AVALIDE®

COMBINATION OF:

IRBESARTAN, (BMS-186295) PLUS HYDROCHLOROTHIAZIDE

NDA 20-758 Supplement 037

BRIEFING DOCUMENT

FOR MEETING WITH FDA ADVISORY COMMITTEE

Applicant:

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1 INTRODUCTION

This background document is provided to the FDA's Cardio-Renal Advisory Committee for the April 18, 2007 Committee meeting. At the meeting the Committee will review new clinical trial data on Avalide to provide guidance for the labeling for Avalide, which is currently approved for the treatment of hypertension, after titration with either irbesartan or hydrochlorothiazide (HCTZ) alone has not resulted in desired blood pressure control.

Avalide, a fixed-dose combination of irbesartan and HCTZ, was approved in 1997 and has labeling consistent with the policies and data available at that time. Post-marketing data now include over 10,000,000 patient-years of exposure to Avalide worldwide. Data from 2 new clinical trials (Study 176 in severe hypertension and Study 185 in moderate hypertension), in addition to the post-marketing experience suggest that the current labeling should be revised.

The proposed labeling no longer requires titration of irbesartan or HCTZ before using Avalide to treat patients with severe hypertension. Thus, Avalide would be a first-line agent in these patients. It also notes that the benefits and risks of initial treatment with Avalide need to be considered for each patient. Information from clinical trials is provided to help physicians make that assessment.

1.1 Clinical and Regulatory Issues

Severe hypertension (SBP ≥180 mmHg and/or DBP ≥110 mmHg) is a serious condition with life-threatening sequelae including the risk of hypertensive emergencies and cardiovascular events. Successful short-term treatment of severe hypertension requires prompt and substantial reduction of blood pressure without causing syncope and orthostatic hypotension. To treat severe hypertension confidently and safely, physicians must choose between the following 2 strategies.

- Start with a single medication, titrate when necessary, and later consider adding another medication if needed; or
- Start with 2 medications at once to get patients quickly on a multi-drug regimen that they will most likely need.

The best approach for a given patient is not always clear. Increasing doses of a monotherapy based on blood pressure response might successfully treat some patients

with as few medications as possible. But this stepwise approach may easily result in important and avoidable delays in achieving prompt control of blood pressure, which is a particular concern for patients with severe hypertension. Delay in achieving blood pressure control means greater exposure of the patient to the serious risks of uncontrolled severe hypertension.

The second treatment option, starting immediately with combination therapy, will almost certainly provide earlier and more complete reduction of blood pressure. But this approach exposes patients initially to a second medication with the attendant risk of agent-specific, non-dose-related adverse effects if their blood pressure could be controlled on monotherapy. The optimal approach must individualize care to yield a favorable benefit/risk profile for each patient.

Current guidelines recognize the need for initial combination therapy for severe hypertension. The Joint National Committee Guideline (JNC 7) suggests that physicians consider initiating therapy with more than one medication whenever blood pressure is elevated at least 20 mmHg systolic or 10 mmHg diastolic above target.[1] These guidelines recognize that severe hypertension requires prompt and effective treatment. They also recognize that most patients with even moderate hypertension require at least 2 drugs to achieve their blood pressure goals. This has been shown in recent, large clinical trials including ALLHAT, VALUE, ASCOT, and CONVINCE.

JNC 7 guidelines also emphasize the importance of individualizing care. They describe risk factors, clinical signs, and symptoms that may suggest a need for a more aggressive treatment. They describe special considerations for treating Blacks, and they include lower blood pressure goals for those with diabetes or renal disease. The choice of initial therapy should be made in this context.

The main regulatory issue hinges on the degree to which the current labeling of Avalide still applies today to patients with severe hypertension. This supplemental NDA requests that the labeling be changed to specifically allow initial use in these patients. The proposed additional indication is:

Avalide is indicated for initial treatment of severe hypertension.

The basis of this request lies in the safety and tolerability profile of irbesartan and low-dose HCTZ and the need for prompt and substantial blood pressure reduction in patients with severe hypertension.

Data to establish the favorable tolerability of Avalide come from several sources, including the 7-week trial (Study 176) in severe hypertension and the 12-week trial (Study 185) in moderate hypertension; and the clinical trials included in the original NDA. Published meta-analyses of a large number of clinical studies establish the safety and tolerability of HCTZ. The data collected during 10 years of post-marketing surveillance provide a reassuring long-term safety profile.

Data to establish the short-term efficacy of Avalide in severe hypertension come from Study 176, and are supported by other clinical efficacy studies in severe hypertension included in the original NDA. The prompt blood pressure reductions observed in these studies are expected to reduce the risks of severe hypertension. More substantial benefits are expected to derive from the observation that differences in blood pressure obtained with a more effective initial therapy have persisted for months or years in several clinical studies. [2,3,4,5,6]

The central clinical issue for the prescribing physician concerns the importance of making a balanced and appropriate benefit/risk assessment for each patient when considering initial use of Avalide. The physician will need to carefully consider risk factors for individual patients, including baseline blood pressure, race, co-morbidities, and the risks of excessive BP lowering such as syncope and dizziness when considering whether to initiate therapy with Avalide.

1.2 Regulatory Background

Labeling of fixed-dose combination products for hypertension usually restricts the use of the combination until after titration with one of its components has failed to achieve desired blood pressure control. This approach intends to avoid dose-independent and dose-dependent adverse events that might be associated with the second drug, until the need for the second drug has been demonstrated clinically. When approved in 1997, Avalide labeling reflected this approach. The current label still requires failure of the titration of irbesartan or HCTZ before using Avalide.

The recent clinical program set out to provide data that would support a change to this labeling. The program consisted of Study 176 in severe hypertension and a supportive study, Study 185, in moderate hypertension. Study 176 was intended to show that Avalide was well tolerated and effective in patients that are "very unlikely" to reach blood pressure goals with irbesartan alone. The expectation was that <10% of patients would achieve a diastolic blood pressure < 90 mmHg on irbesartan monotherapy. This followed a regulatory precedent established by the approval of losartan/HCTZ for initial therapy in patients with severely elevated blood pressure.

The results of Study 176 showed that Avalide was significantly more effective than irbesartan monotherapy as initial treatment for severely hypertensive (mean baseline DBP ≥ 110 mmHg) patients and that irbesartan monotherapy was effective in some patients (47.2% with Avalide vs 33.2% with irbesartan achieved the primary endpoint, DBP<90 mmHg at Week 5; P=0.0005). The study did not identify a population of patients very unlikely to reach diastolic blood pressure <90 mmHg with irbesartan alone, because 33.2% of patients treated with irbesartan monotherapy reached that level. Yet the efficacy results with Avalide were clinically meaningful: Avalide treatment resulted in blood pressure reductions of 10/5 mmHg greater than with irbesartan alone. Avalide also showed a tolerability profile similar to that of irbesartan monotherapy, with no increase in adverse events. Importantly, these data demonstrate that there is no increase in possible short-term risks of initial combination therapy compared to initial irbesartan monotherapy.

Although the results of Study 176 did not enable approval according to one established pathway for initial use of a combination product, the new data on Avalide suggest that another path to approval can be charted. Historically, labeling for combination products restricts initial use mainly to avoid dose-independent and dose-dependent adverse effects that might be associated with the second component. But initial use of an effective combination product may also be appropriate if the incidence of dose-independent side effects associated with the components is low, in particular if some dose-dependent side effects of one component are lessened in the presence of the other component. The combination product must be shown to be more effective than monotherapy with the constituent drugs in the intended population. Because the second component will have some risk of side effects, even if very low, its appropriate use should be targeted to the patients who will benefit most from initial combination therapy.

Avalide's profile matches the criteria for this proposed path to approval. The current labeling states that the "overall incidence of adverse events reported with the combination is comparable to placebo," and irbesartan labeling notes that the "side effects are generally mild and transient with no relationship to dose of irbesartan. " With HCTZ, published reports suggest that the dose-independent adverse events are very rare and that there are few dose-dependent side effects at the low doses present in Avalide (12.5-25mg). Moreover, hypokalemia, the primary dose-dependent adverse effect of HCTZ, is reduced in the presence of irbesartan.

The new clinical trial data in severe (Study 176) and moderate (Study 185) hypertension are consistent with this established, favorable tolerability profile. More importantly, they provide reassuring information on other dose-dependent adverse effects, hypotension (<1%) and syncope (none observed on Avalide). And they show that the initial use of Avalide results in greater and earlier blood pressure reductions than on irbesartan monotherapy, particularly in those patients with the greatest need for combination therapy.

Following review of the data from Study 176, the FDA issued an Approvable letter on 13 October, 2006, indicating that although the submission did not meet a previously established criterion for approval, they were reconsidering the evidence needed to approve combination products for initial use, partly because of the data in the Avalide program.

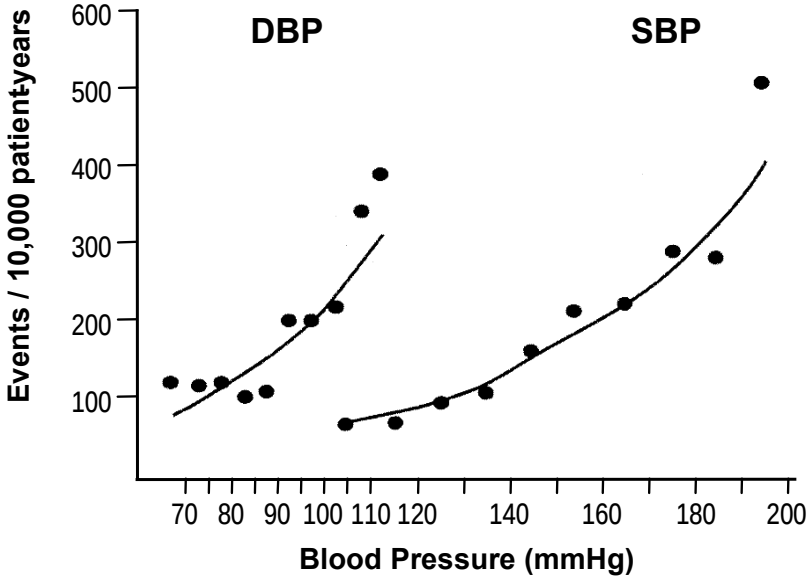
This background document provides clinical evidence of Avalide's efficacy and tolerability from the Avalide program along with evidence from post-marketing safety surveillance for irbesartan and Avalide, supporting the rationale for approval of Avalide for initial treatment of severe hypertension. That rationale relies on the safety and tolerability profile of the combination of irbesartan and low-dose HCTZ and the ability of the combination to deliver reductions in blood pressure that are greater and earlier than those achieved on monotherapy in patients at greatest risk.

2 UNMET MEDICAL NEED

Severe hypertension (≥180 systolic or ≥ 110 diastolic) represents an important unmet medical need. According to the National Health and Nutrition Examination Survey III (NHANES III), approximately 4% of the US adult hypertensive population has severe hypertension.[7] This represents more than 2 million people. Severe hypertension still leads

to hypertensive emergencies which include events such as progressive retinopathy, nephropathy, encephalopathy, hospitalization for severe hypertension, and heart failure; and cardiovascular events like myocardial infarction, stroke, and cardiovascular death. The Framingham Study[8] established the close relationship between higher blood pressure and greater risk of these events (Figure 2).

Figure 2: Framingham Study: Incidence of CV Events during 18 Years of Follow-up



Severe hypertension is not always managed successfully. Part of the problem in treating severe hypertension in actual clinical practice relates to the realities of the healthcare process. Physicians often do not see patients frequently enough to increase dose or add other medications fast enough to establish rapid control of blood pressure. Once initial therapy is established, additional meaningful reductions in blood pressure often take 2 years or more to achieve, whether in actual practice or in controlled clinical trials (Syst-Eur, SCOPE, ASCOT, ALLHAT, VALUE).[2,3,4,5,6]

There is extensive literature on the treatment of severe hypertension, but much of it is based on very small clinical studies or anecdotal experiences. A substantial portion of the literature covers medications like short-acting nifedipine and clonidine whose use has diminished because of safety concerns.

There remains a need for a well-tolerated drug whose efficacy and safety in severe hypertension are established. This drug should be able to treat severe hypertension in a simple manner, with few titration steps. The drug should reduce blood pressure within days to weeks in an outpatient setting. The appropriate use should be guided by data from controlled clinical studies that physicians need in order to individualize care.

3 CLINICAL PROGRAM SUPPORTING INITIAL TREATMENT OF SEVERE HYPERTENSION WITH AVALIDE

The development program for Avalide as initial treatment for severe hypertension included pivotal Study CV131176 (Study 176) in patients with severe hypertension and supportive Study CV131185 (Study 185) in moderately hypertensive patients. Study 185 provides supportive data regarding safety and the relative efficacy of irbesartan and hydrochlorothiazide as monotherapies. These 2 studies in more than 1200 patients, 796 of whom received Avalide, provide a robust data base to evaluate Avalide as initial treatment for severe hypertension.

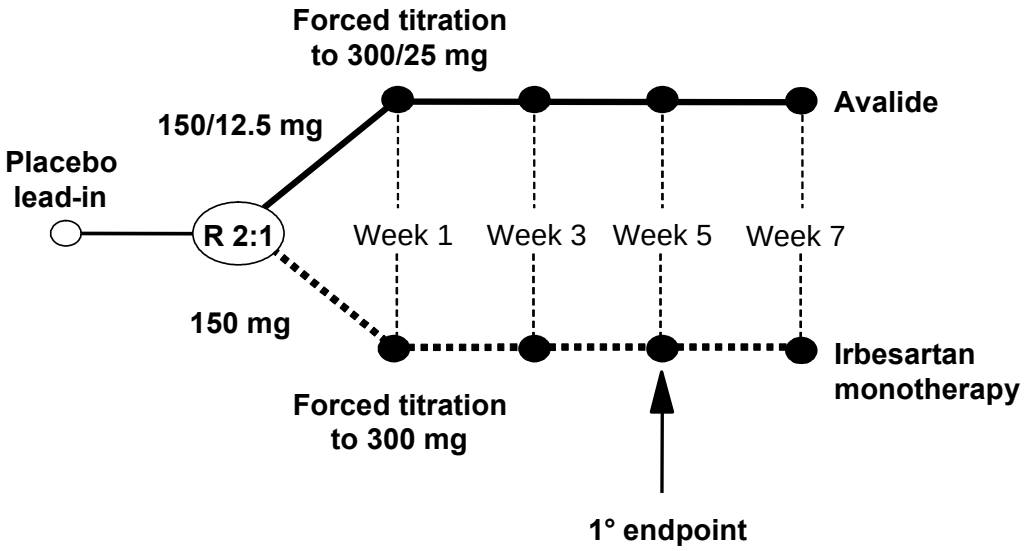
3.1 Pivotal Trial 176

3.1.1 Design of Study 176

Study 176 was designed to show safety and efficacy of Avalide as initial treatment of severe hypertension. The trial compared Avalide to irbesartan monotherapy and incorporated, after 1 week of therapy, a forced-titration step to ensure that the safety of Avalide would be evaluated at maximum dose.

Study 176 was a multicenter, randomized, double-blind, active-controlled, 7-week, parallel-arm study in patients with severe hypertension. After 1 week of placebo lead-in, patients with DBP ≥ 110 mmHg were randomized in a 2:1 ratio to receive either Avalide or irbesartan monotherapy for 7 weeks. The starting doses for Avalide and irbesartan monotherapy were 150 mg/12.5 mg and 150 mg, respectively. After 1 week at the starting dose, study medication was force-titrated upward to 300 mg/25 mg Avalide, and 300 mg irbesartan monotherapy. The design of Study 176 is presented in Figure 3.1.1 below.

Figure 3.1.1: Design of Study 176



Because of ethical considerations, Study 176 did not have a placebo control. Placebo-controlled studies in severe hypertension have shown that patients with severe hypertension are at high risk for hypertensive emergencies and that risks are almost immediately eliminated with prompt blood pressure lowering.[9,10,11] Thus, only an active control was allowed in Study 176.

Study 176 also required that severe hypertension be documented at 2 consecutive visits before patients were randomized and that each visit included an average of several measures. These steps were taken to avoid regression to the mean.

The primary objective was to compare the proportion of patients with severe hypertension who achieved a DBP ≤ 90 mmHg at Week 5. Other objectives included comparing combination therapy and monotherapy in terms of other time points and other blood pressure parameters. Blood pressure control to the guideline-recommended target of < 140/90 mmHg was examined at Weeks 1, 3, 5, and 7, as were changes from baseline in SBP and DBP at Weeks 1, 3, 5, and 7.

Study 176 also evaluated the safety of the Avalide regimen, in particular the frequency of treatment discontinuations due to prespecified adverse events, and the frequencies of

those events (hypotension, dizziness, syncope; headache, hypokalemia, and hyperkalemia).

Six hundred ninety-seven (697) patients from North America and Europe were randomized and 695 received double-blind treatment in Study 176: there were 468 on Avalide and 227 on irbesartan monotherapy. The mean age of patients was approximately 52 years (13% ≥65 years); 58% were male, 84% white, 14% black, and 12% diabetic. Mean weight was approximately 90 kg; 50% of patients had a BMI ≥ 30 kg/m^2. Mean baseline blood pressure was approximately 171/113 mmHg. Mean duration of exposure to study medication was about 47 days for each treatment group. Approximately 92% of patients in each treatment group were exposed to treatment for at least 31 days during the study.

3.1.2 Results in Study 176

Avalide was significantly more effective in reducing severe blood pressure in every parameter evaluated and at every time point when compared to irbesartan monotherapy. Moreover, Avalide was as well tolerated as irbesartan monotherapy even when force-titrated after 1 week in severely hypertensive patients.

Efficacy Results in Study 176

1) A greater proportion of patients on Avalide (47.2%) achieved a DBP < 90mmHg than those on irbesartan monotherapy (33.2%) did at the primary endpoint (Week 5; P=0.0005).
2) Avalide controlled blood pressure of a greater proportion of patients (34.6%) to a target of <140/90 mmHg than irbesartan monotherapy did (19.2%) at Week 5 (P<0.0001).
3) Avalide reduced both mean baseline systolic and diastolic blood pressures further than irbesartan monotherapy did at Week 5: SBP, 31 vs 21 mmHg; DBP, 24 vs 19 mmHg (Avalide vs irbesartan monotherapy, respectively; P<0.0001 for both comparisons).
4) Avalide reduced both mean systolic and diastolic blood pressures significantly more than irbesartan monotherapy did at every time point assessed (Weeks 1, 3, 5, and 7). The blood pressure reductions achieved with irbesartan monotherapy at Week 7 were seen approximately one month earlier with Avalide.
5) Initial therapy with Avalide led to a distribution of blood pressures with significantly fewer patients having moderate and severe blood pressure levels. At the time of the primary endpoint (Week 5)

- The proportion of patients who still had severe blood pressure levels was 5.4% for those on Avalide and 13.8% for those on irbesartan monotherapy (P= 0.0003; post hoc analysis).
- The proportion of patients who still had moderate blood pressure levels was 15.5% for those on Avalide and 29.8% for those on irbesartan monotherapy (P= 0.0003; post hoc analysis).

6) Patients with higher baseline blood pressures had a lower probability of achieving goals for blood pressure control on irbesartan monotherapy (post hoc analysis).
7) Response among subgroups (race, diabetic status, elderly, obese) was consistent with the results of the main analysis. Avalide was more effective than irbesartan monotherapy in each of these subgroups.

Table 3.1.2A provides details of the results at Week 5.

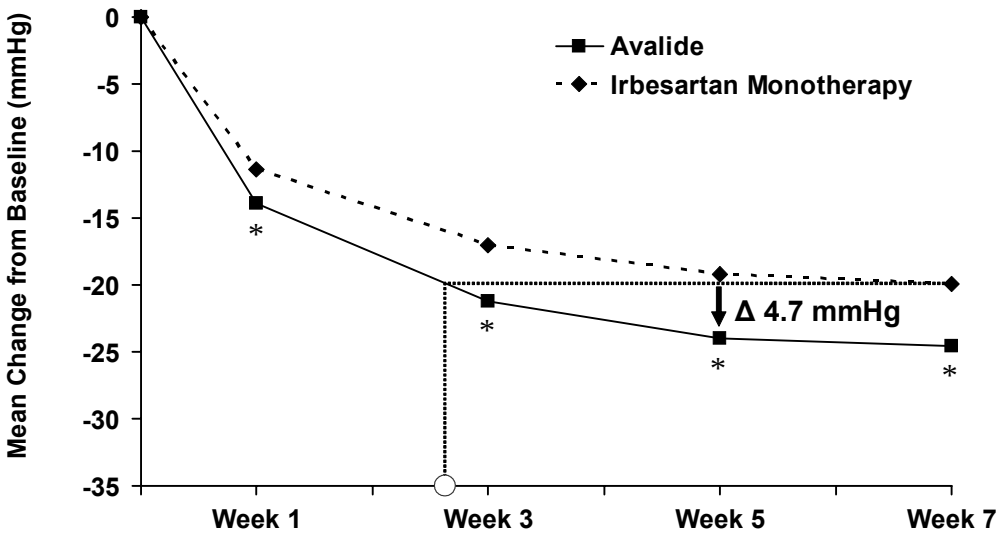
Table 3.1.2A: Efficacy Results in Study 176 at Primary Endpoint (Week 5)

Treatment Comparison of Proportions Controlled				
	Trough DBP < 90 mmHg		**Trough DBP < 90 mmHg AND Trough SBP < 140 mmHg**	
	Avalide N = 468	**Irbesartan N = 229**	**Avalide N = 468**	**Irbesartan N = 229**
N	423	206	423	206
Proportion (No.) Controlled	0.472 (221)	0.332 (76)	0.346 (162)	0.192 (44)
Est. Difference between Treatments	0.140		0.154	
95% CI for Estimated Difference	(0.061 , 0.220)		(0.084 , 0.224)	
P-value for Between Group Comparison	0.0005		< 0.0001	
Mean Changes from Baseline in Trough DBP and SBP				
	Trough DBP (mmHg)		**Trough SBP (mmHg)**	
Baseline Mean (SD)	113.5 (3.5)	113.2 (3.2)	171.6 (16.4)	171.3 (16.3)
Double-blind Period (B) On-Therapy Mean (SD)	89.4 (9.3)	93.9 (10.2)	140.8 (15.3)	150.3 (16.9)
Adj. Mean Change from Baseline (SD)	-24.0 (0.5)	-19.3 (0.7)	-30.8 (0.7)	-21.1 (1.0)
Difference in Adjusted Mean Change	-4.7		-9.7	
95% CI for Estimated Difference	(-6.3 , -3.1)		(-12.0 , -7.3)	
P-value	< 0.0001		< 0.0001	

Note: N = number of patients randomized into double-blind treatment
n = number of patients with available efficacy during double-blind treatment

Figure 3.1.2A shows the mean changes from baseline in trough DBP at each time point during double-blind treatment in Study 176. At Week 5 the difference in reduction in DBP was 4.7 mmHg in favor of Avalide. At Week 7, the adjusted mean change from baseline in DBP was -19.9 mmHg for monotherapy, whereas a greater change of -21.2 mmHg for Avalide therapy was noted 4 weeks earlier before Week 3 (see dotted line). This efficacy advantage translates into less exposure of patients to severe elevations of DBP.

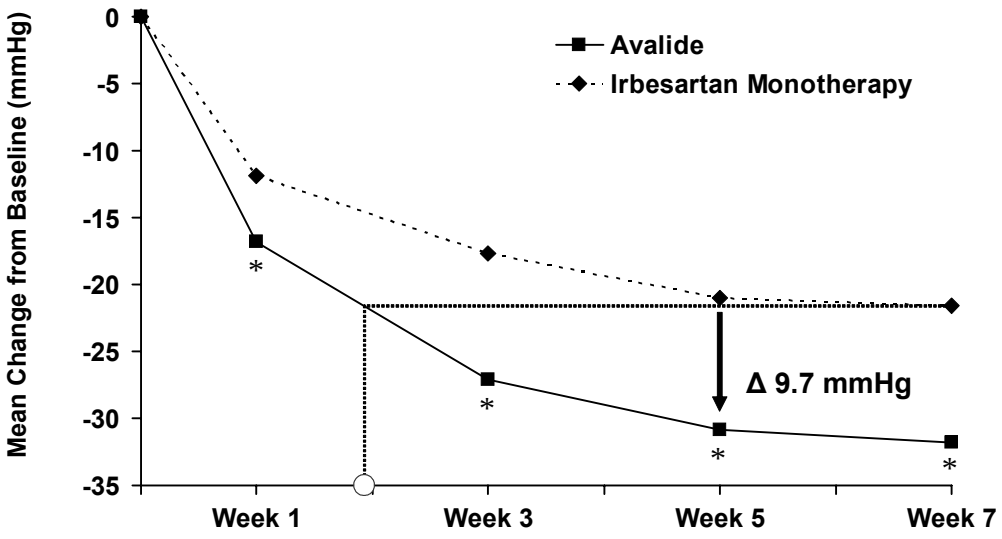
Figure 3.1.2A: Change from Baseline in DBP in Study 176



*Significant difference; all *P*<0.001

Figure 3.1.2B shows the mean changes from baseline in trough SBP at each time point during double-blind treatment in Study 176. At Week 5 the difference in SBP reduction was 9.7 mmHg. Avalide achieved a mean reduction in SBP between Week 1 and Week 3 that was only reached at Week 7 by irbesartan monotherapy (see dotted line). These superior blood pressure reductions of approximately 10/5 mmHg (SBP/DBP) are clinically meaningful.

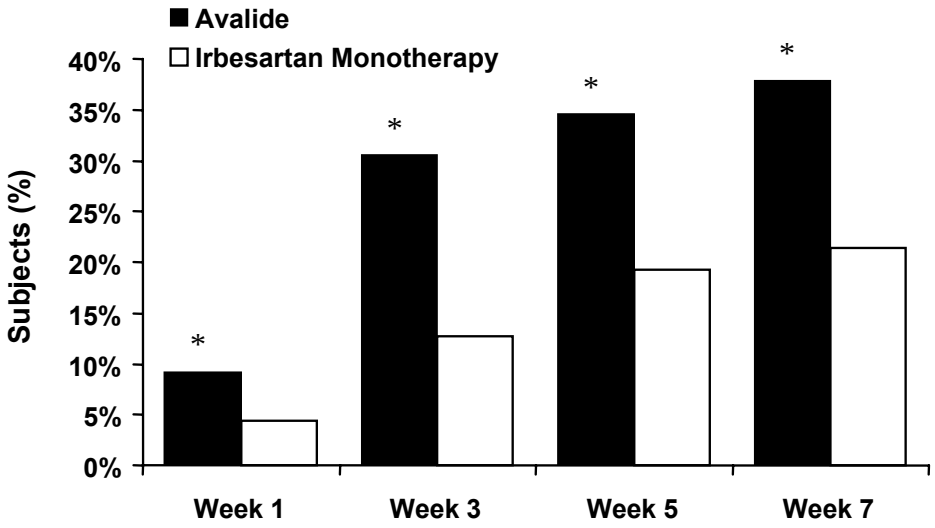
Figure 3.1.2B: Change from Baseline in SBP in Study 176



*Significant difference; all *P*<0.001

Figure 3.1.2C displays by week the proportions of patients with blood pressure controlled (<140/90) in Study 176. The difference between the 2 treatment groups in proportion of patients with blood pressure controlled was significant by Week 1 and continued to be significant at each week in favor of Avalide.

Figure 3.1.2C: Proportions of Patients Controlled to <140/90 mmHg in Study 176

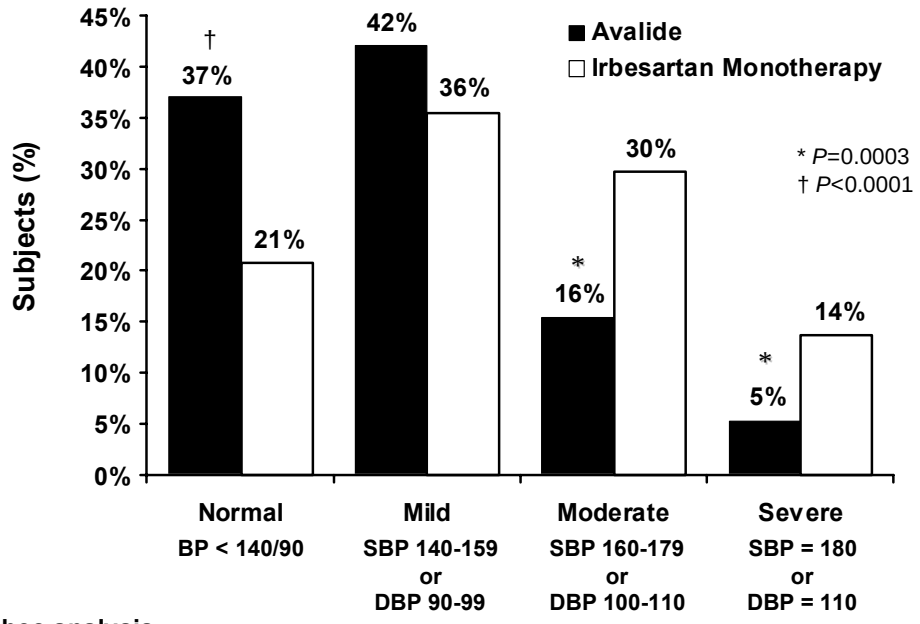


*Significant difference; Week 1 P=0.023; Weeks 3, 5, & 7: P<0.0001

Because the primary and secondary results of the trial were statistically significant in favor of Avalide, post hoc analyses were also performed.

The differences in attainment of blood pressure goal (BP<140/90 mmHg) at Week 5 reflect a broad shift in blood pressure distributions between the 2 treatment arms, with fewer Avalide-treated patients exposed to either moderate (SBP 160-179 mmHg or DBP 100-110 mmHg) or severe (≥180/110 mmHg) blood pressure levels (LOCF analysis). The proportions with persistent severe blood pressure levels were 13.8% on irbesartan monotherapy and 5.4% on Avalide (P = 0.0003). The differences are displayed in Figure 3.1.2D.

Figure 3.1.2D: Blood Pressure Distributions at Week 5 in Study 176



Post-hoc analysis

These results illustrate how the proportion achieving a target such as 140/90 mmHg is only one part of a broader population distribution of blood pressures. An important goal of treatment is to avoid persistent dangerous blood pressure levels. Treatment with Avalide did that significantly better than irbesartan monotherapy in Study 176.

Analyses of proportions controlled to DBP ≤90 mmHg or BP ≤140/90 mmHg were performed in subgroups by age group, gender, race, BMI, diabetes status, and glomerular filtration rate. Avalide was more effective than irbesartan in all subgroups.

Among black patients, DBP < 90 mmHg was achieved by 40.3% on Avalide and 14.7% on irbesartan monotherapy. Among non-black patients, DBP < 90 mmHg was achieved by 48.4% on Avalide and 36.4% on irbesartan monotherapy. This shows the higher need for combination therapy with HCTZ for black patients.

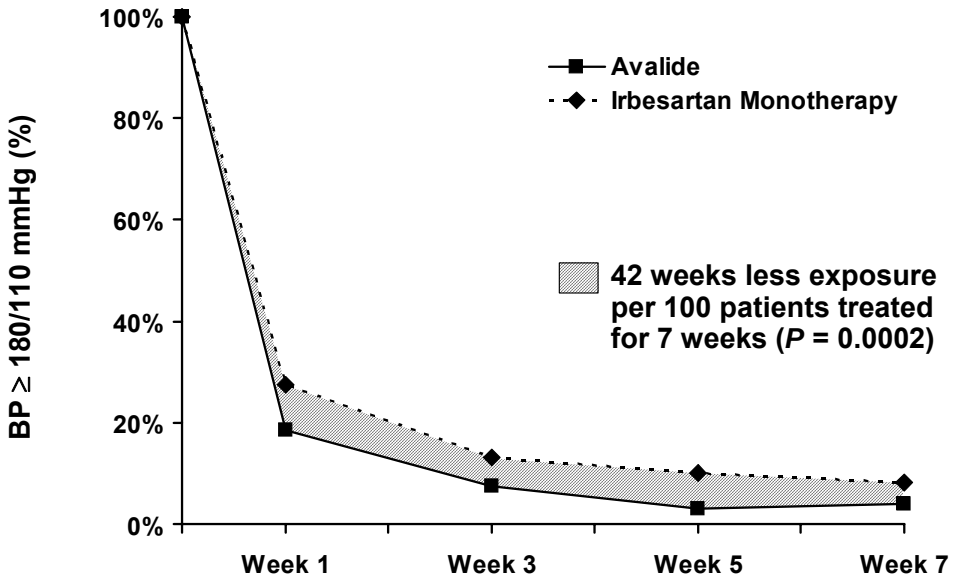
The target blood pressure for hypertensive diabetic patients is 130/80 mmHg. Among diabetic patients in this study, 5.8% on Avalide and none on irbesartan achieved this target. Among non-diabetic patients, the proportions were 10% on Avalide and 3% on irbesartan. Almost all diabetics with severe hypertension will require a combination of drugs to achieve a target of 130/80 mmHg.

In view of the elevated risk associated with exposure to severe hypertension, a post-hoc analysis was performed to quantify the reduction in exposure associated with Avalide therapy relative to irbesartan monotherapy. This reduction can not be defined precisely without very frequent BP measurements, particularly over the early weeks of therapy.

Avalide reduced exposure to severe blood pressure levels as reflected by the difference in areas under the curves in Figure 3.1.2E. The estimated benefit has been expressed in terms of patient-weeks of exposure per 100 patients. A population of 100 patients treated with Avalide for 7 weeks, (ie, 700 patient weeks of exposure to treatment) during the study has 102 patient-weeks of exposure to severe hypertension (area under the Avalide curve) whereas a population treated with irbesartan monotherapy has 144 weeks of exposure (area under the irbesartan curve). The difference (144 weeks-102 weeks = 42 weeks) is significant (P=0.0002).

This estimate may understate the true difference, since additional exposure to severe hypertension was not imputed to patients who discontinued prematurely (more irbesartan patients discontinued prematurely while still experiencing severe hypertension).

Figure 3.1.2E: Exposure to Severe Hypertension in Study 176



Post-hoc analysis

Common slope logistic regression models were performed to assess the relationship between baseline blood pressure and the probability of reaching blood pressure targets. Figures 3.1.2F and 3.1.2G present the fitted probabilities of achieving an SBP <140 mmHg and a DBP < 90 mmHg, respectively, as a function of the corresponding blood pressure. The analyses use all patients who met protocol-specified baseline BP eligibility criteria (DBP 110-130 mmHg and SBP <230 mmHg). Patients with higher baseline blood pressures are less likely to achieve their targets on one drug alone, so they have a greater need for combination therapy.

Figure 3.1.2F: Achievement of SBP <140 mmHg

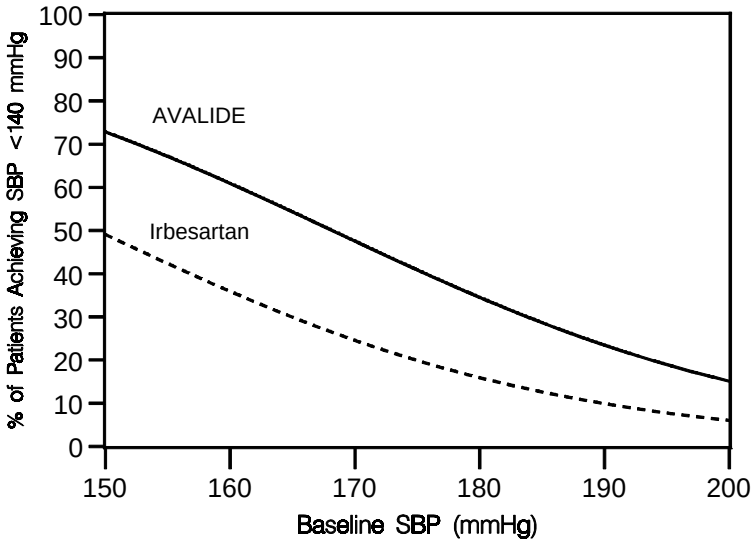
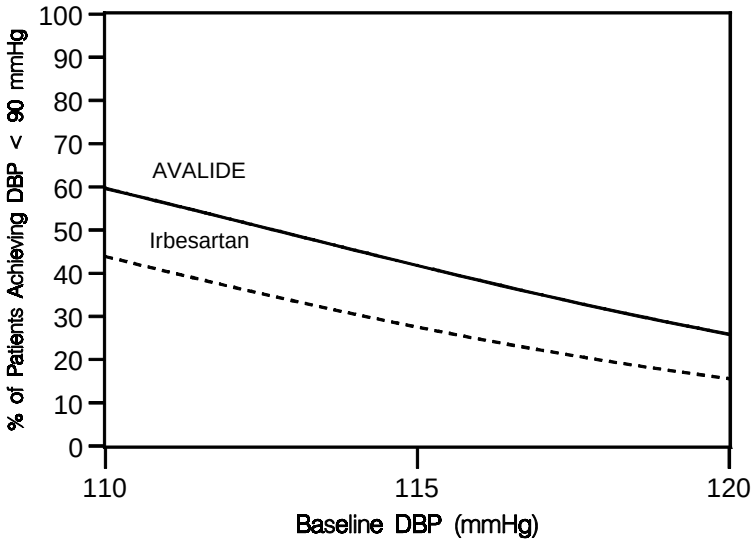


Figure 3.1.2G: Achievement of DBP < 90 mmHg



Safety Results in Study 176

Avalide was safe and well tolerated in severe hypertension patients with no unexpected adverse events. In Study 176:

1) No deaths occurred in either treatment arm.
2) Overall incidence of adverse events (AEs) was similar between the 2 treatment groups: 29.9% for Avalide vs 36.1% for irbesartan monotherapy.
3) There was no syncope in either treatment arm.
4) There was no increase in the incidence of dizziness for Avalide (3.6%) compared to irbesartan monotherapy (4.0%).
5) There was no increase in the incidence of discontinuations for AEs for Avalide (1.9%) compared to that for irbesartan monotherapy (2.2%).
6) The incidence of hypotension on Avalide was low (<1%). Only 1 patient on Avalide discontinued because of hypotension.
7) Only 2 patients reported SAEs in the study (colitis secondary to irritable bowel syndrome and pyelonephritis of moderate intensity in a patient receiving Avalide; and renal artery stenosis of mild intensity in a patient receiving irbesartan monotherapy). Both were categorized as unrelated to study therapy.
8) The incidence of AEs was not higher in elderly (≥65 years) patients than it was overall in either treatment group.

Table 3.1.2B summarizes adverse event experience in Study 176.

Table 3.1.2B: Overall Adverse Events in Study 176

	Number (%) of Patients	
	Avalide	**Irbesartan monotherapy**
	N=468	**N=227**
Any AE	140 (29.9)	82 (36.1)
Treatment-related AE	53 (11.3)	23 (10.1)
Serious AE	1 (0.2)	1 (0.4)
Discontinuations due to AEs	9 (1.9)	5 (2.2)
Deaths	0	0

The most common AEs reported during the 7-week double-blind treatment period are shown in Table 3.1.2C. The overall frequency of AEs reported during this period was similar in the 2 treatment groups. The most common (experienced by ≥3%) AEs in either treatment group were headache, dizziness, and nasopharyngitis.

Table 3.1.2C: Most Common Adverse Events as Reported by at Least 1 Percent of Patients in Either Treatment Group During Double-Blind Period, by Preferred Term: Study 176

	Number (%) of Patients	
PREFERRED TERM (PT)	Avalide N = 468	Irbesartan N = 227
TOTAL PATIENTS WITH AT LEAST ONE AE	140 (29.9)	82 (36.1)
HEADACHE	19 (4.1)	15 (6.6)
DIZZINESS	16 (3.4)	9 (4.0)
NASOPHARYNGITIS	8 (1.7)	10 (4.4)
BRONCHITIS	6 (1.3)	6 (2.6)
FATIGUE	6 (1.3)	1 (0.4)
UPPER RESPIRATORY TRACT INFECTION	6 (1.3)	4 (1.8)
ERECTILE DYSFUNCTION	5 (1.1)	0
NAUSEA	5 (1.1)	5 (2.2)
DIARRHOEA	4 (0.9)	3 (1.3)
SINUSITIS	4 (0.9)	3 (1.3)
COUGH	3 (0.6)	4 (1.8)
MUSCLE SPASMS	2 (0.4)	3 (1.3)

Abbreviations: N = number of patients who received study drug.

Table 3.1.2D presents the most common AEs considered related to study drug.

Table 3.1.2D: Most Common Adverse Events Considered Related to Study Drug (Reported by at Least 1 Percent of Patients in Either Treatment Group During Double-Blind Period) by Preferred Term: Study 176

	Number (%) of Patients	
PREFERRED TERM (PT)	Avalide N = 468	Irbesartan N = 227
TOTAL PATIENTS WITH AT LEAST ONE AE	53 (11.3)	23 (10.1)
DIZZINESS	12 (2.6)	7 (3.1)
HEADACHE	6 (1.3)	5 (2.2)
ERECTILE DYSFUNCTION	5 (1.1)*	0
FATIGUE	5 (1.1)	1 (0.4)
NAUSEA	3 (0.6)	3 (1.3)

* 1.9% of males
Abbreviations: N = number of patients who received study drug.

Adverse events (AEs) and laboratory abnormalities of prespecified interest (dizziness, hypotension, syncope, headache, and abnormalities of serum potassium) were found to occur collectively with similar frequency in the 2 treatment groups (8.8% with Avalide vs 11.5% with irbesartan monotherapy; Table 3.1.2E).

The 95% confidence intervals for the difference between treatment groups in the incidences of the prespecified events, individually and collectively, suggest that the trial data are consistent with underlying rates for Avalide that may be lower than those for irbesartan, or at most one to two percentage points higher. These data provide reassurance that the dose-dependent side effects of HCTZ 12.5mg and 25mg are low.

Note that incidences of AEs in Table 3.1.2C differ from those presented in Table 3.1.2E because each term in Table 3.1.2E represents a collection of more than one preferred term in the dictionary of AE terms (MedDRA).

Table 3.1.2E: Number (Percent) of Patients with Prespecified Events and 95% Confidence Interval for the Estimates of Difference Between Treatment Groups: Study 176

Event	Avalide (N= 468)	Irbesartan (N=227)	Difference (95% CI)
At least one Pre-Specified AE or MA	41 (8.8)	26 (11.5)	-2.7 (-8.0, 2.0)
Pre-specified AEs			
Headache	20 (4.3)	15 (6.6)	-2.3 (-6.6, 1.2)
Dizziness	17 (3.6)	9 (4.0)	-0.3 (-3.9, 2.5)
Hypotension	3 (0.6)	0 (0)	0.6 (-0.9, 1.9)
Syncope	0 (0)	0 (0)	0 (-1.6, 0.9)
Hyperkalemia	1 (0.2)	0 (0)	0.2 (-1.4, 1.3)
Hypokalemia	3 (0.6)	1 (0.4)	0.2 (-1.8, 1.6)
Lab MAs			
Potassium<3.0 mEq/L	0 (0)	0 (0)	0 (-1.6, 0.9)
Potassium>6.0 mEq/L	3 (0.6)	3 (1.3)	-0.7 (-3.1, 0.9)
Discontinued for AE	9 (1.9)	5 (2.2)	-0.3 (-3.2, 1.9)
Overall AE	140 (29.9)	82 (36.1)	-6.2 (-13.8, 1.2)

Dataset: Treated Patients

MA = marked abnormality

Note: Confidence intervals are exact by method of Santner & Snell.

Note: A patient may appear in more than one category of pre-specified AEs so the total who experienced at least one pre-specified AE is not the sum of the rows above it.

Nine patients (1.9%) in the Avalide group and 5 patients (2.2%) in the irbesartan monotherapy group were discontinued from the study due to AEs. Discontinuations from the study are summarized in Table 3.1.2F.

Table 3.1.2F: Discontinuations in Study 176

	% of Patients	
	Avalide	**Irbesartan monotherapy**
	N=468	**N=229***
Total discontinued	48 (10.3)	28 (12.2)
AE	9 (1.9)	5 (2.2)
Lack of efficacy	15 (3.2)	12 (5.2)
Other reasons**	24 (5.2)	11 (4.8)

* Note that the 229 patients who were randomized include 2 who did not receive medication.
** Includes patients who withdrew consent, were lost to follow up, no longer met study criteria, were non-compliant, became pregnant, or were withdrawn for administrative reasons.

Three (3; 0.6%) patients reported hypotension as an AE during treatment with Avalide. Only 1 of these patients (248-1) discontinued the study. In none of these 3 cases were blood pressures dangerously low. Table 3.1.2G presents data on these 3 cases.

Table 3.1.2G: Hypotension Adverse Events on Avalide in Study 176

PID	**Blood Pressure mmHg**					**Reported AE**
Age/Gender	**Pre-rand**	**Week 1**	**Week 3**	**Week 5**	**Week 7**	
248-1 32/F	140/111	133/86	133/83	136/96[a]	NA	Left-sided neck pain, hypotension (onset Day 30, mild intensity)
288-4 62/F	160/111	153/105	131/79[b]	133/81	133/78	Dizziness, orthostatic hypotension (onset Day 19, moderate intensity)
293-2 38/F	190/125	145/109	133/97[c]	142/103	134/96	Headache, hypotension symptomatic (onset Day 16, mild intensity)

a Systolic BP 125 mmHg on standing
b Systolic BP 124 mmHg on standing
c Systolic BP 136 mmHg on standing

During treatment 9 patients (1.9%) on Avalide had at least one SBP <110 mmHg. All of these patients were <65 years old. None of these SBPs occurred during Week 1. Six (6) had BP <140/90 at Week 1. Three (3) had dizziness (2 mild and 1 moderate).

One (1) patient (0.2%) had DBP <60 mmHg. This patient was < 65 years old. Baseline BP was 151/111 mmHg. At Week 1 the BP was 121/73 mmHg, so the patient's dose would not have been titrated in actual clinical practice. At Week 7 the BP was 103/56 mmHg. The patient completed the study with no AEs.

Safety results among the elderly are of particular interest. In this study, 92 (13%) patients were ≥65 years old. None of these patients experienced hypotension or syncope. Among those on Avalide, dizziness occurred in 1.9% of the elderly patients vs 3.9% of non-elderly patients; overall, AEs occurred in 26.4% of elderly patients vs 30.4% of non-elderly.

The data from Study 176 provide reassurance that in severe hypertension the incidence of dose-dependent side effects of Avalide is low. Most importantly, hypotension was less than 1% and syncope was not observed.

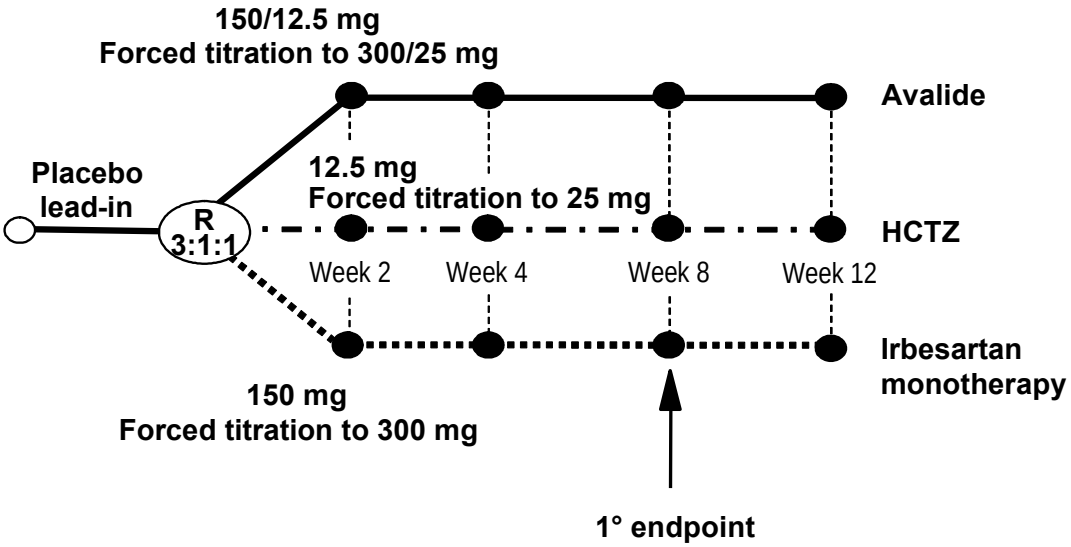
3.2 Supportive Study 185

3.2.1 Design of Study 185

The second trial in the program, Study 185, was designed to evaluate the safety and efficacy of Avalide as initial treatment of moderate hypertension (SBP 160 to 179 mmHg and DBP 100 to 109 mmHg). The maximum dose of Avalide was assessed to provide reassurance of its safety. After placebo lead-in, patients were randomized (3:1:1) to receive Avalide therapy, irbesartan monotherapy, or HCTZ monotherapy for 12 weeks.

The starting doses for Avalide, irbesartan monotherapy, and HCTZ monotherapy were 150 mg/12.5 mg, 150 mg, and 12.5 mg, respectively. After 2 weeks at starting dose, study medications were force-titrated to 300 mg/25 mg for Avalide, 300 mg for irbesartan, and 25 mg for HCTZ. The design of Study 185 is presented in Figure 3.2.1.

Figure 3.2.1: Design of Study 185



The primary objective of this study was to compare the change from baseline in systolic blood pressure (SBP) between the Avalide arm and each of the 2 monotherapy arms at Week 8.

Other objectives were to examine the change from baseline in DBP among treatment arms at Weeks 8 and 12, and in SBP at Week 12. The percent of patients in each treatment arm with BP <140/90 at Weeks 8 and 12 was also compared.

Safety objectives included overall frequency of AEs, frequency of discontinuations due to AEs, and AEs of special interest (hypotension, dizziness, syncope, headache, hypokalemia and hyperkalemia).

Five hundred thirty-eight (538) patients from North America and Europe received double-blind therapy in Study 185: there were 328 on Avalide, 106 on irbesartan monotherapy, and 104 on HCTZ monotherapy. The mean age of patients was approximately 55 years (21% ≥65 years); 54% were male, 84% white, 14% black, and 14% diabetic. Mean weight was approximately 88 kg; 48% had BMI ≥30 kg/m^2. Mean baseline blood pressure was approximately 162/98 mmHg. Mean duration of exposure to study medication was about 78 days for each treatment group. Almost 90% of patients in each treatment group were exposed to treatment for at least 61 days during the study.

3.2.2 Results in Study 185

Study 185 demonstrated efficacy and safety results that were consistent with those seen in Study 176.

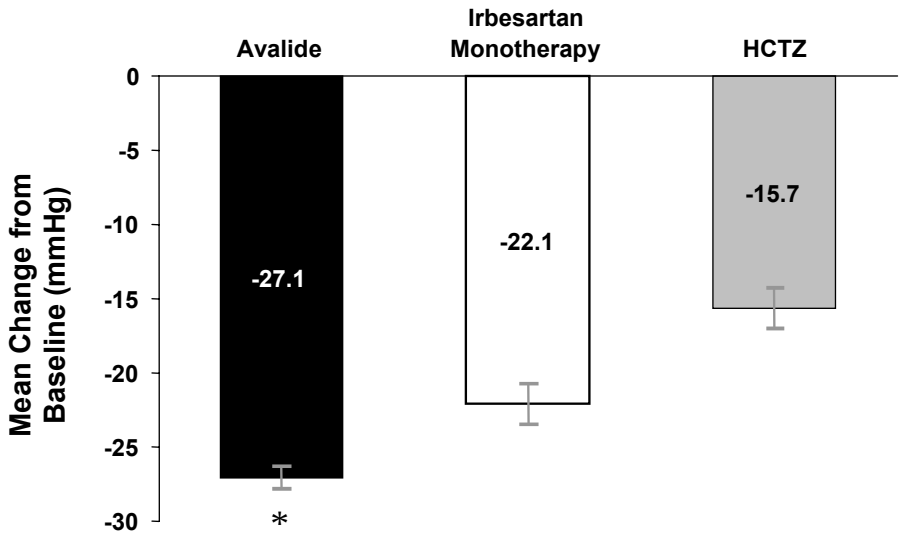
Efficacy Results in Study 185

In Study 185 Avalide was more effective than monotherapy with either irbesartan or HCTZ in moderately hypertensive patients. In Study 185:

1) At Week 8, mean blood pressure reductions with Avalide (27.1 mmHg SBP and 14.6 mmHg DBP) were significantly greater than with irbesartan monotherapy (P= 0.0016 for SBP, P=0.0013 for DBP) or HCTZ monotherapy (P<0.0001 for both SBP and DBP).
2) At Week 8, mean blood pressure reductions with irbesartan monotherapy (22.1 mmHg SBP and 11.6 mmHg DBP) were greater than those with HCTZ monotherapy (15.7 mmHg SBP and 7.3 mmHg DBP). The 95% confidence interval for the difference between the reduction for irbesartan monotherapy and that for HCTZ monotherapy was 2.6 to 10.2 mmHg for SBP and 2.1 to 6.6 mmHg for DBP.

Figure 3.2.2A displays the primary endpoint at Week 8. At Week 8 Avalide achieved a significantly greater reduction in SBP than irbesartan or HCTZ did (27.1 mmHg, 22.1 mmHg, and 15.7 mmHg, respectively). These differences of approximately 5 to 10 mmHg SBP (compared to irbesartan and HCTZ) are clinically meaningful.

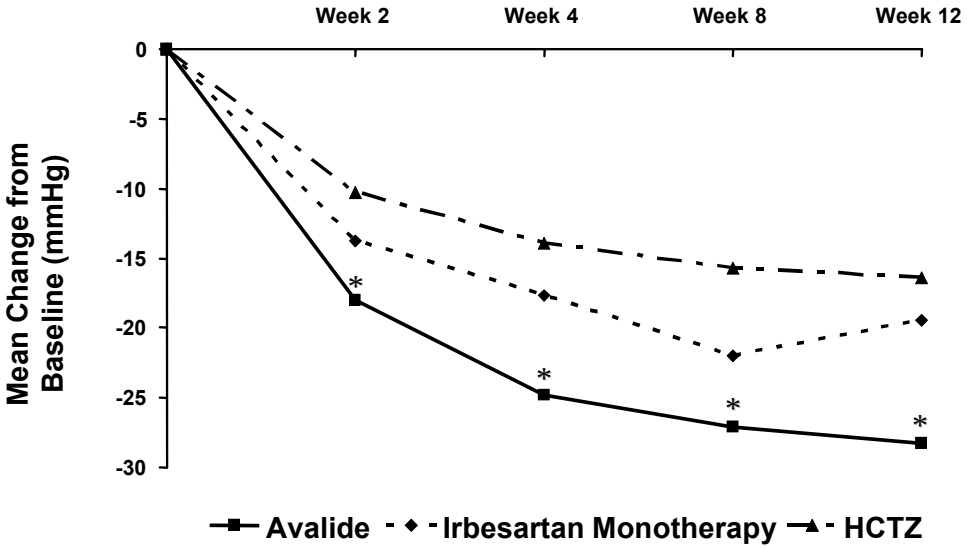
Figure 3.2.2A: Change from Baseline in SBP at Week 8 in Study 185



*P<0.0001 vs HCTZ; P<0.01 vs irbesartan

Figure 3.2.2B shows the mean changes from baseline in trough SBP at each time point during double-blind treatment in Study 185. The mean reduction in SBP was significantly greater for patients on Avalide compared to those on irbesartan or on HCTZ. This difference was noted at Week 2 and at each subsequent week assessed.

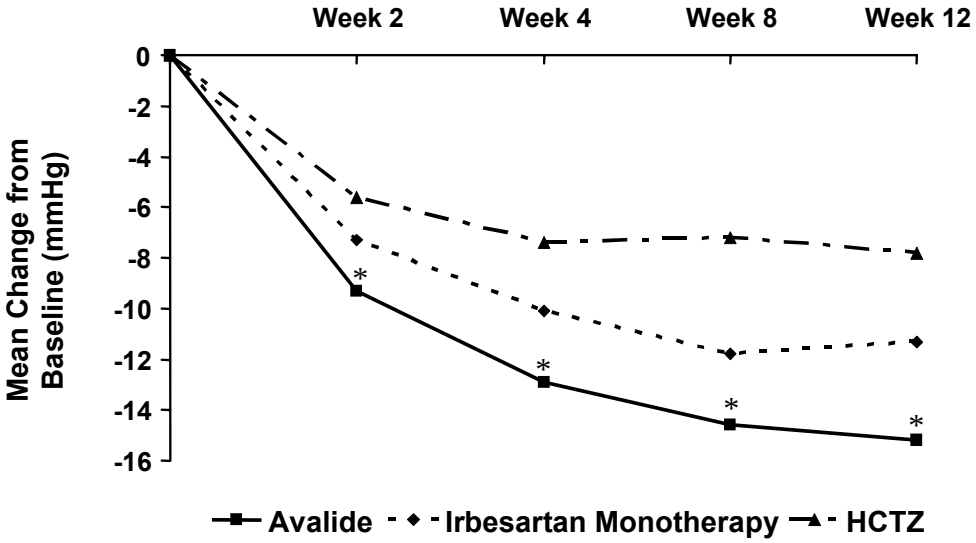
Figure 3.2.2B: Change from Baseline in SBP in Study 185



*P<0.0001 vs HCTZ; P<0.01 vs irbesartan

Figure 3.2.2C shows the mean changes from baseline in trough DBP at each time point during double-blind treatment in Study 185. The mean reduction in DBP was significantly greater for patients on Avalide compared to those on irbesartan or on HCTZ. This difference was noted at Week 2 and at each subsequent week assessed.

Figure 3.2.2C: Change from Baseline in DBP in Study 185



**P*<0.0001 vs HCTZ; *P*<0.05 vs irbesartan

Safety Results in Study 185

Avalide was well tolerated in patients with moderate hypertension with no unexpected adverse events. In Study 185:

1) No deaths occurred in any treatment arm.
2) Overall incidences of AEs were 47.0% for Avalide, 45.3% for irbesartan monotherapy, and 39.4% for HCTZ monotherapy.
3) There was no syncope on Avalide or irbesartan monotherapy.
4) Overall incidences of discontinuations for AEs were: 6.7% for Avalide, 3.8% for irbesartan, and 4.8% for HCTZ.
5) Dizziness occurred in only 3.0% of patients treated with Avalide. Hypotension was uncommon, occurring in <1% of patients on Avalide. These frequencies are consistent with the current product label. Among patients on irbesartan monotherapy, dizziness occurred in 3.8% and hypotension in none. Among those on HCTZ monotherapy, dizziness occurred in 1.0% and hypotension in none.

6) Among patients on Avalide, discontinuations due to dizziness or hypotension were 2.1% compared to 0.9% among those on irbesartan monotherapy and none on HCTZ monotherapy.
7) Avalide demonstrated good safety in elderly patients, with no excess of dizziness, no hypotension, and the same overall rate of adverse events as in younger patients.

Note: The incidences of adverse events on Avalide and irbesartan in Study 185 were higher than in Study 176; this reflects the longer duration of Study 185 which had a 12-week follow-up period. Table 3.2.2B summarizes AE experience in Study 185.

Table 3.2.2B: Overall Adverse Events in Study 185

	% of Patients		
	Avalide N=328	**Irbesartan monotherapy N=106**	**HCTZ monotherapy N=104**
Any AE	154 (47.0)	48 (45.3)	41 (39.4)
Treatment-related AE	47 (14.3)	12 (11.3)	8 (7.7)
Serious AE	6 (1.8)	0	3 (2.9)
Discontinuations due to AEs	22 (6.7)	4 (3.8)	5 (4.8)
Deaths	0	0	0

The most common AEs reported during the 12-week double-blind treatment period are shown in Table 3.2.2C. The most common (experienced by ≥ 3%) AEs in the Avalide group were headache, upper respiratory tract infection, and dizziness. In the irbesartan monotherapy group they were nasopharyngitis, dizziness, and upper respiratory tract infection. In the HCTZ monotherapy group they were headache and nasopharyngitis.

Table 3.2.2C: Most Common AEs (Reported by At Least 1 Percent Of Patients In Any Treatment Group During Double-blind Treatment), by Preferred Term: Study 185

PREFERRED TERM (PT)	Number (%) of Patients: Avalide N = 328	Irbesartan N = 106	HCTZ N = 104
TOTAL PATIENTS WITH AT LEAST ONE AE	154 (47.0)	48 (45.3)	41 (39.4)
HEADACHE	14 (4.3)	3 (2.8)	5 (4.8)
UPPER RESPIRATORY TRACT INFECTION	13 (4.0)	4 (3.8)	1 (1.0)
DIZZINESS	10 (3.0)	4 (3.8)	1 (1.0)
NASOPHARYNGITIS	9 (2.7)	5 (4.7)	4 (3.8)
BACK PAIN	8 (2.4)	2 (1.9)	2 (1.9)
MUSCLE SPASMS	6 (1.8)	2 (1.9)	0
SINUS CONGESTION	6 (1.8)	0	2 (1.9)
ASTHENIA	5 (1.5)	0	0
DIARRHOEA	5 (1.5)	3 (2.8)	1 (1.0)
COUGH	4 (1.2)	2 (1.9)	2 (1.9)
FATIGUE	4 (1.2)	2 (1.9)	1 (1.0)
NAUSEA	4 (1.2)	0	1 (1.0)
PAIN IN EXTREMITY	4 (1.2)	2 (1.9)	2 (1.9)
SINUS HEADACHE	4 (1.2)	1 (0.9)	0
SINUSITIS	4 (1.2)	2 (1.9)	1 (1.0)
ARTHRALGIA	2 (0.6)	2 (1.9)	0
MUSCLE STRAIN	2 (0.6)	2 (1.9)	0
OEDEMA PERIPHERAL	2 (0.6)	2 (1.9)	0
SHOULDER PAIN	2 (0.6)	1 (0.9)	2 (1.9)
URINARY TRACT INFECTION	2 (0.6)	3 (2.8)	2 (1.9)
CONTUSION	1 (0.3)	0	2 (1.9)

Abbreviations: N = number of patients who received study medication.

Table 3.2.2D presents the most common AEs considered related to study drug.

Table 3.2.2D: Most Common Related AEs (Reported by At Least 1 Percent of Patients in Any Treatment Group During Period B, by Preferred Term): Study 185

PREFERRED TERM (PT)	Number (%) of Patients: Avalide N = 328	Irbesartan N = 106	HCTZ N = 104
TOTAL PATIENTS WITH AT LEAST ONE AE	47 (14.3)	12 (11.3)	8 (7.7)
DIZZINESS	8 (2.4)	2 (1.9)	0
ASTHENIA	4 (1.2)	0	0
NAUSEA	4 (1.2)	0	1 (1.0)
HEADACHE	2 (0.6)	1 (0.9)	3 (2.9)
DIARRHOEA	1 (0.3)	2 (1.9)	0

Abbreviations: N = number of patients receiving study medication

The incidences of adverse events and laboratory abnormalities of pre-specified interest (dizziness, hypotension, syncope, headache, and abnormalities of serum potassium) were 10.7% with Avalide therapy, 6.6% with irbesartan monotherapy, and 6.7% with HCTZ monotherapy (Table 3.2.2E). Headache was the most frequent of the prespecified AEs.

Patients with moderate hypertension are presumed to be more susceptible to the hypotensive effects of Avalide, especially after forced-titration to the highest dose, than are patients with higher initial blood pressure levels. Yet there was no syncope in the Avalide group in Study 185, and the incidence of hypotension was still low (0.9%; consistent with current label). Furthermore there was no increase in dizziness with Avalide compared to irbesartan monotherapy.

Table 3.2.2E: Number (%) of Patients with Prespecified AEs: Study 185

	Avalide		Irbesartan		HCTZ	
	N=328		N=106		N=104	
	N	%	N	%	N	%
Patients with pre-specified AEs	35	10.7	7	6.6	7	6.7
Dizziness	10	3.0	4	3.8	1	1.0
Headache	18	5.5	4	3.8	5	4.8
Hyperkalemia	4	1.2	0	-	1	1.0
Hypokalemia	3	0.9	0	-	0	-
Hypotension	3	0.9	0	-	0	-
Syncope	0	-	0	-	1	1.0
Serum potassium <3.0	0	-	0	-	0	-
Serum potassium>6.0	4	1.2	0	-	0	-

Note: A patient may appear in more than one category of pre-specified AEs so the total of patients who experienced at least one pre-specified AE is not the sum of the rows below it.

No deaths occurred during Study 185. Serious AEs were reported in 6 patients (1.8%) treated with Avalide, 3 patients (2.9%) treated with HCTZ, and in no irbesartan-treated patients. All but one SAE was classified by the investigator as either not related or not likely to be related to study treatment. The only SAE considered by the investigator to be probably related to study drug occurred in an Avalide-treated patient. It was characterized as “symptomatic hypokalemia,” but was only a minor decrease in potassium (3.2 mEq/L

at one isolated measurement) and the symptoms of atypical chest pain were not consistent with this value.

Twenty-two (22; 6.7%) patients in the Avalide group, 4 (3.8%) in the irbesartan monotherapy group, and 5 (4.8%) in the HCTZ monotherapy group were discontinued from the study due to AEs. Seven patients (7; 2.1%) in the Avalide group discontinued due to AEs of dizziness or hypotension, 4 of which occurred after forced titration to irbesartan 300 mg/HCTZ 25 mg. Discontinuations in Study 185 are summarized in Table 3.2.2F.

Table 3.2.2F: Discontinuations in Study 185

	% of Patients		
	Avalide N=328	**Irbesartan monotherapy N=106**	**HCTZ monotherapy N=104**
Total patients discontinued	41 (12.5)	12 (11.3)	13 (12.5)
Adverse Event	22 (6.7)*	4 (3.8)	5 (4.8)
Lack of efficacy	1 (0.3)	1 (0.9)	1 (1.0)
Other reasons**	18 (5.4)	7 (6.6)	7 (6.7)

*2.1% of patients discontinued Avalide due to dizziness or hypotension.

** Includes patients who withdrew consent, were lost to follow up, no longer met study criteria, were not compliant, or the subinvestigator withdrew.

Avalide was well tolerated among the 68 elderly (≥65 years old) patients. None of the elderly patients on Avalide experienced hypotension or syncope. Dizziness occurred in 3.1% of those ≥65 years old compared to 3.0% overall. Overall AEs occurred in 47.1% of those ≥65 years old compared to 47.0% overall.

Thus, results of Study 185 support the safety and efficacy seen in Study 176. The incidence of adverse events was similar between Avalide (47.0%) and irbesartan monotherapy (45.3%). The lowest overall incidence of adverse events was with HCTZ monotherapy, indicating the tolerability of low doses (12.5 mg and 25 mg). Dose-dependent side effects of Avalide were low, with hypotension still less than 1% and no syncope despite forced titration in a population with only moderate hypertension.

3.3 Safety Data from Original NDA

The original NDA for Avalide provides substantial clinical trial data to support its safety and tolerability. In the 4 main studies with irbesartan/HCTZ (Protocols CV131-037, -038, -039, and -040) there were 12 Avalide dosing groups, 5 irbesartan monotherapy dosing groups, 3 HCTZ dosing groups, and a placebo group. A total of 898 subjects received Avalide, 400 received irbesartan monotherapy, 380 received HCTZ monotherapy, and 236 received placebo.

In these studies, the incidence of adverse events was similar between subjects on Avalide (59.1%) and those in the control groups (irbesartan monotherapy 56.0%, HCTZ monotherapy 58.2%, and placebo 53.4%). No case of first-dose hypotension was reported in subjects given Avalide and no pattern of postural hypotension was observed when irbesartan was given to hypertensive subjects already receiving HCTZ in a double-blind study. Three subjects experienced orthostatic hypotension during treatment with Avalide. These events were described as moderate and all resolved.

In Avalide studies the SAE rate was low and events occurred with similar frequencies in patients treated with Avalide, irbesartan, or HCTZ. SAEs were reported by 12/898 (1.3%) on Avalide, 5/400 (1.2%) on irbesartan monotherapy, 7/380 (1.3%) on HCTZ monotherapy, and 1/236 (0.4%) on placebo.

The tolerability and safety shown in this original NDA are reflected in the product label, which states that the side effects of Avalide are “comparable to placebo.”

4 POST-MARKETING SAFETY

The safety profile of Avalide observed during 10 years of post-marketing surveillance is consistent with what has been demonstrated in clinical studies. To compare the reporting rates of certain adverse effects that might be anticipated to occur more frequently with the combination of irbesartan plus HCTZ than with irbesartan monotherapy, an assessment was conducted using all spontaneous reports collected by BMS during the entire post-marketing surveillance periods for both Avalide and irbesartan. This assessment demonstrates that the safety profiles of both drugs as used in day-to-day practice are well known, and closely reflect the current labeling for both drugs.

Table 4 provides the cumulative spontaneous reporting rates for AEs of special interest for both Avalide and irbesartan. AEs of special interest include those events that, based on the pharmacologic classes of angiotensin II receptor blockers and thiazide diuretics, might be anticipated to occur more frequently with the combination of irbesartan plus HCTZ than with irbesartan monotherapy. These data represent 10,589,729 patient-years of exposure to Avalide and 17,837,852 patient-years of exposure to irbesartan. Numbers of cases are presented per 1,000,000 patient-years of exposure. Reporting ratios have been calculated to look for significant differences in spontaneous reporting rates of these AEs between the two treatments. For each event of interest, we calculated a reporting rate ratio (RRR) by dividing the reporting rate estimated for Avalide exposure by the reporting calculated for irbesartan exposure. The two sided 95% confidence interval (95% CI) for this ratio was calculated according to the normal approximation of the binomial distribution as suggested by Tubert et al.[12]

Overall, the safety profiles appear to be similar, including hypotension and syncope (reporting ratios of ≤1 for the majority of events). Most cases of hypotension and syncope in the Avalide group occurred in patients who were over age 65 (66% and 71% for hypotension and syncope, respectively), and many had underlying CV risks (39% and 43%, respectively) or were on other medications potentially contributing to the event (42% and 33%, respectively). The absolute numbers of reports of these adverse events were low for both treatments (less than 10 reports per 1 million patient-years of exposure).

Reporting ratios greater than one were observed for hypokalemia, hyperglycemia, and acute pancreatitis. Because the absolute numbers of events reported were very small for hyperglycemia and acute pancreatitis (<3 reports per one million patient-years of exposure and <1 report per one million patient-years of exposure, respectively), and the confidence intervals are wide, these results are not reliable indications of increased risk of these events for Avalide. The absolute numbers of cases of acute pancreatitis were so low that the reporting ratio for this event is very unstable, and subject to significant change from even a single additional case in either group

Analysis of individual case reports of acute pancreatitis on Avalide demonstrated that six of nine reports included confounders such as other medications with the potential to cause pancreatitis, or co-morbid conditions associated with pancreatitis such as diabetes

mellitus, biliary calculi, and pancreatic pseudocysts. All of these cases had resolved or were in the process of resolving at the time of this report.

Individual case reports of hyperglycemia show similar clinical features for both Avalide and irbesartan. Most were non-serious reports in patients with pre-existing diabetes, and approximately 50% were reported by patients.

Most reports of hypokalemia for both Avalide and irbesartan were from health care professionals. The difference in reporting rates suggests that in general use, health care professionals are more likely to associate Avalide with hypokalemia compared to irbesartan monotherapy. This is consistent with a known effect of HCTZ, and supports the validity of the post-marketing reporting data. Most of these cases were accompanied by hyponatremia and occurred in the setting of potentially contributing clinical conditions such as dehydration, nausea and vomiting, and inappropriate ADH. All of the cases resolved with appropriate treatment. This profile is consistent with the clinical trial data and the current Avalide label.

Although interstitial pneumonitis is reported in the literature as a dose-independent effect of hydrochlorothiazide, no spontaneous reports have been received for Avalide.

Table 4: Rates of Adverse Event Reporting in Post-marketing Surveillance, Expressed in Terms of Estimated Total Patient-years of Exposure

	Avalide* **Cases per 1,000,000 patient-years of exposure (number of events)**	**Irbesartan*** **Cases per 1,000,000 patient-years of exposure (number of events)**	**Reporting ratio†** **(95% CI)**
Dizziness	18.3 (194)	27.4 (488)	0.7 (0.6 - 0.8)
Hypotension	7.2 (77)	8.7 (156)	0.8 (0.6 -1.1)
Syncope	1.9 (20)	2.1 (38)	0.9 (0.5 - 1.5)
Allergic reactions	3.4 (36)	3.9 (70)	0.9 (0.6 - 1.3)
Blood creatinine increased	3.1 (33)	5.4 (97)	0.6 (0.4 - 0.9)
Renal failure	4.4 (47)	7.6 (144)	0.6 (0.4 - 0.8)
Hypokalemia	2.5 (26)	1.0 (17)	2.6 (1.4 - 4.7)
Blood glucose increased	2.8 (30)	1.9 (35)	1.4 (0.9 - 2.4)
New-onset diabetes mellitus	0.3 (3)	0.3 (6)	0.8 (0.3 - 3.4)
Pancreatitis	0.8 (9)	0.6 (11)	1.3 (0.6 - 3.3)
Interstitial pneumonitis	0.0 (0)	0.5 (8)	0.2 (0.02 - 1.7)**

*Total patient years of exposure are approximately **17,837,852** for irbesartan monotherapy and **10,589,729** for Avalide. Calculation based on quantity of drug sold (IMS Global Service 2007) and estimated average duration of treatment (NGPS November 2006) for both Avalide and irbesartan.

** Reporting rate was calculated after adjustment for the nonexistence of cases under Avalide

†Reporting ratio used irbesartan as reference rate

There are several limitations to these data. Due to the fact that irbesartan is indicated for the treatment of diabetic nephropathy, the reporting ratios for renally-related adverse events may be influenced by indication bias (ie, irbesartan may be used in a population at greater risk for renal failure than the population treated with Avalide). Furthermore, patients with heart failure are at risk for renal failure, and these patients may be more likely to be prescribed irbesartan than Avalide, since loop diuretics and spironolactone are often preferred to thiazides in the setting of heart failure.

It is assumed that many cases in the Avalide group are patients who may have been previously exposed to irbesartan alone because of the current labeling indication, and therefore this group may be less likely to include patients who were unable to tolerate

irbesartan alone. This may impact reporting for several reactions but it should not affect the reporting of those that might be solely attributed to HCTZ (pancreatitis and interstitial pneumonitis).

It is therefore reassuring that dose-independent side effects of Avalide are rare. Reports of pancreatitis (which is not clearly dose-dependent) are less than 1 per million patient years of exposure, and interstitial pneumonitis has not been reported.

In conclusion, post marketing surveillance data indicates that Avalide is safe and well-tolerated in current use, and has a safety profile that is consistent with that observed in the clinical trial program and the current product label. With the possible exception of the well-known adverse effect of hypokalemia, these data suggest that the safety profile for Avalide used in clinical practice does not appear to differ from that of irbesartan alone.

5 BENEFIT/RISK PROFILE

5.1 Rationale

In Study 176 Avalide reduced exposure to severe blood pressure levels, reduced blood pressure by approximately 10/5 mmHg more than irbesartan monotherapy did, and showed no overall increase in adverse events. The findings are also consistent with the original NDA and post-marketing surveillance data. The data form the basis of a favorable benefit/risk profile.

A benefit/risk profile of initial combination therapy for hypertension has been previously published by Law and colleagues.[13] It supports that benefit/risk of Avalide and is based on the same concept of the tolerability of both irbesartan and low-dose HCTZ.

Law and colleagues examined results from 354 randomized, blinded, placebo-controlled studies and a total of over 55,000 patients to examine the efficacy and safety of monotherapy and combination therapy in the treatment of hypertension.

They found that the efficacy of fixed-dose combinations was additive, almost exactly the sum of the efficacy of the individual components. Yet fixed-dose combinations had significantly fewer adverse effects than would be expected from the sum of the adverse effects of the individual components.

This was attributed to the effective use of low doses of at least one of the individual components, where adverse effects are the same as placebo. In particular, Law and colleagues reviewed several potential dose-dependent adverse effects of thiazides and concluded that they did not pose serious health risks.

Law and colleagues went on to perform a benefit/risk assessment for combination therapy compared to monotherapy. Since low doses of an individual component enhance efficacy without incurring adverse effects, the benefit/risk was based entirely on the blood pressure benefits of combination therapy. They concluded, "Low-dose combination treatment should be used as a first option in lowering blood pressure, and the indications for using blood pressure-lowering drugs should be broadened."[13]

5.2 Risks

The main concern regarding risks in initial use of Avalide vs irbesartan monotherapy is the possible increased exposure of patients to the dose-independent and dose-dependent side effects associated with the added component, HCTZ. The dose-dependent side effects with HCTZ include dizziness, syncope, hypotension, hypokalemia, and allergic reactions. The dose-independent side effects include interstitial pneumonitis and may include pancreatitis (although the relationship to dose is not clear).

Regarding the dose-dependent side effects, there was no significant increase of these for Avalide vs irbesartan monotherapy in Study 176, Study 185, or the original NDA. Post-marketing data in Table 4 indicate a slightly higher incidence on Avalide than on irbesartan monotherapy for hypokalemia and increased blood glucose. All cases of hypokalemia resolved with appropriate measures and the majority of glucose elevations reported were not serious. The clinical magnitude of the difference for these 2 events is very small (<2 per 1,000,000 patient-years of exposure). Therefore, there is no additional clinically significant risk of these 2 events to patients on Avalide. The incidences of dizziness, hypotension, syncope, allergic reactions, increased creatinine, and new-onset diabetes for Avalide are all lower than for irbesartan monotherapy in post-marketing data.

Regarding dose-independent adverse effects associated with HCTZ, neither one was seen in Study 176 or 185. In post-marketing data (Table 4) only pancreatitis shows a slight excess (0.2 per 1,000,000 patients-years) on Avalide vs irbesartan monotherapy. These events are reported so rarely that precise quantification of their incidence is impossible.

The safety profile for Avalide seen in Study 176, Study 185, and in post-marketing surveillance demonstrated no appreciable increased risk for dose-independent or dose dependent adverse events associated with HCTZ. Therefore, the actual risk of Avalide vs irbesartan monotherapy is extremely low.

In particular, the current Avalide product label states that irbesartan's action in elevating potassium can offset the tendency of HCTZ to reduce it. The label also states that HCTZ has the potential to unmask latent diabetes. The label includes a precaution for patients with hypovolemia.

There may be concern that diuretics can lead to increases in creatinine or blood urea nitrogen, or decrease glomerular filtration rate in patients with hypovolemia or renal insufficiency. Yet mild diuresis (as seen with low-dose HCTZ) can actually be beneficial to patients with renal disease, since they have sodium retention. Diuretics and irbesartan were given safely as concomitant medications to patients with renal disease in the morbidity/mortality trial known as IDNT.[14]

Interstitial pneumonitis and pancreatitis may be considered in a benefit/risk analysis because they have the potential to be life-threatening, and they have been described in the medical literature.[15,16,17] An estimate for each of these for Avalide can be obtained from the upper 95% confidence interval of its relative reporting ratio compared to irbesartan monotherapy in Table 4. Yet post-marketing surveillance can under-report adverse events, so a 10-fold greater incidence of these events may be considered. So there is the potential for 0 to 1 cases of interstitial pneumonitis and 0-2 cases of pancreatitis for every 100,000 patients treated with Avalide.

5.3 Benefits

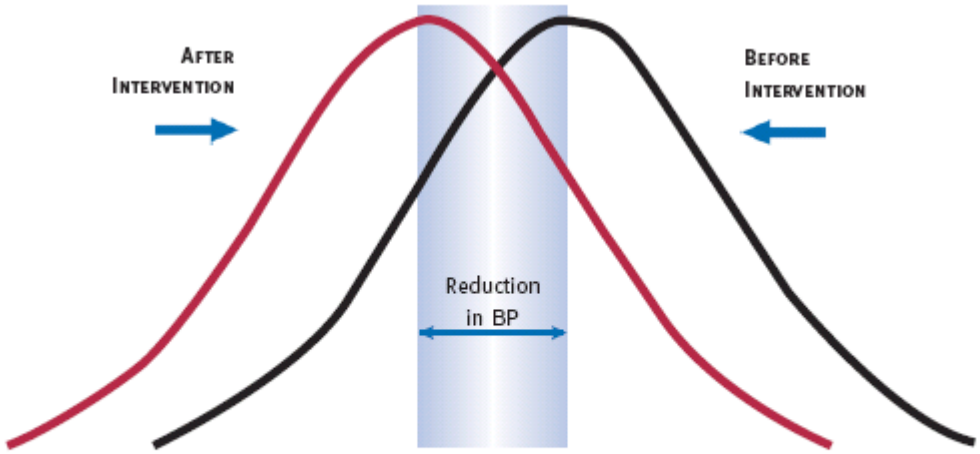
Given the low risk of Avalide compared to irbesartan monotherapy, it is important to consider whether the blood pressure benefits are clinically meaningful. A general perspective of this can be obtained by considering the baseline risks of a population with severe hypertension and the potential risk reduction of blood pressure lowering.

The Framingham data in Figure 2 show cardiovascular event rates in a broad range of 250 to 500 events per 10,000 patient-years of follow-up. In a population of 100,000 individuals with severe hypertension, this means 2,500 to 5,000 events per year. These

risks are much greater than the potential for serious adverse events from the HCTZ component of Avalide.

The potential for better risk reduction with Avalide depends on its superior blood pressure lowering. In Study 176 this was approximately 10 mmHg SBP compared to irbesartan monotherapy. Even 5 mmHg or smaller differences in SBP are meaningful, as shown in Figure 5.3 from JNC 7 guidelines.[18] In a population of 100,000 individuals with severe hypertension, these risk reductions suggest the potential to prevent hundreds of cardiovascular events.

Figure 5.3: Potential Risk Reduction Based on Lowering of Blood Pressure



Reduction in SBP mmHg	% Reduction in Mortality Stroke	CHD	Total
2	-6	-4	-3
3	-8	-5	-4
5	-14	-9	-7

The quantification of benefits is an imprecise task. It relies on a surrogate marker of clinical outcome, blood pressure, and a careful examination of the literature. Questions may relate to the timing and duration of benefit.

In this respect, two types of projections are considered. The first is based on the risk of hypertensive emergencies, which represent the most immediate concern of severe hypertension. The second is based on the incremental 10/5 mmHg that was seen with

Avalide compared to irbesartan monotherapy. It considers the potential for these blood pressure advantages of Avalide to persist for several months or more.

5.3.1 Avoiding Hypertensive Emergencies

Though Study 176 was a short-term study, the results achieved are meaningful to patients. The Initial Cohort of the original VA Cooperative study (patients with DBP 115-129 mmHg) demonstrated the early (within weeks of starting treatment) and meaningful effect of initial combination therapy (including HCTZ): the reduction in hypertensive emergencies was significant when compared with results on placebo.[9] Though the placebo arm of this study had only 70 patients, there was a substantial excess of morbid events in that arm. After 8 weeks there were 5 events on placebo and none on active treatment. After 24 weeks there were 9 events on placebo and none on active treatment. Most of the morbid events were hypertensive emergencies. The study was stopped early when the difference in event rates was seen.

The second cohort of the VA study (patients with DBP 105-114 mmHg) also demonstrated the benefit of short-term reduction in blood pressure resulting from initial use of combination therapy in patients with severe hypertension.[10] In this group of 210 patients (100 treated and 110 on placebo) there were 21 hypertensive emergencies on placebo and only 1 on combination therapy; and there were 20 cases of DBP ≥125 mmHg on placebo and none on combination therapy. The exact timing of the events in this cohort is not given, but the authors stated that the benefits were seen early and accumulated steadily throughout the study.

The National Heart Lung and Blood Institute (NHLBI) study showed that effective treatment of severe hypertension with combination therapy reduced morbid events and the benefit was seen within 24 weeks. Within 2 years, among 42 placebo patients there was an excess of 13 morbid events.[11]

Based on experience in the VA Cooperative Study and the NHLBI, the risk of hypertensive emergencies in uncontrolled severe hypertension is approximately 10% 20% per patient-year. These classic trials are consistent with events seen today. Preston and colleagues examined management of severe hypertension at a teaching hospital. Of 74 patients managed on an outpatient basis, 10 returned in an average of 33 days with new evidence of acute organ damage.[19] An initial review of outcomes in over 2,000

patients with severe hypertension seen at Christiana Medical Center (Delaware) indicates an approximately 15% risk for an emergency room visit or cardiovascular hospitalization within one year (personal communication, Dr. William Weintraub).

In Study 176 Avalide was estimated to reduce exposure to severe hypertension compared to irbesartan monotherapy by approximately 42 patient-weeks (from 144 patient-weeks to 102 patient-weeks; P=0.0002) of exposure for every 100 patients treated for 7 weeks with Avalide vs irbesartan monotherapy. Qualitatively, this reduction is relevant in terms of concerns that physicians and patients have about the potential for hypertensive emergencies. The reduction in exposure for every 100 patients is approximately 0.8 years (42weeks/52weeks/year=0.8 years). In a population of 100,000, that suggests 800 fewer patient years of exposure to severe blood pressure levels with initial Avalide compared to irbesartan monotherapy.

Therefore, this reduction of 800 patient-years in exposure to severe blood pressure has the potential to prevent 80 to 160 hypertensive emergencies per 100,000 patients.

The estimates are derived as follows. The lower range is

(0.8 patient-years/100 patients)* 100,000 patients *0.1(events/patient-year) = 80 events.

The upper range is

(0.8 patient-years/100 patients)* 100,000 patients *(0.2events/patient-year) = 160 events.

The projected benefit is within the context of frequent office visits and prompt titration, as conducted in Study 176. If in actual practice physicians intervene less frequently, then the time during which patients are exposed to either irbesartan 150 mg or Avalide 150/12.5 mg is prolonged. Similarly, the time during which patients are exposed to irbesartan 300 mg compared to Avalide 300mg/25 mg is also prolonged.

5.3.2 Avoiding Cardiovascular Events

Reducing blood pressure by a mean of 10/5 mmHg with the initial use of Avalide compared to monotherapy with irbesartan is also expected to be beneficial. The meta-analyses conducted by MacMahon examined the results of observational studies and predicted substantial reductions in heart disease (21%) and stroke (34%) with a 5 mmHg reduction of DBP.[20] The meta-analysis of Collins examined the results of clinical trials

and confirmed over 40% reduction in stroke and 14% reduction in coronary heart disease when DBP was reduced by approximately 5 mmHg.[21]

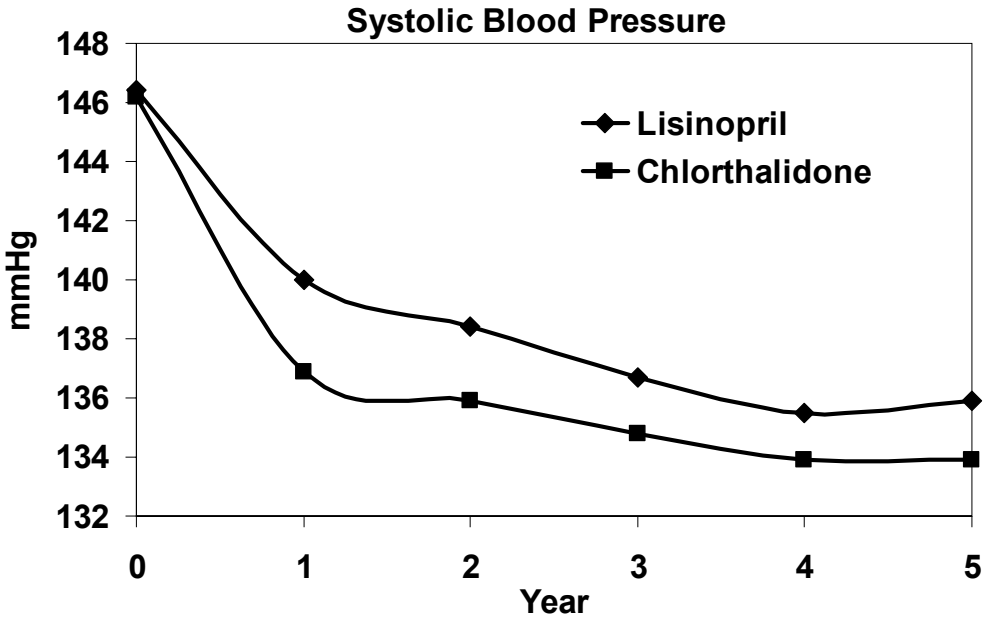
The superior blood pressure reductions with Avalide in Study 176 were seen for the length of the study, approximately 0.1 year. But in clinical practice the benefit may extend to many months or years beyond this short period because physicians do not always intensify antihypertensive treatment sufficiently. In large clinical trials initial differences in blood pressure are sustained even when clinical protocols instruct physicians to titrate to goal.

The delays in increasing therapy were shown in a landmark study in the New England Journal of Medicine conducted by Dr. Dan Berlowitz.[22] In a large cohort of patients, physicians were slow to increase medication. More recently Dr. Berlowitz has also shared preliminary data specifically in severe hypertension. Physicians will increase therapy at 40% of visits when blood pressure levels are severe, but with moderate and mild blood pressure elevations, they are less likely to take action, and the interval between visits is greater. If a physician continued to titrate medication 40% of the time and sees patients approximately 6 times a year, then it can take 8 months or more to take a population from full dose of irbesartan to full dose of Avalide.

The estimate of 8 months is a conservative one. In large clinical trials comparing hypertension treatments, it has often taken at least 2 years for early differences in blood pressure lowering to be reduced by the addition of adjunctive therapy. This was seen in Syst-Eur, SCOPE, ASCOT, ALLHAT (for chlorthalidone vs lisinopril) and VALUE.[2,3,4,5,6] Physicians know that blood pressure varies considerably from visit to visit, so they often wait to see a consistent pattern of persistent blood pressure elevations before changing therapy.

The time course of blood pressure change in ALLHAT is shown in Figure 5.3.2 for the chlorthalidone and lisinopril arms.[5] This is similar to that seen in other hypertension trials. Initial efficacy is substantial, but once patients respond further progress is slow. And both treatment arms continue to improve over time because most patients in both treatment arms will need even more therapy than provided by the initial treatment regimen. So the advantage of a better initial therapy can persist for years.

Figure 5.3.2: Time Course of Blood Pressure Changes in ALLHAT



So the benefit/risk estimates below are based on a 10/5 mmHg blood pressure benefit of Avalide that persists over a range of 0.1 years (the duration of Study 176) to 8 months (0.67 years) more for a total of 0.77 years.

The cardiovascular benefits seen in the meta-analysis of Collins are described in the World Health Organization hypertension guidelines, which state that blood pressure reductions of 10/5 mmHg can prevent from 5 to more than 10 cardiovascular events per 1000 patient-years of exposure for patients who are at medium to very high cardiovascular risk.[23]

The potential to prevent cardiovascular events is estimated as follows. The lower range is

(0.1 patient-years/patient) * 100,000 patients * 10 events/1000 patient-years = 50 events.

The upper range is

(0.77 patient-years/patient)*100,000 patients * 10 events/1000 patient-years=770 events.

5.4 Summary of Benefits/Risks

Weighing the potential benefits against the risks yields a highly positive benefit/risk profile (Table 5.4). While these numbers are only intended to provide a rough estimate, they highlight the clinical concepts underlying initial combination therapy: avoiding persistent exposure to severe blood pressure levels, and providing a more effective initial therapy whose incremental benefits may persist for months or more. The estimates suggest that initial use of Avalide in a large population can benefit patients by preventing hundreds of events for every 100,000 patient-years of exposure. At the same time, anywhere from 0 to 3 cases of pancreatitis or interstitial pneumonitis are possible (per 100,000 patient-years), although in post-marketing data these risks were too low to be quantified with any precision.

Table 5.4: Potential Benefits and Risks in a Population of 100,000 Patients with Severe Hypertension Treated with Initial Use of Avalide Instead of Irbesartan Monotherapy

Potential Benefits	Additional events prevented
Hypertensive emergencies	80 to 160
Cardiovascular events (for 10/5 mmHg reduction lasting from 0.1 to 0.77 years)	50 to 770
Potential Risks	**Additional cases**
Pancreatitis	0 to 2
Interstitial pneumonitis	0 to 1

The data indicate that the benefit/risk profile for initial use of Avalide in severe hypertension is highly favorable. The reductions in exposure to severe hypertension and the approximately 10/5 mmHg early advantage in blood pressure reduction with initial use of Avalide have the potential to prevent hypertensive emergencies and cardiovascular events.

As with all drugs, the benefit/risk will not be the same in all patients, and physicians should have information allowing them to individualize care.

5.5 Guidance to Physicians

The treatment of severe hypertension should be individualized based on the benefits and risks for each patient. With respect to the benefits of initial combination therapy, the physician may consider the overall cardiovascular risk of the patient. For example, a patient with a major risk factor such as diabetes or a history of stroke may benefit more from initial combination therapy. Blacks are also at particularly high risk, because they are more prone to renal complications. They also do not respond as well as other populations to monotherapy with agents acting on the renin angiotensin system.

Physicians may also consider the risks of combination therapy. While no serious risks have been seen in Study 176, greater caution is appropriate in treating a patient with a history of orthostatic hypotension or volume depletion.

One of the most important elements in determining benefit/risk is the baseline blood pressure. Patients with higher baseline blood pressures are at higher cardiovascular risk. Furthermore, it is logical that patients with higher blood pressure are less likely to achieve their goals on monotherapy. Therefore, their risks of unnecessary exposure to HCTZ in initial combination therapy are low.

Figures 5.5A and 5.5B below can help the physician understand how baseline blood pressure levels relate to the need for combination therapy. These figures, coupled with the knowledge of expected reductions in SBP and DBP for Avalide and irbesartan, can help guide treatment decisions. Given such data, physicians may be better informed to make sound clinical judgments regarding the choice between initial combination and monotherapy for their patients.

Another consideration is how far patients are from their BP goals. Some patients may be adequately treated by monotherapy. For example, a patient with a baseline blood pressure of 160/110 mmHg may have a reasonable chance of achieving a blood pressure target of 140/90 mmHg on monotherapy. However, a patient with a blood pressure of 190/110 mmHg and a major risk factor such as diabetes will likely need combination therapy to achieve a lower goal. At Week 5, the mean reduction of SBP on irbesartan was 21.1 mmHg. Therefore, as Figure 5.5A shows, patients whose BP is 30 mmHg above SBP goal are likely to need combination therapy. Some patients need to achieve lower blood pressure goals such as 130/80 mmHg, and they likewise have a greater need for combination therapy

Figure 5.5A: Achievement of SBP <140 mmHg

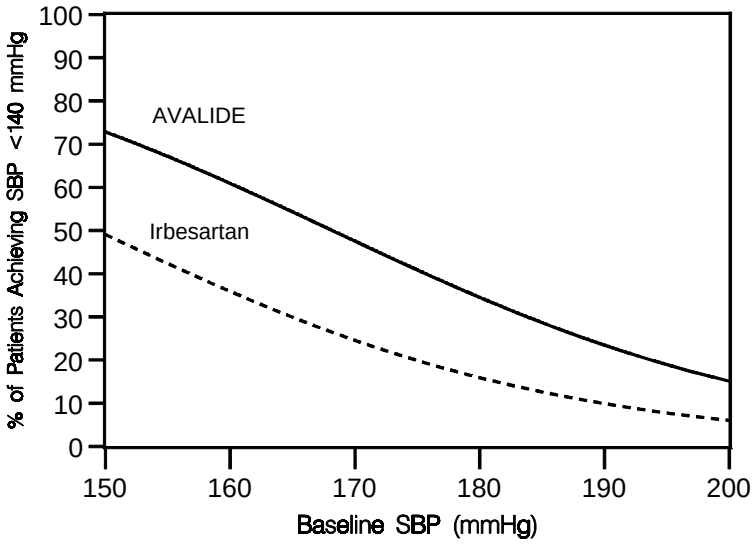
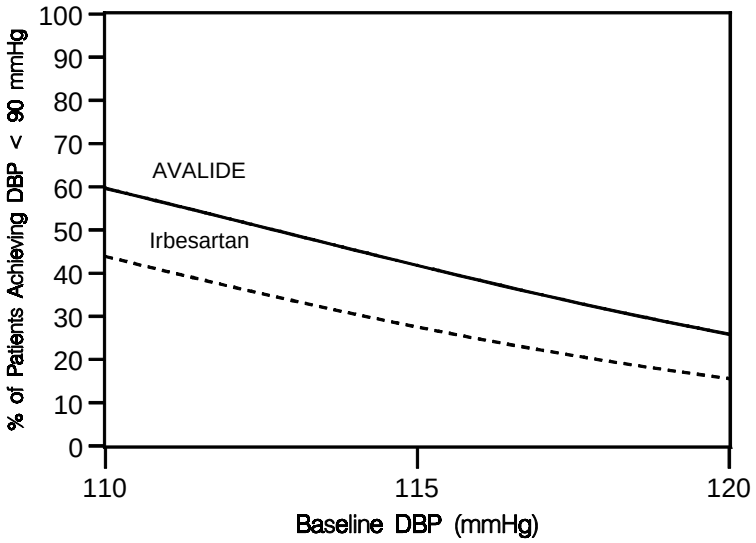


Figure 5.5B: Achievement of DBP < 90 mmHg



6 CONCLUSIONS

- The clinical trial program demonstrated a favorable benefit/risk profile for Avalide as initial therapy for severe hypertension.
- The need for combination therapy is greatest in those who are furthest away from their target blood pressure levels or have important CV risks.
- The results of pivotal Study 176 can help physicians individualize treatment for severe hypertension most effectively.
- The Avalide label should be changed to allow first-line treatment of severe hypertension.

LIST OF ABBREVIATIONS

AE	Adverse event
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
DBP	Diastolic blood pressure
HCTZ	Hydrochlorothiazide
IMS	International Medical Statistics
JNC	Joint National Committee
MedDRA	Medical Dictionary for Regulatory Activities
NGPS	Next Generation Prescription Services
NHLBI	National Heart Lung an Blood Institute
SBP	Systolic blood pressure
SeDBP	Seated diastolic blood pressure
VA	Veterans Administration

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