse reactions compared with 38% of the placebo patients. The number in each group is given below:

Group	Number in Group	Number experiencing new Adverse Reactions	Percent
2.5 mg bid	40	19	47.5%
5 mg bid	40	17	42.5%
7.5 mg bid	41	23	56.1%
10 mg bid	41	23	56.1%
Placebo	41	16	39.0%

The percent of patients experiencing newly occurring adverse reactions at the two higher dose levels of Dynacirc is somewhat larger than that in the placebo group and the two lower dose levels, but it is not statistically significant (Chi-Square=3.96, $df=4$, $p=.41$). The body systems experiencing the most adverse reactions were the cardiovascular and central nervous systems. There were no significant differences

between the groups for the number of adverse reactions in any specific body system.

3. Reviewer's Comments

This study clearly demonstrates that Dynacirc is effective in reducing blood pressure. The results for all of the blood pressure variables were highly significant when compared with baseline or placebo. This study involved multiple comparisons for each efficacy variable. In all cases the p-value for the comparison with baseline or placebo was small enough that it would remain significant even using the conservative Bonferroni approach and multiplying each p-value by the number of comparisons. This is not true for the comparisons between the various doses of Dynacirc. Because the time of the visit was not specified, it is not possible to know for sure whether these are peak or trough values, but since the morning dose was taken before the evaluation it is more likely that they are peak values. The length of time between the dose and the evaluation appears to have varied from patient to patient within the study.

The sponsor's claim of a dose-response relationship between the four doses is not substantiated by this study. Figures 3 and 4 show that the larger three doses demonstrate a greater reduction in blood pressure than does the lowest dose studied, however there does not seem to be an obvious relationship between these three higher doses. In some cases the 7.5 mg bid group had a moderately greater reduction than the 5 mg bid group, but in other cases they were essentially equivalent. In no case did the 10 mg bid group out-perform the 7.5 mg bid group, and in many cases the decrease was substantially less than that of the 7.5 mg bid group, and sometimes even less than that of the 5 mg dose. Because of this, this reviewer would recommend that 5 mg bid be the largest dose recommended.

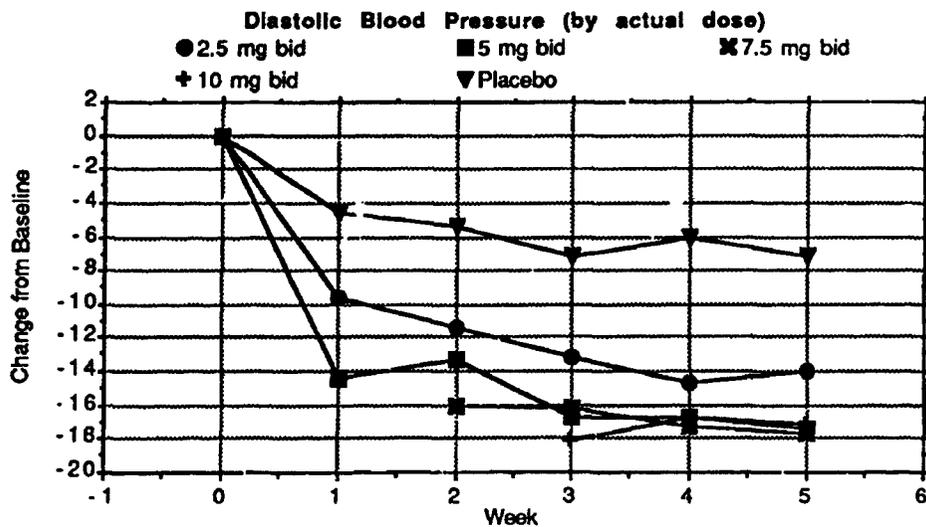


Figure 3

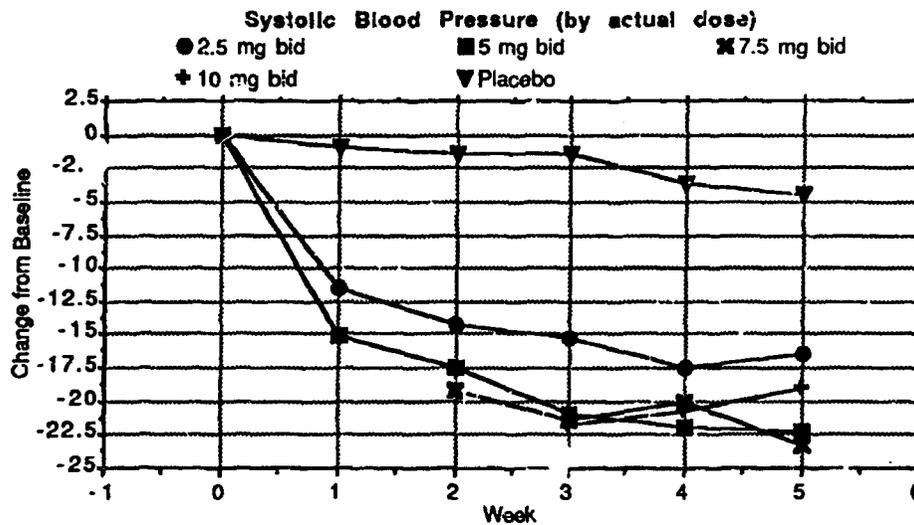


Figure 4

Because of the rather large mean reductions in blood pressure at the 2.5 mg bid dose level (10.73 to 13.89 mmHg for diastolic and 14.92 to 16.96 mmHg for systolic), this reviewer wonders if a smaller dose might be adequate for some patients. Of the 40 patients in the 2.5 mg bid group, the maximum change at endpoint in supine diastolic blood pressure was -36 mmHg with 9 patients having a reduction of at least 20 mmHg and 19 having a reduction of at least 15 mmHg. For standing diastolic blood pressure the maximum change at endpoint was -32 mmHg with 4 patients having a reduction of at least 20 mmHg and 11 having a reduction of at least 15 mmHg. The maximum change at endpoint in supine systolic blood pressure was -54 mmHg with 6 patients having a reduction of at least 30 mmHg and 16 having a reduction of at least 20 mmHg. For standing systolic blood pressure the maximum change at endpoint was again -54 mmHg with 8 patients having a reduction of at least 30 mmHg and 13 having a reduction of at least 20 mmHg.

The results of the 38 patients who remained on 2.5 mg bid for the entire study period clearly indicate that a longer titration period would be advisable. The Phase II and Phase III placebo-controlled titration studies increased the dose at weekly intervals if the supine diastolic blood pressure had not normalized (≤ 90 mmHg) and the Phase III active-controlled studies increased the dose at biweekly intervals. The results shown below indicate that it may require three to four weeks for the effect of the drug to reach steady state.

	Systolic Mean Decrease	Diastolic Mean Decrease	Number Normalized
Week 1	11.55	9.59	17
Week 2	14.32	11.38	27
Week 3	15.21	13.20	30
Week 4	17.53	14.07	31
Week 5	16.41	13.94	33

The continual decrease up to four weeks was also clearly seen in Figures 2 and 3. This time-response should be considered when the drug is titrated to avoid giving a larger dose than is necessary.

III.B. STUDY 302

1. Study Description

Study 302 was a randomized, double-blind, two parallel groups, four-center, titration trial to determine the efficacy and safety of Dynacirc administered twice-a-day in patients with mild to moderate essential hypertension. This was planned as a three center study, but a fourth center was added because of slow patient enrollment. The double-blind portion of the study lasted four weeks. The initial dose of the study drug was either 2.5 mg bid Dynacirc or a matching placebo capsule. The dose was increased by one capsule at the end of each of the first three weeks if the supine diastolic blood pressure remained above 90 mmHg. During week 4, nine Dynacirc patients remained at the 2.5 mg bid dose level, seven were at the 5 mg bid dose level, 13 were at the 7.5 mg bid dose level, and nine had been titrated to the 10 mg bid dose level. One of the placebo patients was at the 1 capsule dose level, three were at the 2 capsule dose level, seven were at the 3 capsule dose level, and 28 had been titrated to the 4 capsule dose level.

A total of 98 patients were enrolled in this study, 29.6% from Center A, 22.4% from Center B, 26.5% from Center C, and 21.4% from Center D. The patients were randomized to the two parallel groups based on a stratified schedule. Patients with supine diastolic blood pressure between 100 and 105 mmHg were randomized separately from those with a supine diastolic blood pressure over 105. The 49 patients randomized to each group were comparable in terms of age, sex, race, and various laboratory values.

77 patients were considered valid for efficacy, as shown below. Seven Dynacirc patients and three placebo patients were considered partially valid, because of loss to follow-up, adverse reactions, or lack of cooperation. Four Dynacirc patients and seven placebo patients were considered totally invalid because of non-qualifying baseline value, and lack of compliance.

2. Sponsor's Analysis

A two-way analysis of variance/covariance model with repeated measurements was used to justify the pooling of the data from the four centers. The treatment x investigator interaction analysis for the endpoint values indicated interaction in the supine pulse ($p=.018$). The sponsor claimed this was because Center A had a high baseline value which resulted in both treatments demonstrating a reduction in pulse, instead of the slight increase indicated by the other centers and other studies. Because there was no interaction in the blood pressure variables, pooling was considered acceptable.

A one-way analysis of variance/covariance with repeated measures was performed for the valid patients for week 4 and for the valid and partially valid patients for weeks 1, 2, and 3. An "all patient" analysis of variance/covariance was done on the endpoint values. Table 5 gives the results for the valid patients for week 4 and the results of the "all patient" endpoint analysis. In both analyses, the Dynacirc group demonstrated changes from baseline that were highly statistically significant ($p=.0001$) for all the blood pressure variables. The comparisons with placebo were also highly statistically significant for all the blood pressure variables ($p=.0001$). The changes in pulse rate, although sometimes statistically significant, were never large enough to be considered clinically significant (all < 4 beats/minute).

51% of the Dynacirc patients experienced newly occurring adverse reactions compared with 49% of the placebo patients. The body systems most affected in both groups were the central nervous system, cardiovascular system, and gastrointestinal system. There were no statistically significant differences between the groups for any body system. One patient in the Dynacirc group died during this study. The cause of death was a myocardial infarction and the investigator did not feel it was related to the study drug.

3. Reviewer's Comments

This study gives very strong evidence of the ability of Dynacirc to reduce both systolic and diastolic blood pressure. As discussed in the review of Study 301, the length of time before titration was too short for the full effect of the lower doses to be apparent. In many cases, patients who were titrated to a higher dose would possibly have normalized at the lower dose given two to four weeks at that level.

IV. PHASE III ACTIVE-CONTROLLED STUDIES

Four Phase III active-controlled studies were submitted by the sponsor. The studies were similar in design but with a different active-control in each case. Three of the studies, 303 (hydrochlorothiazide), 304 (propranolol), and 305 (prazosin), were direct comparisons of Dynacirc with a single active agent. The fourth study, 307, was a combination study comparing Dynacirc in combination with hydrochlorothiazide to

propranolol in combination with hydrochlorothiazide.

The patients involved in all of these studies were people with benign mild to moderate essential hypertension. Subjects entered into these studies were required to be at least 18 years old and to exhibit a sitting diastolic blood pressure of at least 95 mmHg on at least two consecutive visits during the washout period, including the final visit (baseline). Severe hypertensives (average sitting diastolic blood pressure >120 mmHg on two consecutive evaluation days during the washout period) were excluded from the trial. Other reasons for exclusion from the study included: clinically apparent secondary forms of hypertension; malignant or accelerated hypertension; angina pectoris; history of myocardial infarction; cardiac arrhythmias; congestive heart failure; bradycardia; a history of alcohol or drug abuse or mental dysfunction; cerebral vascular insufficiency; presence of any disease or abnormal condition which compromised the function of the gastrointestinal tract, kidney and/or liver; patients with known serious adverse reactions to drugs similar to the study drug; patients who received any other investigational new drug within 4 weeks prior of entering the study; patients who required the use of medication which might interfere with the evaluation of the study drug; and pregnant and lactating females. Medication which was disallowed during the study (beginning with the wash-out period) included: all antihypertensive agents except the study drugs; adrenergic-augmenting drugs; antiarrhythmic drugs; psychotropic drugs; oral contraceptives; and antacids with high sodium content.

IV.A. STUDY 303

1. Study Description

Study 303 was a randomized, double-blind, parallel group, multicenter, active-controlled trial design comparing Dynacirc with hydrochlorothiazide (HCTZ), a diuretic commonly used to control hypertension. 98 patients were enrolled in the active-treatment phase of the study at three treatment centers (Center B consisted of two study sites both within the same city). Center A contributed 29% of the total number of patients enrolled in the study, Center B contributed 31% (both sites combined), and Center C contributed 41%. An initial three to five week single-blind placebo washout period was followed by a ten week randomized double-blind treatment period. Patients were randomized to the study groups based on their average sitting diastolic blood pressure at baseline, with those patients with a baseline value between 95 and 105 randomized according to one schedule and those patients with a baseline value over 105 randomized according to another schedule. 48 patients were randomized to receive Dynacirc and 50 patients to receive HCTZ. The groups were comparable with respect to age, size, race, and various laboratory values. All patients began with one 5 mg dose of Dynacirc or one 25 mg dose of HCTZ given twice daily, before breakfast and after supper. The dose was doubled at the week 4 evaluation if the average sitting diastolic blood pressure was still greater than 90 mmHg or at the end of weeks 2 or 3 if the average sitting diastolic blood pressure was greater than 110 mmHg or posed a hazardous state to the patient. Therefore the dose

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levels during the plateau period (weeks 5-10) ranged from 5 mg to 10 mg, bid for Dynacirc and from 25 mg to 50 mg bid for HCTZ. A total of ten patients in the Dynacirc group and 12 patients in the HCTZ group were titrated to the higher dose. The other patients were maintained at the lower dose throughout the study.

Patients were monitored weekly throughout the study, with visits at approximately the same time each evaluation day. The efficacy variables were average sitting diastolic blood pressure, average sitting systolic blood pressure, and average sitting pulse. Two readings were taken at least three minutes apart after the patient had rested in the prescribed position for at least 30 minutes. The same arm and the same size blood pressure cuff were used throughout the study, and the same individual performed the evaluation as often as possible. Safety was monitored by a physical examination, vital signs recordings, clinical laboratory analysis, electrocardiogram, cardiopulmonary evaluation and recording of the concomitant medications, compliance and adverse reactions.

36 Dynacirc patients and 37 HCTZ patients were considered completely valid. Nine Dynacirc patients and 10 HCTZ patients were considered partially valid. The reasons included adverse reactions, lack of cooperation, and patients leaving town. Three Dynacirc and three HCTZ patients were considered totally invalid. Two had a nonqualifying blood pressure at baseline and four were noncompliant.

2. Sponsor's Analysis

A two-way (treatment x investigator) analysis of variance/covariance with repeated measures was used to evaluate the blood pressure response for the valid patients during the plateau period (weeks 5-10). This analysis examined the treatment x time, treatment x investigator, and treatment x time x investigator interactions to determine if pooling the efficacy data across centers was justified. A one-way analysis of variance/covariance was used to assess treatment group differences during the double blind portion of the study. This was performed for the valid patients for weeks 1-4 and for the plateau period. It was also performed for the valid and partially valid patients for the endpoint of the plateau period and for all the randomized patients at the endpoint of the study. Table 6 gives the results for the valid and partially valid patients over the plateau period and the "all patient" endpoint analysis. The Dynacirc group demonstrated a statistically significantly greater reduction in the average sitting diastolic blood pressure than did HCTZ in both cases ($p=0.0057$ for plateau period and $p=0.0198$ for endpoint). The reduction in average sitting systolic blood pressure was similar for the two drugs. The change in the pulse rate was statistically significant but not clinically significant.

69 percent of the patients in the Dynacirc group and 76 percent of the patients in the HCTZ group reported at least one newly-occurring adverse reaction during the double-blind portion of this study. The most frequently reported adverse reactions in the Dynacirc group were edema, cardiac arrhythmias, and palpitations, which accounted for 50% of the occurrences. The HCTZ group experienced cardiac arrhythmias, palpitations, and chest pains, and weakness.

3. Reviewer's Comments

This study indicates that Dynacirc is probably at least as effective as HCTZ in controlling benign essential hypertension. Twice daily dosing of Dynacirc at these levels appears to result in an equivalent reduction in the systolic blood pressure while giving a somewhat larger reduction in diastolic blood pressure.

There appeared to be some confusion among those working on the statistical report for this study as to whether it should be considered a three center or a four center study. Center B, although supervised by a single physician, actually was carried out at two different hospitals within the same town. No treatment x center interactions were found in the analysis of variance.

The reviewer made comparisons between the occurrences of the various adverse reactions experienced by patients on the two drugs. Edema was the only adverse reaction which exhibited a statistically significant difference between the two treatment groups ($p=0.0384$).

IV.B. STUDY 304

1. Study Description

Study 304 was a randomized, double-blind, parallel group, multicenter, active-controlled trial design comparing Dynacirc with propranolol, a beta-blocker used to control benign essential hypertension. 89 patients were enrolled in the active-treatment phase of the study at three treatment centers. Center A contributed 31% of the total number of patients enrolled in the study, Center B contributed 34%, and Center C contributed 35%. An initial three week single-blind placebo washout period was followed by a ten week randomized double-blind treatment period. Patients were randomized to the study groups based on their average sitting diastolic blood pressure at baseline, with those patients with a baseline value between 95 and 105 randomized according to one schedule and those patients with a baseline value over 105 randomized according to another schedule. 46 patients were randomized to receive Dynacirc and 43 patients to receive propranolol. The groups were comparable with respect to age, size, race, and various laboratory values.

The initial dose for all patients was either 2.5 mg Dynacirc or 60 mg propranolol twice daily, shortly after awakening in the morning and before the evening meal. The dose was increased at bi-weekly intervals if the average sitting diastolic blood pressure was still greater than 90 mmHg. Beginning with week 7, the dose remained constant for the rest of the study. Therefore the dose levels during the plateau period (weeks 7-10) ranged from 2.5 mg to 10 mg, bid for Dynacirc and from 60 mg to 240 mg bid for propranolol. During the plateau period, eight patients in the Dynacirc group stayed at the 2.5 mg bid level, 13 remained at the 5 mg bid level, 10 stayed at the 7.5 mg bid level, and 6 were at the 10 mg bid level. In the propranolol group seven

patients were at the 60 mg bid level, 4 remained at the 120 mg bid level, 8 were at the 180 mg bid level, and 12 were at the 240 mg bid level.

Patients were monitored weekly throughout the study, with visits at approximately the same time each evaluation day. The efficacy variables and the procedure were the same as Study 303. 37 Dynacirc patients and 31 propranolol patients were considered completely valid. Five Dynacirc patients and 11 propranolol patients were considered partially valid. The reasons included treatment failure, adverse reactions, lack of cooperation, and loss to follow-up. Four Dynacirc and one propranolol patients were considered totally invalid. Three had a nonqualifying blood pressure at baseline and two were noncompliant.

2. Sponsor's Analysis

A two-way (treatment x investigator) analysis of variance/covariance with repeated measures was used to determine if pooling the efficacy data across centers was justified. A one-way analysis of variance/covariance was used to assess treatment group differences during the double blind portion of the study. This was performed for the valid patients for the plateau period (weeks 7-10). It was also performed for the valid and partially valid patients for weeks 1 and 2, the endpoint of the titration period, and the endpoint of the plateau period. A one-way analysis of variance was also performed for all the randomized patients at the endpoint of the study. Table 7 gives the results for the valid patients over the plateau period and the "all patient" endpoint analysis. The Dynacirc group demonstrated a statistically significantly greater reduction in the average sitting diastolic blood pressure than did propranolol in both cases ($p=0.0060$ for the plateau period and $p=0.0012$ for the endpoint). The reduction in average sitting systolic blood pressure also tended to be greater in the Dynacirc group ($p=0.0717$ for the plateau period and $p=0.0383$ for the endpoint). The change in the pulse rate was very statistically significant, with the Dynacirc group demonstrating a small increase in pulse rate (4 to 5 beats per minute), while the propranolol demonstrated a moderate decrease in pulse rate (11 to 12 beats per minute).

83 percent of the patients in the Dynacirc group and 65 percent of the patients in the propranolol group reported at least one newly-occurring adverse reaction during the double-blind portion of this study. The most frequently reported adverse reactions in the Dynacirc group were in the central nervous and cardiovascular systems. The propranolol group experienced adverse reactions in the central nervous system, gastrointestinal system, and cardiovascular system. One patient in the propranolol group died during this study. The cause of death was cardiac arrest and the investigator did not think it was related to the propranolol therapy.

3. Reviewer's Comments

This study shows that Dynacirc is probably at least as effective as propranolol in controlling benign essential hypertension. Twice daily dosing of Dynacirc at these

levels resulted in a trend of greater reductions in the systolic blood pressure and a statistically significantly greater reduction in diastolic blood pressure. The increase in pulse rate attributable to the Dynacirc group is statistically significant but, according to the sponsor, not clinically significant. The reduction in pulse rate in the propranolol group was highly significant. The vast difference in the pulse rate response to the two drugs could have led the investigators involved in this study to be able to ascertain which patients were on which drug. This unblinding could have led to bias in the reporting of adverse reactions.

The reviewer made comparisons between the occurrences of the various adverse reactions experienced by patients on the two drugs. The Dynacirc group displayed more adverse reactions than did the propranolol group, and the results were marginally statistically significant ($p=.0596$). The sponsor claims that the vast majority of these adverse reactions were considered by the investigator to be mild to moderate in severity and transient in nature. Irregularities in the heart rate were the only adverse reaction which exhibited a statistically significant difference between the two groups, with seven of 36 Dynacirc treated patients experiencing newly occurring heart irregularities while none of the 35 propranolol patients had this problem ($p=.0060$).

IV.C. STUDY 305

1. Study Description

Study 305 was a randomized, double-blind, parallel group, multicenter, active-controlled trial design comparing Dynacirc with prazosin, an alpha-blocker used to control benign essential hypertension. 83 patients were enrolled in the active-treatment phase of the study at three treatment centers. Center A contributed 20% of the total number of patients enrolled in the study, Center B contributed 52%, and Center C contributed 28%. An initial three week single-blind placebo washout period was followed by a ten week randomized double-blind treatment period. Patients were randomized to the study groups based on their average sitting diastolic blood pressure at baseline, with those patients with a baseline value between 95 and 105 randomized according to one schedule and those patients with a baseline value over 105 randomized according to another schedule. 41 patients were randomized to receive Dynacirc and 42 patients to receive prazosin. The groups were comparable with respect to age, size, race, and various laboratory values.

The initial dose for all patients was either 2.5 mg Dynacirc or 1 mg prazosin twice daily, before breakfast and supper. The prazosin dose was automatically titrated to 2 mg bid at the end of the first week. The doses of both drugs were then increased by 2.5 mg Dynacirc or 2 mg prazosin at bi-weekly intervals if the average sitting diastolic blood pressure was still greater than 90 mmHg. Beginning with week 7, the dose remained constant for the rest of the study. Therefore the dose levels during the plateau period (weeks 7-10) ranged from 2.5 mg to 10 mg, bid for Dynacirc and from 2 mg to 8 mg bid for prazosin. During the plateau period, 14 patients in the Dynacirc group remained at the 2.5 mg bid level, nine remained at the 5 mg bid level, three

remained at the 7.5 mg bid level, and 4 had been titrated to the 10 mg bid level. In the prazosin group ten patients were at the 2 mg bid level, seven remained at the 4 mg bid level, nine were at the 6 mg bid level, and seven had been titrated to the 8 mg bid level.

Patients were monitored weekly throughout the study, with visits at approximately the same time each evaluation day. The evaluation procedure were the same as in Study 303. The efficacy variables were sitting diastolic blood pressure, sitting systolic blood pressure, sitting pulse, standing diastolic blood pressure, standing systolic blood pressure, and standing pulse. 30 Dynacirc patients and 33 prazosin patients were considered completely valid. Ten Dynacirc patients and seven prazosin patients were considered partially valid. The reasons included adverse reactions, unrelated illnesses, and loss to follow-up. One Dynacirc and two prazosin patients were considered totally invalid. Two had a nonqualifying blood pressure at baseline and one was noncompliant.

2. Sponsor's Analysis

A two-way (treatment x investigator) analysis of variance/covariance with repeated measures was used to determine if pooling the efficacy data across centers was justified. A statistically significant ($p=.0335$) treatment x investigator interaction was detected for the sitting systolic blood pressure. This interaction could be attributed to Center C which had fairly different results from Centers A and B for this variable, as shown in the results below:

Center	Dynacirc		Prazosin	
	Baseline Mean (N)	Mean change from baseline	Baseline Mean (N)	Mean change from baseline
A	155.8 (6)	-24.86	156.8 (6)	-3.75
B	149.3 (16)	-18.17	153.7 (19)	-7.62
C	145.1 (8)	-7.56	150.8 (8)	-12.63

A similar interaction was not found for standing systolic blood pressure nor for either of the diastolic blood pressure measurements. The sponsor felt that the overall conclusions reached from a pooled analysis would not be greatly affected by this interaction.

A one-way analysis of variance/covariance was used to assess treatment group differences during the double blind portion of the study. This was performed for the valid patients for the plateau period (weeks 7-10). It was also performed for the valid and partially valid patients for weeks 1 and 2, and for the endpoint of the titration period. A one-way analysis of variance was also performed for all the randomized patients at the endpoint of the study. Table 8 gives the results for the valid patients over the plateau period and the "all patient" endpoint analysis. The Dynacirc group

demonstrated a statistically significant greater reduction in sitting systolic, standing systolic, and standing diastolic blood pressure in both analyses. The sitting diastolic blood pressure values were lower for the study drug in both analyses, but were not statistically significant ($p=.0654$ for the plateau period and $p=.0699$ for the endpoint analysis).

56 percent of the patients in the Dynacirc group and 74 percent of the patients in the prazosin group reported at least one newly-occurring adverse reaction during the double-blind portion of this study. The most frequently reported adverse reactions in the Dynacirc group were in the central nervous and cardiovascular systems. The prazosin group experienced adverse reactions in the central nervous system, gastrointestinal system, and cardiovascular system.

3. Reviewer's Comments

This study shows that Dynacirc is probably at least as effective as prazosin in controlling benign essential hypertension. Twice daily dosing of Dynacirc at these levels resulted in a trend to greater reductions in the diastolic blood pressure and a statistically significant reduction in systolic blood pressure. The increase in heart rate in the prazosin group is statistically significant but the increase in the Dynacirc was not.

The reviewer made comparisons between the occurrences of the various adverse reactions experienced by patients on the two drugs. The prazosin group displayed more adverse reactions than did the Dynacirc group, and the results were marginally statistically significant ($p=.0906$). There were also no significant differences in the number of adverse reactions reported in any of the individual body systems.

IV.D. STUDY 307

1. Study Description

Study 307 was a randomized, double-blind, parallel group, multicenter, active-controlled combination trial design comparing Dynacirc with propranolol, when both are given in conjunction with hydrochlorothiazide (HCTZ). Patients entering this study had a diagnosis of benign essential hypertension which did not respond to HCTZ alone. 78 patients were enrolled in the active-treatment phase of the study at four treatment centers. Centers A and B each contributed 26% of the total number of patients enrolled in the study, Center C contributed 27%, and Center D contributed 22%. The study began with an initial two to three week single-blind placebo run-in period during which each patient received a placebo capsule in addition to their usual dose of HCTZ. The dose and dosage of HCTZ remained constant during the run-in period and throughout the duration of the study.

The run-in period was followed by a ten week randomized double-blind treatment

period. Patients were randomized to the study groups based on their average supine diastolic blood pressure at baseline, with those patients with a baseline value between 95 and 110 randomized according to one schedule and those patients with a baseline value over 110 randomized according to another schedule. 40 patients were randomized to receive Dynacirc and 38 patients to receive propranolol. The groups were comparable with respect to age, size, race, and various laboratory values.

The initial dose for all patients was either 2.5 mg Dynacirc or 60 mg propranolol twice daily, before breakfast and supper, which was given in addition to their usual dose of HCTZ (at least 50 mg per day). The doses of both study drugs were then increased by 2.5 mg Dynacirc or 60 mg propranolol at bi-weekly intervals if the average supine diastolic blood pressure was still greater than 90 mmHg. Beginning with week 7, the dose remained constant for the rest of the study. Therefore the dose levels during the plateau period (weeks 7-10) ranged from 2.5 mg to 10 mg bid for Dynacirc and from 60 mg to 240 mg bid for propranolol. During the plateau period, 10 patients in the Dynacirc group remained at the 2.5 mg bid level, four remained at the 5 mg bid level, nine remained at the 7.5 mg bid level, and ten had been titrated to the 10 mg bid level. In the propranolol group ten patients were at the 60 mg bid level, one was at the 90 mg bid level, seven remained at the 120 mg bid level, six were at the 360 mg bid level, and five had been titrated to the 480 mg bid level.

Patients were monitored weekly throughout the study, with visits at approximately the same time each evaluation day. The evaluation procedure were the same as in Study 303. The efficacy variables were supine diastolic blood pressure, supine systolic blood pressure, supine pulse, standing diastolic blood pressure, standing systolic blood pressure, and standing pulse. 33 Dynacirc patients and 29 propranolol patients were considered completely valid. Seven Dynacirc patients and nine propranolol patients were considered partially valid. The reasons included adverse reactions, ineffectiveness of the study drug, and loss to follow-up. No patients were considered totally invalid.

2. Sponsor's Analysis

A two-way (treatment x investigator) analysis of variance/covariance with repeated measures was used to determine if pooling the efficacy data across centers was justified. None of the treatment x investigator, treatment x time and treatment x investigator x time interactions over the plateau period were statistically significant for any of the blood pressure parameters.

A one-way analysis of variance/covariance was used to assess treatment group differences during the double blind portion of the study. This was performed for the valid patients for the plateau period (weeks 7-10). It was also performed for the valid and partially valid patients for weeks 1 through 6, the endpoint of the plateau period and for the endpoint of the study. A one-way analysis of variance was also performed for all the randomized patients at the endpoint of the study. Table 9 gives the results for the valid patients over the plateau period and the "all patient"

endpoint analysis. The reductions in all the blood pressure parameters were very similar between the two groups, and all were highly significant against baseline. The changes in the pulse rate were very different with the Dynacirc group showing a small increase in pulse rate (1.64 to 3.09 beats per minute) while the propranolol group showed a large decrease in pulse rate (-12.08 to -20.14). This difference in the pulse rate was statistically significant with $p < .0001$.

73 percent of the patients in the Dynacirc group and 45 percent of the patients in the propranolol group reported at least one newly-occurring adverse reaction during the double-blind portion of this study. The most frequently reported adverse reactions in the Dynacirc group were in the cardiovascular system, central nervous systems, gastrointestinal system, and respiratory system. The propranolol group experienced adverse reactions in the central nervous system, gastrointestinal system, and musculo-skeletal system. The difference in the total number of patients with a newly occurring adverse reaction was statistically significant with $p = .02$ (Fisher's Exact Test). The differences in the individual symptoms were not significant except for coughing (respiratory system) which was experienced by 5 Dynacirc patients and no propranolol patients ($p=.05$).

3. Reviewer's Comments

This study shows that Dynacirc is probably about as effective as propranolol when used in conjunction with HCTZ for controlling benign essential hypertension. The reductions in all the blood pressure parameters were very similar for the two groups, with no indication of superiority for either drug. The decrease in heart rate in the propranolol group is very statistically significant in all cases, but the increase in heart rate in the Dynacirc was not significant in most cases. In this study, as in Study 304, the vast difference in the pulse rate response to the two drugs could have led the investigators involved in this study to be able to ascertain which patients were on which drug. This unblinding could have led to bias in the reporting of adverse reactions.

The comparison of the results of this study with the results of Study 304 does not indicate an advantage to using Dynacirc in combination with HCTZ. The comparison is hampered by the fact that Study 304 measured sitting blood pressure while Study 307 measured supine and standing blood pressure. However, the two studies were comparable in both size (89 and 78 patients enrolled) and study procedure (patient selection, washout period, titration schedule, etc.) The change from baseline values for the two studies are given below. The addition of HCTZ to propranolol always increased the reduction in systolic or diastolic blood pressure by from 3 to 7 mmHg. The addition of HCTZ to Dynacirc resulted in only slight increases in the reduction of systolic blood pressure and in slight decreases in the reduction of diastolic blood pressure.

Treatment	Variable	Study 304 Sitting (Treatment alone)	Study 307 Supine (Treatment + HCTZ)	Study 307 Standing (Treatment +HCTZ)
Dynacirc	Systolic B.P. (Plateau Average)	-17.28	-19.40	-20.49
Dynacirc	Systolic B.P. (Endpoint)	-18.59	-19.28	-20.88
Dynacirc	Diastolic B.P. (Plateau Average)	-15.44	-15.08	-14.57
Dynacirc	Diastolic B.P. (Endpoint)	-15.55	-15.38	-13.63
Propranolol	Systolic B.P. (Plateau Average)	-11.19	-18.05	-17.85
Propranolol	Systolic B.P. (Endpoint)	-11.65	-15.72	-15.71
Propranolol	Diastolic B.P. (Plateau Average)	-9.96	-15.50	-13.63
Propranolol	Diastolic B.P. (Endpoint)	-9.24	-14.04	-12.45

The large number of newly occurring adverse reactions in the Dynacirc group is of concern. This reviewer made comparisons of the symptoms reported in the various body systems and several gave significant differences. The Dynacirc group experienced significantly more adverse experiences in the cardiovascular system ($p=.0046$) and in the respiratory system ($p=.0112$).

V. OVERALL SUMMARY AND CONCLUSIONS

This group of studies essentially contain only drug effects measured at peak. They demonstrate that at peak Dynacirc is very effective in reducing both systolic and diastolic blood pressure; it is far superior to placebo, and at least as good as the three active agents (Hydrochlorothiazide, propranolol, and prazosin) used in the comparative studies. The only studies with trough data are Study 9, which involved only 16 patients in a Latin Square design, and the last two weeks of Study 11 which involved qd dosing. Based on the twenty-four hour results of Study 9, this reviewer feels that the twice daily dosing schedule is probably adequate for the lower doses. If higher doses are recommended, the dosing schedule should be evaluated more carefully since this study indicates that they lose effectiveness rather rapidly after reaching their peak effects. The qd and bid dosing schedules in Study 11 cannot be compared since the qd values are trough results (taken over 24 hours after the last dose) and the bid values are peak results (taken 2-3 hours after the last dose).

Table 10A gives a summary of all the Phase III studies for diastolic blood pressure at peak. This includes a total of eight study groups assigned to Dynacirc (Study 301 had four different fixed Dynacirc dose groups), two to placebo, and one each to HCTZ, propranolol, and prazosin, Dynacirc plus HCTZ, and propranolol plus HCTZ. Studies 301, 302, and 307 measured supine and standing blood pressure, studies 303 and 304 measured sitting blood pressure, and study 305 measured sitting and standing blood pressure. Table 10B presents a summary of the number of patients achieving a 10 mmHg decrease in diastolic blood pressure (supine or sitting) and the

number whose diastolic blood pressure was normalized to no greater than 90 mmHg for all the Phase III studies.

An initial concern on the part of this reviewer was the fact that the company had submitted this NDA originally with interim reports on all of the Phase III studies. The final reports were submitted after the studies were completed in accordance with the protocols. However, an examination of several of the interim reports and comparison of the interim results with the final results found no significant discrepancies. The wording of the two reports was virtually identical, with only the numbers changed to reflect results of the additional patients. In all cases, the study was completed with at least as many patients as had been required in the protocol, although in most cases the results at the time of the interim analysis were already highly statistically significant (most p-values less than .001).

At the time of the original submission, the interim report on Study 301 was based on 155 of an ultimate 203 patients and the interim report on Study 302 was based on 74 of an ultimate 98 patients, about 75% of the final totals for these placebo-controlled studies. In the active-controlled studies, the interim report on Study 303 was based on 82 of an ultimate 98 patients, the interim report on Study 304 was based on 59 of an ultimate 89 patients, the interim report on Study 305 was based on 39 of an ultimate 83 patients and the interim report on Study 307 was based on 35 of an ultimate 78 patients.

This reviewer compared the results of the two analyses for studies 301 and 304. The changes in the blood pressure parameters in study 301, both systolic and diastolic, supine and standing, for the plateau average and endpoint results, were all very similar, with only one differing by as much as 1.5 mmHg. The changes were evenly distributed with 18 showing a small increase and 22 demonstrating a small decrease. At the time of the interim analysis the p-values versus baseline and placebo were all statistically significant, with most below 0.001. In study 304 there was a little more change, with the plateau average sitting systolic blood pressure for the propranolol group showing an increase of over 3 mmHg from the interim analysis to the final analysis. The other variables all showed increases of less than 1.5 mmHg. None of the blood pressure parameters showed decreases from the interim analysis to the final analysis. At the time of the interim analysis both drug groups demonstrated highly statistically significant ($p < .001$) differences from baseline in the blood pressure results, and from each other in the pulse rate results. If the investigators were aware of the results of the interim analysis, I feel sure the blinding of the study beyond that point was compromised.

Because of its fixed dose schedule, the most informative study reviewed here is Study 301. In all the other studies the dose of Dynacirc was titrated, either based on a fixed titration schedule or based on current readings of diastolic blood pressure. As discussed in the review of Study 301, the time to titration (1-2 weeks) was too short in all of these studies. Both diastolic and systolic blood pressure continued to decrease for about four weeks in the fixed dose study.

dose-response relationship was not demonstrated for doses above 5 mg bid. The reductions at 7.5 mg bid were never significantly greater than those of 5 mg bid and were numerically almost identical. The reductions at 10 mg bid were frequently less than the reductions at 5 and 7.5 mg bid. Because of the excellent results achieved with the lowest dose (2.5 mg bid) it might be worthwhile to study a dose smaller than 2.5 mg bid. Based on the results of these studies, this reviewer feels that the maximal dose should be 5 mg bid in most cases, and should not be increased beyond this point unless the drug was not producing the desired effect after at least a month of therapy.

Study 307, which compared a combination of Dynacirc and HCTZ with a combination of propranolol and HCTZ led to a conclusion of no difference between the two combinations. However, in Studies 303 and 304 Dynacirc had given significantly greater reductions in diastolic blood pressure than had propranolol or HCTZ alone. An across studies comparison of the results for the combination of Dynacirc and HCTZ with the results of Dynacirc given alone do not indicate any advantage to giving a combination of the two drugs. A study directly comparing the combination with Dynacirc monotherapy would be necessary before the combination should be recommended.

In all of these studies the reduction in diastolic blood pressure due to Dynacirc is about the same as the reduction in systolic blood pressure. Table 10D gives a summary of the Phase III monotherapy studies for both systolic and diastolic blood pressure, including the overall mean for the studies and the range of the individual study means for supine, sitting, and standing blood pressure. The values for the sitting parameters are almost identical and those for supine and standing parameters do not indicate much greater reduction in systolic blood pressure than that of the diastolic blood pressure.

Table 10B also includes the number of patients in each group who experience newly occurring adverse reactions. Dynacirc when used as a monotherapy appeared to cause fewer adverse reactions than did the other active drugs. In the combination therapy the reverse was true. The incidence of adverse reactions did appear to be somewhat dose related, with more occurring at higher doses. Table 10C gives a list of the incidence rates of all adverse reactions from studies 7, 11, 301-305, and 307. Headache, edema, and flushing were experienced more frequently by the Dynacirc patients, while fatigue, abdominal discomfort, and nausea were experienced more frequently in the patients taking the active control drugs.

The overall summary and conclusions section may be conveyed to the sponsor.

Nancy D. Smith

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Mathematical Statistician

Concur:

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HFD-110

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HFD-344/Dr. Lisook

HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]

HFD-713/Dr. Chi

HFD-713/Dr. Smith

Chron.

N.Smith/x30263/SERB/WriteNow/10-6-88

This review contains 28 pages of text and 13 pages of attached tables.

TABLE 1
STUDY 7 - CHANGE FROM BASELINE (PEAK)

Variable	Treatment Group	N	ENDPOINT		P-value vs baseline	P-value vs placebo
			Baseline Mean (S.D.)	Mean Change (S.D.)		
Supine Systolic B.P. (mmHg)	Dynacirc	12	160.3 (23.48)	-18.5 (20.18)	0.0088	0.1301
	Placebo	11	164.5 (19.39)	-5.5 (19.45)	0.3743	
Supine Diastolic B.P. (mmHg)	Dynacirc	12	99.8 (5.13)	-13.2 (8.47)	0.0002	0.0051
	Placebo	11	100.5 (6.33)	-1.5 (9.51)	0.6230	
Supine Pulse Rate (beats/min.)	Dynacirc	12	66.3 (8.12)	3.3 (7.44)	0.1489	0.9564
	Placebo	11	71.0 (7.29)	3.5 (10.79)	0.3015	
Standing Systolic B.P. (mmHg)	Dynacirc	12	156.1 (21.69)	-12.4 (19.11)	0.0459	0.5285
	Placebo	11	163.5 (22.47)	-7.9 (13.93)	0.0891	
Standing Diastolic B.P. (mmHg)	Dynacirc	12	97.8 (7.36)	-7.3 (9.32)	0.0197	0.1462
	Placebo	11	102.0 (6.76)	-1.5 (9.05)	0.5835	
Standing Pulse Rate (beats/min.)	Dynacirc	12	72.4 (10.18)	3.0 (8.43)	0.2434	0.4999
	Placebo	11	76.8 (12.85)	0.3 (10.58)	0.9336	

PLATEAU AVERAGE

Variable	Treatment Group	N	ENDPOINT		P-value vs baseline	P-value vs placebo
			Baseline Mean (S.D.)	Mean Change (S.D.)		
Supine Systolic B.P. (mmHg)	Dynacirc	10	158.0 (21.52)	-18.8 (18.26)	0.0099	0.4451
	Placebo	9	161.3 (19.65)	-12.78 (14.91)	0.0330	
Supine Diastolic B.P. (mmHg)	Dynacirc	10	99.6 (5.46)	-14.1 (5.61)	0.0001	0.0016
	Placebo	9	100.2 (5.78)	-3.8 (6.42)	0.1154	
Supine Pulse Rate (beats/min.)	Dynacirc	10	67.4 (8.54)	6.7 (6.37)	0.0088	0.1468
	Placebo	9	71.9 (7.25)	0.3 (11.44)	0.9325	
Standing Systolic B.P. (mmHg)	Dynacirc	10	54.8 (21.25)	-13.75 (15.89)	0.0230	0.6897
	Placebo	9	158.3 (21.51)	-11.11 (11.87)	0.0229	
Standing Diastolic B.P. (mmHg)	Dynacirc	10	96.6 (7.25)	-9.4 (8.18)	0.0055	0.0589
	Placebo	9	100.9 (6.86)	-2.7 (6.00)	0.2191	
Standing Pulse Rate (beats/min.)	Dynacirc	10	73.0 (10.95)	5.2 (9.70)	0.1241	0.1155
	Placebo	9	78.9 (13.01)	-2.3 (10.09)	0.0576	

TABLE 2A

STUDY 9 - CHANGE FROM BASELINE
DIASTOLIC **SYSTOLIC**

Dose	Mean Change	P-Value	P-Value	P-Value	Mean Change	P-Value	P-Value	P-Value
		versus 2.5 mg	versus 5 mg	versus 10 mg		versus 2.5 mg	versus 5 mg	versus 10 mg
9 HOURS								
2.5 mg	-5.36				-4.00			
5 mg	-7.46	0.3350			-11.43	0.0534		
10 mg	-13.55	0.0006	0.0081		-21.24	0.0001	0.0127	
20 mg	-15.53	0.0001	0.0007	0.3624	-23.78	0.0001	0.0023	0.49
12 HOURS								
2.5 mg	-5.43				-2.17			
5 mg	-7.03	0.4298			-10.14	0.0451		
10 mg	-12.11	0.0022	0.0161		-18.29	0.0002	0.0407	
20 mg	-14.14	0.0001	0.0012	0.3158	-21.46	0.0001	0.0058	0.4119
21 HOURS								
2.5 mg	-5.37				-0.81			
5 mg	-5.98	0.7774			-6.94	0.1514		
10 mg	-9.34	0.0722	0.1250		-14.88	0.0021	0.0665	
20 mg	-12.15	0.0034	0.0069	0.1963	-17.19	0.0005	0.0199	0.5831

TABLE 2B

STUDY 9 - CHANGE IN BLOOD PRESSURE

Hours after Dosing	2.5 mg	5 mg	10 mg	20 mg	Placebo
0.0	0.000	0.000	0.000	0.000	0.000
0.5	-3.750	-6.625	-8.688	-3.750	-0.950
1.0	-6.375	-10.125	-14.438	-16.875	0.450
1.5	-6.125	-11.250	-18.313	-17.125	1.575
2.0	-6.375	-10.000	-17.188	-17.875	1.000
2.5	-4.625	-9.750	-15.688	-19.000	1.225
3.0	-3.875	-6.625	-14.688	-20.000	1.750
4.0	-5.125	-7.125	-16.063	-18.375	-2.475
5.0	-4.375	-4.875	-14.063	-17.875	-3.125
6.0	-4.750	-6.500	-13.813	-16.500	-3.675
7.0	-7.750	-7.375	-11.813	-15.250	-4.275
8.0	-6.625	-8.000	-12.813	-14.375	-2.463
9.0	-6.125	-7.625	-9.313	-10.250	-1.975
10.0	-4.875	-5.625	-5.563	-9.375	-0.775
11.0	-5.875	-5.250	-8.563	-10.750	-1.400
12.0	-6.375	-5.000	-8.813	-9.250	-2.050
15.0	-4.875	-4.250	-5.063	-11.000	-2.150
21.0	-5.375	-4.875	-4.750	-7.375	-2.450
24.0	-1.375	0.250	-3.438	-3.125	0.313

TABLE 3
STUDY 11
CHANGE FROM BASELINE (PEAK)

WEEK 3

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs placebo
Supine Systolic B.P. (mmHg)	Dynacirc	12	149.0 (11.61)	-13.9 (11.99)	0.0020	0.0004
	Placebo	12	150.8 (13.44)	4.3 (9.00)	0.1300	
Supine Diastolic B.P. (mmHg)	Dynacirc	12	102.3 (5.99)	-14.8 (7.58)	0.0001	0.0007
	Placebo	12	103.4 (3.63)	-3.8 (6.09)	0.0517	
Supine Pulse Rate (beats/min.)	Dynacirc	12	68.3 (6.37)	6.8 (12.18)	0.0780	0.1316
	Placebo	12	67.2 (10.37)	0.8 (5.27)	0.5949	
Standing Systolic B.P. (mmHg)	Dynacirc	12	143.0 (13.56)	-19.5 (14.92)	0.0009	0.0017
	Placebo	12	146.3 (10.87)	-1.3 (9.62)	0.6614	
Standing Diastolic B.P. (mmHg)	Dynacirc	12	100.4 (6.97)	-17.2 (8.34)	0.0001	< 0.0001
	Placebo	12	101.9 (6.27)	-2.3 (4.96)	0.1441	
Standing Pulse Rate (beats/min.)	Dynacirc	12	78.4 (7.88)	5.9 (12.25)	0.1225	0.1503
	Placebo	12	78.1 (12.84)	0.2 (5.34)	0.9158	

TABLE 4A

STUDY 301

CHANGE FROM BASELINE (PEAK) - PLATEAU AVERAGE

Variable	Treatment Group	N	Baseline Mean (S.D.)	Change Mean (S.D.)	P-Value	P-Value	P-Value	P-Value	P-Value
					versus Baseline	versus Placebo	versus 2.5 mg	versus 5 mg	versus 7.5mg
Supine	2.5 mg bid	35	156.9 (16.48)	-16.1 (10.51)	0.0001	<.0001			
Systolic	5 mg bid	34	160.4 (14.32)	-22.0 (13.78)	0.0001	<.0001	0.0614		
B.P.	7.5 mg bid	38	158.6 (20.72)	-22.4 (17.70)	0.0001	<.0001	0.0429	0.9170	
(mmHg)	10 mg bid	41	154.0 (13.52)	-20.5 (12.45)	0.0001	<.0001	0.1449	0.6169	0.5324
	Placebo	39	151.1 (13.69)	-3.4 (9.17)	0.0274				
Supine	2.5 mg bid	35	104.2 (4.48)	-13.9 (6.20)	0.0001	<.0001			
Diastolic	5 mg bid	34	104.3 (4.35)	-17.1 (6.89)	0.0001	<.0001	0.0486		
B.P.	7.5 mg bid	38	103.5 (3.65)	-17.2 (7.99)	0.0001	<.0001	0.0341	0.9256	
(mmHg)	10 mg bid	41	103.5 (3.97)	-17.3 (5.87)	0.0001	<.0001	0.0301	0.9146	0.9900
	Placebo	39	104.0 (4.44)	-7.0 (6.45)	0.0274				
Supine	2.5 mg bid	35	78.4 (10.22)	1.5 (7.00)	0.2066	0.1944			
Pulse	5 mg bid	34	74.8 (8.55)	4.4 (7.37)	0.0014	0.0024	0.0824		
(beats/	7.5 mg bid	38	74.6 (9.36)	4.0 (7.40)	0.0025	0.0045	0.1322	0.7879	
min.)	10 mg bid	41	75.6 (8.22)	2.6 (5.59)	0.0044	0.0386	0.4800	0.2679	0.3940
	Placebo	39	75.7 (8.91)	-0.6 (6.87)	0.6190				
Standing	2.5 mg bid	35	153.3 (17.56)	-14.9 (10.89)	0.0001	<.0001			
Systolic	5 mg bid	34	156.2 (13.24)	-18.8 (15.15)	0.0001	<.0001	0.2498		
B.P.	7.5 mg bid	38	154.7 (14.42)	-22.9 (16.00)	0.0001	<.0001	0.0158	0.2140	
(mmHg)	10 mg bid	41	148.5 (12.48)	-18.2 (13.36)	0.0001	<.0001	0.3031	0.8620	0.1394
	Placebo	39	146.5 (14.83)	-1.2 (11.98)	0.5366				
Standing	2.5 mg bid	35	103.6 (6.97)	-10.7 (5.11)	0.0001	<.0001			
Diastolic	5 mg bid	34	105.9 (7.89)	-16.3 (6.86)	0.0001	<.0001	0.0002		
B.P.	7.5 mg bid	38	104.4 (6.08)	-17.0 (9.96)	0.0001	<.0001	0.0003	0.6743	
(mmHg)	10 mg bid	41	104.8 (5.78)	-16.9 (7.13)	0.0001	<.0001	0.0003	0.7124	0.9496
	Placebo	39	102.4 (8.79)	-2.8 (6.60)	0.0126				
Standing	2.5 mg bid	35	86.6 (9.55)	1.3 (7.74)	0.3168	0.2094			
Pulse	5 mg bid	34	83.8 (9.87)	4.7 (8.25)	0.0021	0.0026	0.0814		
(beats	7.5 mg bid	38	83.3 (6.42)	3.8 (7.73)	0.0055	0.0103	0.2020	0.6140	
/min.)	10 mg bid	41	82.7 (9.74)	4.8 (8.30)	0.0007	0.0015	0.0655	0.9844	0.5835
	Placebo	39	82.9 (9.25)	-1.1 (8.07)	0.4323				

TABLE 4B

STUDY 301

CHANGE FROM BASELINE (PEAK) - ENDPOINT

Variable	Treatment Group	N	Baseline Mean (S.D.)	Change Mean (S.D.)	P-Value versus Baseline	P-Value versus Placebo	P-Value versus 2.5 mg	P-Value versus 5 mg	P-Value versus 7.5mg
Supine Systolic B.P. (mmHg)	2.5 mg bid	40	158.2 (17.04)	-17.0 (14.30)	0.0001	0.0001			
	5 mg bid	39	159.0 (14.28)	-20.3 (15.75)	0.0001	<.0001	0.3249		
	7.5 mg bid	41	157.6 (20.40)	-23.2 (18.12)	0.0001	<.0001	0.0616	0.3827	
	10 mg bid	41	154.0 (13.52)	-19.1 (14.10)	0.0001	<.0001	0.5307	0.7126	0.2093
	Placebo	41	151.5 (14.40)	-3.3 (11.76)	0.0773				
Supine Diastolic B.P. (mmHg)	2.5 mg bid	40	104.2 (4.42)	-13.8 (8.28)	0.0001	0.0001			
	5 mg bid	39	104.8 (4.14)	-15.8 (8.92)	0.0001	<.0001	0.2049		
	7.5 mg bid	41	103.5 (3.81)	-17.2 (7.95)	0.0001	<.0001	0.0405	0.4691	
	10 mg bid	41	103.5 (3.95)	-17.1 (8.07)	0.0001	<.0001	0.0493	0.4934	0.9683
	Placebo	41	103.9 (4.36)	-6.1 (8.4)	0.0274				
Supine Pulse (beats/min.)	2.5 mg bid	40	78.7 (10.5)	1.0 (7.4)	0.3993	0.1694			
	5 mg bid	39	75.7 (9.0)	3.7 (9.3)	0.0168	0.0043	0.1328		
	7.5 mg bid	41	74.5 (9.0)	3.8 (8.7)	0.0086	0.0037	0.1227	0.9753	
	10 mg bid	41	75.6 (8.2)	2.2 (6.9)	0.0536	0.0437	0.5238	0.3777	0.3581
	Placebo	41	75.7 (9.3)	-1.5 (7.9)	0.2361				
Standing Systolic B.P. (mmHg)	2.5 mg bid	40	154.6 (17.4)	-16.3 (14.7)	0.0001	0.0001			
	5 mg bid	39	155.1 (12.7)	-17.0 (13.0)	0.0001	<.0001	0.8476		
	7.5 mg bid	41	154.8 (13.9)	-23.3 (19.2)	0.0001	<.0001	0.0624	0.0965	
	10 mg bid	41	148.5 (12.5)	-16.7 (16.4)	0.0001	<.0001	0.9127	0.9327	0.0772
	Placebo	41	146.9 (17.1)	-1.2 (15.4)	0.6190				
Standing Diastolic B.P. (mmHg)	2.5 mg bid	40	104.0 (6.8)	-11.0 (7.5)	0.0001	<.0001			
	5 mg bid	39	105.7 (7.7)	-15.2 (10.0)	0.0001	<.0001	0.0471		
	7.5 mg bid	41	105.0 (6.3)	-17.2 (10.4)	0.0001	<.0001	0.0037	0.3583	
	10 mg bid	41	104.8 (5.8)	-16.4 (9.1)	0.0001	<.0001	0.0102	0.5708	0.7187
	Placebo	41	102.0 (9.1)	-2.1 (9.5)	0.1640				
Standing Pulse (beats/min.)	2.5 mg bid	40	86.6 (10.5)	1.1 (9.2)	0.4417	0.1454			
	5 mg bid	39	84.1 (10.0)	4.9 (9.7)	0.0032	0.0014	0.0757		
	7.5 mg bid	41	82.8 (6.6)	4.2 (9.1)	0.0062	0.0038	0.1465	0.7365	
	10 mg bid	41	82.7 (9.7)	4.1 (10.1)	0.0122	0.0038	0.1495	0.7203	.9843
	Placebo	41	83.1 (9.34)	-1.9 (8.7)	0.1658				

TABLE 5

STUDY 302 - CHANGE FROM BASELINE (PEAK)

WEEK 4

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs placebo
Supine Systolic B.P. (mmHg)	Dynacirc	38	155.67 (14.14)	19.21 (12.79)	0.0001	0.0001
	Placebo	39	161.44 (14.23)	-3.60 (12.87)	0.0853	
Supine Diastolic B.P. (mmHg)	Dynacirc	38	103.56 (3.58)	-13.82 (6.97)	0.0001	0.0001
	Placebo	39	104.09 (3.60)	-4.71 (7.01)	0.0001	
Supine Pulse Rate (beats/min.)	Dynacirc	38	74.85 (11.36)	1.00 (9.44)	0.5159	0.3917
	Placebo	39	76.08 (11.43)	-0.86 (9.50)	0.5735	
Standing Systolic B.P. (mmHg)	Dynacirc	38	150.77 (15.33)	-17.13 (14.11)	0.0001	0.0001
	Placebo	39	157.77 (15.42)	-4.05 (14.20)	0.0792	
Standing Diastolic B.P. (mmHg)	Dynacirc	38	103.96 (7.69)	-12.92 (8.41)	0.0001	0.0001
	Placebo	39	103.73 (7.74)	-3.28 (8.46)	0.0181	
Standing Pulse Rate (beats/min.)	Dynacirc	38	80.63 (12.38)	2.72 (9.38)	0.0783	0.0781
	Placebo	39	83.36 (12.46)	-1.12 (9.44)	0.4623	

ENDPOINT

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs placebo
Supine Systolic B.P. (mmHg)	Dynacirc	49	154.76 (15.10)	-17.11 (12.67)	0.0001	0.0001
	Placebo	49	159.10 (15.15)	-4.00 (12.70)	0.0299	
Supine Diastolic B.P. (mmHg)	Dynacirc	49	103.47 (4.69)	-12.86 (7.54)	0.0001	0.0001
	Placebo	49	103.21 (4.71)	-5.13 (7.56)	0.0001	
Supine Pulse Rate (beats/min.)	Dynacirc	49	75.68 (11.65)	2.12 (9.43)	0.1184	0.1841
	Placebo	49	75.42 (11.68)	-0.43 (9.46)	0.7510	
Standing Systolic B.P. (mmHg)	Dynacirc	49	150.54 (17.54)	-16.67 (14.29)	0.0001	0.0001
	Placebo	49	156.02 (17.08)	-3.68 (14.33)	0.0756	
Standing Diastolic B.P. (mmHg)	Dynacirc	49	103.85 (8.42)	-12.52 (8.87)	0.0001	0.0001
	Placebo	49	102.29 (8.44)	-2.11 (8.90)	0.1007	
Standing Pulse Rate (beats/min.)	Dynacirc	49	81.81 (13.03)	3.73 (9.74)	0.0087	0.0308
	Placebo	49	82.93 (13.07)	-0.59 (9.77)	0.6729	

TABLE 6

STUDY 303 - CHANGE FROM BASELINE (PEAK)

PLATEAU PERIOD

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs HCTZ
Sitting Systolic B.P. (mmHg)	Dynacirc	40	148.03 (17.19)	-18.71 (17.02)	0.0001	0.9114
	HCTZ	44	149.43 (12.82)	-19.08 (13.01)	0.0001	
Sitting Diastolic B.P. (mmHg)	Dynacirc	40	100.43 (4.34)	-17.70 (8.75)	0.0001	0.0057
	HCTZ	44	99.99 (4.21)	-12.85 (6.85)	0.0001	
Sitting Pulse Rate (beats/min.)	Dynacirc	40	75.58 (10.67)	4.18 (10.46)	0.0158	0.0257
	HCTZ	44	72.38 (9.04)	-0.50 (8.36)	0.6935	

ENDPOINT

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs HCTZ
Sitting Systolic B.P. (mmHg)	Dynacirc	48	148.17 (15.87)	-16.60 (18.11)	0.0001	0.5361
	HCTZ	50	148.29 (13.42)	-18.56 (12.70)	0.0001	
Sitting Diastolic B.P. (mmHg)	Dynacirc	48	100.21 (4.24)	-16.71 (10.34)	0.0001	0.0198
	HCTZ	50	100.16 (4.67)	-12.56 (6.68)	0.0001	
Sitting Pulse Rate (beats/min.)	Dynacirc	48	75.50 (10.28)	4.50 (10.17)	0.0036	0.0105
	HCTZ	50	72.73 (8.63)	-0.34 (8.11)	0.7681	

TABLE 7

STUL Y 304

CHANGE FROM BASELINE (PEAK)

PLATEAU AVERAGE

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs Propranolol
Sitting Systolic B.P. (mmHg)	Dynacirc	37	147.93 (17.17)	-17.28 (15.25)	0.0001	0.0717
	Propranolol	31	150.55 (18.15)	-11.19 (11.45)	0.0001	
Sitting Diastolic B.P. (mmHg)	Dynacirc	37	101.95 (5.35)	-15.44 (7.42)	0.0001	0.0060
	Propranolol	31	101.39 (5.43)	-9.96 (8.51)	0.0001	
Sitting Pulse Rate (beats/min.)	Dynacirc	37	78.58 (10.79)	4.14 (8.92)	0.0078	<0.0001
	Propranolol	31	75.23 (8.77)	-10.99 (7.10)	0.0001	

ENDPOINT

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs Propranolol
Sitting Systolic B.P. (mmHg)	Dynacirc	46	149.74 (17.71)	-18.59 (15.96)	0.0001	0.0383
	Propranolol	43	153.72 (19.02)	-11.65 (15.09)	0.0001	
Sitting Diastolic B.P. (mmHg)	Dynacirc	46	101.57 (5.10)	-15.55 (6.16)	0.0001	0.0012
	Propranolol	43	102.57 (5.82)	-9.24 (9.53)	0.0001	
Sitting Pulse Rate (beats/min.)	Dynacirc	46	76.61 (11.47)	5.34 (12.15)	0.0047	<0.0001
	Propranolol	43	74.71 (8.00)	-11.62 (7.71)	0.0001	

TABLE 8
STUDY 305 - CHANGE FROM BASELINE (PEAK)

PLATEAU AVERAGE

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs Prazosin
Sitting Systolic B.P. (mmHg)	Dynacirc	30	149.50 (15.36)	-16.68 (13.65)	0.0001	0.0078
	Prazosin	33	153.56 (13.05)	-8.13 (10.95)	0.0002	
Sitting Diastolic B.P. (mmHg)	Dynacirc	30	100.85 (5.10)	-15.60 (6.62)	0.0001	0.0654
	Prazosin	33	102.39 (5.51)	-12.64 (5.89)	0.0001	
Sitting Pulse Rate (beats/min.)	Dynacirc	30	76.67 (11.28)	1.68 (9.61)	0.3464	0.9278
	Prazosin	33	82.56 (12.90)	1.48 (7.27)	0.2496	
Standing Systolic B.P. (mmHg)	Dynacirc	30	150.05 (17.07)	-17.08 (14.19)	0.0001	0.0059
	Prazosin	33	152.46 (15.09)	-6.41 (15.39)	0.0227	
Standing Diastolic B.P. (mmHg)	Dynacirc	30	102.97 (6.00)	-16.12 (8.81)	0.0001	0.0142
	Prazosin	33	101.33 (6.51)	-10.85 (7.75)	0.0001	
Standing Pulse Rate (beats/min.)	Dynacirc	30	81.68 (14.26)	2.61 (9.76)	0.1538	0.1628
	Prazosin	33	84.94 (13.38)	5.66 (7.27)	0.0001	

ENDPOINT

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs Prazosin
Sitting Systolic B.P. (mmHg)	Dynacirc	41	151.76 (15.09)	-14.94 (16.84)	0.0001	0.0399
	Prazosin	42	153.49 (13.67)	-8.16 (12.49)	0.0001	
Sitting Diastolic B.P. (mmHg)	Dynacirc	41	102.11 (5.86)	-14.95 (10.10)	0.0001	0.0699
	Prazosin	42	102.21 (5.23)	-11.23 (8.32)	0.0001	
Sitting Pulse Rate (beats/min.)	Dynacirc	41	76.83 (11.38)	2.20 (12.26)	0.2584	0.7577
	Prazosin	42	82.13 (12.22)	3.00 (11.42)	0.0962	
Standing Systolic B.P. (mmHg)	Dynacirc	41	153.06 (16.49)	-18.82 (14.53)	0.0001	0.0023
	Prazosin	42	151.26 (14.53)	-6.92 (19.52)	0.0268	
Standing Diastolic B.P. (mmHg)	Dynacirc	41	105.90 (5.97)	-15.81 (10.96)	0.0001	0.0096
	Prazosin	42	101.74 (6.22)	-9.85 (9.46)	0.0001	
Standing Pulse Rate (beats/min.)	Dynacirc	41	81.94 (13.12)	3.16 (11.39)	0.0834	0.2604
	Prazosin	42	85.07 (12.63)	6.00 (11.45)	0.0015	

TABLE 9

STUDY 307 - CHANGE FROM BASELINE

PLATEAU AVERAGE

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs Propranolol
Supine Systolic B.P. (mmHg)	Dynacirc	33	151.71 (19.50)	-19.40 (14.59)	0.0001	0.6995
	Propranolol	29	153.81 (16.29)	-18.05 (12.45)	0.0001	
Supine Diastolic B.P. (mmHg)	Dynacirc	33	104.53 (7.62)	-15.08 (4.90)	0.0001	0.769
	Propranolol	29	105.12 (7.23)	-15.50 (6.21)	0.0001	
Supine Pulse Rate (beats/min.)	Dynacirc	33	78.12 (13.15)	2.95 (8.30)	0.0496	<.0001
	Propranolol	29	77.74 (10.67)	-13.59 (10.56)	0.0001	
Standing Systolic B.P. (mmHg)	Dynacirc	33	146.49 (20.31)	-20.49 (17.13)	0.0001	0.4764
	Propranolol	29	145.71 (15.98)	-17.85 (10.65)	0.0001	
Standing Diastolic B.P. (mmHg)	Dynacirc	33	104.34 (9.70)	-14.57 (7.94)	0.0001	0.6037
	Propranolol	29	103.55 (8.63)	-13.63 (5.91)	0.0001	
Standing Pulse Rate (beats/min.)	Dynacirc	33	88.92 (13.36)	3.08 (10.02)	0.0875	<.0001
	Propranolol	29	88.81 (11.83)	-20.14 (9.34)	0.0001	

ENDPOINT

Variable	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs Propranolol
Supine Systolic B.P. (mmHg)	Dynacirc	40	152.26 (21.84)	-19.28 (16.41)	0.0001	0.3857
	Propranolol	38	155.83 (18.08)	-15.72 (19.48)	0.0001	
Supine Diastolic B.P. (mmHg)	Dynacirc	40	104.84 (7.66)	-15.38 (7.18)	0.0001	0.5288
	Propranolol	38	105.83 (7.58)	-14.04 (11.14)	0.0001	
Supine Pulse Rate (beats/min.)	Dynacirc	40	79.00 (13.43)	1.64 (10.12)	0.3126	<.0001
	Propranolol	38	77.54 (10.70)	-12.08 (12.13)	0.0001	
Standing Systolic B.P. (mmHg)	Dynacirc	40	145.98 (20.96)	-20.88 (18.34)	0.0001	0.2013
	Propranolol	38	148.00 (18.30)	-15.71 (16.57)	0.0001	
Standing Diastolic B.P. (mmHg)	Dynacirc	40	105.00 (10.13)	-13.63 (9.88)	0.0001	0.6297
	Propranolol	38	104.61 (9.37)	-12.45 (11.58)	0.0001	
Standing Pulse Rate (beats/min.)	Dynacirc	40	90.11 (14.07)	3.09 (11.11)	0.0866	<.0001
	Propranolol	38	88.54 (12.23)	-18.47 (11.13)	0.0001	

TABLE 10A

SUMMARY OF STUDIES 301-305 and 307

Study Number	Treatment Group	N	Baseline Mean (S.D.)	Mean Change (S.D.)	P-value vs baseline	P-value vs control
Supine Diastolic Blood Pressure - Endpoint						
301	Dynacirc/2.5 mg bid	40	104.2 (4.4)	-13.8 (8.3)	0.0001	0.0001
	Dynacirc/5 mg bid	39	104.8 (4.1)	-15.8 (8.9)	0.0001	<0.0001
	Dynacirc/7.5 mg bid	41	103.5 (3.8)	-17.2 (8.0)	0.0001	<0.0001
	Dynacirc/10 mg bid	41	103.5 (4.0)	-17.1 (8.1)	0.0001	<0.0001
	Placebo	41	103.9 (4.4)	-6.1 (8.4)	0.0274	
302	Dynacirc	49	102.5 (4.7)	-12.9 (7.5)	0.0001	0.0001
	Placebo	49	103.2 (4.7)	-5.1 (7.6)	0.0001	
307	Dynacirc/HCTZ	40	104.8 (7.7)	-15.4 (7.2)	0.0001	0.5288
	Propranolol/HCTZ	38	105.8 (7.6)	-14.1 (11.2)	0.0001	
Sitting Diastolic Blood Pressure - Endpoint						
303	Dynacirc	48	100.2 (4.2)	-16.7 (10.3)	0.0001	0.0198
	HCTZ	50	100.2 (4.7)	-12.6 (6.7)	0.0001	
304	Dynacirc	46	101.6 (5.1)	-15.6 (8.2)	0.0001	0.0012
	Propranolol	43	102.6 (5.8)	-9.2 (9.5)	0.0001	
305	Dynacirc	41	102.1 (5.9)	-15.0 (10.1)	0.0001	0.0699
	Prazosin	42	102.2 (5.2)	-11.2 (8.3)	0.0001	
Standing Diastolic Blood Pressure - Endpoint						
301	Dynacirc/2.5 mg bid	40	104.0 (6.8)	-11.0 (7.5)	0.0001	<0.0001
	Dynacirc/5 mg bid	39	105.7 (7.7)	-15.2 (10.0)	0.0001	<0.0001
	Dynacirc/7.5 mg bid	41	105.0 (6.3)	-17.2 (10.4)	0.0001	<0.0001
	Dynacirc/10 mg bid	41	104.8 (5.8)	-16.4 (9.1)	0.0001	<0.0001
	Placebo	41	102.0 (9.1)	-2.1 (9.5)	0.1640	
302	Dynacirc	49	103.9 (8.4)	-12.5 (8.9)	0.0001	0.0001
	Placebo	49	102.3 (8.4)	-2.1 (8.9)	0.1007	
305	Dynacirc	41	103.9 (6.0)	-15.8 (11.0)	0.0001	0.0096
	Prazosin	42	101.7 (6.2)	-9.9 (9.5)	0.0001	
307	Dynacirc/HCTZ	40	105.0 (10.1)	-13.6 (9.9)	0.0001	0.6297
	Propranolol/HCTZ	38	104.6 (9.4)	-12.5 (11.6)	0.0001	

TABLE 10B

SUMMARY OF STUDIES 301-305 and 307

CATEGORICAL ANALYSIS AND ADVERSE REACTIONS

Endpoint of Study - Valid Patients
Results by Drug Treatment

Treatment	Diastolic Blood Pressure		Adverse Reactions (%)
	≥ 10 mmHg Decrease (%)	Normalized to ≤ 90 mmHg (%)	
Monotherapy			
Dynacirc	232/288 80.6%	208/288 72.2%	186/345 53.9%
Placebo	25/78 32.1%	10/78 12.8%	40/90 44.4%
HCTZ	23/37 62.2%	28/37 75.7%	38/50 76.0%
Propranolol	12/31 38.7%	13/31 41.9%	28/43 65.1%
Prazosin	24/33 72.7%	20/33 60.6%	31/42 73.8%
Combination Therapy			
Dynacirc/HCTZ	27/33 81.8%	20/33 60.6%	29/40 72.5%
Propranolol/HCTZ	21/29 72.4%	18/29 62.1%	17/38 44.7%

TABLE 10C

ADVERSE REACTIONS (by Percent)

SUMMARY OF STUDIES 7, 11, 301-305, AND 307

Adverse Reaction	Dynacirc (n=410)	Placebo (n=113)	Active Controls (n=173)
Headache	18	11	14
Edema	12	5	5
Flushing	5	0	2
Palpitation	5	<1	3
Chest Pain	4	3	3
Tachycardia	3	<1	1
Dizziness	8	6	10
Fatigue	6	2	12
Abdominal Discomfort	5	2	10
Nausea	3	3	8
Musculo-Skeletal Complaints	10	6	14
Respiratory Complaints	8	8	7
Skin Reactions	5	2	4

TABLE 10D

SUMMARY OF STUDIES 301-305

CHANGE FROM BASELINE - ENDPOINT

Variable	Treatment Group	Number of Studies	Number of Study Groups	Number of Patients	Mean Change	Range for Means of Various Studies
Supine Systolic B.P. (mmHg)	Dynacirc	301,302	5	210	-19.24	(-23.21 to -16.96)
Supine Diastolic B.P. (mmHg)	Dynacirc	301,302	5	210	-15.26	(-17.16 to -12.86)
Sitting Systolic B.P. (mmHg)	Dynacirc	303,304,305	3	135	-16.77	(-18.59 to -14.94)
Sitting Diastolic B.P. (mmHg)	Dynacirc	303,304,305	3	135	-15.78	(-16.71 to -14.95)
Standing Systolic B.P. (mmHg)	Dynacirc	301,302,305	6	251	-18.09	(-23.28 to -16.26)
Standing Diastolic B.P. (mmHg)	Dynacirc	301,302,305	6	251	-14.63	(-17.15 to -11.03)