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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name Melanie Blank, MD
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Established Name Telmisartan/Amlodipine
(Proposed) Trade Name Twynsta
Therapeutic Class Combination Antihypertensive
Applicant Boehringer-Ingelheim

Priority Designation S

Formulation Tablet
Dosing Regimen Once a day
Indication First-line treatment for moderate
to severe hypertension
Intended Population Stage I and Stage II hypertension

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Trial No. / Report No. (Name)	Objectives	Trial Design	Patient Population	Treatment Duration	Key Endpoints	Treatment Groups*	Number of Subjects (total)
Phase IIIb/IV Trials with Telmisartan in Hypertensive Diabetics (by concomitant use of amlodipine)							
502.236 U04-1945-01 (DETAIL)	To compare the renal consequences of telmisartan and enalapril treatment in patients with hypertension and concurrent type 2 diabetes and diabetic nephropathy	Randomized, double-blind, double dummy, forced titration, parallel group comparison	Male or female patients with documented history of mild to moderate hypertension (with on-treatment DBP \leq 95 mmHg and mean seated SBP \leq 180 mmHg) and concurrent type 2 diabetes mellitus and diabetic nephropathy (UAER $>$ 10 and $<$ 1000 μ g/min)	5 years	Efficacy: Glomerular filtration rates, urinary albumin excretion rates, creatinine, and blood pressure Safety: Incidence of clinical endpoints, all-cause mortality, and safety	T40 mg (Micardis®) uptitrated to 80 mg Enalapril 10 mg uptitrated to 20 mg (A allowed as background therapy; only patients on T \pm concomitant A analyzed in SCS.)	T: 120 Enalapril: 130 (250 total) Analyzed in SCS: 82 T w/o con. A, 38 T with con. A
502.396 U06-1367-01 (VIVALDI)	To compare the effects of telmisartan 80 mg and valsartan 160 mg on proteinuria in hypertensive patients with type 2 diabetes and overt nephropathy after 1 year of treatment.	Randomized, double-blind, double dummy, forced titration, parallel-group comparison	Male and female patients with type 2 diabetes mellitus, hypertension (untreated SBP $>$ 130 mm Hg or DBP $>$ 80 mm Hg, or currently receiving antihypertensive medication), and overt nephropathy (serum creatinine \leq 265 μ mol/L and UPER \geq 900 mg/24 hr)	1 year	Primary: Change from baseline in UPER Secondary: 24-hr UAER, 24-hr urine sodium excretion, serum creatinine, CrCl, eGFR, ADMA levels, 8-iso-prostaglandin F2 α levels; high sensitive CRP; BP; time to a composite of a doubling of serum creatinine concentration, ESRD, or all-cause death Safety: AEs, PEs, laboratory parameters, ECG, and vital signs	T40 mg (Micardis®) uptitrated to 80 mg Valsartan 80 mg uptitrated to 160 mg (A allowed as background therapy; only patients on T \pm concomitant A analyzed in SCS.)	T: 443 Valsartan: 442 (885 total) Analyzed in SCS: 278 T w/o con. A, 165 T with con. A

* Study medication was in tablet form, administered orally once daily unless otherwise noted.

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Twynsta, the subject of this NDA review, is an angiotensin II receptor blocker (telmisartan) and a dihydropyridine calcium channel blocker (amlodipine) combination drug product intended to treat hypertension. The proposed indication for Twynsta is:

- In patients not adequately controlled on antihypertensive monotherapy
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals

Pivotal trial 1235.1 and other supportive phase 3 and 4 trials submitted in NDA 22401, including the ONTARGET trial (Mann et al, Lancet 2008 Aug 16; 372:547-53), demonstrate that Twynsta is safe and effective and is appropriate to use as a combination antihypertensive therapy drug for patients that are uncontrolled on monotherapy as well as a first line therapy for patients that are likely to require combination antihypertensive therapy.

The primary efficacy endpoint, a demonstration of superiority of highest marketed doses of the key combinations of telmisartan (T) and amlodipine (A) (T40mg + A5mg, T40mg + A10mg, T80mg + A5mg and T80mg + A10mg) over the individual monotherapies in lowering seated trough diastolic blood pressure (DBP), was met ($p < 0.0001$) in trial 1235.1. Additionally, there were no compelling safety issues. In fact, the dose-limiting side effect of peripheral edema caused by amlodipine 10 mg was substantially less with the co-administration of telmisartan.

Notable points on the Trial 1235.1 include the following:

EFFICACY ANALYSIS

1. The full efficacy analysis set included 1423 patients. The safety analysis included 1461 patients.
2. The trial was conducted in over 100 sites in 4 U.S. regions, Mexico, Argentina, Brazil, and South Africa
3. There was a race distribution reflective of the U.S. population: approximately 15% Blacks, approximately 4% Asians, and approximately 81% Whites. The sexes were represented equally.
4. All patients who were in one of the amlodipine 10 mg + telmisartan or placebo cells were started on a fixed dose of amlodipine 5 mg + telmisartan or placebo and titrated up to amlodipine 10 mg + telmisartan or placebo after one week.
5. 8% of the patients discontinued the trial. The most common reasons for discontinuation were: adverse events (2.6%), consent withdrawn (1.8%), and lack of efficacy, (1.1%) were the most. This was a low drop out rate.

6. The drop in seated trough diastolic blood pressure in mmHg between the key (to be marketed) combination treatments and each individual component was statistically significant at each dose studied.
7. The placebo subtracted effect on trough seated DBP for the highest combination dose, T80 +A10 was 13.7 mmHg.
8. For all the dose combinations, the additive trough seated delta DBP effect was between 60 and 70% of the effect one would have expected if the drug effects were fully additive. This is within the range of what is seen with other combination drugs. When looking at the pooled data, in the A10 + T combinations, amlodipine made the larger contribution to the additive effect whereas the A and T contributions were approximately equal in the A5 + T combinations.
9. The majority of the DBP antihypertensive effect in mono- and combination therapy was attained in by the time of the initial visit at two weeks and the maximum antihypertensive effect occurred by 4 weeks after therapy initiation.
10. ABPM hourly mean reductions in DBP and SBP over the 24-hour dosing interval for combination therapy were consistently of a greater magnitude than the respective monotherapies. Additionally, it was demonstrated that there is consistent 24 hour blood pressure control for the combination products. The dose relationship for the combination product is small but demonstrable and provides evidence that there is a dose relationship among the combination product with the T80A10 combination being the most effective dose, followed by the T40A10, followed by the T80A5, followed by the T40A5.
11. Twynsta was demonstrated to be more effective at lowering SBP than each of the monotherapies (all analyses had a p value <0.0001 except for the T40A10 combination vs. A10 which had a p value = 0.018).
12. The responder analysis demonstrated that the combination product is superior to the individual monotherapies for attainment of goals of DBP < 90 mmHg, DBP < 80 mmHg, SBP < 140 mmHg and SBP < 130 mmHg. This analysis confirms the appropriateness of first-line use of Twynsta. However, it is prudent to cut off the responder analysis graphs at >95mmHg baseline DBP on the left and ≤ 110 mmHg baseline DBP on the right of the x axis because of the very few patients that were studied outside of this range.
13. Subgroup analyses did not show much difference between subgroups other than a generally larger effect in women compared to men (but there was also a considerably larger placebo effect in women) and in patients ≥ 65 years of age compared to patients <65. Of interest, in Blacks there was little if any difference between the delta DBP between the amlodipine monotherapy groups and most of the combination therapy groups, suggesting that there is probably less benefit from a pure efficacy perspective of switching Blacks from amlodipine to Twynsta.

SAFETY ANALYSIS

1. The only death reported in Trial 1235.1 was a 50-year-old male patient who experienced fatal choking starting 28 days after initiation of treatment with telmisartan 80 mg. No other AEs were reported for the patient during the course of the trial, and no concomitant medication was used. The causal relationship between the drug and this event is unknown. Choking is an unusual event and has not been associated with telmisartan use in the past.

2. AEs occurred in 37.3% of treated patients and the occurrence of AEs was well balanced between active treatment groupings
3. There were approximately 8% of the patients in each treatment group that had AEs while approximately 15% of patients in the placebo group had AEs. Only 1-2% of the patients in the trial had SAEs.
4. According to my analysis, the most frequently reported adverse events in the pooled combination therapies in Trial 1235.1 were peripheral edema (4.8%), headache (4.7%), dizziness (3.0%), and back pain (2.2%). There was no great difference in incidence of these common AEs between the combination and monotherapy treatment cells except for dizziness which was twice as common in the combination therapy cells and for peripheral edema which was lower in the pooled combination therapies than in the pooled amlodipine monotherapies.
5. The total number of AEs leading to treatment discontinuation in this trial was 33. This number is so low that it is difficult to make any comparative treatment group analyses. There were comparable percentages of patients that discontinued due to AEs in the pooled combination and in the monotherapies
6. The increased incidence of peripheral edema in amlodipine monotherapy patients was most prevalent in those patients randomized to A10. There was a dose dependent effect for patients on amlodipine (17.8% in A10 treatment group, 0.7% in A5 treatment group). No dose dependent effect was seen in telmisartan monotherapy treated patients. In the combination therapy groups, there were 6.2% and 11.3% peripheral edema AEs in the T40A10 and the T80A10 treatment groups, respectively. Although the study was not powered to detect statistical differences among treatment groupings for any individual AE and there was no prespecified efficacy endpoint for reduction in edema, a post-hoc analysis of the occurrence of peripheral edema demonstrated a significant difference among treatment groups $p < 0.0001$.
7. Clinically meaningful orthostatic changes were defined as a decrease in DBP > 10 mmHg and/or decrease in SBP > 20 mmHg, a reasonable definition. A total of 99 (7.0%) patients experienced orthostatic changes in SBP and/or DBP during the trial. Orthostatic changes were observed in placebo: 4.3%, telmisartan monotherapy: 6.1% to 7.1%, amlodipine monotherapy: 8.1% to 12.5% and combination: 2.5% to 10.6%. Since clinically meaningful orthostatic changes rarely translated to symptomatic orthostasis, and there were only 2 syncopal events in this trial, these orthostatic changes are less worrisome.
8. Overall, the observed laboratory changes were in accordance with the existing labeling of its respective components, telmisartan and amlodipine. Telmisartan is associated with an increased risk of hemoglobin drop than placebo according to the package insert. While it is possible that the combination product could augment this adverse effect, I do not think that this is an overriding safety concern.
9. The overall safety profile of these combinations treatments was comparable to their monotherapy components.

1.2 Risk Benefit Assessment

There are no safety concerns aside from need to avoid drug in pregnancy, potential concerns for orthostatic hypotension and risk for peripheral edema (which is mitigated by the combination product) and angioedema (risks that are germane to the already approved drug components). These risks can be stated in the label and patient information sheets. There is a proven antihypertensive benefit for these drugs. Therefore, there is a favorable risk benefit assessment.

1.3 Recommendations for Postmarketing

15-day safety reports and PSURs as per CFR21 314.80

1.4 Risk Management Activities

Patient information sheet that informs patients on the following risks is recommended:

- Women should not take drug when pregnant, breast feeding or when planning pregnancy
- Elderly patients (≥ 75 years of age) should start on the lowest dose of the combination drug
- Patients at risk for peripheral edema should start on the A5 + T combinations
- Patients allergic to either of the components should not take Twynsta

1.5 Recommendations for other Post Marketing Study Commitments

- No recommendations for post-marketing studies

2 Introduction and Regulatory Background

2.1 Product Information

Twynsta is a combination product of two already approved antihypertensive drugs, amlodipine, a dihydropyridine calcium channel blocker, and telmisartan, an angiotensin receptor blocker.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are multiple combination drugs. Capozide, Hyzaar, Ziac, Azor and Exforge are approved for first line use. All currently approved combination antihypertensive therapy drugs are listed in Table 1.

Table 1: Combination Drugs for the Treatment of Hypertension

Combination Type*	Fixed-Dose Combination, mg†	Trade Name
ACEIs and CCBs	Amlodipine-benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20)	Lotrel Lexxel
	Enalapril-felodipine (5/5)	Tarka
	Trandolapril-verapamil (2/180, 1/240, 2/240, 4/240)	
ACEIs and diuretics	Benazepril-hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25)	Lotensin HCT
	Captopril-hydrochlorothiazide (25/15, 25/25, 50/15, 50/25)	Capozide
	Enalapril-hydrochlorothiazide (5/12.5, 10/25)	Vasoretic
	Fosinopril-hydrochlorothiazide (10/12.5, 20/12.5)	Monopril/HCT
	Lisinopril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Prinzide, Zestoretic,
	Moexipril-hydrochlorothiazide (7.5/12.5, 15/25)	Uniretic
	Quinapril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Accuretic
CCBs and ARBs	Amlodipine-valsartan (5/160, 10/160, 5/320, 10/320)	Exforge
	Amlodipine-Olmesartan (5/20, 5/40, 10/20/10/40)	Azor
CCBs and ARBs and diuretics	Amlodipine- -hydrochlorothiazide-valsartan (5/12.5/160, 5/25/160, 10/12.5/160, 10/25/160, 10/25/320)	Exforge/HCT
ARBs and diuretics	Candesartan-hydrochlorothiazide (16/12.5, 32/12.5)	Atacand HCT
	Eprosartan-hydrochlorothiazide (600/12.5, 600/25)	Teveten-HCT
	Irbesartan-hydrochlorothiazide (150/12.5, 300/12.5)	Avalide
	Losartan-hydrochlorothiazide (50/12.5, 100/25)	Hyzaar
	Olmesartan medoxomil-hydrochlorothiazide (20/12.5,40/12.5,40/25)	Benicar HCT
	Telmisartan-hydrochlorothiazide (40/12.5, 80/12.5)	Micardis-HCT
	Valsartan-hydrochlorothiazide (80/12.5, 160/12.5,	Diovan-HCT

	160/25) Aliskiren Hemifumarate-hydrochlorothiazide (150/12.5, 150/25, 300/12.5, 300/25)	Tekturna HCT
BBs and diuretics	Atenolol-chlorthalidone (50/25, 100/25) Bisoprolol-hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25) Metoprolol-hydrochlorothiazide (50/25, 100/25) Nadolol-bendroflumethiazide (40/5, 80/5) Propranolol LA-hydrochlorothiazide (40/25, 80/25) Timolol-hydrochlorothiazide (10/25)	Tenoretic Ziac Lopressor HCT Corzide Inderide LA Timolide
Centrally acting drug and diuretic	Methyldopa-hydrochlorothiazide (250/15, 250/25, 500/30, 500/50) Reserpine-chlothalidone (0.125/25, 0.25/50) Reserpine-chlorothiazide (0.125/250, 0.25/500) Reserpine-hydrochlorothiazide (0.125/25, 0.125/50)	Aldoril Demi-Regroton, Regroton, Diupres Hydropres
Diuretic and diuretic	Amiloride-hydrochlorothiazide (5/50) Spironolactone-hydrochlorothiazide (25/25, 50/50) Triamterene-hydrochlorothiazide (37.5/25, 75/50)	Moduretic Aldactazide Dyazide, Maxzide

Source: JNC 7

*Drug abbreviations: BB, beta-blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker

†Some Drug combinations are available in multiple fixed doses. Each drug dose is reported in milligrams.

2.3 Availability of Proposed Active Ingredient in the United States

There is no concern about the availability of active ingredients in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

It should be recommended that clinicians consider discontinuing other angiotensin receptor blockers (ARBs) and/or dihydropyridine calcium channel blockers (DHP CCBs) and angiotensin converting enzyme inhibitors (ACEIs) when prescribing Twynsta. Patients at risk for renal failure should not combine this drug with an ACE inhibitor.

Summary of Presubmission Regulatory Activity related to this submission
 The IND for this drug is 71,882. A Type C meeting occurred on April 9, 2008.

Discussion points included:

- 1) FDA expressed concern that since the lowest dose of amlodipine would not be used, there might be limitations placed on the population that will be considered for initial therapy. The Sponsor acknowledged this potential limitation and suggested that limitations might be placed on use in the elderly, diabetics and patients with renal or hepatic failure. The FDA encouraged the Sponsor to address difference seen in the study with respect to these subgroups and other subgroups where differences were seen.
- 2) FDA suggested that orthostatic measurements at peak drug effect should be assessed.
- 3) The Sponsor was told that they should consider how well they can defend the safe use of the product in patients with elevated blood pressure when the patient population is old and frail. The Sponsor acknowledged that there was limited data in patients ≥ 75 years old.
- 4) The FDA informed the Sponsor that it was not clear at the time that labeling for (b) (4) (b) (4) would be acceptable. This might require data from post-marketing studies.
- 5) The FDA was concerned that the histograms that reflect achievement of goal by baseline blood pressure reading may be affected by small numbers of outliers and suggested that the Sponsor redo those figures excluding the outliers for further review.

2.5 Other Relevant Background Information

Hypertension is a prevalent disease affecting millions of people world-wide and is a significant risk factor for stroke, ischemic heart disease, vascular disease and renal failure. The National Heart, Lung, and Blood Institute (NHLBI) released The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC VII) and reported that approximately one billion people worldwide and 50 million individuals in the U.S. have high blood pressure. According to the Joint National Committee (JNC VI), “the goal of prevention and management of hypertension is to reduce morbidity and mortality by the least intrusive means possible.” Achieving and maintaining blood pressure below 140/90 mmHg (and preferably lower, if tolerated) is one way to accomplish this.

According to the JNC VII, more than 66% of hypertensive patients have uncontrolled blood pressure. Large scale studies have demonstrated that the majority of hypertensive patients can not be successfully controlled with one therapeutic agent alone. Most patients with hypertension, including those with co-existing diseases, require multiple antihypertensive agents to achieve blood pressure goals.

In a meta-analysis by Lewington¹ involving one million adults across 61 prospective studies, vascular and overall mortality risk reductions were shown to be strongly and directly related to blood pressure (BP) reductions without evidence of a blood pressure threshold to at least the 115/75 mmHg level. This analysis indicated that the relationship is approximately log-linear and differences of 20 mmHg systolic blood pressure (SBP) and 10 mmHg diastolic blood pressure (DBP) reductions directly correlate to a two-fold reduction in stroke mortality and in death rates for ischemic heart disease and other vascular deaths.

¹Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-1913.

Table 2 provides current guidelines for the management of hypertension. The severity of hypertension is now categorized as Stage 1, defined as blood pressure (BP) = 140-159/90-99 and Stage 2, defined as BP \geq 160/100.

Table 2: Classification and management of blood pressure for adults*

BP Classification	SBP* mmHg	DBP* mmHg	Lifestyle Modification	Initial drug therapy	
				Without Compelling Indication	With Compelling Indications (Heart failure, MI prevention, CAD risk, D.M, CKD, stroke prevention)
Normal	<120	and <80	Encourage	No antihypertensive drug indicated.	Drug(s) for compelling indications.‡
Prehypertension	120–139	or 80–89	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.	Drug(s) for the compelling indications.‡ Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
Stage 1 Hypertension	140–159	or 90–99	Yes	Two-drug combination for most† (usually thiazide-type diuretic and ACEI or ARB or BB or CCB).	
Stage 2 Hypertension	\geq 160	or \geq 100	Yes		

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Drug abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

* Treatment determined by highest BP category.

† Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

‡ Treat patients with chronic kidney disease or diabetes to BP goal of <130/80 mmHg.

Source: JNC 7

Micardis (telmisartan) is a member of the second generation of angiotensin II receptor antagonists with sustained blood pressure control over the full 24-hour dosing interval (source: package insert). It was developed by Boehringer Ingelheim and is an orally active, non-peptide

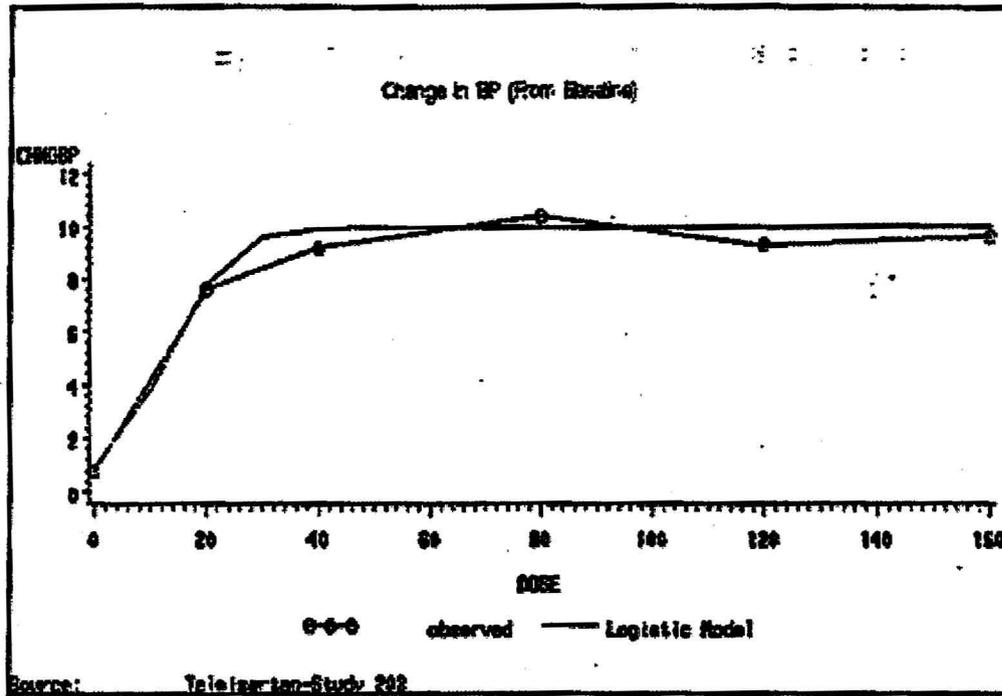
Type I angiotensin II receptor antagonist that lowers blood pressure with once-daily dosing by blocking the Type I angiotensin II receptor, thus selectively inhibiting the pressor effects of the renin angiotensin aldosterone system (RAAS). Micardis was approved for use in hypertension by the United States Food and Drug Administration (FDA) in November 1998 and is approved and marketed in many countries throughout the world. Despite its antihypertensive effects, there is little association with orthostatic changes. Following the subtraction of the placebo effect, a dosage of Micardis 40 mg once-daily reduces the SBP/DBP by an average of 9-13/6-8 mmHg; and a dosage of Micardis 80 mg once-daily reduces the SBP/DBP by an average of 12-13/7-8 mmHg. The antihypertensive activity occurs within three hours after single-dose administration and is maintained for the full 24-hour dosing interval. With ambulatory blood pressure monitoring (ABPM), the 24-hour trough-to-peak ratio for Micardis was determined to be 70–100% for both SBP and DBP.

Micardis has been evaluated for safety in clinical trials in more than 11,016 patients, including 1,683 patients treated for one year or more, and 1,165 patients treated for two years or more (Boehringer Ingelheim, data on file). The majority of adverse experiences have been of mild or moderate intensity and transient in nature; only infrequently have they required discontinuation of therapy. In placebo-controlled trials involving 2,739 patients treated with various doses of Micardis (20-160 mg) monotherapy for up to 26 weeks, the overall incidence of adverse events was comparable to placebo (Boehringer Ingelheim, data on file). The incidence of adverse events was not found to be dose-related. In studies where Micardis was compared with angiotensin converting enzyme (ACE) inhibitors, the incidence of dry cough was consistently greater (more than double) in the ACE inhibitor groups. In contrast, the overall incidence of dry cough on Micardis was comparable to placebo (Boehringer Ingelheim data).

The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range 20-160 mg, with greater than proportional increases of plasma concentrations (C_{max} and AUC) with increasing doses. Telmisartan shows bi-exponential decay kinetics with a terminal elimination half life of approximately 24 hours. Trough plasma concentrations of telmisartan with once daily dosing are about 10-25% of peak plasma concentrations, despite having a 24 hour effect. (Source: Telmisartan label)

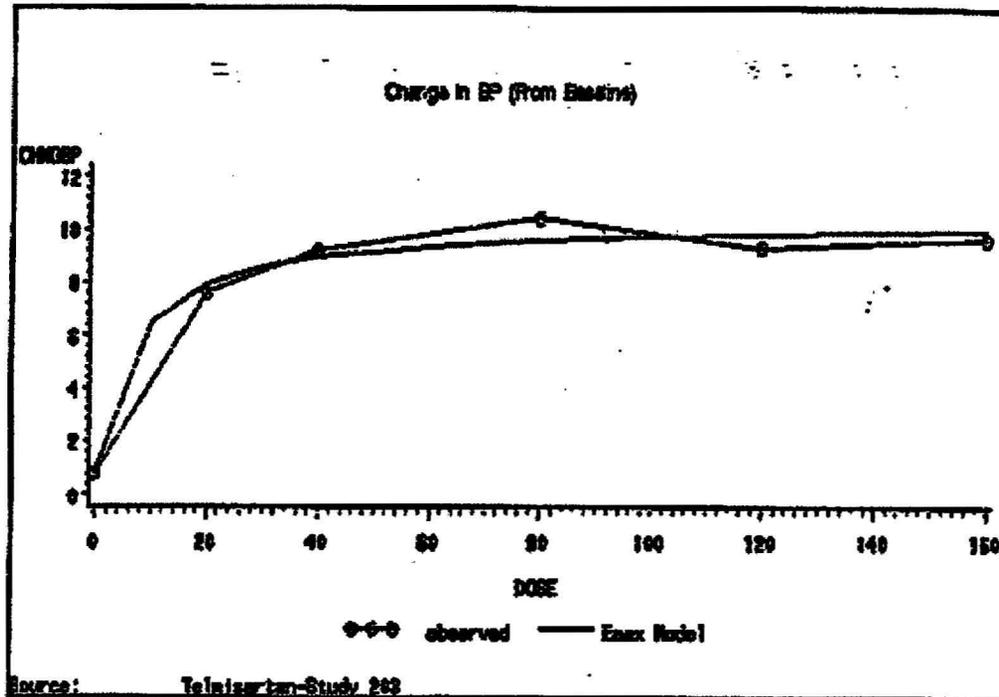
In Figure 1, Figure 2, and Figure 3 the statistician who reviewed the original telmisartan NDA provided figures that display the dose relationship in two of the original studies used for approval. The statistician concluded that, “the three dose response curves seem to have reached a plateau at some dose level between telmisartan 20 mg and 80 mg.” It is not clear that there is much of an advantage of the 80 mg dose over the lower doses. The maximum marketed dose of telmisartan is 80 mg. This finding of peak drug effect was also mirrored in the current NDA application (Figure 4).

Figure 1: Observed Changes from Baseline in Supine Diastolic Blood Pressure and the Estimated Logistic Model for Dose Response (Study 502.203)



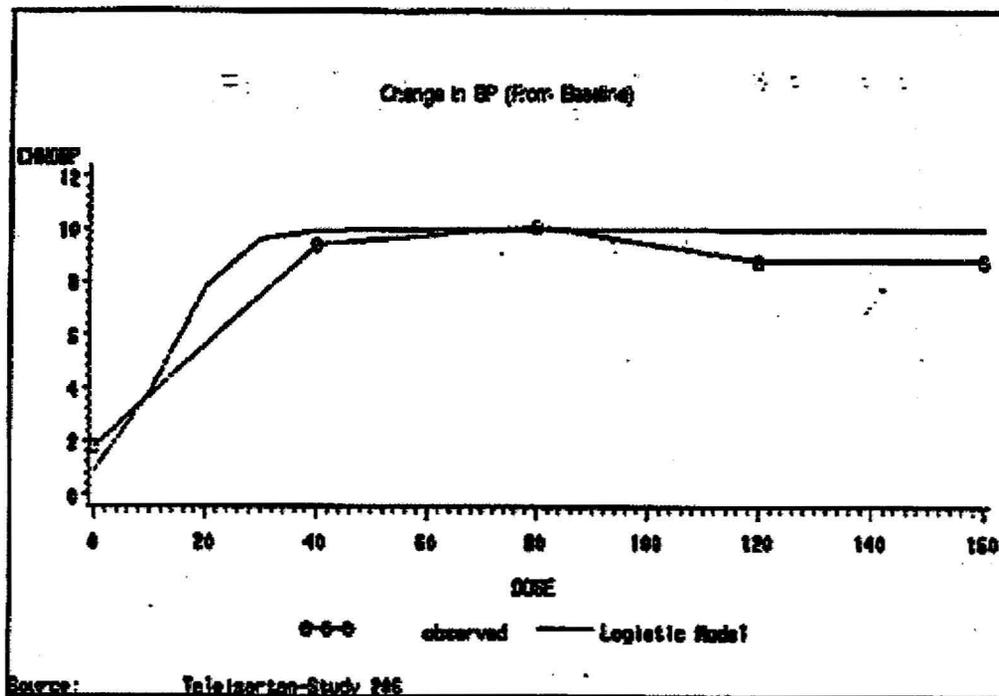
Source: Statistics review from original telmisartan NDA

Figure 2: Observed changes from baseline in Supine diastolic blood Pressure and the estimated Emax model for dose response. (Study 502.203)



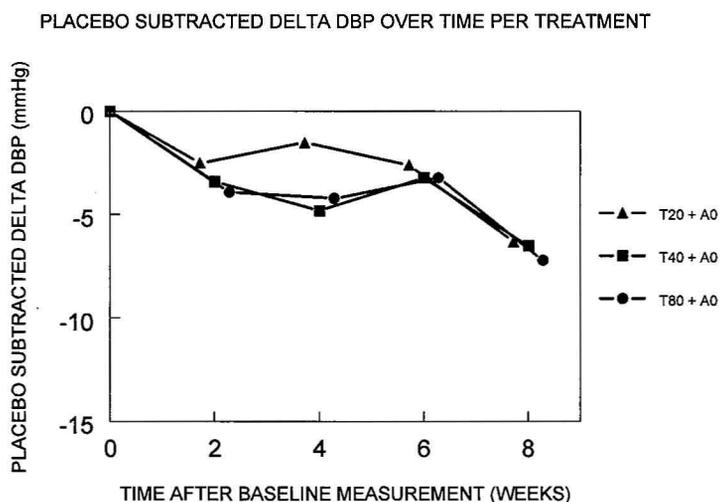
Source: Statistician Review from original Telmisartan NDA

Figure 3: Observed Changes from Baseline in Supine Diastolic Blood Pressure and the Estimated Logistic Model for Dose Response (Study 502.206)



Source: Statistician Review from original Telmisartan NDA

Figure 4: Placebo-subtracted DBP flat dose response for Telmisartan over 8 week trial 1235.1 FAS (current NDA 22401 pivotal trial) after 20 mg Dose



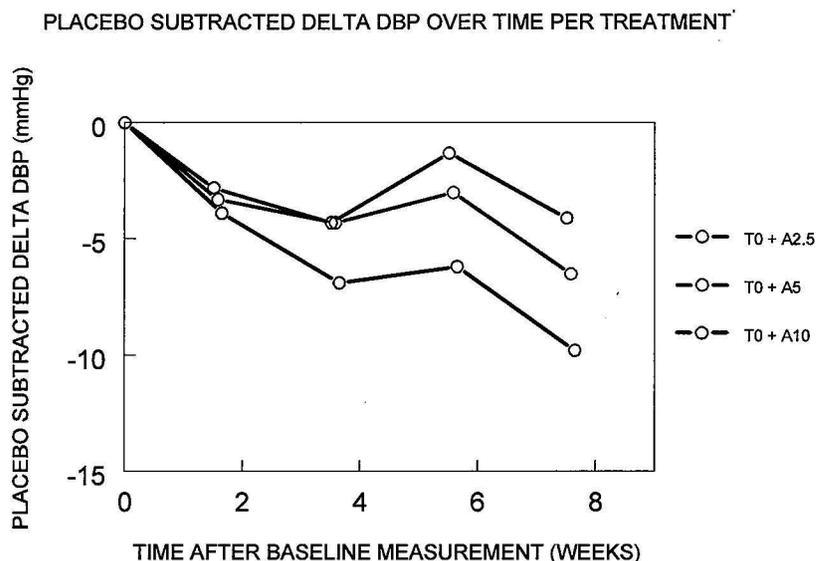
Norvasc® is a dihydropyridine (DHP) calcium antagonist [calcium ion antagonist or calcium channel blocker (CCB)] that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. It is a peripheral arterial vasodilator that acts directly on vascular smooth muscle to cause a reduction in peripheral vascular resistance and reduction in blood pressure.

The antihypertensive efficacy of Norvasc has been demonstrated in a total of 15 double-blind, placebo-controlled, randomized studies involving 800 patients on Norvasc and 538 on placebo. Once daily administration produces statistically significant placebo-corrected reductions in supine and standing blood pressures at 24 hours post-dose, averaging about 12/6 mmHg in the standing position and 13/7 mmHg in the supine position in patients with mild to moderate hypertension. Maintenance of the blood pressure effect over the 24-hour dosing interval was observed in the clinical trials, with little difference in peak and trough effect. Tolerance was not demonstrated in patients studied for up to 1 year. The parallel, fixed dose, dose response studies showed that the reduction in supine and standing blood pressures was dose-related within the recommended dosing range. Effects on diastolic pressure were similar in young and older patients. The effect on systolic pressure was greater in older patients, possibly because of greater baseline systolic pressure. Effects were similar in black patients and in white patients.

Norvasc has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with Norvasc is well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with Norvasc were of mild or moderate severity. In controlled clinical trials directly comparing Norvasc (n = 1730) in doses up to 10 mg to placebo (n = 1250), discontinuation of Norvasc due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. Edema, dizziness, flushing and palpitation have been noted to occur in a dose-related manner. Some adverse events (edema, flushing, palpitations and somnolence) appear to be drug and dose related and were reported with a greater incidence in women than men.

In contrast to the absence of a substantial dose response for telmisartan past the 20 mg dose, amlodipine does have a dose response across the spectrum of the marketed dose range. This dose response curve is demonstrated in Figure 5.

Figure 5: Placebo subtracted DBP dose response for Amlodipine over 8 week trial 1235.1 (current NDA 22401 pivotal trial)



The purpose of trial 1235.1 was to determine whether the combinations of Micardis (telmisartan) and Norvasc (amlodipine) are more effective in reducing blood pressure than their respective monotherapies after eight weeks of randomized treatment in patients with Stage 1 and 2 hypertension.

3 Ethics and Good Clinical Practices

This randomized, double-blind, double-dummy, placebo-controlled, 4x4 factorial design, comparison trial is an ethical and widely accepted trial design to compare the efficacy of different combination therapies. The placebo run-in/washout period is a standard portion of the trial that establishes that the patient has hypertension. This run-in period was aimed to familiarize the patient with trial procedures and to perform any necessary wash out of excluded medication. Patient safety was monitored throughout the trial. All patients who signed informed consent and completed Visit 1, meeting all inclusion and exclusion criteria, were provided an electronic home blood pressure monitor for home use. In addition, in-clinic visits were held approximately every two weeks to monitor blood pressure levels.

There were no specific benefits guaranteed or implied to the patients who participated in this trial. Participation was purely voluntary and patients were made aware of the chance of randomization to placebo (1:32).

3.1 Submission Quality and Integrity

All data files were accessible. According to the criteria set by the Sponsor on inclusion of subjects into the Full Analysis Set (FAS), the correct numbers of subjects were found to be included. While certain criteria for exclusion from the FAS were not stated in the originally submitted protocol or in any of the amendments submitted for review, (subjects who had ambulatory blood pressure monitoring before either the baseline or final BP readings were excluded as well as patients who had follow-up visit(s) after test drug was initiated but had not taken it), the numbers of subjects that should have been included by these standards were included in the data sets. There were 23 patients excluded from the FAS for these reason and adding them back into the primary efficacy analysis did not affect the results. I examined the primary data files for vital signs (VS.xpt) and found that the blood pressures were assessed as explained in the protocol (average of 3 DBP readings at each visit).

3.2 Compliance with Good Clinical Practices

Patients who met all inclusion/exclusion criteria were randomized to treatment at visit 3 by assignment to the next lowest numbered medication kit available at the center. Originally, the randomization to treatment was to be assigned by IVRS but this was change in Amendment 1. The randomization schedule was prepared and reviewed by personnel not directly involved in the conduct or analysis of the trial. According to the Sponsor, the randomization schedule was generated by a validated system that involved a pseudo-random number generator so that the resulting treatment sequence was both reproducible and non-predictable. Access to the randomization code was restricted to the Pharmaceuticals Department and Clinical Trial Support Group who generated the randomization code and labels and packaged the clinical supplies. Investigators, subjects and statisticians did not have access to the treatment allocation prior to the database lock that took place after the trial was clinically complete.

REVIEWER'S COMMENT(S): This method of randomization would not allow an overabundance of any one treatment group at any particular site. This method of randomization is acceptable.

Data Collection: All clinical data with the exception of lab data was captured using the ORACLE Clinical (O*C) Report Data Capture system, a WEB-based tool. The Investigator or designated site staff entered and edited the data via a secure network, with secure access features (username, password and Secure ID – an electronic password system). Data discrepancies were resolved via the secure network. A complete electronic audit trail was maintained. The Investigator, using an electronic signature, compliant with 21 Code of Federal Regulations (CFR) Part 11, approved the data, and this approval was used to ensure the accuracy of the data recorded. Copies of the electronic case report forms (eCRFs) with all data changes were supplied to the Investigator at the end of the study.

REVIEWER'S COMMENT(S): This is an acceptable data capturing system.

Protocol violations:

Refer to Table 3 for listing of reasons for protocol violations. The subjects with the protocol violations listed in this table were included in the FAS-TC.

There were a minimal amount of important protocol violations (IPVs) (only 321/1423). The most prevalent were:

- Use of concomitant medications that were not allowed (88, 6.2% of total randomized population)
- Subjects did not have stage 1 or 2 hypertension at baseline. (64, 4.5% of total randomized population).
- Incorrect Timing:
 - There were 50 subjects (3.5%) that had no other visits after the first treatment exposure to target therapy.
 - There were 49 subjects (3.4%) final in-clinic BPs who were not at trough levels.

C1 (incorrect trial medication taken) and C2 (randomization not followed) are zero and therefore suggest that the trial was well conducted.

Table 3: Important protocol violations related to efficacy –overall (FAS-TC)

	N (%)
Number of patients in FAS-TC	1423 (100.0)
Entrance criteria not met	
A2.3 Patient does not have Stage 1 or Stage 2 hypertension at baseline	64 (4.5)
A2.4 Patient's work is during the night shift	0 (0.0)
A2.5 Known or suspected secondary hypertension	0 (0.0)
Trial medication and randomization	
C1 Incorrect trial medication taken during the randomized treatment period	0 (0.0)
C2 Randomization not followed	0 (0.0)
C3.1 Noncompliant during the randomized treatment period	19 (1.3)
Concomitant medication	
D1.1 Improper medication washout	10 (0.7)
D2 Prohibited medication use during the randomized treatment period	88 (6.2)
Incorrect timing	
F1.2 Insufficient treatment exposure to target therapy	50 (3.5)
F4.3 Baseline in-clinic BPs not at trough	32 (2.2)
F4.4 Final in-clinic BPs not at trough	49 (3.4)
Trial specific	
G1 Same arm not used for cuff BP measurements at baseline and final visits	8 (0.6)
G2 Information on arm used for cuff BPs at baseline or final visit is missing	1 (0.1)

Source: Table 15.1.2.1:1 p. 195 of study report

3.3 Financial Disclosures

Most investigators and sub-investigators were certified by BI regarding the absence of financial arrangements as defined in 21 CFR 54.2. However, there were several investigators who did not provide information and therefore were not certified. Most of the uncertified investigators did not

participate, were no longer at site or were lost to follow-up. There were few whose reason for lack of certification was “no response.” Two investigators were compensated in excess of the allowed amount of \$25,000 because of speaking engagements. The amount of money that they were paid was not provided. One of the investigators enrolled (b) (6) subjects (b) (6) and the other, (b) (6). There is no great cause for concern. I looked specifically at the clearances for 8 investigators that had the largest numbers of enrolled subjects (30 and up). Each had obtained financial clearance.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There are no concerns regarding chemistry, manufacturing and controls.

4.2 Clinical Pharmacology

4.2.1. Mechanism of Action

The two components of Twynsta, telmisartan and amlodipine are both peripheral vasodilators and decrease blood pressure by lowering systemic arterial resistance.

4.2.2 Pharmacokinetics

The systemic exposure of amlodipine is not affected by the co-administration of telmisartan and the systemic exposure of telmisartan is not affected by the co-administration of amlodipine. For more details, please refer to the clinical pharmacology review.

Food, conversely, has a great impact on the peak levels and AUC of telmisartan. Fatty food significantly reduces telmisartan $AUC_{0-\infty}$ by 24.3% and C_{max} 60.1%. There is no effect of food on amlodipine absorption. Since there was no significant hypotension seen in the pivotal trial 1235.1, directions to take the medication with food are probably not warranted.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

There was one clinical study, 1235.1. This will be described in detail in the following sections.

5.2 Review Strategy

FDA Audits: There were no DSI audits requested. The components of the combination product are approved. The Division considered it unlikely that any unusual safety concerns would be detected by individual site reviews. Furthermore, the Division considered the likelihood of finding significant deviations from the protocol, which might alter its conclusions as small, since there were a large number of study sites, none of which accounted for a significant proportion of the overall population. The yield from inspecting any one or two sites, therefore, appeared minimal.

REVIEWER'S COMMENT(S): I reviewed the study report for 1235.1 and the clinical summaries for safety and efficacy which included analyses of supportive phase 3 and 4 studies in diabetics and the ONTARGET trial as well as the 4-month safety update report. I did my own data analyses and creation of tables except where noted.

5.3 Discussion of Individual Studies

The one pivotal trial for review and analysis was:

Study: 1235.1/U07-3503-02

Dates: April 4, 2006 – March 12, 2007

Title of trial: A randomized, double-blind, double-dummy placebo-controlled, 4x4 factorial design trial to evaluate telmisartan 20, 40 and 80 mg tablets in combination with amlodipine 2.5, 5 and 10 mg capsules after eight weeks of treatment in patients with Stage I or II hypertension, with an ABPM sub-study

Principal/Coordinating

Investigator:

Thomas Littlejohn III, MD
Piedmont Medical Research Associates
1901 S. Hawthorne Road, Suite 306
Winston-Salem, NC 27103

Trial sites: Multicentre Study

Clinical phase: III

Objectives: To demonstrate that for both active therapies of telmisartan and amlodipine there exists an overall dose response, thereby showing that combinations of telmisartan and amlodipine are more effective in reducing diastolic blood pressure than each of the respective monotherapies in patients with Stage I or II hypertension.

Design: Randomized, double-blind, double-dummy, placebo-controlled, international, multi-centre, parallel group, 4x4 factorial design comparison trial of 16 treatments over eight weeks. A subset of patients also participated in an ambulatory blood pressure monitoring (ABPM) sub-study.

Number of subjects:

Planned: Approximately 1280 randomized male and female subjects with Stage I or II hypertension. (It was expected that as many as 1830 patients would need to be screened, and each center was expected to randomize approximately 8 -10 patients within 12 months of trial initiation). Additionally, approximately 50% (640) of randomized patients were to participate in an ABPM sub-study evaluating the effects of trial medication over the 24-hour dosing interval. All patients that were randomized into the study were also randomized into the sub-study until enrollment into the sub-study had ended.

Actual: 2607 patients enrolled; 1461 randomized to one of 16 treatments

Enrollment Criteria:

Patients with Stage I or II hypertension, as defined by a mean-seated DBP of ≥ 95 mm Hg and ≤ 119 mm Hg at the baseline visit, were eligible for randomization. Patients had to be 18 years or older with a medical condition that allowed for the stopping of current antihypertensive therapy without any unacceptable risk. For all inclusion and exclusion criteria, see the lists below.

Criteria for Inclusion

1. Ability to provide written informed consent
2. Hypertension as defined by a mean seated cuff diastolic blood pressure of ≥ 95 mmHg and ≤ 119 mmHg at Visit 3

Note: In order for patients to qualify after only three weeks (as opposed to after four weeks of run-in treatment, mean seated cuff diastolic blood pressure must be ≥ 100 mmHg and ≤ 119 mmHg

3. Age 18 years or older
4. Ability to stop any current antihypertensive therapy without unacceptable risk to the patient (at the investigator's discretion). Male and female patients ≥ 18 years of age with Stage I or II hypertension defined as: a mean seated cuff diastolic blood pressure (DBP) ≥ 95 and ≤ 119 mmHg.

Criteria for Exclusion:

1. Pre-menopausal women (last menstruation ≤ 1 year prior to signing informed consent) who:

- a) Are not surgically sterile; or
 - b) Are nursing, or
 - c) Are pregnant, or
 - d) Are of childbearing potential and are NOT practicing acceptable methods of birth control, or do NOT plan to continue practicing an acceptable method throughout the trial. The only acceptable methods of birth control are: Intra-Uterine Device (IUD), oral, implantable or injectable contraceptives and estrogen patch
2. Night shift workers
 3. Known or suspected secondary hypertension
 4. Mean in-clinic seated cuff DBP ≥ 120 mmHg and/or SBP ≥ 180 mmHg during any visit prior to randomization
 5. Renal dysfunction as defined by the following laboratory parameters:
Serum creatinine >3.0 mg/dL (or >265 $\mu\text{mol/L}$)
 6. Bilateral renal artery stenosis, renal artery stenosis in a solitary kidney, post-renal transplant patients or patients with only one kidney
 7. Clinically relevant hypokalemia or hyperkalemia
 8. Uncorrected sodium or volume depletion
 9. Primary aldosteronism.
 10. Hereditary fructose intolerance
 11. Biliary obstructive disorders (e.g., cholestasis) or hepatic insufficiency
 12. Congestive heart failure NYHA functional class CHF III-IV
 13. Contra-indication to a placebo run-in period (e.g., stroke with-in the past six months, myocardial infarction, cardiac surgery, percutaneous transluminal coronary angioplasty, unstable angina or coronary artery bypass graft within the past three months prior to start of run-in period)
 14. Clinically significant ventricular tachycardia, atrial fibrillation, atrial flutter
 15. Hypertrophic obstructive cardiomyopathy, severe obstructive coronary artery disease, aortic stenosis, hemodynamically relevant stenosis of the aortic or mitral valve
 16. Patients whose diabetes has not been stable and controlled for at least the past three months as defined by an HbA1C $\geq 10\%$
 17. Patients who have previously experienced symptoms characteristic of angioedema during treatment with ACE inhibitors or angiotensin-II receptor antagonists
 18. History of drug or alcohol dependency within six months prior to signing the informed consent form
 19. Concomitant administration of any medications known to affect blood pressure, except medications allowed by the protocol
 20. Any investigational drug therapy within one month of signing the informed consent
 21. Known hypersensitivity to any component of the trial drugs (telmisartan, amlodipine, or placebo)
 22. History of non-compliance
 23. Any other clinical condition which, in the opinion of the investigator, would not allow safe completion of the protocol and safe administration of the trial medication

REVIEWER'S COMMENT(S): These enrollment criteria were defined to select an appropriate patient population for this drug combination, a population of patients likely to need more than one antihypertensive medication for BP control.

Test product: Telmisartan (T) and amlodipine (A) combination therapy

Doses: Telmisartan: 20, 40 or 80 mg. and Amlodipine: 2.5, 5 or 10 mg. Patients assigned to treatment with amlodipine 10 mg were dosed with amlodipine 5 mg for the first two weeks and up-titrated to target dose for the remaining six weeks of treatment. Patients randomized to combination therapy received one of nine treatment combinations:

T20+A2.5 or T20+A5 or T20+A10 or

T40+A2.5 or T40+A5 or T40+A10 or

T80+A2.5 or T80+A5 or T80+A10

(A10 mg was supplied as two 5 mg capsules)

The formulation that is planned to be marketed (one compressed combination tablet) was not used in this or any other clinical trial. For this reason, bioequivalence studies will need to be completed.

Mode of administration: Oral

Methodology:

All patients underwent a three to four week single-blind run-in period in order to wash out all antihypertensive medications so that baseline blood pressure measurements would be established. Following the run-in period, eligible patients were randomized to one of 16 treatment groups as shown in Table 4. The first half of the enrolled patients was also assigned to the ambulatory blood pressure monitoring (ABPM) part of the trial. (Originally, each treatment group was to be randomly assigned to ABPM or no-ABPM. A protocol amendment changed this).

Table 4: Target number of patients per treatment group

	Placebo	Amlodipine 2.5 mg	Amlodipine 5 mg	Amlodipine 10 mg
Placebo	40	40	120	120
Telmisartan 20 mg	40	40	40	40
Telmisartan 40 mg	120	40	120	120
Telmisartan 80 mg	120	40	120	120

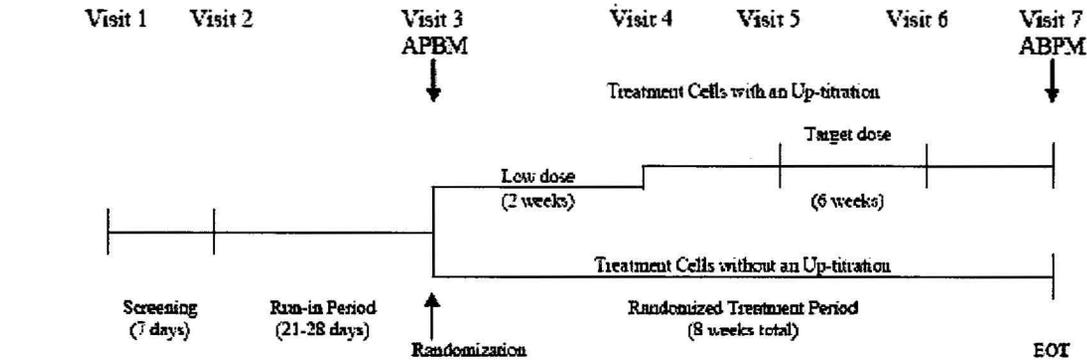
Source: clinical overview

REVIEWER'S COMMENT(S): There is unequal randomization. The Sponsor targeted their study to look for BP effects in patients treated with monotherapy (T40, T80, A5 and A10) and the combinations that they planned to market (T40 + A5, T40 + A10, T80 + A5, and T80 + A10). This is not a serious deficiency for the efficacy analysis because the arms that include the doses that we are mostly interested in (T40 + A5, T40 + A10, T80 +

A5, and T80 + A10) have 120 planned patients. For the safety analysis, it would have been more favorable to have more patients enrolled in all dose ranges and combinations so that a better dose relationship analysis for AEs could have been done.

A diagrammatic presentation of the trial is presented in Figure 6. Only patients with mean seated at “visit 3” (week three after “visit 2”) could be randomized and receive treatment. The others had to come back at week 4 for a second “visit 3” and would be enrolled as long as they had a diastolic BP of no less than 90. The treatment period was 8 weeks. The patients received the first dose of single-blind placebo trial medication at the beginning of the run-in period (“visit 2”). After three weeks if the patients did not meet the DBP inclusion criteria (DBP of ≥ 95 mmHg and ≤ 119) the “visit 2” run-in medication kit was re-dispensed and the patient returned the next week for re-evaluation when randomization would only occur if the diastolic BP was ≥ 90 mmHg. Therefore, randomization day which occurred on “visit 3” could occur on two separate days that were one week apart depending on the patient’s blood pressure. All qualifying patients were assigned to the next lowest numbered medication kit available at the center at “visit 3” following completion of all visit procedures (including the baseline 24-hour ABPM procedure for sub-study patients). Patients that were randomized to receive amlodipine 10 mg, alone or in combination, started with a low dose (5 mg) treatment for the first 2 weeks starting at “visit 3” and were automatically titrated up to 10 mg at “visit 4”.

Figure 6: Diagrammatic presentation of the study design



EOT – End of Trial

Treatment Cells with an Up-titration: A10, T20A10, T40A10, T80A10

Low Dose:	Target Dose:
A5	A10
T20A5	T20A10
T40A5	T40A10
T80A5	T80A10

Treatment Cells without an Up-titration: Placebo, A2.5, A5, T20, T40, T80, T20A2.5, T40A2.5, T80A2.5, T20A5, T40A5, T80A5

Source: clinical overview

REVIEWER'S COMMENT(S): As in any antihypertensive trial, there is an expected regression to the mean effect, meaning that the blood pressure readings of individual patients will approach the untreated mean blood pressure reading of the population being studied. Since the monotherapy + placebo treatment cells will also share a comparable degree of regression to the mean as the combination therapy cells, a fair comparison can be made. For calculation of absolute blood pressure lowering effects of all treatment cells, the placebo effect will have to be subtracted.

Methodology for Blinding:

Telmisartan 20, 40, and 80 mg tablet doses were provided by using the respective active or placebo tablets in a double-dummy fashion. Over-encapsulation was performed for amlodipine; encapsulating a single placebo tablet, a single capsule of amlodipine 2.5 mg, or a single capsule of amlodipine 5 mg. For the amlodipine 10 mg dose group, two capsules of over-encapsulated amlodipine 5 mg capsules were used. The following batches were available for randomization.

T20 Matching Placebo – PD-2749
T40 Matching Placebo – PD-2746
T80 Matching Placebo – PD-2751
T20 - PD-2677
T40 – PD-2679
T80 – PD-2681
A2.5 and 5 Matching Placebo – PD-2687
A2.5 – PD-2682
A5 – PD-2683

According to the sponsor, the blind was maintained until the database was locked and populations for analysis had been defined.

Trial drug was taken as three tablets and two capsules (one row from the blister card), orally, once-daily with water, in the morning at 8 a.m. \pm 1 hour. Trial drug was allowed to be taken with or without food. Dosing on each day of the trial occurred at approximately the same time. If a dose was missed, the patient was instructed to take the next dose as scheduled.

REVIEWER'S COMMENT(S): If one were to open the amlodipine placebo capsules one could readily see the difference between placebo and amlodipine. In a verbal communication with the sponsor, the reasons that the amlodipine were not made to look like a placebo and vice-versa were related to cost. Therefore, if the subject or physician were sufficiently motivated, it would not be difficult to unblind the amlodipine part of the trial. Since blood pressure monitoring is relatively objective, I think that the potential for amlodipine unblinding is not a great concern.

Methodology for BP readings:

Seated cuff blood pressure readings and pulse rate were taken at every visit. As well, at Visits 3, 4, 5, 6 and 7 standing cuff blood pressure readings were taken. The following procedures followed:

- 1) Blood pressure measurements were performed with standard blood mercury manometry and were recorded to the nearest 2 mmHg. Blood pressure measurements were performed on the same arm and, if possible, by the same person at all study visits.
- 2) After patients had rested quietly in the seated position for five minutes, three blood pressure measurements were taken two minutes apart.
- 3) The seated pulse rate was taken during the two-minute interval between the second and third seated blood pressure readings.
- 4) Following the third seated measurement the patients stood and immediately had their blood pressure taken, followed by two more standing measurements taken two minutes apart.

ABPM measurements:

- 1) On the mornings that the ABPM equipment was applied (Visits 3 and 7), patients were asked to arrive at approximately 7:30 a.m. to allow additional time for

ABPM procedures such that dosing of medication occurred as close to 8:00 a.m. as possible.

- 2) It was important that the dosing time for the baseline ABPM (Visit 3) was the same as the dosing time for the final ABPM (Visit 7).
- 3) The daytime and nighttime activities of the patient during the 24 hours had to be similar for each. For example, if the baseline ABPM fell on a normal workday, then the final ABPM should have been scheduled for a normal workday, not a weekend or vacation day. The idea was to have the same environment for both ABPMs.
- 4) The ABPM monitors were programmed to measure blood pressure every 20 minutes throughout the day and night. Patients were advised not to move the arm during each blood pressure measurement and were also given instructions concerning interruption of measurement in case of malfunction of the device or repositioning of the cuff if it slips.

REVIEWER'S COMMENT(S): The blood pressure monitoring protocol is standard and acceptable.

Subject Discontinuation: Subjects were evaluated for compliance at every visit. The trial medication compliance had to be 80 -120%. Otherwise, the subject would be counseled. Any decision to discontinue subjects based on compliance issues was discussed with the Clinical Monitoring Committee. Last observation carried forward (LOCF) was used for the analysis of those patients that were discontinued.

Subjects were discontinued at any time during the trial for having a mean in-clinic seated DBP \geq 120 mmHg and/or SBP \geq 180 mmHg, or for having intolerable adverse events. If the subject was a randomized subject, the end of trial/Visit 7 procedures were completed and included in the primary efficacy analysis.

REVIEWER'S COMMENT(S): The choice to include the subjects who met these discontinuation criteria in the primary efficacy analysis is important because we are then able to get an idea of the treatment effect on the likelihood of having to discontinue for this reason. Also, it is important to factor these data into the primary efficacy analysis.

For those subjects that participated in the ABPM sub-study, a final ABPM was conducted upon termination only if:

- The patient had at least 6 weeks of double-blind treatment, AND
- The patient could take a last dose of double-blind medication, AND
- The patient had not already started taking an excluded medication.

REVIEWER'S COMMENT(S): Including only the subjects specified in the bullet points above in the primary analysis of the ABPM substudy is acceptable because the analysis then lends itself to providing a cleaner view of the ambulatory effects of the treatments over time. For instance, if the plateau effect isn't reached until 5 weeks after initiation, including patients with only 3 weeks of treatment would be misleading. If the

patient could not take a last dose of medication prior to the last ABPM, the effect of the treatment would be underestimated. Additionally, if the patient was on an excluded medication for the last ABPM reading, the effect of treatment would possibly be under- or over-estimated.

Criteria for evaluation: Efficacy / clinical pharmacology:

Primary: Change from baseline (visit 3, visit of randomization) in the in-clinic seated trough cuff DBP after eight weeks of treatment (visit 7)

Secondary:

- Change from baseline in the in-clinic seated trough cuff systolic blood pressure (SBP) after eight weeks of treatment
- Changes from baseline in the in-clinic standing trough cuff DBP and SBP after eight weeks of treatment ABPM Sub-study
- Changes from baseline in the 24-hour ABPM mean (relative to dose time) for DBP and SBP after eight weeks of treatment
- Responder analysis

REVIEWER'S COMMENT(S): These are appropriate endpoints for the purpose of demonstrating the product is superior to each monotherapy

Safety: Adverse events (AEs), laboratory parameters, electrocardiogram (ECG), orthostatic changes in SBP and DBP (calculated for both SBP and DBP as the mean seated BP at a particular visit subtracted from the first standing BP at the same visit), and changes from baseline pulse rate.

REVIEWER'S COMMENT(S): While this 8-week trial provides less safety information than normally required, the sponsor included a great deal of safety information on the combination product from other studies.

Statistical methods: Analysis of covariance with main effects of treatment with telmisartan, treatment with amlodipine, and country/region, with baseline as a covariate; response surface analysis; Mantel-Haenszel test.

Only patients who received at least one dose of active treatment were included in the safety analysis.

Missing Data: The last observation carried forward (LOCF) principle was applied to all efficacy variables. Baseline values and values obtained at doses of telmisartan and/or amlodipine other than the final assigned randomized dose were not carried forward.
For a missing day of the month, the 15th was used.

REVIEWER'S COMMENT(S): The statistical methods chosen by the sponsor are appropriate for this trial.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Antihypertensive therapy for patients not controlled on a single antihypertensive agent or a first-line treatment for those patients who are likely to require a combination therapy for adequate antihypertensive control.

6.1.1 Methods

The proposed indication for Twynsta is:

- In patients not adequately controlled on antihypertensive monotherapy
- As initial therapy in patients likely to need multiple drugs to achieve their blood pressure goals

This first primary objective was pre-specified in the Trial Protocol (TP) and trial statistical analysis plan (TSAP) to be met by first showing that there was an overall significant ($\alpha=0.05$) effect among both the dosages of telmisartan and among both the dosages of amlodipine, and second by showing a lack of any significant ($\alpha=0.10$) telmisartan-by-amlodipine interaction. The second primary objective involving only the patients with Stage 2 hypertension was predefined in the trial statistical analysis plan to only be evaluated and conclusions drawn if the primary objective involving all patients with Stage 1 or 2 hypertension was achieved.

The primary endpoint in Trial 1235.1 was the change from baseline (visit 3) in trough seated DBP after 8 weeks of treatment (visit 7) in patients with moderate hypertension (up to 99 mm Hg). BP was assessed using a manual mercury sphygmomanometer; the average of three replicate measurements at each visit was used. If there was at least one visit after visit 3, the last observation carried forward (LOCF) was used to define the final end-of-study blood pressure (visit 7) with the following exception: When the target therapy dose did not occur until visit 4 (as with the patients randomized to receive amlodipine 10mg) there had to be a visit 5 or 6 to impute the 7th visit BP. In order for the trial to be successful, the combination product had to be superior to the two separate products at the different doses at lowering diastolic blood pressure.

For the ABPM aspect of the trial, although the measurements were taken every 20 minutes, there was an average taken of all BPs taken for the hour and this average was used for the analysis. If there was an outlier BP (define) it would be excluded from the average. Clearly this method of would smooth out the effect of the trial medications over the course of the 24 hour period and would likely provide a more favorable drug effect for all doses.

REVIEWER'S COMMENT(S): These methods are appropriate for establishing the validity of the proposed indication.

6.1.2 Demographics

A total of 136 sites participated in this international study. One hundred and one sites were located in the USA, 6 in Argentina, 5 in Brazil, 10 in Mexico and 14 in South Africa. Sites that were closed prior to enrolling patients were replaced as needed to insure that enrollment goals were met. Most of the enrolled patients were from the U.S (877, [61.6%]). Of these, there were 210 (14.8%) patients from So. Africa, 169 (11.9%) from Mexico, 87 (6.1%) from Brazil, and 80 (5.6%) from Argentina.

Table 5: Demographics in treatment groups (FAS)

	T/A	T mono	A mono	Placebo
Number of patients, N	765	303	309	46
Age [years]				
Mean(SD)	53.0 (11.4)	52.7 (11.1)	53.5 (10.7)	52.5 (12.3)
Range	22.0 – 84.0	23.0 – 81.0	21.0 – 82.0	19.0 – 75.0
Age group, N (%)				
<65 years	657 (85.9)	259 (85.5)	265 (85.8)	40 (87.0)
>=65 to <75 years	83 (10.8)	38 (12.5)	35 (11.3)	5 (10.9)
>=75 years	25 (3.3)	6 (2.0)	9 (2.9)	1 (2.2)
Sex, N (%)				
Male	381 (49.8)	148 (48.8)	160 (51.8)	29 (63.0)
Female	384 (50.2)	155 (51.2)	149 (48.2)	17 (37.0)
Race, N				
White	607 (79.3)	239 (78.9)	244 (79.0)	40 (87.0)
Black	127 (16.6)	49 (16.2)	51 (16.5)	5 (10.9)
Asian	31 (4.1)	15 (5.0)	14 (4.5)	1 (2.2)
Weight [kg]				
Mean(SD)	88.89 (21.04)	87.94 (21.18)	89.85 (20.08)	90.18 (23.05)
Range	46.50 – 163.0	43.80 – 167.6	50.80 – 154.3	52.00 – 153.5
Height in cm				
Mean(SD)	168 (11.2)	168 (11.4)	168 (10.9)	170 (11.0)
Range	133 – 205	122 – 198	142 – 196	144 – 193
BMI [kg/m ²]				
Mean(SD)	31.44 (6.69)	31.00 (6.30)	31.59 (5.64)	31.14 (7.23)
Range	18.20 – 64.90	16.30 – 61.60	21.20 – 50.80	18.80 – 50.20

Source: Table A.1.2.1:2 in ISE

There was a race distribution reflective of the U.S. population: approximately 15% Blacks, approximately 4% Asians, and approximately 81% Whites. The sexes were represented equally. When looking at the 16 different treatment groups there were demographic differences between them but these differences were not great. The placebo group had fewer Blacks and Asians. The distribution of time with diagnosis of hypertension differed among treatment groups more than any other demographic criterion. Time with hypertension diagnosis < 1 year ranged from 6.9% – 23.9%, 1-5 years ranged from 20% – 42.2, and >5 years from 44.7% to 71.4%.

REVIEWER'S COMMENT(S): The small demographic differences in the treatment cells is not likely to affect the results of the trial. Most importantly, as can be seen in Table 6, the patients in the FAS-TC did not differ by much in baseline DBP, SBP and pulse by treatment group.

Table 6: Baseline in-clinic seated trough blood pressure and pulse rate by treatment group (treated set)

			A0	A2.5	A5	A10	Total
T0	DBP (mmHg)	N	46	50	140	129	365
		Mean (SD)	102.5 (4.79)	102.4 (4.60)	102.3 (4.62)	101.1 (3.95)	101.9 (4.43)
	SBP (mmHg)	N	46	50	140	129	365
Mean (SD)		152.6 (11.20)	157.5 (13.22)	153.9 (12.60)	152.6 (12.14)	153.8 (12.41)	
	PR (bpm)	N	46	50	140	129	365
		Mean (SD)	72.9 (9.87)	75.4 (9.16)	74.3 (9.02)	73.6 (8.56)	74.0 (8.98)
	T20	DBP (mmHg)	N	42	44	46	44
Mean (SD)			101.6 (3.45)	102.3 (4.79)	102.7 (5.22)	100.8 (3.84)	101.9 (4.43)
SBP (mmHg)		N	42	44	46	44	176
	Mean (SD)	150.3 (11.81)	157.3 (14.09)	156.7 (10.89)	153.2 (10.68)	154.4 (12.16)	
	PR (bpm)	N	42	44	46	44	176
		Mean (SD)	74.1 (7.76)	73.6 (9.93)	74.7 (7.49)	74.0 (10.27)	74.1 (8.88)
	T40	DBP (mmHg)	N	130	47	143	129
Mean (SD)			102.2 (4.68)	101.1 (3.98)	101.6 (4.12)	101.6 (3.76)	101.7 (4.18)
SBP (mmHg)		N	130	47	143	129	449
	Mean (SD)	153.1 (11.89)	149.3 (11.55)	153.0 (11.79)	152.7 (11.90)	152.6 (11.84)	
	PR (bpm)	N	130	47	143	129	449
		Mean (SD)	74.6 (9.60)	74.1 (10.91)	75.0 (9.50)	75.0 (9.34)	74.8 (9.61)
	T80	DBP (mmHg)	N	135	48	146	142
Mean (SD)			101.5 (4.45)	101.4 (3.84)	101.8 (4.51)	101.3 (3.88)	101.5 (4.24)
SBP (mmHg)		N	135	48	146	142	471
	Mean (SD)	152.1 (12.18)	153.3 (13.37)	153.8 (11.72)	153.1 (11.79)	153.0 (12.03)	
	PR (bpm)	N	135	48	146	142	471
		Mean (SD)	74.9 (8.98)	74.1 (9.36)	73.8 (9.09)	74.9 (9.83)	74.5 (9.30)

SD - Standard Deviation

Source data: Appendix 16.2, Listing 3.1, 4.2.1

t15base.sas

The patients in the FAS-TC-MS (Stage 2 sub-group) dataset did not differ much from group to group in baseline readings as well. The overall mean seated trough cuff SBP/DBP at baseline was 153.2/101.7 mmHg for all treated patients (TS) and 154.7/103.5 mmHg for treated patients with moderate or severe hypertension at baseline (TS-MS). The groups were not distinctly different

The overall baseline characteristics of the FAS and the FAS-TC-MS (Stage 2 sub-group) did not differ in frequency of smokers, h/o alcohol use, BMI, diabetes status, renal impairment status or use of NSAIDs. T/A, T mono, A mono and placebo treatment groups were assessed in these categories for baseline characteristic similarities and dissimilarities. In the placebo group there

were fewer diabetics (approximately 9% compared to approximately 15% in the other groups), and no renally impaired subjects (compared to approximately 5% in the other groups). Overall, the populations were well-balanced for each baseline characteristic across the key combination and respective monotherapies. The proportion of non-smokers ranged from 53% (observed in the T40/A10 treatment cell) to 68% (T80/A10). Ex-smokers comprised from 16% to 29% and current smokers from 16% to 26% of patients in key combination and respective monotherapies.

In the FAS-TC-MS analysis, T/A, T mono, A mono and placebo treatment groups were assessed in these categories for baseline similarities and dissimilarities. The 4 major treatment groups did not differ greatly in regard to baseline characteristics. However, placebo treated subjects were more likely to be current smokers and less likely to be diabetic or have renal impairment.

REVIEWER'S COMMENT(S): The minor demographic differences among treatment groups were not of great concern and were not felt to be important when considering safety or efficacy.

6.1.3 Patient Disposition

Treatment compliance was approximately 98% in each group, meaning that 98% of the patients in each group took between 80 -120% of their medications between visits.

Out of the 8% of the patients that discontinued the trial, adverse events (2.6%), consent withdrawn (1.8%), and lack of efficacy, (1.1%) were the most common reasons. This was a low drop out rate. Subjects who prematurely discontinued were not replaced.

There was a trend toward increase in dropout rate for subjects that were treated with placebo + placebo (15.2%), or placebo + 2.5 mg amlodipine (14%). The range was 2.4% to 15.2% drop out rate by group. There was no dose related increase in subject drop out rate.

Of the total 1461 patients randomized/treated with study drug, 1078 were identified as having moderate or severe hypertension (defined as: DBP \geq 100mmHg) at baseline. Of the 1078 patients, 997 (92.5%) patients completed the eight-week trial and 81 (7.5%) patients were prematurely discontinued. No major differences were observed in the frequency of premature discontinuation in this subset of patients as compared to the overall randomized/treated population. (Source 15.1.1:3 and 15.1.1:4 of study report).

REVIEWER'S COMMENT(S): The relatively low drop out rate in all groups reflects good study conduct and suggests a good safety profile.

6.1.4 Analysis of Primary Endpoint(s)

In Table 7, the analysis sets are broken down into the various categories. It can be seen that 2607 patients were screened, 1461 were randomized, 1423 were included in the full analysis set – trough cuff (FAS-TC) and of those, 1050 patients were included in the full analysis set- trough cuff-moderate/severe (FAS-TC-MS). Only 373 (26%) subjects had Stage 1 hypertension when defined by their baseline BP. This small number of stage 1 subjects explains why there is little – no difference in outcomes between the full analysis set and the full analysis set-moderate/severe. The enrollment criteria selected patients with baseline DBP that would be most likely to meet the stage 2 criteria. It is presumed that if a blood pressure medication is effective in one stage of hypertension it is also effective in the other.

Table 7: Patient Analysis Sets

Analysis Set	Total
Screened Set	2607
Randomized Set	1461 (56.0 of the screened set)
Treated Set	1461 (100.0 of the randomized set)
Full analysis set-trough cuff (FAS-TC)	1423 (97.4)
Per-protocol analysis set-trough cuff (PPS-TC)	1155 (79.1)
Full analysis set- ABPM (FAS-ABPM)	562 (38.5)
Treated Set- Moderate/severe (TS-MS)	1078 (73.8)
Full analysis set-trough cuff (FAS-TC-MS)	1050 (71.9)
Per-protocol set-trough cuff-moderate/severe (PPS-TC-MS)	892 (61.1)
Full analysis set-ABPM –moderate/severe (FAS-ABPM-MS)	403(27.6)

Source data: Table 15.1.3:1, study report

CHANGES IN THE CONDUCT OF THE TRIAL OR PLANNED ANALYSES

In the course of this trial, 1 amendment was issued, which was implemented only after documented approval by the IRB/IEC. The important changes introduced by this amendment are listed below. The following changes resulting from Amendment 1, issued on 14 February 2006, were:

- Randomization method was changed to remove the Interactive Voice Response System (IVRS)
- Medical history assessment would only include current conditions
- Ambulatory Blood Pressure Monitoring (ABPM) screening rules were revised
- Participation in the ABPM substudy was further clarified prior to data base lock
- Finalization of the trial statistical analysis plan (TSAP)

Additional changes to the planned analysis of the study were agreed upon by the clinical team.

These changes included:

A second primary objective was defined to demonstrate an overall dose response in patients with moderate or severe hypertension at baseline for both active therapies of telmisartan and amlodipine

Pooling of centers would be performed by country with four regions defined within the USA and would be included in the primary and secondary analyses. An analysis to evaluate any treatment-by-country/region interaction on the primary endpoint was also performed.

Three additional response variables were going to be evaluated as secondary endpoints were defined: SBP response (SBP <140 mmHg or ≥ 15 mmHg reduction), BP Control 1 (SBP <140 mmHg and DBP <90 mmHg) and BP Control 2 (SBP <130 mmHg and DBP <80 mmHg).

The 24-hour ABPM mean DBP and SBP at baseline and final visits, as well as the change from baseline, were going to be summarized using descriptive statistics due to the limited number of patients participating in the sub-study.

Patients with clinically meaningful orthostatic changes were going to be identified and listed in a separate table from all orthostatic changes.

Patients with any AE with a preferred term relating to edema, including peripheral edema were summarized by the four key treatment groupings.

All primary and secondary efficacy endpoints and safety analyses were performed on the subset of patients with moderate or severe hypertension at baseline as well as the full data set.

In order to differentiate among individual treatments for the secondary endpoints of the various response variables, logistic regression were going to be performed.

From the ABPM sub-study results, peak changes from baseline in DBP hourly means were identified as the maximal reduction for the period of hours 2-8 relative to dosing

The statistical analyses were done after excluding patients treated with double placebo because of the T-by A interaction. When involving all treatment groups there was, as anticipated, a significant T-by-A interaction ($p=0.0317$). However, when excluding patients treated with placebo the T-by-A interaction effect ($p=0.1777$) was not significant. This statistical plan was prespecified in the original protocol.

REVIEWER'S COMMENT(S): These amendments were agreed upon prospectively by the clinical team. Excluding the double placebo group from the primary efficacy analysis is acceptable because we are most interested in knowing that drug A (amlodipine) + different doses of drug T (telmisartan) is better than each drug with placebo alone. It is therefore not necessary to compare the combination to the double-placebo group. The placebo group is useful for calculating absolute mean blood pressure

differences from baseline to end-of-trial (absolute differences must be placebo-subtracted) and for purposes of assessing safety.

Table 8: Effect of treatment with Telmisartan alone on change from baseline to end of study (LOCF) in in-clinic seated trough DBP (mmHg) (FAS-TC)

	Overall T0 effect	Overall T20 effect	Overall T40 effect	Overall T80 effect	Level of significance
N	355	171	440	457	
Adj mean† (SE)	-12.5 (0.45)	-16.8 (0.63)	-16.6 (0.41)	-17.2 (0.40)	P<0.0001

† Adjusted for country/region effect and baseline value

SE – Standard Error

Source data: Table 15.2.1.1.1: 2

Table 9: Effect of treatment with Amlodipine alone on change from baseline to end of study (LOCF) in in-clinic seated trough DBP (mmHg) (FAS-TC)

	Overall A0 effect	Overall A2.5 effect	Overall A5 effect	Overall A10 effect	Level of significance
N	349	185	466	423	
Adj mean† (SE)	-12.2 (0.46)	-15.3 (0.60)	-16.2 (0.40)	-19.3 (0.42)	P<0.0001

† Adjusted for country/region effect and baseline value

SE – Standard Error

Source data: Table 15.2.1.1.1: 2

Table 8 and Table 9 demonstrate that there was a clinically significant dose effect of the individual components of Twynsta on DBP when compared to placebo. A similar effect was seen in the moderate – severe hypertension subgroup.

Table 10: Adjusted* mean DBP change from baseline in key combinations and respective monotherapies in Trial 1235.1 (FAS)

A0			A5	A10
Number of patients, N	T0	46	137	124
End of trial, Mean (SE)		-6.2 (1.19)	-13.4 (0.69)	-17.1 (0.73)
Number of patients, N	T40	129	141	123
End of trial, Mean (SE)		-13.4 (0.71)	-16.5 (0.68)	-20.2 (0.73)
Difference to A component			-3.1 (0.97)	-3.1 (1.02)
95% CI			(-5.0, -1.2)	(-5.1, -1.1)
p-value			0.0013	0.0023
Difference to T component, Mean (SE)			-3.1 (0.98)	-6.8 (1.01)
95% CI			(-5.0, -1.2)	(-8.8, -4.8)
p-value			0.0016	<0.0001
Number of patients, N	T80	132	143	136
End of trial, Mean (SE)		-14.0 (0.71)	-18.2 (0.68)	-20.1 (0.70)
Difference to A component, Mean (SE)			-4.9 (0.96)	-3.0 (1.00)
95% CI			(-6.7, -3.0)	(-5.0, -1.1)
p-value			<0.0001	0.0024
Difference to T component, Mean (SE)			-4.2 (0.97)	-6.1 (0.98)
95% CI			(-6.1, -2.3)	(-8.0, -4.1)
p-value			<0.0001	<0.0001

SE = Standard error, CI = Confidence interval

* adjusted for baseline and country effect

Note: DBP result presented in mm Hg

Source: Module 5.3.5.3, Table A.2.1.1.3.1

It is clear from Table 10 that the drop in seated trough diastolic blood pressure in mmHg between the key (to be marketed) combination treatments and each individual component was statistically significant at each dose studied. The analysis was done using the analysis of covariance (ANCOVA) approach that included all 16 treatment cells. The data showed that each of the 4 key combinations reduced in-clinic seated trough DBP to a significantly greater degree than each individual monotherapy.

The primary analysis involved an Analysis of Covariance (ANCOVA) using DBP, country, effects of treatment with telmisartan (T) and treatment with amlodipine (A) as covariates and showed that treatment with each active therapy resulted in a significant ($\alpha=0.05$) dose response in the reduction in the in-clinic trough cuff DBP after eight weeks of treatment.

Table 11: Mean (SD) non-placebo subtracted observed changes from baseline in in-clinic seated trough cuff DBP (mmHg) (FAS-TC)

	A0	A2.5	A5	A10
T0	n=46 -5.9 (9.4)	n=48 -10.4 (9.9)	n=137 -13.0 (7.9)	n=124 -16.5 (7.1)
T20	n=42 -13.2 (9.0)	n=44 -18.0 (7.8)	n=45 -15.7 (6.5)	n=40 -18.7 (7.0)
T40	n=129 -13.1 (10.1)	n=47 -16.2 (8.2)	n=141 -16.0 (7.6)	n=123 -19.6 (7.9)
T80	n=132 -13.6 (8.7)	n=46 -15.3 (7.5)	n=143 -17.8 (8.5)	n=136 -19.6 (7.9)

(SD) – Standard Deviation

Source: Study report trial 1235.1 p.74

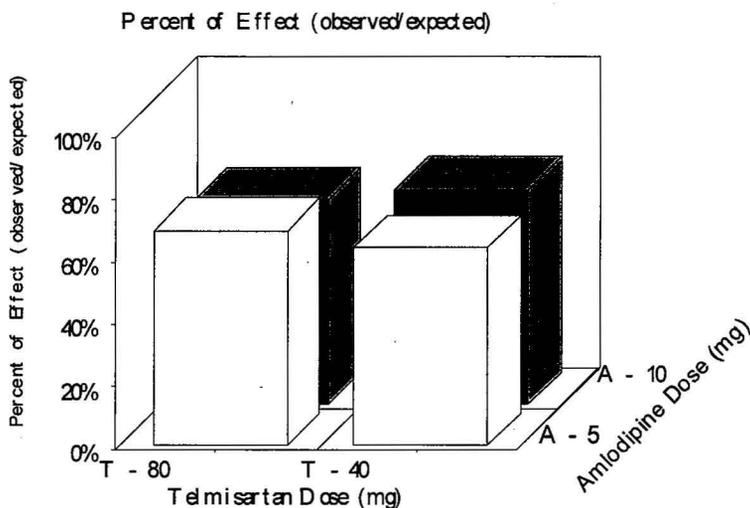
Table 12: Mean (SD) placebo subtracted observed changes from baseline in in-clinic seated trough cuff DBP (mmHg) (FAS-TC)

	A0	A2.5	A5	A10
T0	n=46 0	n=48 -4.5	n=137 -7.1	n=124 -10.6
T20	n=42 -7.3	n=44 -12.1	n=45 -9.8	n=40 -12.8
T40	n=129 -7.2	n=47 -10.3	n=141 -10.1	n=123 -13.7
T80	n=132 -7.7	n=46 -9.4	n=143 -11.9	n=136 -13.7

Table 11 and Table 12 provide the mean non-placebo-subtracted and placebo-subtracted, respectively, trough seated cuff DBP drops for each combination of drugs with the standard deviation from the mean in parentheses. Of note, the combination of A10 with T40 is no different in its effect on DBP than the combination of A10 with T80. Also, of important note, the effects of the two treatments are not additive, meaning when you add the effect of each drug when taken alone with the other drug alone, the sum expected effect is considerably higher than the effect of the combination product. In the four major combinations, the effect of adding telmisartan to amlodipine resulted in only an observed DBP decrement of approximately 2 to 4 mm Hg whereas the expected effect of adding amlodipine to telmisartan would be a decrement of approximately 13 mmHg if the effect were fully additive. Using the sponsor's data I constructed Figure 7 to demonstrate this point.

REVIEWER'S COMMENT(S): For all the dose combinations, the additive delta DBP effect is between 60 and 70% of the effect one would expect if the drug effects were fully additive. This is within the range of what is seen with other combination drugs.

Figure 7: Observed/Expected delta DBP effect (if DBP effect of both drugs were fully additive)



I constructed my own table from the raw data to corroborate the primary efficacy analysis of the sponsor's. My table differed in the number of patients in each treatment group because I included in my analysis two subgroups of patients that were excluded from the sponsor's data set. These subjects were ones who had not taken study medication even though they kept one of their post visit 3 or 4 visits (6 subjects) or subjects who had their ambulatory monitor device done before their baseline BP measurement or before their final BP measurement (17 subjects scattered among different treatment groups). The changes in DBP results that I arrived at were different from the sponsor's only in those treatment groups where the n was different. I spot-checked the data on the subjects that the sponsor had excluded from the FAS-TC. I found that the reason for exclusion of the ABPM protocol violation subjects from the FAS-TC was specified in the study report but not in the last finalized protocol. The rationale for excluding these latter 17 subjects was that the sponsor thought that the ambulatory blood pressure cuff could erroneously alter the seated BP readings.

I did a sensitivity analysis to see if the results would be different from the sponsor's if I included the subjects with ABPM protocol violations into the FAS. The results of this analysis are tabulated in Table 13. When compared to the table derived from the sponsor's data set (Table 11), the addition of these subjects did not change the results of the analysis by much. For this reason, the rest of the analyses were done using the sponsor's full analysis set.

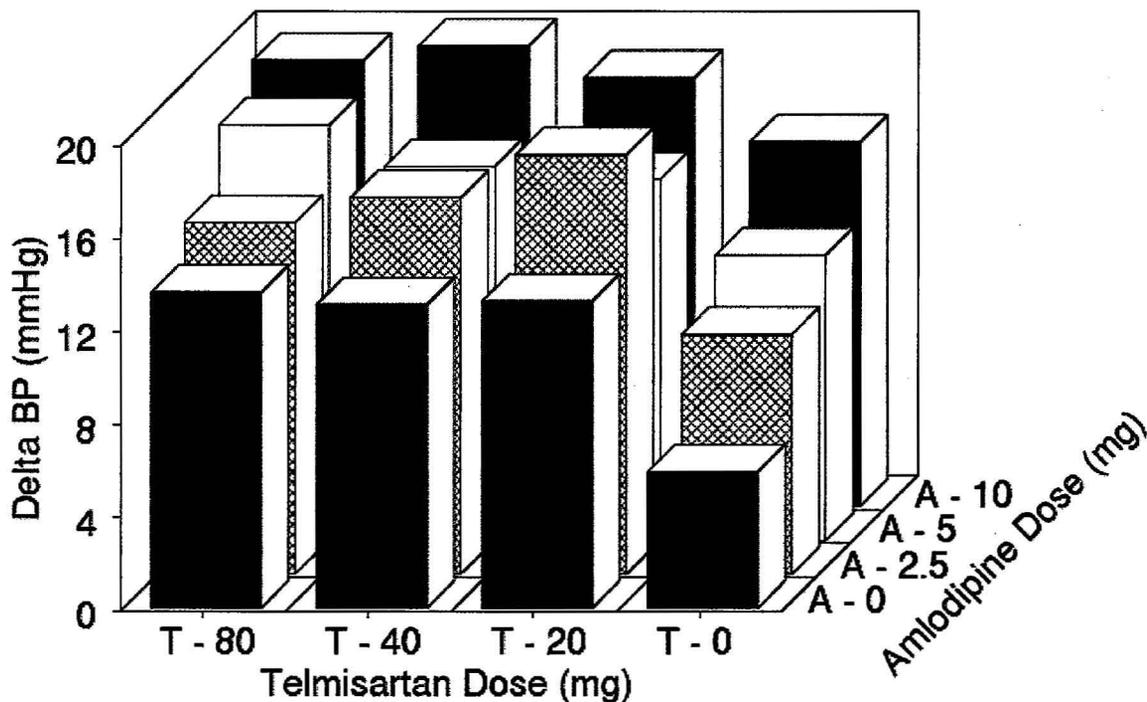
Table 13: Mean (SD) non-placebo-subtracted observed changes from baseline in in-clinic seated trough cuff DBP (mmHg) (FAS-TC) when subjects with ABPM protocol violations were included

	A0	A2.5	A5	A10
T0	n=46 -5.9 (9.4)	n=49 -10.3 (9.8)	n=140 -13.0 (7.9)	n=126 -16.5 (7.0)
T20	n=42 -13.2 (9.0)	n=44 -18.0 (7.8)	n=46 -15.5 (6.6)	n=40 -18.7 (7.0)
T40	n=130 -13.1 (10.1)	n=47 -16.2 (8.2)	n=142 -16.1 (7.7)	n=124 -19.7 (7.9)
T80	n=140 -13.6 (8.6)	n=47 -15.1 (7.6)	n=145 -17.9 (8.6)	n=138 -19.5 (8.0)

(SD) – Standard Deviation

The effect of each drug is graphically represented in Figure 8. The bar at amlodipine 10 and telmisartan 40 is actually somewhat higher than the bar at amlodipine 10 and telmisartan 80.

Figure 8: Delta Sitting Diastolic Mean BP, Baseline to Final (mmHg) from FAS-TC



Moderate To Severe Subgroup Analysis

Table 14 demonstrates that the combinations of important doses of telmisartan and amlodipine are significantly superior to each monotherapy in the moderate to severe hypertension groups.

Table 14: Comparison of key combination therapies to individual components on change from baseline (LOCF) in in-clinic seated trough cuff DBP (FAS-TC-MS)

		A0	A5	A10
T0	N	35	101	83
	Adj mean [†] (SE)	-5.8 (1.39)	-13.3 (0.82)	-17.6 (0.90)
T40	N	100	108	96
	Adj mean [†] (SE)	-14.2 (0.83)	-17.2 (0.79)	-20.1 (0.84)
	<u>Diff versus T</u>			
	Adj mean [†] (SE)		-3.0 (1.14)	-5.9 (1.17)
	95% CI		(-5.2, -0.7)	(-8.2, -3.6)
	p-value		0.0090	<0.0001
	<u>Diff versus A</u>			
	Adj mean [†] (SE)		-3.9 (1.14)	-2.5 (1.23)
	95% CI		(-6.1, -1.7)	(-4.9, -0.0)
	p-value		0.0006	0.0459
T80	N	89	106	100
	Adj mean [†] (SE)	-14.1 (0.87)	-19.1 (0.80)	-21.0 (0.83)
	<u>Diff versus T</u>			
	Adj mean [†] (SE)		-5.0 (1.18)	-6.8 (1.20)
	95% CI		(-7.3, -2.7)	(-9.2, -4.5)
	p-value		<0.0001	<0.0001
	<u>Diff versus A</u>			
	Adj mean [†] (SE)		-5.8 (1.14)	-3.3 (1.22)
	95% CI		(-8.1, -3.6)	(-5.7, -0.9)
	p-value		<0.0001	0.0065

Adjusted for country/region effect and baseline value

SE – Standard Error

Source data: Table 15.2.1.1.3: 4

Table 15: Mean (SD) non-placebo subtracted observed changes from baseline in in-clinic seated trough cuff DBP (mmHg) (FAS-TC-MS) in moderate to severe hypertensives

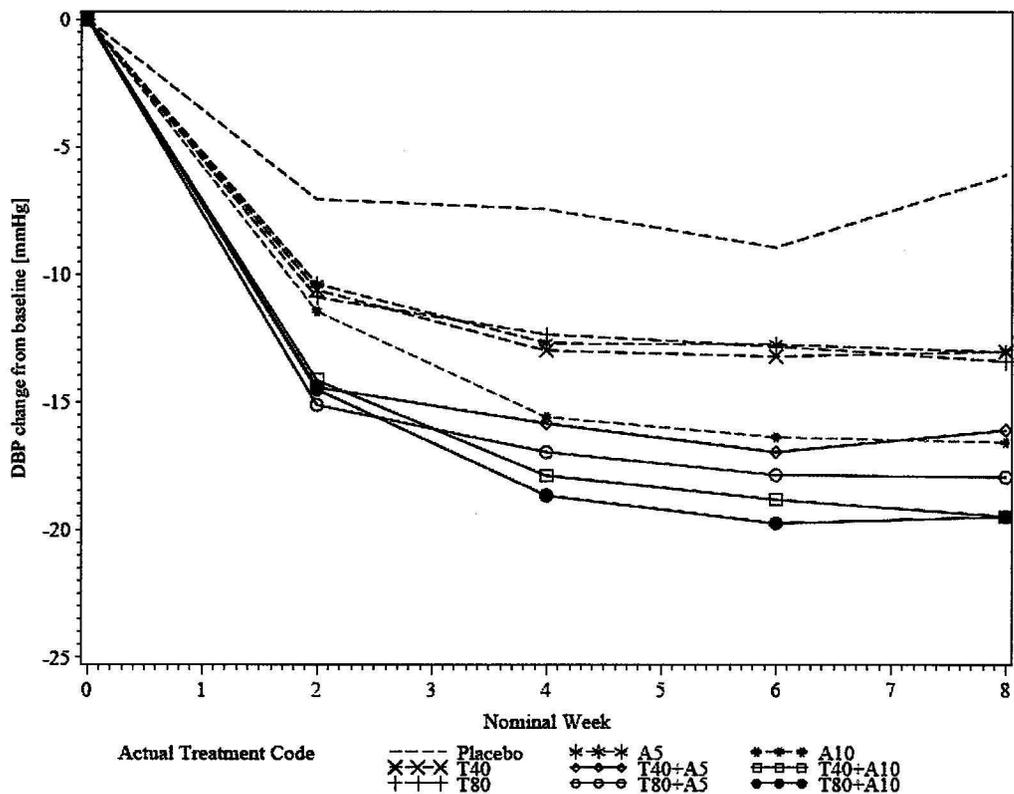
	A0	A2.5	A5	A10
T0	n=35 -5.5 (10.1)	n=37 -11.4 (8.3)	n=101 -13.1 (8.1)	n=83 -17.1 (7.6)
T20	N=33 -13.9 (9.4)	N=34 -18.4 (7.9)	n=34 -15.8 (6.4)	n=28 -19.5 (7.2)
T40	n=100 -13.8 (10.2)	n=30 -18.7 (7.9)	n=108 -16.8 (7.5)	n=96 -19.6 (8.3)
T80	n=89 -13.9 (9.2)	n=36 -16.3 (7.7)	n=106 -18.8 (9.0)	n=100 -20.4 (7.3)

(SD) standard deviation
Source: Study report trial 1235.1 p.74

REVIEWER'S COMMENT(S): The diastolic BP was lowered more by the A10/T80 combination than the A10/T40 in the FAS-TC-MS subgroup analysis, but only by an average of 0.8 mmHg with large standard deviations. There is a very small difference in effect between these doses. As will be seen later, the ABPM sub-study, and the benign safety profile provide sufficient rationale for approving the higher dose combinations.

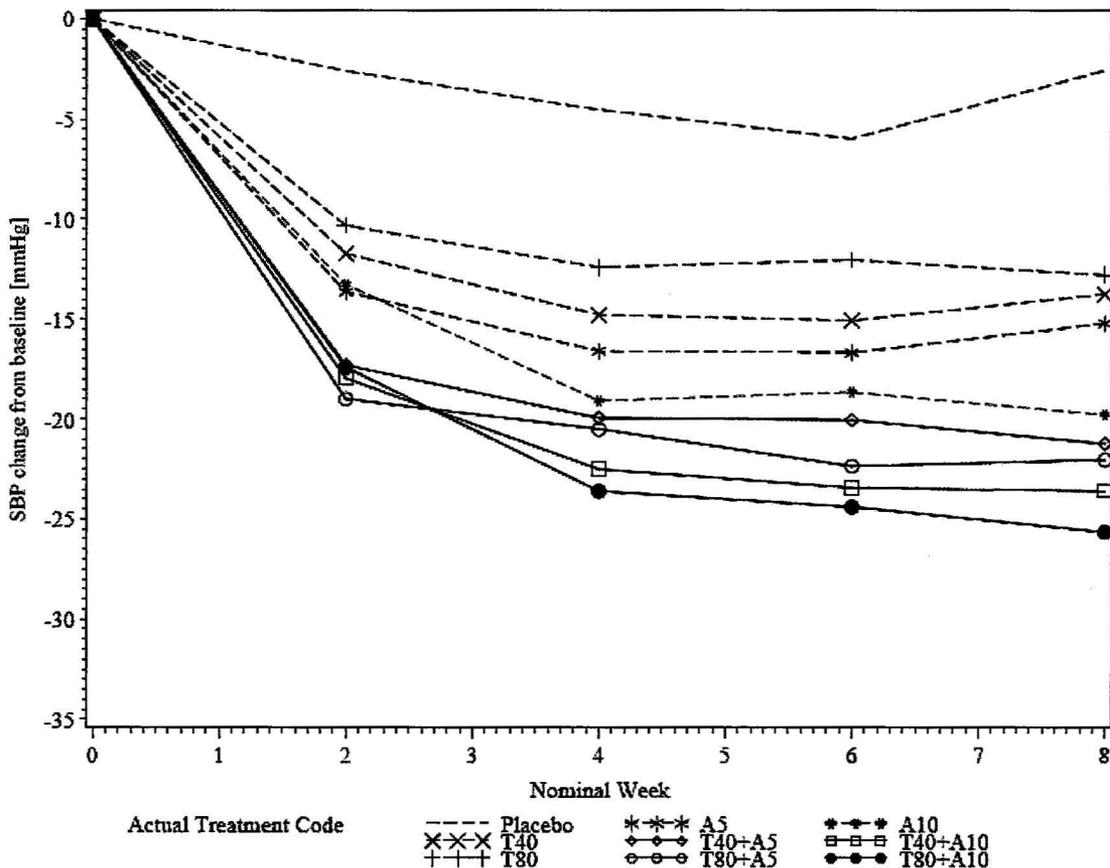
The majority of the antihypertensive effect in mono- and combination therapy was attained in diastolic pressure by the time of the initial evaluation at two weeks and the maximum antihypertensive effect occurred by 4 weeks after therapy initiation. See Figure 9 for a graphic representation of the effects of combined and monotherapy over time on DBP. The maximum effect on the systolic BP was also reached by week 4 in both combination and monotherapies. Similar effects occurred for SBP (Figure 10) and for the FAS-TC-MS subgroup. Figure 9 and Figure 10 also illustrate a small but consistent dose response effect.

Figure 9: Mean DBP in mmHg change from baseline over time [FAS]



Source: module 5.3.5.3, Figure 1:1

Figure 10: mean SBP (mm Hg) change from baseline over time (FAS)



Source: Module 5.3.5.3, Figure 1: 2

Figure 11 demonstrates placebo-subtracted delta diastolic BP for the combinations that contain amlodipine 5 mg. This graph shows no difference between T20+A5 and T40+A5. Figure 12 also demonstrates that there is little difference between the T20+A10 and T40+A10 combinations. Note that the improved apparent placebo-subtracted effect for all doses at week 8 shown in Figure 11 and Figure 12 is due to a decrease in the placebo effect at week 8 as illustrated in Figure 9.

REVIEWER'S COMMENT(S): Once again, even with the lower dose of telmisartan (20 mg) there is no convincing difference between the combinations with 20 mg, 40 mg or 80 mg in obtaining reduction in DBP. Nevertheless, as stated in my prior comment, there is sufficient other supportive information to warrant approval of the higher dose combinations.

Figure 11: Placebo- subtracted Diastolic Blood Pressure by week for Amlodipine 5 mg in Combination with Varying Doses of Telmisartan (FAS)

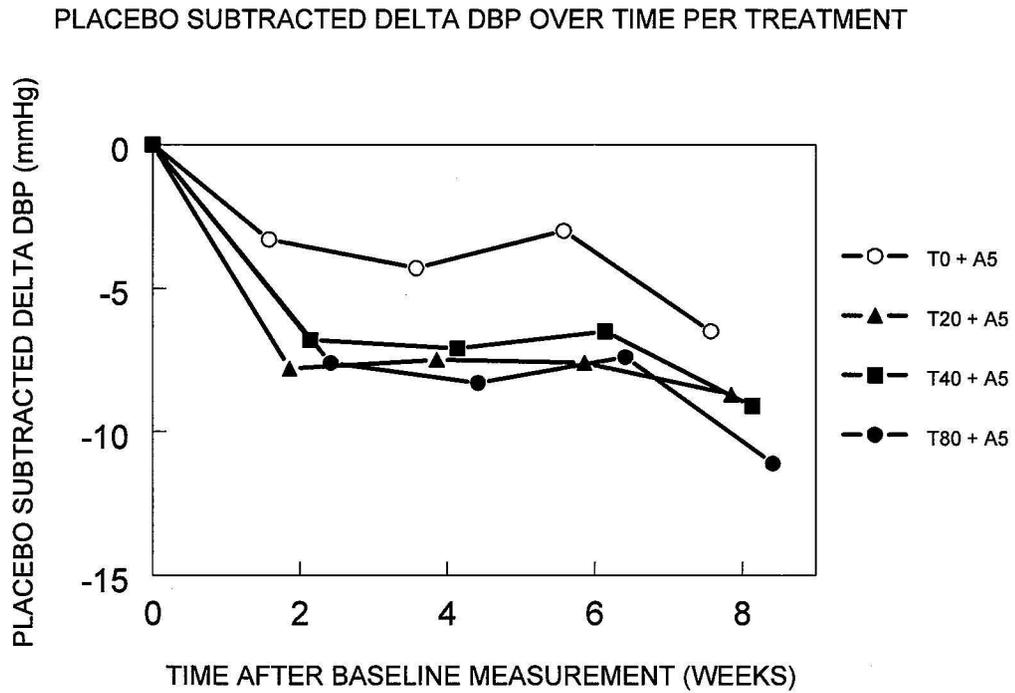
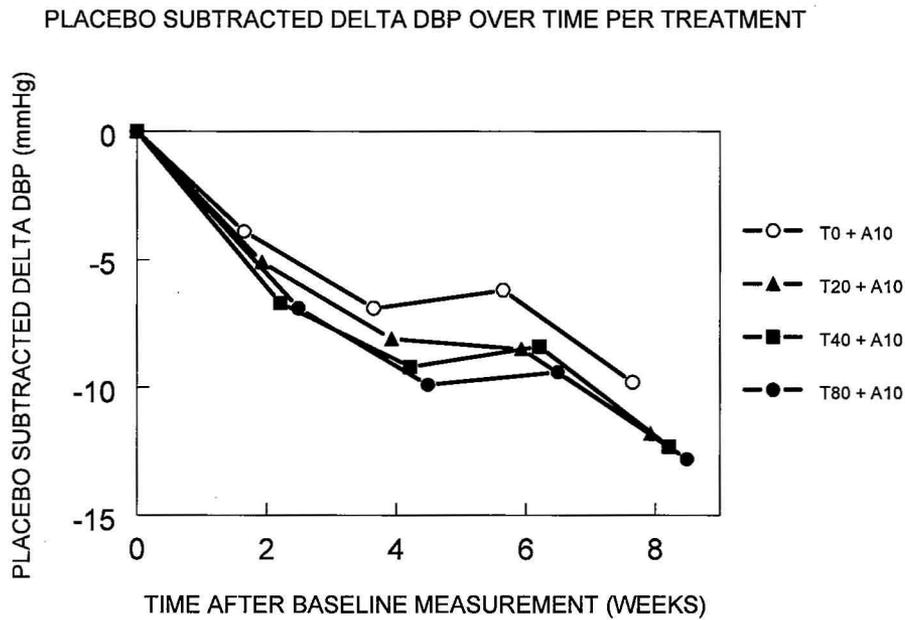


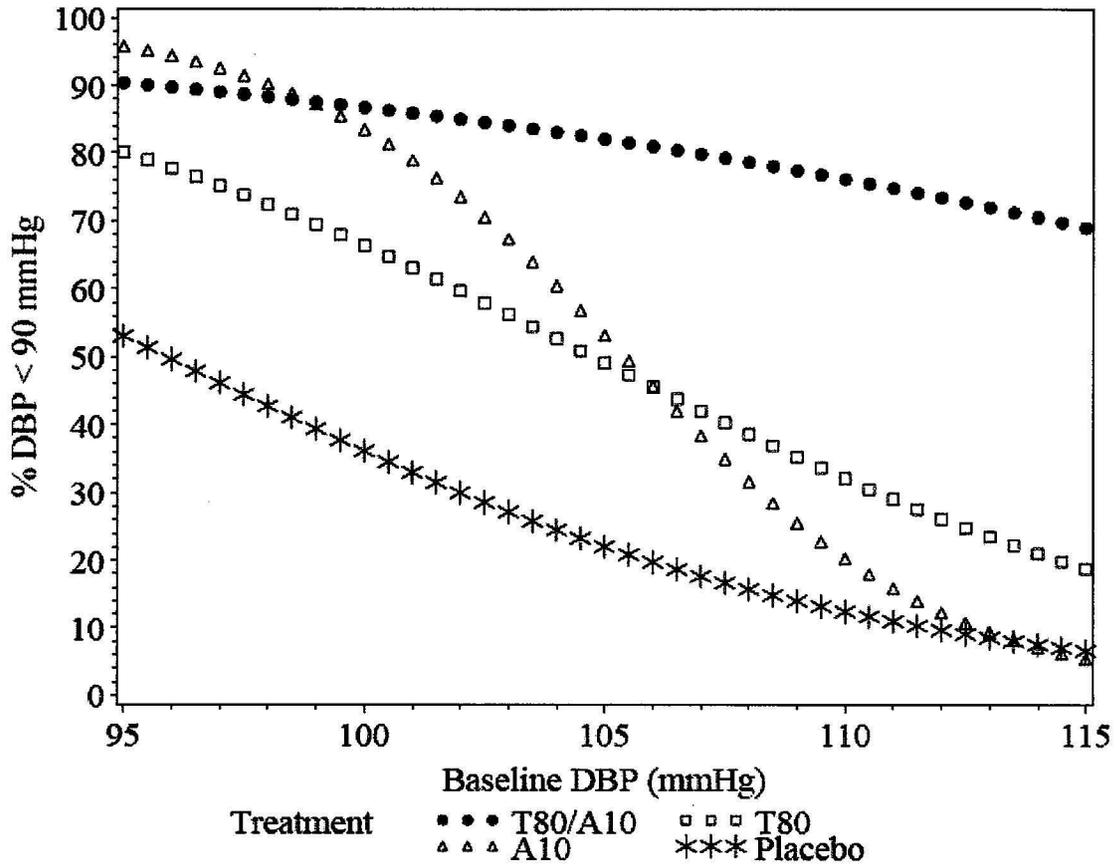
Figure 12: Placebo- subtracted Diastolic Blood Pressure by week for Amlodipine 10 mg in Combination with Varying Doses of Telmisartan (FAS)



Reaching Goal

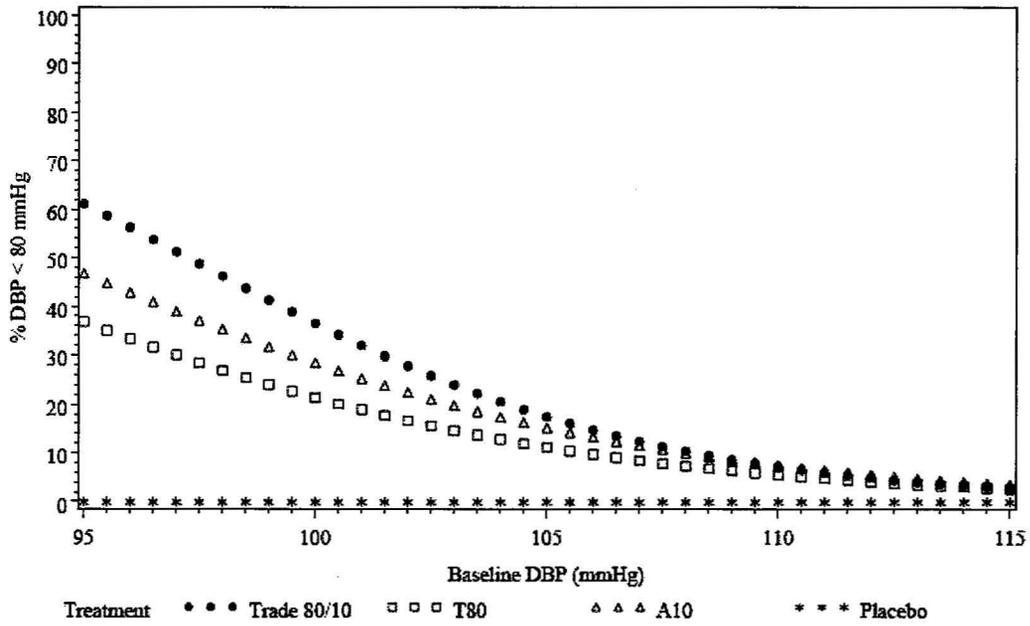
In order for a combination product to be marketed for first line use, superiority at reaching SBP goals of <140 and <130 than each monotherapy and at reaching DBP goals of < 90 and <80 than each monotherapy at all levels of baseline systolic and diastolic blood pressures must be demonstrated. The sponsor did a logistic regression model graph that demonstrated an impressive difference between the highest combination therapy and the respective monotherapies. These graphs are included in this review as Figure 13, Figure 14, Figure 15, and Figure 16. As shown in Table 16, there are very few patients in the baseline DBP ≥ 110 mmHg. I created Figure 17 by plotting the mean chance of reaching the DBP goal of <90 by batched groups defined by 5 mmHg increments in baseline DBP, eliminating the patients with DBP ≥ 110 mmHg.

Figure 13: Probability of achieving Goal DBP of DBP <90 mmHg modeled by sponsor including all data in FAS



Source: ISE

Figure 14: Probability of achieving Goal DBP of DBP <80 mmHg modeled by sponsor including all data in FAS



Source: Proposed Label

Figure 15: Probability of achieving goal of SBP < 140 mmHg with high dose combination and each monotherapy by sponsor using modeling analysis of FAS

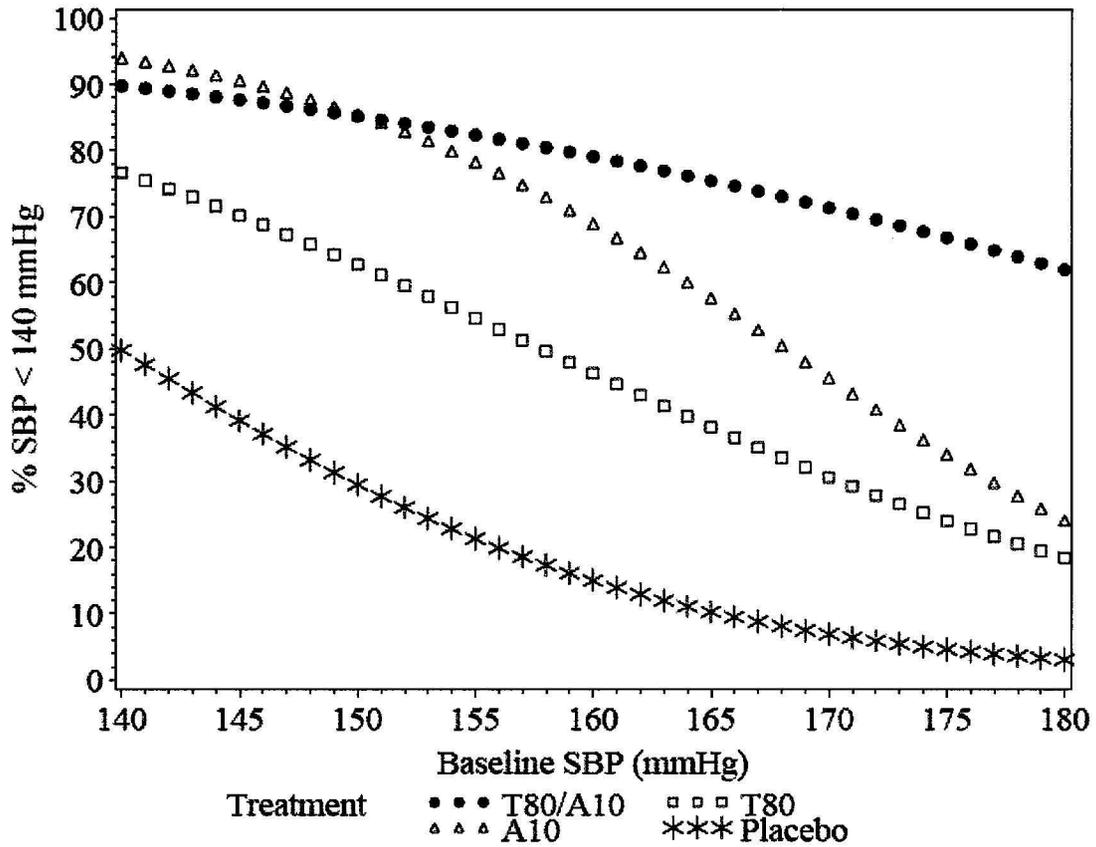
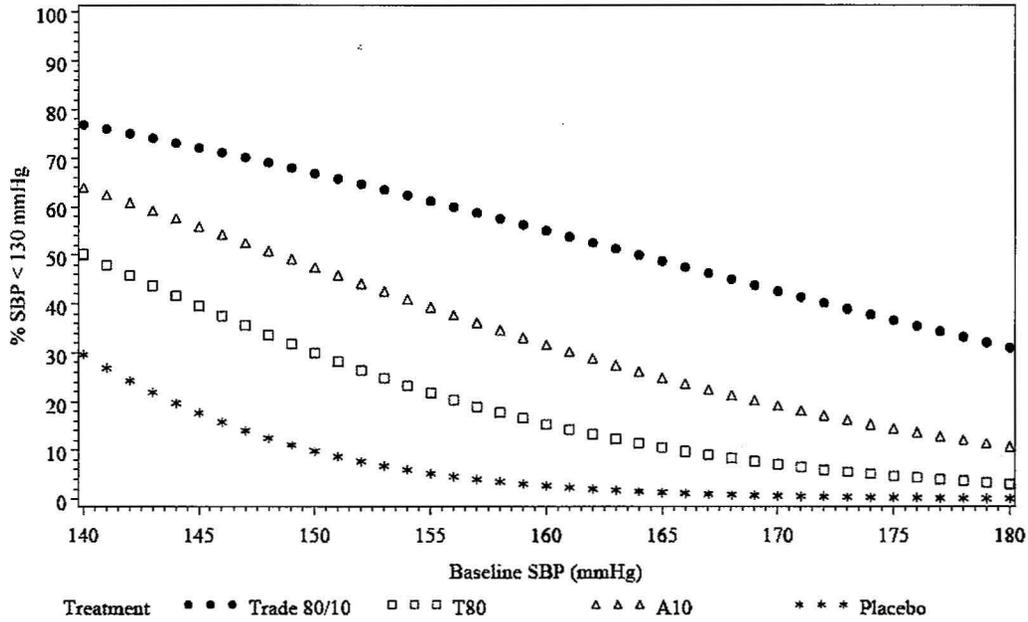


Figure 2.3: 4 Probability of achieving SBP control (<140 mmHg) by baseline SBP

Source: ISE

Figure 16: Probability of achieving goal of SBP < 130 mmHg with high dose combination and each monotherapy by sponsor using modeling analysis of FAS



Source: proposed label

Table 16: Numbers of patients in FAS in each baseline BP batch

N	<95mmHg		≥95mmHg		<100mmHg		≥100mmHg		<105mmHg		≥105mmHg		<110mmHg		≥110mmHg		<115mmHg		≥115mmHg		
	N	n RG <90	N	n RG <90	N	n RG <90	N	n RG <90	N	n RG <90	N	n RG <90	N	n RG <90	N	n RG <90	N	n RG <90	N	n RG <90	
Placebo	1	1	11	4	23	8	9	1	1	0	1										
T80	4	4	48	36	54	29	19	8	7	3	0										
A10	2	2	52	45	47	37	21	7	2	0	0										
T80/A10	2	1	51	46	66	58	13	7	3	3	1										

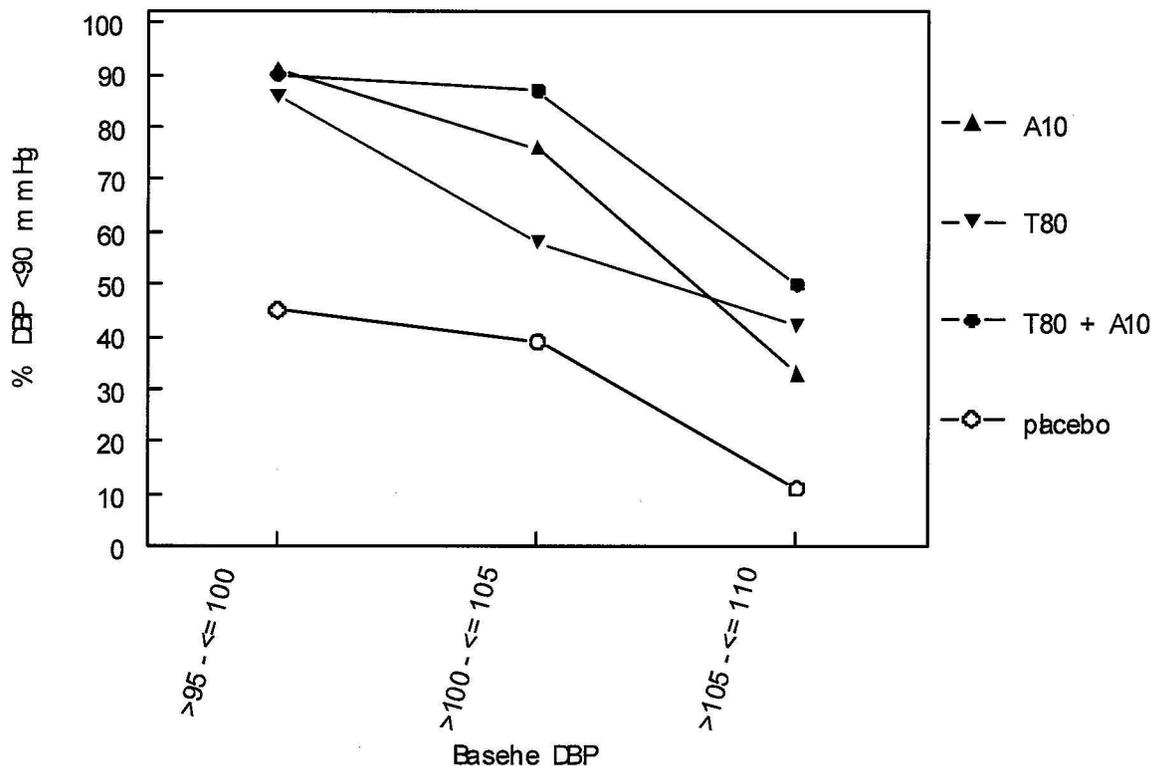
n RG = number of patients that met goal of DBP <90

Table 17: Data used to Create Figure 17.

BP baseline	Percent Reaching Goal by Treatment			
	A10	T80	A10/T80	Placebo
>95 - ≤100	91	86	90	45
>100 - ≤105	76	58	87	39
>105 - ≤110	33	42	50	11

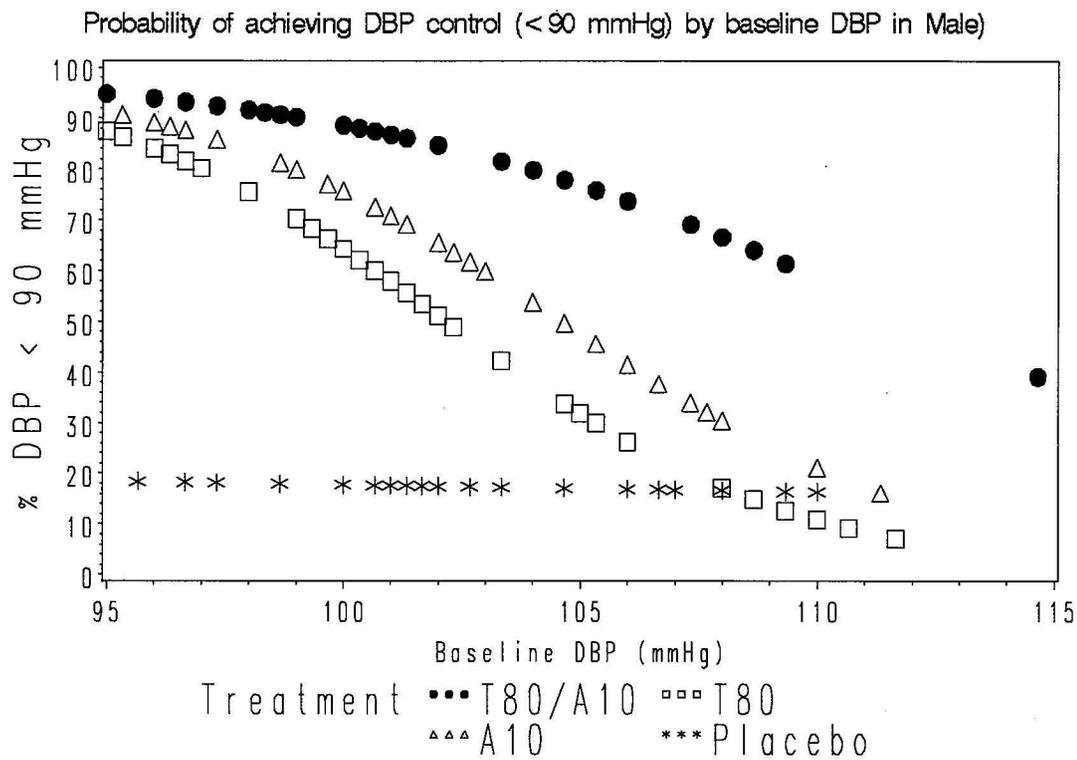
Data truncated to include only patients with baseline DBP between >95 and ≤ 110 because of the paucity of patients outside of this range.

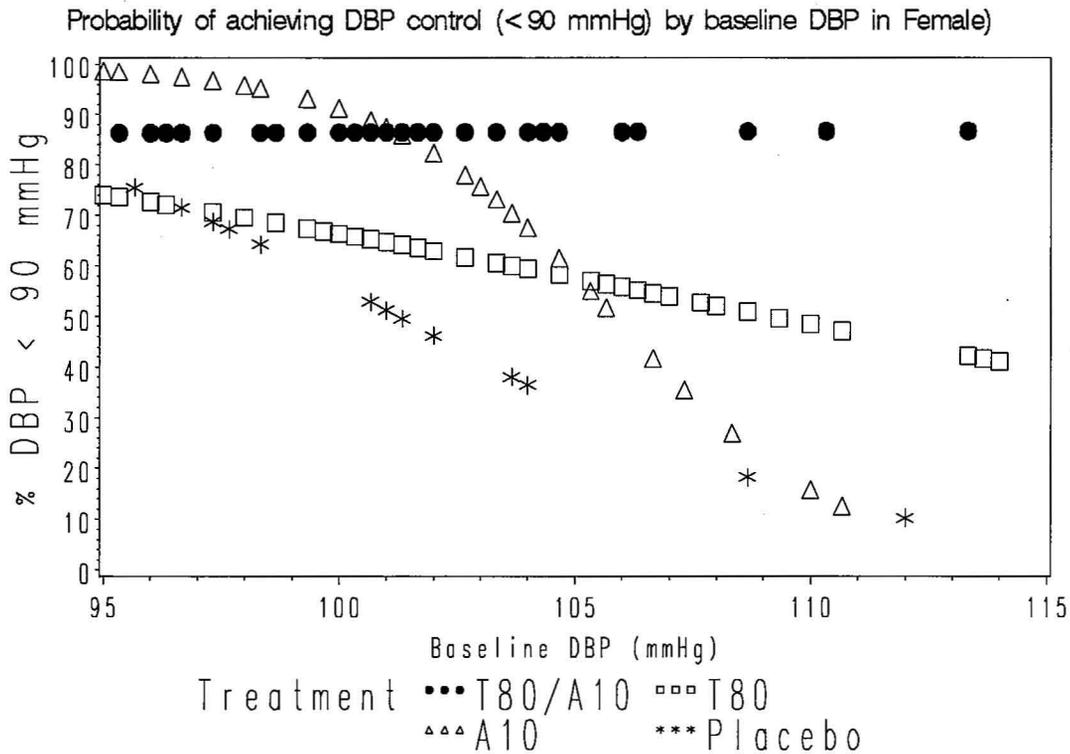
Figure 17: Probability of Meeting Goal DBP <90 by baseline DBP, excluding the patients with baseline DBPs ≤ 95 mmHg and ≥ 110 mmHg (only 24 patients excluded in all). No data modeling, batched analysis



REVIEWER'S COMMENT(S): Regardless of the data used or model used to construct the figures for the responder analysis, it is clear that the highest combination dose is superior to the monotherapies for achieving a diastolic blood pressure goal of <90 mmHg. It is prudent to cut off the responder graphs at >95mmHg baseline on the left and ≤ 110 baseline DBP on the right of the x axis because of the very few patients that were studied outside of this range. It is apparent that patients with baseline DBPs < 100 mmHg achieve goal of 90 DBP as well as with A10 as with T80A10. For achieving DBP <80 mmHg, there is little difference between treatments, including placebo. For achieving SBP < 130 mmHg, however, the T80A10 combination is more effective at reaching goal than the monotherapies or placebo regardless of baseline SBP.

Since, as will be discussed later, there is a larger delta DBP effect in women than in men, a responder analysis was done in women and men for achieving DBP goal of < 90 mmHg with the highest combination and the respective monotherapies and placebo. See graphs below. While no conclusions can be made from these graphs, it is curious that the patterns of baseline DBP effects on meeting goal look very different between the men and women.





6.1.5 Analysis of Secondary Endpoints(s)

Secondary Endpoints

The main secondary endpoints included:

1. Change from baseline in the in-clinic seated trough cuff systolic blood pressure (SBP) after 8 weeks of treatment
2. Change from baseline in the in-clinic standing trough cuff DBP after 8 weeks of treatment.
3. Change from baseline in the in-clinic standing trough cuff SBP after 8 weeks of treatment.
4. Ambulatory Blood Pressure Monitoring (ABPM) substudy

1. Change from baseline in the in-clinic seated trough cuff systolic blood pressure (SBP) after eight weeks of treatment

Combination therapy produced greater reductions in SBP than monotherapy. Mean placebo-subtracted SBP changes from baseline ranged from -12.8mmHg to -18.2 mmHg in the monotherapies to -19mmHg to 23.9mmHg for the key combination therapies at the last on-therapy evaluation.

For systolic BP in the FAS and FAS-MS, the doses that are planned to be marketed showed statistically significant improvements compared to each drug alone. The T80/A10 dose appears superior to the T40/A10 for controlling systolic BP by point estimate (by 2 mmHg). However, there is little difference between the T40/A5 and T80/A5 dose for lowering systolic BP (0.3 mmHg). This is demonstrated in Table 18 and Table 19.

Table 18: Comparison of treatment effects on the change from baseline in in-clinic seated trough SBP (LOCF) for combination therapy of important doses versus the individual components (FAS-TC)

		A0	A5	A10
T0	N	46	137	124
	Adj* mean (SE)	-2.5 (1.82)	-15.4 (1.06)	-20.7 (1.11)
T40	N	129	141	123
	Adj* mean (SE)	-14.6 (1.09)	-21.8 (1.05)	-24.7 (1.12)
	Diff versus T			
	Adj* mean (SE)		-7.2 (1.50)	-10.1 (1.55)
	95% CI		(-10.2, -4.3)	(-13.2, -7.1)
	p-value		<0.0001	<0.0001
	Diff versus A			
	Adj* mean (SE)		-6.4 (1.48)	-4.0 (1.57)
95% CI		(-9.3, -3.5)	(-7.1, -0.9)	
p-value		<0.0001	0.0108	
T80	N	132	143	136
	Adj* mean (SE)	-14.3 (1.08)	-22.1 (1.04)	-26.4 (1.07)
	Diff versus T			
	Adj* mean (SE)		-7.8 (1.49)	-12.1 (1.51)
	95% CI		(-10.8, -4.9)	(-15.1, -9.2)
	p-value		<0.0001	<0.0001
	Diff versus A			
	Adj* mean (SE)		-6.7 (1.47)	-5.7 (1.53)
95% CI		(-9.6, -3.8)	(-8.7, -2.7)	

Source: Study report p.307

Table 19: Comparison of treatment effects on the change from baseline of in-clinic seated trough SBP (LOCF) for combination therapy of important doses versus the individual components (FAS-TC-MS)

		A0	A5	A10
T0	N	35	101	83
	Adj* mean (SE)	-1.9 (2.07)	-14.8 (1.23)	-21.0 (1.35)
T40	N	100	108	96
	Adj* mean (SE)	-15.4 (1.23)	-22.2 (1.18)	-25.3 (1.26)
	Diff versus T			
	Adj* mean (SE)		-6.8 (1.70)	-9.9 (1.75)
	95% CI		(-10.1, -3.5)	(-13.4, -6.5)
	p-value		<0.0001	<0.0001
	Diff versus A			
	Adj* mean (SE)		-7.4 (1.69)	-4.3 (1.83)
95% CI		(-10.8, -4.1)	(-7.9, -0.7)	
p-value		<0.0001	0.0194	
T80	N	89	106	100
	Adj* mean (SE)	-15.4 (1.30)	-22.5 (1.20)	-26.5 (1.23)
	Diff versus T			
	Adj* mean (SE)		-7.0 (1.76)	-11.1 (1.78)
	95% CI		(-10.5, -3.6)	(-14.6, -7.6)
	p-value		<0.0001	<0.0001
	Diff versus A			
	Adj* mean (SE)		-7.7 (1.70)	-5.5 (1.82)
95% CI		(-11.0, -4.3)	(-9.0, -1.9)	
p-value		<0.0001	0.0026	

Source: p. 314 study report

REVIEWER'S COMMENT(S): It appears from these figures that the telmisartan 40mg combinations do as well at controlling SBP as the telmisartan 80 mg combinations.

2. In-Clinic Standing DBP and In-Clinic Standing SBP

Treatment with the combination therapy on standing DBP and SBP over 8 weeks was superior to each monotherapy for each of the combinations, as one might expect.

The results are provided in Table 20.

Table 20: Improved BP control demonstrated with standing BP readings

Treatment	Delta standing DBP in mmHg	P value for superiority of combination therapy over Amlodipine monotherapy	P value for superiority of combination therapy over Telmisartan monotherapy	Delta standing SBP in mmHg	P value for superiority of combination therapy over Amlodipine monotherapy	P value for superiority of combination therapy over Telmisartan monotherapy
T40 + A5	-14.2	p=0.0053	p=0.0046	-20.0	p=0.0004	p<0.0001
T40	-10.9			-13.2		
A5	-11			-14.7		
T40 + A10	-18	p=<0.0001	p=0.0494	-22.8	p=0.0195	p<0.0001
A10	-15.5			-19.1		
T80 + A5	-17.3	p=<0.0001	p=<0.0001	-21.2	p <0.0001	p <0.0001
T80	-11.3			-14.7		
T80 + A10	-19.2	p=<0.0001	p=0.0032	-24.9	p=0.0002	p <0.0001

Data source: clinical trial report

3. Ambulatory Blood Pressure Monitoring

A total of 562 (38.5%) of the 1461 treated patients in Trial 1235.1 were included in the ABPM sub-study; most of these patients (403/71.7%) had moderate or severe hypertension at baseline. Patients in this sub-study had ABPM assessments performed at their baseline and at their end-of-study visits. Hourly DBP and SBP values were summarized and calculations based on these data were performed to determine the following: 24-hour mean DBP and SBP, last 6-hour mean DBP and SBP, mean TP ratios, and smoothness indices for each treatment group.

The peak effects of the key doses of monotherapies and the key doses of the combination therapy occurred between hours 4 and 8 in the FAS and FAS-MC sub-group.

The mean hourly untreated DBP has an expected diurnal trough at 15 -20 hours post-dosing which occurs at some point between 10 PM and 3 PM. This diurnal trough makes it difficult to interpret Figure 18 which is the graph of the mean BP at each hour after treatment dose. Refer to Figure 19 for a better assessment that allows one to assess the stability of effect over time. To construct Figure 19, I used placebo subtracted values. This eliminated the diurnal variation effect and better demonstrates the stability of effect of the combination therapy over the 24 hour time period. While the error bars are very large, we can have confidence in the superiority of the combination therapy because there is more improvement in the point estimate compared to monotherapy at each measured time point. It is important to note that at each time point the mean

change in DBP is more than for each of the individual components for the T80 +A10 combination. This pattern held true for all of the key combinations for the DBP and the SBP, but not for the smaller dose combinations which were much more variable. The same effect held true for the FAS-MC ABPM sub-group. When comparing the different key combinations, it appeared that the group treated with the T40 +A5 combination had a smaller delta in DBP measurements (approximately -10 to -15 mmHg from baseline throughout the 24 hours period) than the groups treated with the other key combinations where the delta DBPs were approximately -15 to -20 mmHg). This was similar to the pattern seen for the systolic BPs where the group treated with the T40 +A5 combination had a smaller delta (approximately -15 to -20 mmHg) than the groups treated with the other key combinations where the delta SBPs were approximately -20 to -25 mmHg. This observation suggests a dose effect.

Figure 18: ABPM for FAS, Change in DBP over time (average of 3 every 20 minute readings per time point) for T80 + A 10 dose

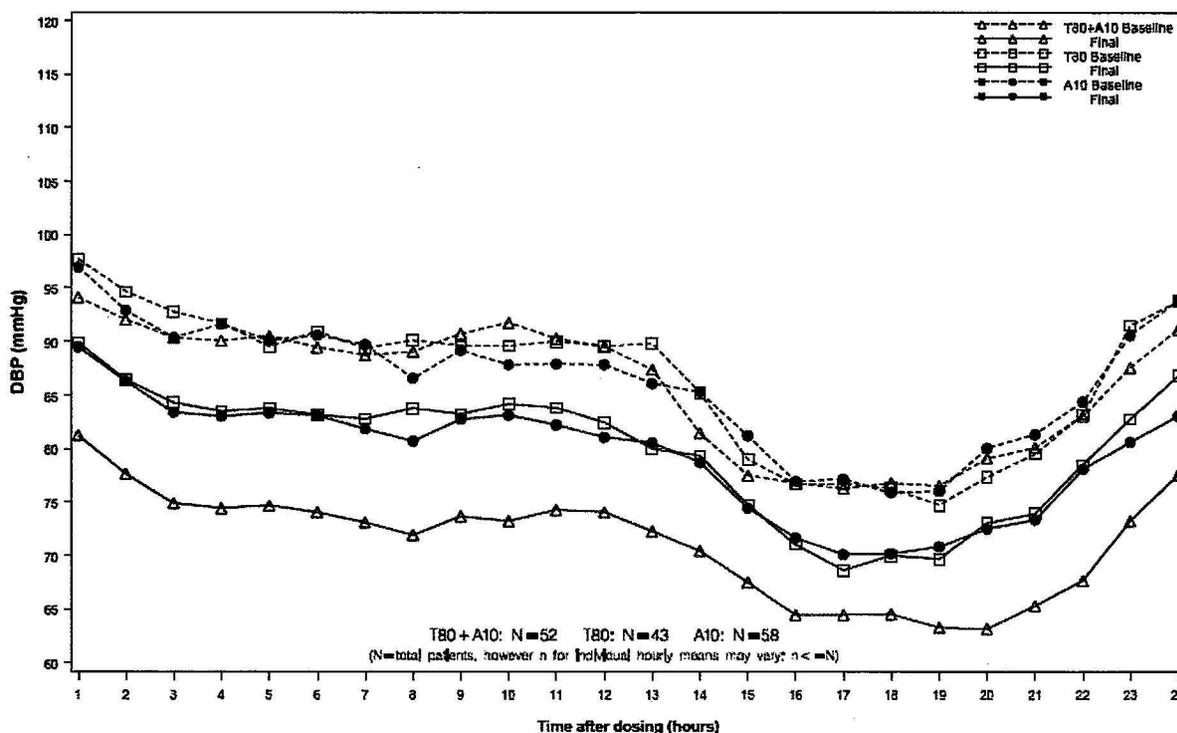
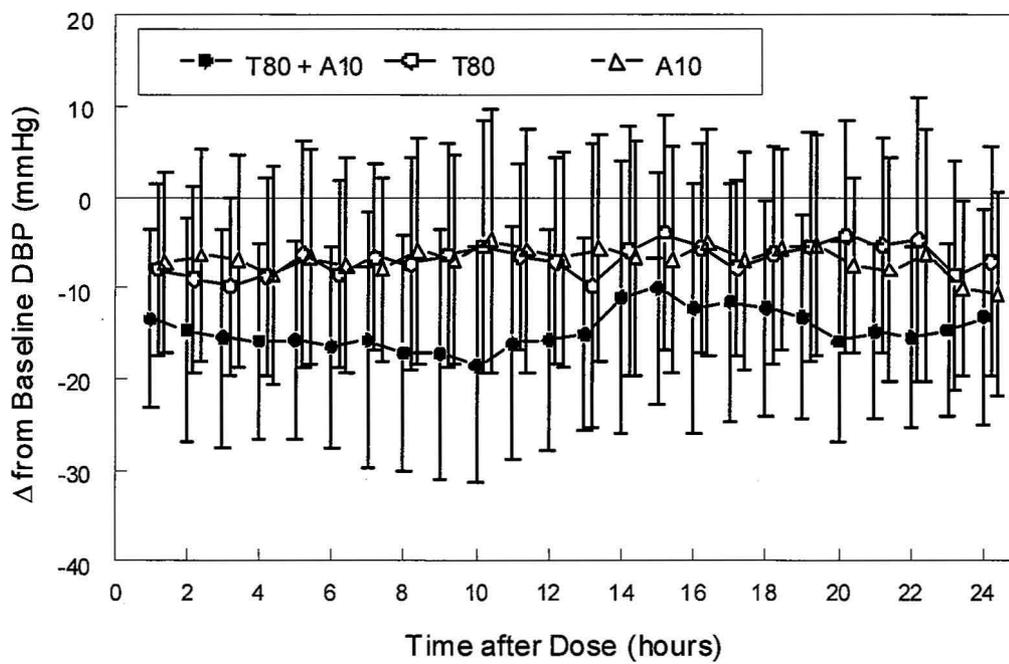


Figure 15.2.3.1.1: 17 Profile of ABPM DBP hourly means for T80+A10 and individual components [FAS-ABPM]

Source data: Section 15, Table 2.3.1.2: 1

f15hm.sas 05JUL2007

Figure 19: ABPM change from baseline for treatment groups T80, A10 and T80/A10



Dose Relationship Exploration Using ABPM Measurements

In Table 21 the mean delta ABPM blood pressures were calculated over the 24 hour period for each dose and dose combination. The dose relationship for the combination product is small but demonstrable and provides evidence that there is an, albeit small, dose relationship among the combination product with the T80A10 combination being the most effective dose, followed by the T40A10, followed by the T80A5, followed by the T40A5. The dose relationship is also demonstrated graphically in Figure 20 and Figure 21.

Table 21: Mean Delta ABPM BPs for entire 24 hour period from baseline to final

Dose	Mean Δ Systolic BP mmHg	Mean Δ Diastolic BP mmHg
Placebo	-5.2	-2.6
A2.5	-9.3	-5.3
A5	-11	-6.6
A10	-11.9	-6.8
T20	-7.1	-5.2
T40	-8.4	-4.7
T80	-12.1	-7
T20+A2.5	-13	-6.5
T20+A5	-17.8	-11.8
T20+A10	-14.1	-9.4
T40+A2.5	-12.5	-9.5
T40+A5	-16.4	-10.5
T40+A10	-21.1	-13.4
T80+A2.5	-16.2	-9.8
T80+A5	-19.1	-11.9
T80+A10	-22.5	-14

Figure 20: Change in DBP per hour from ABPM measurements over 24 hours for each key dose combination

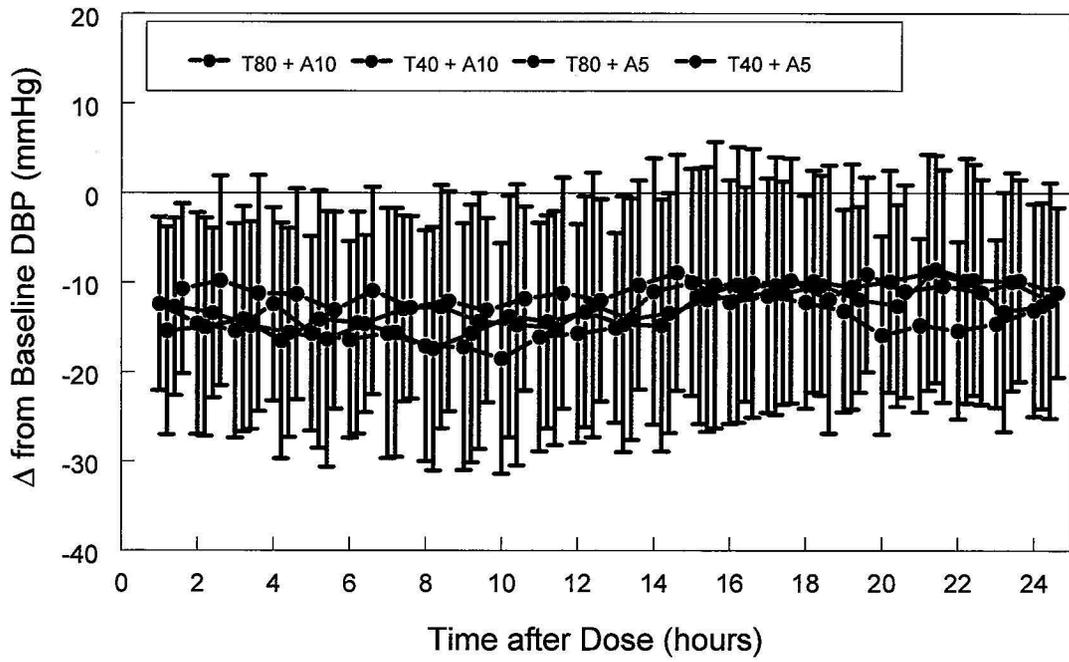
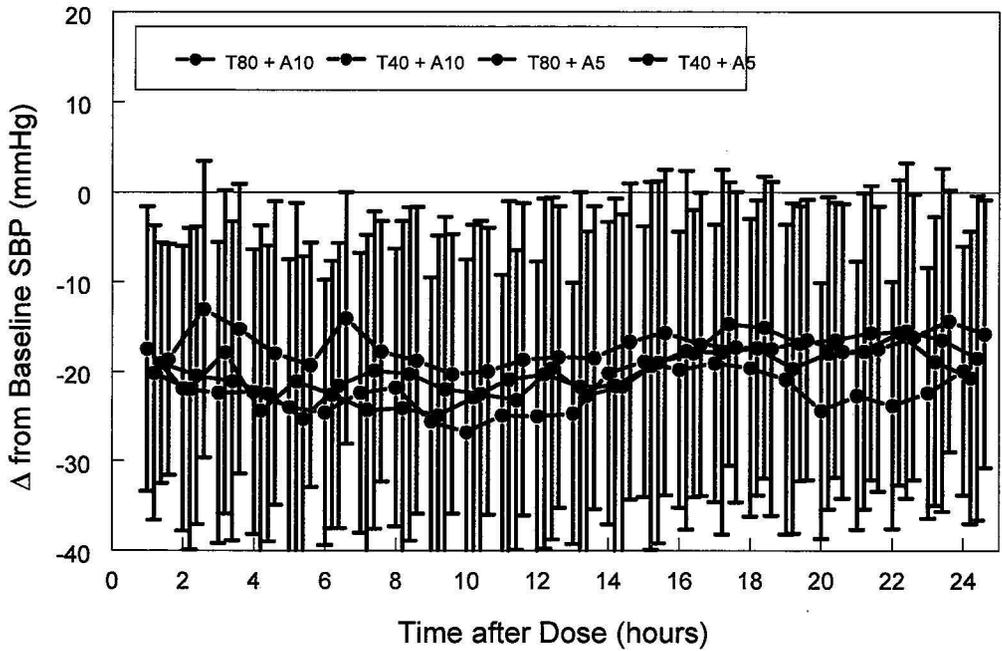


Figure 21: Change in SBP per hour from ABPM measurements over 24 hours for each key dose combination



6.1.6 Subpopulations

Subgroup analyses were conducted to evaluate the consistency of treatment effect on BP.

Sex differences:

As demonstrated in Table 22, there was a small but consistently larger decrease in DBP in females for all treatment groups including placebo. In this study we cannot presume that the sex difference seen is due to a drug effect because it was also seen in the placebo group. It is unclear if females are more subject to a regression to the mean effect with hypertension treatment because of white coat hypertension or possibly they have a greater placebo effect. In an article written by Banegas et al and published in *Am J Med.* 2008, Dec;121(12):1078-84, it was noted in a cohort of ~15,000 men and ~14,000 women that the probability of achieving ambulatory BP control was higher in women than in men (49% vs. 39%, <0.001) even after controlling for age, number of antihypertensive drugs, hypertension duration and risk factors. Women also had a higher frequency of isolated office hypertension which may have accounted for this finding. In an article by White et al (*Am J Hypertens.* 2001 Dec;14(12):1239-47), in a meta-analysis of

~400 hypertensive patients, treatment with extended release verapamil resulted in a greater response in women than in men. The results of trial 1235.1 stratified by sex are provided in Table 22.

Table 22: Mean DBP changes from baseline at end of trial in key combinations by sex

		A0	A5	A10
Male, N	T0	29	70	63
Mean change (SD)		-3.9 (9.6)	-11.2 (7.1)	-14.9 (6.5)
Female, N		17	67	61
Mean change (SD)		-9.3 (8.3)	-15.0 (8.2)	-18.2 (7.3)
Male, N	T40	65	70	60
Mean change (SD)		-12.0 (9.8)	-14.5 (7.1)	-19.3 (9.1)
Female, N		64	71	63
Mean change (SD)		-14.2 (10.4)	-17.4 (7.9)	-20.0 (6.6)
Male, N	T80	57	71	62
Mean change (SD)		-12.5 (7.8)	-17.4 (8.3)	-18.9 (8.0)
Female, N		75	72	74
Mean change (SD)		-14.4 (9.3)	-18.2 (8.8)	-20.1 (7.8)

Age differences:

Since the majority of patients within each treatment group were <65 years of age, comparison across age categories is difficult. There was a small but consistently larger decrease in DBP in patients ≥ 65 years of age when compared to those <65 years of age for all treatment groups except placebo. Since there is a small placebo effect, there is an even larger decrease in placebo subtracted DBP in patients ≥ 65 years of age for all treatment groups.

Difference in effect by diabetic status:

Diabetic status did not correlate with any notable differences in efficacy in any subgroups. Approximately 17% of patients in the key combination therapy groups were diabetic.

Racial Differences: The combination drug was as effective in all races. However, the primary contribution to this effect was amlodipine. See Table 23.

Geographical differences:

It was not possible to compare the efficacy in each region because of the relatively small numbers of patients in regions outside of the U.S. Appendix 4 shows a break-down of effectiveness by country and US region.

Other: BMI and concomitant use of NSAIDs/COX-2 inhibitors did not appear to affect efficacy as the changes from baseline DBP were generally comparable between the subgroups. Too few patients in Trial 1235.1 were ≥ 75 years of age, were of Asian race, or were renally impaired to allow for conclusive determination of efficacy in comparison to their complementary subgroups for age, race and renal status.

Relative contributions of telmisartan and amlodipine to Twynsta effect by subgroups:

The smaller the delta between the monotherapy effect and the combination, the lesser the contribution of the other monotherapy there is on the final blood pressure. As you can see in Table 23, in Blacks there is no extra Δ DBP effect gained from adding T80 to A10. The T80 Δ DBP effect is less than the A10 Δ DBP effect in Caucasians as well, but there is at least some contribution of T80 to the Δ DBP seen with Twynsta T80 + A10. In Asians, the pattern is the opposite for the T80A10 dose, i.e., T80 makes the larger contribution to the combination Δ DBP effect. For the T40 + A10 dose combination and the T40 + A5 dose contribution there is also a lower telmisartan Δ DBP effect in Blacks, but the T80 + A5 dose contribution shows an equal Δ DBP telmisartan and amlodipine effect. Therefore, it is unlikely that switching Black patients to Twynsta from amlodipine will have much of a Δ DBP effect.

In the Telmisartan original studies, all pivotal studies demonstrated that the change in supine DBP from baseline for T40 and T80 in Blacks was between -1.0 and -8.3 mmHg while the change in supine DBP from baseline for Caucasians was between -8.0 and -14.3 mmHg. The placebo subtracted effect was between -1.2 and -11.4 mmHg in Blacks and between -5.4 and -10.4 in Caucasians. There was a larger placebo effect in Caucasians than Blacks in most but not all studies which accounts for the lessening of the difference between races when placebo-subtracted values are used for comparison. Nevertheless, there appears to be a race difference that favors Caucasians somewhat for telmisartan.

In males and females the A10 Δ DBP effect supersedes the T80 Δ DBP effect. The A10 Δ DBP effect supersedes the T80 Δ DBP effect more in females than in males. In the other dose combinations the difference between the amlodipine and telmisartan Δ DBP effect is the same in females, but disappears to a large extent in males. Females will not be as likely as men to benefit from switching from amlodipine to Twynsta.

In patients ≥ 65 years and patients < 65 years, the A10 Δ DBP effect also supersedes the T80 Δ DBP effect. In patients ≥ 65 years old, the difference is magnified. This difference between the age groups is only apparent for the A10 combinations. Patients ≥ 65 years of age will be less likely to benefit from switching from A10 to Twynsta.

Table 23: Amlodipine vs. Telmisartan contribution to delta (Δ) DBP effect of combination therapy by race, sex and age

	T80 + A10 Δ DBP effect In mmHg	T80 – (T80 + A10) Δ DBP effect in mmHg	A10 – (T80 + A10) Δ DBP effect in mmHg	T40 + A10 Δ DBP effect In mmHg	T40 – (T40 + A10) Δ DBP effect in mmHg	A10 – (T40 + A10) Δ DBP effect in mmHg	T80 + A5 Δ DBP effect In mmHg	T80 – (T80 + A5) Δ DBP effect in mmHg	A5 – (T80 + A5) Δ DBP effect in mmHg	T40 + A5 Δ DBP effect in mmHg	T40 – (T40 + A5) Δ DBP effect in mmHg	A5 – (T40 + A5) Δ DBP effect in mmHg
Race												
Black	-17.2	-3.6	0.3	-20.9	-10.4	-3.4	-16.7	-3.1	-3.0	-13.7	-3.2	0.0
Caucasian	-20.6	-6.4	-3.7	-20.3	-6.7	-3.4	-15.6	-1.4	-2.5	-17.0	-3.4	-3.9
Asian	-25.4	-5.4	-9.0	-16.1	1.0	3.9	-20.6	-6.2	-4.4	-19.3	-2.2	-3.2
Sex												
Female	-20.5	-5.8	-2.1	-20.5	-6.0	-2.1	-18.7	-4.0	-3.4	-17.3	-2.8	-2.0
Male	-19.5	-6.4	-3.8	-19.5	-7.3	-3.8	-17.7	-4.6	-6.2	-15.0	-2.8	-3.5
Age												
< 65	-19.6	-5.8	-3.1	-19.9	-7.4	-3.4	-17.6	-4.1	-4.7	-16.3	-3.8	-4.6
\geq 65	-22.7	-7.4	-2.6	-21.6	-5.0	-1.5	-23.2	-7.9	-7.7	-17.5	-0.9	-2.0

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

The pivotal study was done using the combinations of T40 and T80 with A5 as treatment for the entire trial or as initiation treatment with planned titration to T+A10 combinations after the first week. Additionally, the peak effect of each combination dose was not attained until at least two weeks after initiation of therapy. For these reasons, the drug should be initiated with the T40+A5 combination or the T80+A5 combination and titrated up if necessary after 2 weeks.

There was an incremental BP change when increasing doses of each component. However, none of the doses were far superior to the others. If patients have dose limiting side effects of amlodipine (usually edema), it is reasonable to switch those patients to one of the doses containing T+A5.

It is reasonable from the data presented to label Twynsta as an initial therapy for hypertension when it is suspected that more than one drug will be required or as replacement therapy in patients not adequately controlled by a monotherapy.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

The efficacy of amlodipine and telmisartan has been tested over longer periods of time than 8 weeks in many other trials (at least one year). There is no reason to suspect that the efficacy of the combination product would diminish over time.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The three facets of the safety analysis for TWYNSTA were, 1) the pivotal trial (1235.1), 2) Supportive phase 3 and 4 studies and 3) ONTARGET

7.1.2 Adequacy of Data

The data is adequate considering the fact that the components of TWYNSTA are two drugs that have been approved for several years.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The studies are of completely different study designs and cannot be pooled.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the pivotal trial, the maximum exposure to the combination therapy was 83 days with a total of 118.1 patient years. The exposure data is provided in Table 24. This extent of exposure is not sufficient for a safety analysis. However, the Sponsor provided other non-randomized studies that contained longer exposure to the combination therapy. This overall exposure is sufficient for conducting a safety analysis

Table 24: Exposure by treatment group in treated set of patients in 1235.1

	Placebo	Telmisartan monotherapy	Amlodipine monotherapy	Combination	Total in FAS-Treatment Set	Total in MS-FAS Treatment subset
Number of Patients	46	307	319	789	1461	1078
Days						
Mean	51.3	54.7	54.5	54.7	54.5	54.8
Median	56	56	56	56	56	56
Range	14-63	2-72	5-70	1-83	1-83	1-72
Patient Years	6.5	45.9	47.6	118.1	218.2	161.9

1 Patient years = Σ (days on treatment for each patient / 365.25)

Source data: Appendix 16.2, Listings 3.1, 7.1

The mean age of the subjects was between 52 and 55 for all of the 16 treatment groups. All but one of the 16 groups had between 12 -16% of subjects ≥ 65 . The one group with only 6.4% of subjects ≥ 65 was T40 +A2.5. The sex distribution was usually between 40 and 60% for each sex for each of the 16 groups. There were only about 5% of subjects who considered themselves Asian and they were relatively equally distributed among the groups. There were approximately 81% Caucasians and approximately 15% Blacks. The different racial groups were relatively well distributed among the different treatment groups. The mean height of 167 -169 cm didn't vary much among the treatment groups. The mean weight of 87 to 90 kg also did not vary much among the treatment groups.

REVIEWER'S COMMENT(S): The racial distribution and other demographic factor distribution of pivotal trial 1235.1 is reflective of the U.S. population that is likely to be treated with this combination drug.

In the phase 1 trials which were of short duration, the overall exposure was low and therefore, the data from these trials were not included in the safety analysis. This choice was agreed upon with FDA in a pre-NDA meeting.

In the supportive Phase 3b and 4 trials, described in Appendix 1, the exposure to telmisartan without concomitant amlodipine was 955.3 patient years and the exposure to telmisartan with concomitant amlodipine was 336.9 patient years (21.2 in patients ≥ 75 years of age). In these trials, amlodipine was not a study drug and was used only as a concomitant background medication. Not all patients in this group used amlodipine for the entire treatment period, and various amlodipine dosages could have been used. The demographics in this trial were different from the pivotal trial 1235.1 in that the patients were all diabetics, many patients had abnormal renal function (~40%), the mean age was 60, there were overall more males than females (~60% males), there were only ~7% Blacks and ~27% Asians. However, the demographic distribution among the groups that were treated with concomitant amlodipine and the groups that were not treated with concomitant amlodipine were very similar.

In the ONTARGET trial, a large trial of diabetic patients treated with telmisartan and/or ramipril is described in Appendix 1. The exposure to telmisartan/ramipril without CCBs was 15,860 patient years and the exposure to telmisartan/ramipril with CCBs was 12,146 patient years. Most patients were exposed between 1462 and 1827 days. In this trial, CCBs were not study drugs and were used only as an uncontrolled concomitant background medication. The demographics in this trial was similar to the phase 3 and 4 supportive trials except that there were very few Blacks, ~15% Asians. A greater relative proportion of Asian hypertensive patients used concomitant CCBs than did hypertensive patients in the other racial categories.

DISPOSITION

Table 25 presents the disposition of all patients in Trial 1235.1 irrespective of dose, according to whether the patients were randomized to the monotherapy, combination or placebo treatment groups. The pooled combination and monotherapies had comparable percentages of patients discontinued for any reason (range 7.5%-8.5%) and due to AEs (range 2.0%-2.8%), with higher percentages in both categories in the placebo group (15.2% and 4.3%, respectively). The low numbers of overall discontinuations, the similar percentages of AEs across active treatment groups and the higher incidence of placebo group AEs and drop outs provide evidence of a favorable safety profile for TWYNSTA.

Table 25: Disposition of patients enrolled in pivotal trial 1235.1

	T/A (T20/A2.5– T80/A10)	T mono (T20-T80)	A mono (A2.5-A10)	Placebo
Entered and treated	789	307	319	46
Not prematurely discontinued	729 (92.4)	284 (92.5)	292 (91.5)	39 (84.8)
Prematurely discontinued	60 (7.6)	23 (7.5)	27 (8.5)	7 (15.2)
Adverse events	22 (2.8)	6 (2.0)	8 (2.5)	2 (4.3)
Worsening of disease under study	1 (0.1)	2 (0.7)	2 (0.6)	1 (2.2)
Worsening of other pre-existing disease	2 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)
Other adverse events	19 (2.4)	3 (1.0)	5 (1.6)	1 (2.2)
Lack of efficacy*	3 (0.4)	8 (2.6)	3 (0.9)	2 (4.3)
Lack of efficacy*	27 (3.4)	7 (2.3)	13 (4.1)	3 (6.5)
Administrative	6 (0.8)	2 (0.7)	5 (1.6)	0 (0.0)
Non compliant with protocol	7 (0.9)	3 (1.0)	0 (0.0)	0 (0.0)
Lost to follow-up	14 (1.8)	2 (0.7)	8 (2.5)	3 (6.5)
Consent withdrawn	8 (1.0)	2 (0.7)	3 (0.9)	0 (0.0)
Other reasons				

* According to Investigator's assessment Source: Module 5.3.5.3, Table B.1.2.1.1:1

Patients ≥ 75 years were more likely to discontinue treatment (~16%) compared to younger patients (~5%) regardless of treatment group. Aside from this subgroup, there were no other demographic or baseline factors that appeared to influence risk for discontinuation.

Disposition of Patients in Phase 3/Phase 4 Trials

As shown in Table 26, when the supportive phase 3 and 4 studies were pooled together, the disposition between the two treatment arms (treated with concomitant use of amlodipine and telmisartan and treatment groups treated with telmisartan without concomitant use of amlodipine were essentially identical).

Table 26: Disposition of patients in the supportive Phase 3 and 4 trials

	Telmisartan Without Concomitant Amlodipine n (%)	Telmisartan With Concomitant Amlodipine† n (%)
Entered and treated	607 (100.0)	375 (100.0)
Not prematurely discontinued	487 (80.2)	302 (80.5)
Prematurely discontinued	120 (19.8)	73 (19.5)
Adverse events	68 (11.2)	40 (10.7)
Worsening of disease under study	22 (3.6)	13 (3.5)
Worsening of other pre-existing disease	7 (1.2)	4 (1.1)
Other adverse events	39 (6.4)	23 (6.1)
Lack of efficacy*	4 (0.7)	1 (0.3)
Administrative	39 (6.4)	26 (6.9)
Non compliant with protocol	14 (2.3)	7 (1.9)
Lost to follow-up	2 (0.3)	5 (1.3)
Consent withdrawn	23 (3.8)	14 (3.7)
Other reasons	9 (1.5)	6 (1.6)

Disposition of Patients in ONTARGET

As demonstrated in Table 27, the only notable difference between the groups of patients in this trial with hypertension who were treated with telmisartan + dihydropyridine calcium channel blockers (DHP CCBs) and those treated with telmisartan without DHP-CCBs is the lower death rate in the patients treated with telmisartan + DHP CCBs. This statistic favors combining telmisartan with DHP CCBs. It must be kept in mind that the effect of amlodipine alone can not be teased out from this analysis. I.e., the beneficial effect could have might be attributable to or associated with other DHP CCBs such as verapamil or diltiazem.

Table 27: Disposition of ONTARGET patients randomized to telmisartan by concomitant use of DHP CCBs, with and without hypertension as concomitant diagnosis

	Patients without hypertension (N=1487)		Patients with hypertension (N=7055)		Total (N=8542)	
	Telmisartan without DHP CCBs	Telmisartan with DHP CCBs*	Telmisartan without DHP CCBs	Telmisartan with DHP CCBs*	Telmisartan without DHP CCBs	Telmisartan with DHP CCBs*
Entered/randomized to telmisartan	1234	253	3996	3059	5230	3312
Completed#	1230 (99.7)	252 (99.6)	3986 (99.7)	3056 (99.9)	5216 (99.7)	3308 (99.9)
Deaths	118 (9.6)	14 (5.5)	567 (14.2)	290 (9.5)	685 (13.1)	304 (9.2)
Not completed	4 (0.3)	1 (0.4)	10 (0.3)	3 (0.1)	14 (0.3)	4 (0.1)
Lost to follow-up	2 (0.2)	1 (0.4)	8 (0.2)	3 (0.1)	10 (0.2)	4 (1)
Consent withdrawn	2 (0.2)	0 (0.0)	2 (0.1)	0 (0.0)	4 (0.1)	0 (0.0)
Permanently discontinued trial medication^b	198 (16.0)	45 (17.8)	713 (17.8)	498 (16.3)	911 (17.4)	543 (16.4)
Serious adverse event (excluding specified outcomes)	11 (0.9)	0 (0.0)	17 (0.4)	16 (0.5)	28 (0.5)	16 (0.5)
Adverse events^c	106 (8.6)	22 (8.7)	328 (8.2)	245 (8.0)	434 (8.3)	267 (8.1)
Patient request^d	11 (0.9)	1 (0.4)	56 (1.4)	24 (0.8)	67 (1.3)	25 (0.8)
Other	116 (9.4)	25 (9.9)	452 (11.3)	287 (9.4)	568 (10.9)	312 (9.4)

Overall Adverse Events

Table 28 displays the general safety of the combination of telmisartan and amlodipine during the 8 week treatment phase of pivotal trial 1235.1. The prevalence of all AEs, SAEs and serious AEs was comparable for all groups including placebo, providing further evidence of a favorable safety profile for the combination product. This pattern was similar for the FAS-MS subgroup. A table of all AEs is presented in Appendix 2. The most common AEs were headache, sore throat/congestion, infection, chest pain and peripheral edema. There were no cases of angioedema. The only notable difference among treatment groups was that peripheral edema was more commonly seen in the amlodipine 10 mg treatment group than in the combinations of telmisartan and amlodipine 10 mg treatment groups. Percentages of patients with any AEs during the entire study tended to be higher in the A10 and T80/A10 groups (39.5% and 43.7%, respectively) than in the other active-treatment groups (range 32.9%-37.2%). This was mainly due to the higher rate of peripheral edema in patients treated with A10. The overall pattern of other adverse event terms was comparable across treatment cells. However, the overall small numbers of AEs in all treatment groups made it difficult to make a fair assessment of differences in incidence of AEs among the treatment groups or by different demographic characteristics.

Table 28: Overall AE prevalence

	Placebo	Telmisartan monotherapy	Amlodipine monotherapy	Combination	Total
Total treated	46(100.0)	307(100.0)	319(100.0)	789(100.0)	1461(100.0)
Total with any AE	18 (39.1)	113 (36.8)	115 (36.1)	299 (37.9)	545 (37.3)
Serious AEs	0 (0.0)	1 (0.3)	2 (0.6)	5 (0.6)	8 (0.5)
Severe AEs	0 (0.0)	7 (2.3)	9 (2.8)	17 (2.2)	33 (2.3)
Other significant AEs	2 (4.3)	5 (1.6)	8 (2.5)	16 (2.0)	31 (2.1)

Source data: Table 15.3.1.2.1: 1-5 study report

In Table 29, it can be seen that the combination dose is associated with a somewhat greater incidence of hypotension related AEs. Because of the relatively low incidence of AEs, this is not a great concern. Also, dizziness was 3% in the combination therapy, 1.3% in the monotherapies, and 2% in the placebo group. Therefore, the incidence of dizziness was only 1% over placebo for the combination therapy and therefore, is of low concern. Also, while dizziness was associated with female sex, there were no other specific patterns seen for this AE. There was no association between these hypotension-related AEs and up titration to the T+A10 combinations. There was only one case of severe dizziness, a 53 year old female patient in the T40+A10 treatment group. Two patients had not recovered from dizziness as of the last follow-up: A 62 year old female in the T80+A5 treatment group and a 61 year old female in the T40+A10 treatment group. There were two cases of syncope, only in the combination therapy groups. These were not classified as serious or severe AEs and did not result in study discontinuation.

Table 29: Incidence [n(%)] of AEs of special interest in pooled combination and monotherapies in Trial 1235.1 (all patients)

MedDRA system organ class Preferred term	T/A (T20/A2.5- T80/A10)	T mono (T20- T80)	A mono (A2.5- A10)	Placebo
Treated	789	307	319	46
Total with AEs of special interest	69 (8.7)	7 (2.3)	29 (9.1)	1 (2.2)
General disorders and administration site conditions	38 (4.8)	2 (0.7)	25 (7.8)	0 (0.0)
Edema peripheral	38 (4.8)	2 (0.7)	25 (7.8)	0 (0.0)
Nervous system disorders	27 (3.4)	5 (1.6)	4 (1.3)	1 (2.2)
Dizziness	24 (3.0)	4 (1.3)	4 (1.3)	1 (2.2)
Dizziness postural	2 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Syncope	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	6 (0.8)	0 (0.0)	1 (0.3)	0 (0.0)
Hypotension	5 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Orthostatic hypotension	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)

7.2.2 Explorations for Dose Response

There were no glaring differences in disposition, AEs, or SAEs, among the 16 treatment groups except that patients on amlodipine 10 mg and amlodipine 10 mg combinations had a higher incidence of peripheral edema than the lower doses of amlodipine (and combination with lower doses of amlodipine), patients on higher dose combinations had a higher incidence of orthostatic changes in blood pressure and the placebo group had the largest percentage of premature discontinuation (15.2%). The groups of patients were too small to make further assessments regarding dose relationship to safety.

7.3 Major Safety Results

7.3.1 Deaths

The only death reported in Trial 1235.1 was a 50-year-old male patient who experienced fatal choking starting 28 days after initiation of treatment with telmisartan 80 mg. No other AEs were reported for the patient during the course of the trial, and no concomitant medication was used. The causal relationship between the drug and this event is unknown. Choking is an unusual event and has not been associated with telmisartan use in the past.

The only patients that died in the supportive phase 3 and phase 4 studies were patients with concomitant amlodipine. One 56 year old male diabetic with history of coronary artery disease died of sudden death, one 62 year old male diabetic with history of heart failure and coronary artery disease died of circulatory collapse and one 64 year old male on coumadin with a gastric ulcer that developed while on treatment died of an upper gastrointestinal hemorrhage. The causal relationship between the drug and these events is unknown. These events are not relatively

common causes of death. There were also many deaths in the trial in patients that were on telmisartan without amlodipine.

A total of 750 patients receiving telmisartan in the ONTARGET trial died during treatment. Of those, 213 were hypertensive patients taking telmisartan with concomitant DHP CCBs (out of 3059 patients in this subgroup, for a death rate of 7.0%) and 436 were hypertensive patients taking telmisartan without concomitant DHP CCBs (out of 3996 patients in this subgroup, for a death rate of 10.9%). Therefore, the death rate for any cause in hypertensive patients was lower for patients receiving telmisartan with concomitant DHP CCBs than for patients receiving telmisartan without concomitant DHP CCBs, a reassuring finding. Most of the deaths were due to sudden cardiac death, myocardial infarction and stroke, as would be expected in this older, hypertensive population.

7.3.2 Nonfatal Serious Adverse Events

In the pivotal trial, 1235.1, a total of 14 patients had SAEs: 2 in placebo (4.3%), 5 (0.6%) of 789 in the pooled combination therapies, 1 (0.3%) of 307 in the pooled telmisartan monotherapies and 2 (0.6%) of 319 in the pooled amlodipine monotherapies. There were an additional 4 SAEs in patients who were in the placebo run-in phase of the trial. No glaring differences were seen in SAEs among the active treatment groups.

Table 30: Listing of SAEs

Treatment at AE onset	Patient No.	Age (y) / Sex	AE	Duration	Action	Outcome	Reasons for SAE
Placebo	53262	52/F	Migraine	1	Cont	Rcver	Req hsp
A2.5	58118	56/F	COPD exacerbation	7	Temporarily discontinued	Rcver	Req hsp
T80/A2.5	54208	41/M	Sinusitis	2	Cont	Rcver	Req hsp
T80/A2.5	56189	34/M	Chest pain	1	Cont	Rcver	Req hsp
T40/A5	56027	71/F	Chest pain	3	Cont	Rcver	Req hsp
A5	56883	51/F	Diverticulitis aggravated	14	Cont	Rcver	Req hsp
T80/A5	57113	51/M	Fibula fracture after motorcycle accident	167§	Disc	Nrec#	Req hsp
			Pulmonary embolus		Disc	Nrec#	Req hsp
			Fractured ribs after motorcycle accident	167§	Disc	Nrec#	Req hsp
			Tibia fracture after motorcycle accident	59§	Disc	Nrec#	Req hsp
T80/A5	57543	63/F	Thrombosis of leg deep venous	83§	Cont	Nrec#	Req hsp. And disabled
T80/A5	57633	38/F	Chest pain/ GERD	10	Cont	Rcver	Req hsp
Placebo run-in (A5 group)	54179	56/M	Effusion of knee	37	Cont	Rcver	Req hsp
Placebo run-in and then T80/A5 group	57543	63/F	Osteoarthritis aggravated	45	Cont	Rcver	Req hsp
Placebo run-in (A10 group)	54041	45/F	Cervical neuritis	23	Cont	Rcver	Req hsp
Placebo	58186	59/F	Myocardial Infarction	2	Cont	Rcver	Req hsp
Run-In	56680	52/M	Atypical Chest	4§	Disc	Nrec#	Req hsp

phase			Pain				
(placebo)							
Run-In	56813	68/M	Nausea, Vomiting,	2	Disc	Rcver	Req hsp
phase			epistaxis,				
(placebo)			worsening				
Run-In	58106	59/F	hypertension	2	Disc	Rcver	Req hsp
phase			Malignant				
(placebo			hypertension, chest				
Run-In	57483	57/F	pain	4	Disc	Rcver	Req hsp.
phase			Nausea, Vomiting,				
(placebo)			Chest Pain				

§: recovery days unknown, Nrec#: not recovered, Req hsp: required hospitalization, Rcver: recovered, Disc: discontinued treatment, Cont: treatment continued

Source: safety summary and case report narratives

Table 30 displays the SAEs in pivotal trial 1235.1. There were 3 patients in the placebo run-in period that had SAEs related to increases in blood pressure (58106 whose BP was 210/110 at time of onset of chest pain, 57483 whose BP was 138/105 at time of onset of chest pain, dizziness and vomiting, and 56813 whose BP was 235/115 at onset of vomiting and headache). The only other patient whose BP was reported in the narrative was 56189 whose BP was 136/99 at onset of chest pain. Being in the placebo run-in period may have put patients at risk for hypertension-related AEs.

There were two pregnancy Related AEs that are being listed as SAEs.

- 1) A 36 y/o female discontinued study drug approximately one and one-half months after discovering that she was pregnant by a pregnancy test. She had her last menstrual period 4 days following study drug initiation. She discontinued drug and gave birth to a healthy baby that was born at 33 weeks. She was in the T80 treatment group.
- 2) A 33 y/o female discontinued study drug 6 days after initiation because she discovered she was pregnant. The patient had a therapeutic abortion 8 days later. She was in the T40/A5 treatment group.

SAE information from the supportive phase 3 and phase 4 studies was reassuring regarding the safety of the combination product. The most common SAEs were cardiac failure, MI, pneumonia, congestive heart failure, acute renal failure and pulmonary edema. Each AE occurred at a rate of approximately 1% which is not unexpected in this older, diabetic, (1/2 were hypertensive) population.

There were a total of 72 (19.2%) SAEs in the telmisartan with concomitant amlodipine treatment groups and 195 (25.6%) SAEs in the telmisartan without concomitant amlodipine treatment groups. All categories of SAEs except pulmonary edema occurred more often in patients receiving telmisartan without concomitant amlodipine than in patients receiving telmisartan with concomitant amlodipine. Several other SAEs such as urinary tract infection, diabetic foot, hyperglycemia, renal failure, and chronic renal failure, were only reported in patients receiving telmisartan without concomitant amlodipine.

When looking at subgroups from the phase 3 and 4 supportive trials, the following was observed: the use of NSAIDs/Cox-2 inhibitors, age ≥ 65 years, history of alcohol use and history of tobacco use were associated with an increased risk of SAEs. Renal status did not appear to be associated with risk for AEs using the cut off of eGFR of 60cc/min. This cut off value for abnormal renal function may not be ideal to evaluate the risk of renal function on risk for SAEs. Meaningful comparisons of SAEs by race were limited because of the small numbers of black patients enrolled. In each subgroup, treatment with telmisartan without amlodipine was associated with a greater risk of having an SAE than treatment with telmisartan with amlodipine. Conclusions regarding these SAE findings should be made with caution because the treatment with amlodipine was not randomized and patients may not have stayed on amlodipine during the entire study. However, the data causes no cause concern about the safety of the combination product.

The ONTARGET trial which was a several year nonrandomized trial and had a high percentage of SAEs (>60%) did not show the same pattern with regard to a greater association of SAEs when telmisartan was given without DHP CCBs as opposed to with DHP CCBs. In fact, the pattern was the opposite. Patients on telmisartan with DHP CCBs had a higher incidence of SAEs than patients on telmisartan without CCBs. This finding is somewhat troublesome. However, this trial was also non-randomized and one must be cautious about drawing conclusions. The increased incidence of SAEs in the telmisartan with DHP CCBs was much more apparent in the population of non-hypertensive patients. For the non-hypertensive patients on concomitant DHP CCBs, the SAE incidence was 68.4% compared to 56.7% in non-hypertensive patients not on concomitant CCBs. For the hypertensive patients on concomitant CCBs, the SAE incidence was 67% compared to 64.7% in hypertensive patients not on concomitant CCBs.

Severe AEs

Severe AEs were not frequent in the pivotal trial 1235.1 as can be seen in Table 31. Overall, 33 (2.3%) patients experienced one or more AEs of severe intensity. With the exception of the placebo treatment group in which no severe AEs were reported, the frequency was similar among other treatment groups. The most frequently occurring AE of severe intensity was back pain, reported to occur in the following three patients: Patients 53173 (T40+A5), 57753 (T40+A10) and 53451 (A5). All patients continued study drug, all events were either recovered or determined to be sufficient to follow-up at the end of the trial and none were reported as SAEs.

Table 31: Frequency [N (%)] of patients with AEs of severe intensity by treatment group – (Treated set)

	A0	A2.5	A5	A10
T0	0 (0.0)	0 (0.0)	7 (5.0)	2 (1.6)
T20	2 (4.8)	1 (2.3)	0 (0.0)	0 (0.0)
T40	2 (1.5)	1 (2.1)	3 (2.1)	2 (1.6)
T80	3 (2.2)	1 (2.1)	4 (2.7)	5 (3.5)

Source data: Table 15.3.1.2.1: 11 of study report

Combination therapy severe AEs: 2 streptococcal pharyngitis, 1 pharyngotonsillitis, 1 dizziness, 1 headache and 1 vascular headache. There was one case of deep venous thrombosis, one case of abdominal pain, two cases of back pain, one muscle spasm, one musculoskeletal pain, one nephrolithiasis, one case of erectile dysfunction, two cases of chest discomfort, one of chest pain, one fibula and one rib fracture, and one tibia fracture. The pattern of severe AEs does not provide cause for concern because it does not correlate with the common AEs.

7.3.3 Dropouts and/or Discontinuations

AEs that led to discontinuation

The total number of AEs leading to treatment discontinuation in this trial was 33. This number is so low that it is difficult to make any comparative treatment group analyses. There were comparable percentages of patients that discontinued in the pooled combination and in the monotherapies [2.2% in the T/A groups (17/789), 2.0% for the telmisartan groups, (8/319) 2.5% for the amlodipine groups], and (2/46, 4.3%) in the placebo group. The percentages of AEs leading to discontinuation for the pooled monotherapies in pivotal trial 1235.1 are comparable to those described in telmisartan and amlodipine labeling (1.5% in amlodipine marketing studies compared to 1% in placebo and 2.8% in telmisartan marketing studies compared to 6.1% in placebo) in 8 -12 week trials. The most frequent AEs overall leading to discontinuation in the pooled combination therapies were hypotension (0.4%), dizziness (0.4%), and peripheral edema (0.5%). In the pivotal trial 1235.1, incidences of discontinuation due to AEs in the pooled combination therapy cells were comparable to or lower than the discontinuations due to AEs in the pooled monotherapy cells for all AEs except hypotension, which was reported to cause discontinuation only in the pooled combination therapies (3 cases, 0.4%). This data, albeit limited, is reassuring regarding the safety of the combination therapy.

Demographic subgroup analysis for discontinuations due to AEs did not reveal any gross differences. However, this analysis was limited by the small numbers of patients with AEs that led to discontinuation.

During the course of the phase 3 and phase 4 trials, 9.1% (69/761) of patients receiving telmisartan without concomitant amlodipine and 8.0% (30/375) of patients receiving telmisartan with concomitant amlodipine experienced AEs that led to discontinuation from study treatment. The most frequently reported AE leading to discontinuation in patients receiving telmisartan without and with concomitant amlodipine was hyperkalemia, reported by 8 (1.1%) and 5(1.3%) patients, respectively. The other frequently reported AEs leading to discontinuation in patients receiving telmisartan without amlodipine were related to renal systems and included renal failure and chronic renal failure, reported in 5 and 4 patients, respectively, compared to 0 patients receiving telmisartan with concomitant amlodipine. In these studies, the patients treated with concomitant amlodipine seemed to do better than those who did not receive concomitant amlodipine. However, the lack of randomization makes one hesitant to draw conclusions. In general, there was a low rate of discontinuation with and without concomitant amlodipine over the course of these trials which lasted 1-5 years.

In the ONTARGET trial, approximately 8% to 9% discontinued study medication permanently due to AEs, without regard to the concomitant use of CCBs or hypertensive status. Hypotension and dizziness were the most common AEs that resulted in discontinuation.

7.3.4 Significant Adverse Events

During the course of the study, the treatment code was broken for only one patient, Patient 56189. The 34 y/o male patient was admitted to the hospital with chest pain of severe intensity. The onset of the event occurred after eight days of treatment with study drug. The patient was treated and recovered the same day and study drug was continued. The patient had been randomized to T80/A2.5. This event was unusual because of the patient's young age. However, in my opinion it is unlikely that this AE was related to the combination product.

7.3.5 Submission Specific Primary Safety Concerns

Hypotension

Events related to lowering of blood pressure (dizziness, dizziness postural, syncope, hypotension, and orthostatic hypotension) were reported for 24 patients in the key combination treatment cells (8 in T40/A5, 4 in T40/A10, 8 in T80/A5, and 4 in T80/A10), 8 in the monotherapy treatment cells and 1 in the placebo treatment cells. Most of these AEs were mild or moderate in severity. Most patients with these AEs continued study medication, and all but 2 patients recovered from the AEs as of the last follow-up. Characteristics of patients in the key combination cells reporting specific events related to lowering of blood pressure are summarized below.

Dizziness

There were 18 reported events of dizziness in the 4 key treatment cells, 1 in the T40 treatment cell and none in the other treatment cells.

Severe dizziness was reported by 1 patient in the T40/A10 cell (No. 57502; female, age 53 years) starting on treatment Day 41; the patient recovered from the event after 3 days and continued study medication. Two patients had not recovered from dizziness as of the last follow-up: No. 53213 in the T80/A5 cell (female, age 62 years) reported mild dizziness starting on treatment Day 22 and lasting 70 days as of last follow-up, during which study medication was continued; No. 51150 in the T40/A10 cell (female, age 61 years) reported 2 episodes of mild dizziness starting on treatment Day 32 (the latest lasting 63 days as of last follow-up), for which study medication was discontinued/reintroduced and subsequently discontinued permanently.

Postural Dizziness

Postural dizziness was reported in 1 patient (No. 56512; male, age 34 years) in the T80/A10 treatment cell; 2 episodes of the event occurred on Day 1 (in the titration period, when the patient was on T80/A5) and Day 34 of treatment, respectively. The patient continued treatment and recovered from the events. The events were mild to moderate in severity. There was a case of postural dizziness in a patient in the T40 treatment cell.

Hypotension

Hypotension was reported by 4 patients in the key combination cells and none in the other groups. A 58-year-old male patient in the T40/A5 treatment cell reported hypotension of mild intensity 11 days after start of study medication. A 44-year-old male patient in the T80/A5 treatment cell reported hypotension of moderate intensity following 18 days of treatment with study drug; the event was considered related to study drug, and study drug was discontinued. Hypotension of moderate intensity was reported for 2 female patients in the T80/A10 treatment cell after 17 and 22 days of treatment with study drug, respectively. One patient was 53 years old and one patient with mild hypertension was 77 years old.

Orthostatic hypotension

Orthostatic hypotension was reported by 1 patient in the T80/A5 treatment cell following 29 days of treatment. The patient was 28 years of age. A patient in the A10 group also experienced symptoms of orthostatic hypotension.

Syncope

One patient in the pivotal trial who was in the T40/A10 treatment cell experienced syncope following 56 days of treatment. The event lasted 1 day. The patient was 31 years of age.

Orthostatic Blood Pressure Changes

Clinically meaningful orthostatic changes were defined as a decrease in DBP >10 mmHg and/or decrease in SBP >20 mmHg, a reasonable definition. A total of 99 (7.0%) patients experienced orthostatic changes in SBP and/or DBP during the trial. Orthostatic changes were observed in placebo: 4.3%, telmisartan monotherapy: 6.1% to 7.1%, amlodipine monotherapy: 8.1% to 12.5% and combination: 2.5% to 10.6%. Table 32 displays the frequency of clinically meaningful orthostatic changes by treatment group. Of the 99 patients who experienced clinically meaningful orthostatic changes at study visits, only two instances were associated with symptoms reported as AEs.

The largest single decrease in DBP was 31.3 mmHg in Patient 58181 (A10) at Visit 6 with an increase in SBP of 9 mmHg at the same time. The largest single reduction in SBP was 44.0 mmHg and accompanied by an increase in DBP of 7.7 mmHg in Patient 56580 (T40+A10) at Visit 4. Neither of these more significant orthostatic changes was associated with any reported symptoms.

Orthostatic hypotension is not a major concern because it is usually asymptomatic.

Table 32: Frequency [N(%)] of patients with clinically meaningful orthostatic changes by treatment group – (Treated set)

	A0	A2.5	A5	A10
T0	2 (4.3)	6 (12.5)	12 (8.8)	10 (8.1)
T20	3 (7.1)	4 (9.1)	3 (6.7)	1 (2.5)
T40	8 (6.2)	5 (10.6)	11 (7.8)	9 (7.3)
T80	8 (6.1)	2 (4.3)	5 (3.5)	10 (7.4)

Source data: Table 15.3.3.1.1: 2

Clinically meaningful orthostatic change:

mean seated to first standing decrease in DBP more than 10 mmHg and/or

mean seated to first standing decrease in SBP more than 20 mmHg

REVIEWER'S COMMENT(S): It is clear that the combination therapy increases the frequency of hypotension, orthostatic changes and hypotension related events. While none of these events present major safety concerns, it is important to suggest in that label that dosage reduction be considered if there is symptomatic hypotension, dizziness or syncope.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

To conduct my analysis of common AEs I recategorized the preferred terms into different higher level terms than the sponsor may have chosen. Events could be categorized in more than one higher level term as appropriate. If a patient had more than one higher level term event (as I defined it) I called it as one event. The purpose of this recategorization was to make sure that there were no glaring differences in AEs between the sponsor's and my interpretation. In fact, the differences were minor and I feel comfortable with the sponsor's statistics.

According to my analysis, the most frequently reported adverse events in the pooled combination therapies in Trial 1235.1 were peripheral edema (4.8%), headache (4.7%), dizziness (3.0%), and back pain (2.2%). There was no great difference between the combination and monotherapy treatment cells except for dizziness which was twice as common in the combination therapy cells and for peripheral edema which was lower in the pooled combination therapies than in the pooled amlodipine monotherapies. The incidence rate of peripheral edema was particularly high in the A10 monotherapy cell (17.8%), and lower in the treatment cells where A10 was combined with telmisartan. The incidence of back pain was similar in the pooled combination and amlodipine monotherapies.

According to the sponsor the most common AE was headache (5.4%), with the following occurrences in each treatment group: placebo: 5 (10.9%), telmisartan monotherapy: 18 (5.9%), amlodipine monotherapy: 19 (6.0%), Combination: 37 (4.7%). No evidence of a dose dependent effect was observed. The frequency of headache was similar in each of the four key combination therapies and lower than reported with each respective amlodipine and T40 monotherapies.

Peripheral edema, the second most frequent AE according to the sponsor was reported in 65 (4.4%) patients with the following occurrence in each of the treatment groupings; placebo: 0 (0.0%), telmisartan monotherapy: 2 (0.7%), amlodipine monotherapy: 25 (7.8%), Combination: 38 (4.8%). The increased incidence of peripheral edema in amlodipine monotherapy patients was most prevalent in those patients randomized to A10. There was a dose dependent effect for patients on amlodipine (17.8% in A10 treatment group, 0.7% in A5 treatment group). No dose dependent effect was seen in telmisartan monotherapy treated patients. In the combination therapy groups, there were 6.2% and 11.3% peripheral edema AEs in the T40A10 and the T80A10 treatment groups, respectively. Although the study was not powered to detect statistical differences among treatment groupings for any individual AE and there was no prespecified efficacy endpoint for reduction in edema, a post-hoc analysis of the occurrence of peripheral edema demonstrated a significant difference among treatment groups $p < 0.0001$. In the sponsor's analysis dizziness was much more common in the combination therapy groups than the monotherapy groups. See Table 33.

Table 33: Incidence of Dizziness in Trial 1235.1 FAS

	A0	A2.5	A5	A10
T0	1 (2.2)	0 (0.0)	4 (2.9)	0 (0.0)
T20	2 (4.8)	2 (4.5)	1 (2.2)	1 (2.3)
T40	1 (0.8)	1 (2.1)	7 (4.9)	3 (2.3)
T80	1 (0.7)	2 (4.2)	6 (4.1)	1 (0.7)

7.4.2 Laboratory Findings

In clinical trials supporting this NDA application, evaluation of the clinical laboratory tests included hematology, blood chemistry, and urinalysis parameters.

Mean changes from baseline

Mean changes from baseline in Trial 1235.1 were consistent with laboratory findings described in telmisartan labeling (small decreases in hemoglobin and small increases in liver function tests). No mean changes in creatinine (for which infrequent elevations are described in telmisartan labeling) were observed. When examined by key treatment cell, mean increases from baseline (>10% of baseline values) for ALT and AST occurred in the T40/A5 cell but not in other treatment cells, but overall the mean changes from baseline did not indicate a particular safety concern for the use of T/A combination therapy in the other groups. Mean increases from baseline (>10% of baseline values) for CPK occurred in some subgroups of the pooled combination therapies and in the T40/A5 cell, possibly due to a large reported maximum value of 17815 U/L at the final visit in one patient; a repeat assessment 11 days later for the affected patient (No. 56887) showed a decrease to 614 U/L suggesting that the value was a laboratory error.

Clinical laboratory data from the Phase IIIb/IV trials showed only small mean changes from baseline values with the exception of increases in alkaline phosphatase and creatinine phosphokinase. Changes for these 2 analytes were ~ 10% of baseline values. Alkaline phosphatase elevation is consistent with the occasional LFT elevations described in the telmisartan label. Mean changes in CPK values were 8 and -3 U/L for the telmisartan and telmisartan + amlodipine groups, respectively. These changes were <10% of mean baseline values and are also not clinically meaningful. The clinical significance of these changes is not clear but the observation is probably not worthy of great concern.

Evaluation of laboratory data in the ONTARGET study did not indicate any concerning changes. There were no mean changes from baseline in laboratory variables that were clinically important among patients taking telmisartan, regardless of hypertensive status or the use of calcium channel blockers. The mean reductions in triglycerides and total cholesterol observed in these patients were most likely related to the use of cholesterol-lowering agent.

Frequency of patients categorized by reference range over time

Up to 9% of patients in the pooled combination and monotherapies in Trial 1235.1 had categorical shifts from baseline with respect to reference range in laboratory values to abnormal values. Shifts in hematology values occurred in a higher proportion of patients in the pooled combination (T/A) than in the pooled monotherapies (T mono, A mono), with the greatest difference appearing in shifts to low red blood cell (RBC) counts. In the T+A group, 5.4% of the patients shifted from normal RBC counts to abnormal RBC counts whereas only 2.4% of the patients in the telmisartan group, 1% in the amlodipine group and 2.2% in the placebo group had an abnormal downward shift. Shifts in electrolyte, enzyme, or substrate tests occurred at generally comparable frequencies across the pooled combination and monotherapies.

Laboratory shift data from the Phase IIIb/IV trials showed no unexpected findings for this population except that approximately 12 -14% of patients with normal baseline hemoglobin values had a shift to low hemoglobin during treatment in both treatment groups. There is no clear reason for this shift. However, it may have been due to the population's high prevalence of chronic disease and renal insufficiency.

While there is no biological plausibility for anemia, there is a pattern of shifts to lower hemoglobin in patients treated with the combination therapy and this information should be included in the label.

Frequencies of patients with possibly clinically significant abnormalities

In Trial 1235.1, the frequencies of patients with possible clinically significant abnormalities in the T/A pooled combination group were comparable to, or lower than, the highest frequencies in the monotherapies except in the case of decreased hemoglobin.

There were no differences in the Phase IIIb/IV studies between the two treatment groups (T vs. T+A) in frequency of laboratory abnormalities. However, in both groups there was a higher

frequency (>15%) of abnormalities in potassium, glucose, BUN, creatinine, uric acid, hemoglobin, and hematocrit. These findings are not unexpected in this population (diabetics with micro-/macroalbuminuria).

REVIEWER'S COMMENT(S): Overall, the observed laboratory changes were in accordance with the existing labeling of its respective components, telmisartan and amlodipine. Telmisartan is associated with an increased risk of hemoglobin drop than placebo according to the package insert. While it is possible that the combination product could augment this adverse effect, I do not think that this is an overriding safety concern. The increased risk of decreased hemoglobin and RBC count with the combination product should be included in the label.

7.4.3 Vital Signs

Blood Pressure and Pulse

Mean decreases from baseline in DBP and systolic blood pressure (SBP) were greater in the pooled combination therapies than in the pooled monotherapies. These decreases were substantially greater in the pooled combination and monotherapies than in the placebo group, reflecting the pharmacological action of the drugs. Mean decreases from baseline in DBP and SBP were greater in the key combination cells (T/A 40/5 – 80/10) than in the respective component monotherapy cells. Mean changes from baseline in pulse rate were very small in all the pooled combination, monotherapies and placebo. See section 7.3.5 for an in depth discussion on blood pressure related AEs and clinically significant orthostatic hypotension changes.

The Phase III/IV supportive studies corroborated the findings of decreased blood pressure on treatment with telmisartan when compared to baseline, but addition of amlodipine caused no mean change in BP when compared to telmisartan alone.

Patients taking telmisartan in the ONTARGET trial experienced approximately a 5 mm Hg decrease from baseline in DBP, and approximately a 6 mm Hg decrease from baseline in SBP by the end of the study, regardless of concomitant dihydropyridine (DHP) CCB use. Pulse rate increased slightly from baseline (about 1 bpm) among patients taking telmisartan, regardless of concomitant DHP CCB by the end of the study.

Weight

Mean changes in weight were generally small across treatment groups when analyzed by all demographic factors. There were no substantial mean weight changes in any of the supportive studies.

7.4.4 Electrocardiograms (ECGs)

In the pivotal trial, 1235.1, a 12-lead standard ECG was performed on all patients at Screening (Visit 1) and at the End of Trial visit (Visit 7). The interpretation of the ECGs was performed by the investigator. Seven AEs of clinically relevant findings were reported in five patients randomized to the following treatment groups: T80, A10, T20+A10, T40+A5 and T80+A5. All AEs were of mild intensity. The following AEs were reported as a result of the ECG findings at the final visit: Electrocardiogram repolarization abnormality was reported by Patient 52033 (T20+A10), Electrocardiogram T wave abnormal was experienced by Patients 57996 (T40+A5), 56416 (T80) and 54071 (T80+A5). Events of electrocardiogram QT shortened, electrocardiogram T wave abnormal and QRS axis abnormal were reported by Patient 57255 (A10). These events in Patient 57255 were reported on study Day 34, when the patient prematurely withdrew consent from participating in the trial. Most ECG -related events resolved with or without treatment. There was no information on those that had ECG events that did not resolve except that some were lost to follow up.

These results are not particularly worrisome especially in the light of the absence of concerning postmarketing ECG abnormalities for either amlodipine or telmisartan.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See section 7.2, **Explorations for Dose Response**.

7.5.2 Time Dependency for Adverse Events

There were not enough AEs to determine if there was any time dependency for adverse events.

7.5.3 Drug-Demographic Interactions

There were not enough AEs to determine if there were any worrisome drug-demographic interactions.

7.5.4 Drug-Disease Interactions

As the majority of telmisartan is eliminated by biliary excretion and amlodipine is extensively metabolized by the liver, patients with biliary obstructive disorders or hepatic insufficiency can be expected to have reduced clearance of both components of Twynsta. Therefore, Twynsta should be used with caution in these patients.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with telmisartan. In patients whose

renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure, severe renal insufficiency and renal artery stenosis), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Therefore, these patients should be treated with Twynsta with caution. Additionally, caution should be exercised when administering peripheral vasodilators to patients with aortic insufficiency.

The following is a warning listed in the amlodipine label: "Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated." This warning should also be included in the Twynsta label.

7.5.5 Drug-Drug Interactions

The systemic exposure of amlodipine is not affected by the co-administration of telmisartan and the systemic exposure of telmisartan is not affected by the co-administration of amlodipine. For more details, please refer to the clinical pharmacology review.

Food, conversely, has a great impact on the peak levels and AUC of telmisartan. Fatty food significantly reduces telmisartan AUC_{0-∞} by 24.3% and C_{max} 60.1%. There is no effect of food on amlodipine absorption. Since there was no significant hypotension seen in the pivotal trial 1235.1, directions to take the medication with food are probably not warranted.

While other drug interactions were not studied as part of the NDA, these have been characterized in the past and are currently labeled.

From telmisartan label:

Drug Interactions

Digoxin: When telmisartan was co-administered with digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is, therefore, recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing telmisartan to avoid possible over- or under-digitalization.

Warfarin: Telmisartan administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in International Normalized Ratio (INR).

Other Drugs: Co-administration of telmisartan did not result in a clinically significant interaction with acetaminophen, amlodipine, glibenclamide, simvastatin, hydrochlorothiazide or ibuprofen. Telmisartan is not metabolized by the cytochrome P450 system and had no effects *in vitro* on cytochrome P450 enzymes, except for some inhibition of CYP2C19. Telmisartan is not expected to interact with drugs that inhibit cytochrome P450 enzymes; it is also not expected to interact with drugs metabolized by cytochrome P450 enzymes, except for possible inhibition of the metabolism of drugs metabolized by CYP2C19.

ACE inhibitors: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should be used with caution and should include close monitoring of renal function

From amlodipine label:

Drug Interactions: *In vitro* data indicate that amlodipine has no effect on the human plasma protein binding of digoxin, phenytoin, warfarin, and indomethacin.

Effect of other agents on amlodipine besylate tablets.

Cimetidine: Co-administration of amlodipine besylate tablets with cimetidine did not alter the pharmacokinetics of amlodipine.

Grapefruit juice: Co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine.

Maalox (antacid): Co-administration of the antacid Maalox with a single dose of amlodipine besylate tablets had no significant effect on the pharmacokinetics of amlodipine.

Sildenafil: single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of amlodipine. When amlodipine besylate tablets and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Effect of amlodipine besylate tablets on other agents.

Atorvastatin: Co-administration of multiple 10 mg doses of amlodipine besylate tablets with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin.

Digoxin: Co-administration of amlodipine besylate tablets with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers.

Ethanol (alcohol): Single and multiple 10 mg doses of amlodipine besylate tablets had no significant effect on the pharmacokinetics of ethanol.

Warfarin: Co-administration of amlodipine besylate tablets with warfarin did not change the warfarin prothrombin response time. In clinical trials, amlodipine besylate tablets have been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

While carcinogenicity studies were not repeated, the results of prior studies are included in current labels of the individual products. There is no reason to suspect that there would be a drug interaction that would alter these results.

From telmisartan label:

Genotoxicity assays did not reveal any telmisartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* and *E. coli* (Ames), a gene mutation test with Chinese hamster V79 cells, a cytogenetic test with human lymphocytes, and a mouse micronucleus test.

From amlodipine label:

Mutagenicity studies conducted with amlodipine maleate revealed no drug related effects at either the gene or chromosome level.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women for either drug. The current wording in the individual products' labeling is as follows:

From telmisartan label:

Pregnancy Categories C (first trimester) and D (second and third trimesters). Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

From amlodipine label:

Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while amlodipine is administered.

I did a literature search on telmisartan and birth defects. There is no literature on the subject of first semester exposure and birth defects. However, in the literature it is commonly stated that there has been no association between first semester exposure and birth defects. The label should include a statement on discontinuing the combination drug as soon as pregnancy is discovered. There should be patient information given with a warning of the potential for birth defects in pregnancy.

7.6.3. Pediatrics and Effect on Growth

There are no adequate and well-controlled studies in pediatric patients for either drug. The current wording in the individual products' labeling is as follows:

From telmisartan label:
Safety and effectiveness in pediatric patients have not been established.

From amlodipine label:
The effect of amlodipine on blood pressure in patients less than 6 years of age is not known.

7.6.4 Drug Abuse Potential, Withdrawal and Rebound, Effects on Ability to Drive or Operate Machinery or on Mental Ability

Drug Abuse Potential

The sponsor investigated the drug safety database for any cases of drug abuse for the combination of telmisartan and amlodipine in the pivotal and supportive trials. There were no cases of abuse found in this investigation.

The negative results of the above investigations suggest that the likelihood of abuse of telmisartan/amlodipine is minimal. Prescribing information for telmisartan or amlodipine contains no information on drug abuse.

Withdrawal and Rebound

There is no suspicion of rebound under therapy with either telmisartan or amlodipine. The safety data of the combination product derived from the pivotal and supportive trials as well as the sponsor's post marketing data support the conclusion that rebound hypertension is not a concern.

Effects on Ability to Drive or Operate Machinery or on Mental Ability

The project database and the drug safety database were investigated for any event that may signify any indication of effects on the operation of machinery, e.g., accidents.

The search returned 8 case reports including 20 events. The reported injuries were associated with falls for 3 patients and with bicycle or motorcycle accidents for 3 patients. No potential cause for the reported injuries was stated in case reports for the remaining 2 patients. While it is possible that these events were secondary to hypotension caused by the antihypertensive effects of the antihypertensive therapy, there is no strong evidence to support this possibility. Therefore, special labeling for the potential effects of hypotension on ability to drive or operate machinery is not warranted.

7.7 Additional Submissions

The safety update (SU) submitted by the sponsor on April 16, 2009 includes safety data from the following trials in the telmisartan/amlodipine fixed-dose combination (FDC) clinical development program:

1. Four randomized, double-blind, active-controlled, 8-week Phase III trials (1235.5 and 1235.6 [conducted at multinational sites] and 1235.13 and 1235.14 [conducted in Japan with a slightly different tablet formulation than that used in the multinational trials]) completed since NDA 22-401 was filed

2. Three ongoing long-term open-label extension trials (1235.7 for patients completing 1235.5, 1235.8 for patients completing 1235.6, and 1235.16 for patients completing 1235.13 or 1235.14), for which a data lock point of 13 January 2009 was used for this SU. The above trials provide safety data from a total of 2889 hypertensive patients who received double-blind treatment with telmisartan (158), amlodipine (1120), or T/A FDC (1611) in controlled trials, including initial interim long-term safety data for 2075 of these patients who received telmisartan plus amlodipine in the still-ongoing open-label extension trials.

EXPOSURE

The exposure in the extension trials was up to 182 -365 days in a high percentage of patients. The mean exposure was 133-165 days in the different open-label extension trials, a much greater exposure than in trial 1235.1.

Table 34: Treatment exposure (n[%]) to a combination of telmisartan and amlodipine across trials and irrespective of dose strength

Trial Number	1-30 Days	31-91 Days	92-181 Days	182-365 Days	>365 Days
1235.5/7 (N=1027)	11 (1.1)	55 (5.4)	127 (12.4)	834 (81.2)	0 (0.0)
1235.6/8 (N=907)	19 (2.1)	61 (6.7)	266 (29.3)	561 (61.9)	0 (0.0)
1235.13/14 /16 (N=559)	12 (2.1)	292 (52.2)	33 (5.9)	183 (32.7)	39 (7.0)
Total (N=2493#)	42 (1.7)	408 (16.4)	426 (17.1)	1578 (63.3)	39 (1.6)

Source: SU, Appendix 1, Table 1.2.3

Patients who may have been in more than one study are counted only once.

ANALYSIS OF ADVERSE EVENTS

In the combined double blind trials (1235.5 and 1235.6) there were only 6 serious AEs (out of 1186 patients) (0.5%) in the combination therapy groups. There were 3/ 867 (0.03%) SAEs in the A10 combination therapy groups.

In the open label extension trials, 1235.7 and 1235.8, one death (during T80/A10 treatment) was reported in the trials. This death was due to aortic dissection. Two patients had immediately life-threatening SAEs (coronary artery disease during T40/A5 treatment and hemoptysis during T80/A10 treatment). In the double blind Japanese trials 1235.13 and 1235.14, less than 0.05% of patients had severe AEs. Approximately 2% of the patients discontinued because of an AE.

The most frequent AEs in the short term trials 1235.5 and 1235.6 were peripheral edema, back pain, dizziness and headache. The only AE that was imbalanced between the A10 and combination groups was peripheral edema. There was a 5-6 fold difference in peripheral edema between the combination and the A10 groups (5.1% and 3.6% for A5/T40 and A5/T80, respectively compared to 26.8% for A10) in trial 1235.5. This comparison is not informative because the trial did not include A10+T combination groups. Interestingly, in 1235.6, the A10

treated patients were just as likely to have peripheral edema as the combination therapy treated patients who were treated with the A10 + T combinations.

Nasopharyngitis was the most frequently reported AE in Japanese Trials 1235.13 and 1235.14 (frequency 9.3%-13.0% by treatment group) which studied the A5 dose and dose combinations only. The next most frequent AEs included dizziness, bronchitis, and back pain in Trial 1235.13 and gastroenteritis and abnormal hepatic function in Trial 1235.14. No consistent pattern of relative frequency between combination and monotherapy groups for the most frequent AEs was apparent in either trial. Peripheral edema was reported for only 1 patient (0.4%) in each treatment group in Trial 1235.13 and was not reported in Trial 1235.14. In the open-label Japanese trial 1235.16 that includes no A10 combination therapy group and is ongoing, there were 2 or less events of peripheral edema (<2%).

REVIEWER'S COMMENT(S): The incidence of peripheral edema in the safety update trails was up to 5.1% in combination A5 +T combination therapy groups. The incidence of peripheral edema in these trials in treatment groups treated with A10 was up to 5-6 times higher.

DEATHS

A single patient died during the double-blind period of Trial 1235.6. A male, age 52 years, died of a ruptured cerebral aneurysm occurring 42 days after the start of treatment with T40/A10. A single patient in the open-label Trial 1235.8 died of an aortic dissection occurring during T80/A10 treatment, 113 days after the start of trial treatment.

SAEs

There were no additional concerns arising from the analysis of AEs that occurred during the double blind trials 1235.5 and 1235.6. The SAEs listed in Table 35. The types and numbers of SAEs in the other studies were within expectations for a large population of patients with hypertension.

Table 35: SAEs in Trials Aside from the Death that occurred during the double blind periods of 1235.5 and 1235.6

Trial/ Patient no.	Sex / Age [years]	Treat- ment	AE [MedDRA preferred term]	Start day ₁ / duration [days]	Intensity	Action taken	Outcome
1235.5/ 2244	M/49	A5	Atrial fibrillation	55/12	Mild	Compl	Recovered
1235.5/ 2302	F/55	A5	Chest pain	25/3	Mild	Cont.	Recovered
			Anxiety	25/3	Mild	Cont.	Recovered
1235.5/ 3016	F/48	A10	Breast mass	44/ 21†	Mod	Cont.	Not recovered*
1235.5/ 1698	M/72	T40/A5	Bronchial carcinoma	49/ 46†	Severe	Cont.	Not recovered*
1235.5/ 3146	F/34	T40/A5	Pneumonia	60/6	Moderate	Cont.	Recovered
1235.5/ 1427	M/50	T80/A5	Chest discomfort	8/2	Moderate	Cont.	Recovered
1235.6/ 4270	M / 57	T40/A1 0	Local swelling	50 / 4	Severe	Cont.	Recovered
1235.6/ 5454	M / 53	A10	Bronchitis	1 / 11	Moderate	Disc.	Recovered
1235.6/ 5666	F / 77	T40/A1 0	Cardiac failure	38 / 14	Moderate	Disc.	Recovered

Source: U09-1201-01, Table 15.4.2: 2; U09-1261-01, Table 15.4.2: 2

₁ Start day relative to start of treatment

* Follow-up sufficient

† Censored

TRIAL DISCONTINUATION

Patients with peripheral edema and/or dizziness were the most likely patients to discontinue trial medication. Most patients were on A10 or A10 +T combinations.

LABORATORY RESULTS

There were no clinically relevant laboratory findings.

CONCLUSIONS FROM SAFETY UPDATE

1. The new information provided in the safety update report does not raise additional concerns.
2. The incidence of peripheral edema in the safety update trials was up to 5.1% in combination A5 +T combination therapy groups. The incidence of peripheral edema in

these trials in treatment groups treated with A10 was up to 5-6 times higher. This finding suggests that patients with peripheral edema on A10 alone may benefit from being switched to A5 + T combination therapy.

3. In trial 1235.6 there was no difference in risk of peripheral edema between the group treated with A10 and the groups treated with A10 + T combinations.
4. Considering the totality of evidence from these and the pivotal trials and other studies that have demonstrated the same phenomenon of lowered incidence of amlodipine-induced peripheral edema when an angiotensin II receptor blocker is added, it is appropriate to have a recommendation in the label that clinicians consider changing patients from amlodipine to Twynsta if there is development of peripheral edema. In addition, there should be a suggestion to switch from A10 + T to A5 + T combinations if there is development or persistence of peripheral edema.

8 Postmarketing Experience

The ONTARGET trial enrolled 25,620 patients >55 years old with atherosclerotic disease or diabetes with end-organ damage, randomized them to telmisartan only, ramipril only, or the combination, and followed them for a median of 56 months. Patients receiving the combination of telmisartan and ramipril did not obtain any benefit in the composite endpoint of cardiovascular death, MI, stroke and heart failure hospitalization compared to monotherapy, but experienced an increased incidence of clinically important renal dysfunction (death, doubling of serum creatinine, or dialysis) compared with groups receiving telmisartan alone or ramipril alone. Concomitant use of telmisartan and ramipril is not recommended.

9 Appendices

9.1 Literature Review/References

- Package inserts of amlodipine and telmisartan
- JNC 7 guidelines
- ONTARGET trial, Yusuf S et al, Telmisartan, ramipril, or both in patients at high risk for vascular events. *NEJM* 2008; 358:1547.
- Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903-1913.
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- White et al (*Am J Hypertens.* 2001 Dec;14(12):1239-47).

9.2 Labeling Recommendations

9.3 APPENDICES

9.3.1 APPENDIX 1: Ancillary Studies Used for Safety Analysis

Trial No. / Report No. (Name)	Objectives	Trial Design	Patient Population	Treatment Duration	Key Endpoints	Treatment Groups*	Number of Subjects (total)
Phase IIIb/IV Trials with Telmisartan in Hypertensive Diabetics (by concomitant use of amlodipine)							
502.236 U04-1945-01 (DETAIL)	To compare the renal consequences of telmisartan and enalapril treatment in patients with hypertension and concurrent type 2 diabetes and diabetic nephropathy	Randomized, double-blind, double dummy, forced titration, parallel group comparison	Male or female patients with documented history of mild to moderate hypertension (with on-treatment DBP \leq 95 mmHg and mean seated SBP \leq 180 mmHg) and concurrent type 2 diabetes mellitus and diabetic nephropathy (UAER $>$ 10 and $<$ 1000 μ g/min)	5 years	Efficacy: Glomerular filtration rates, urinary albumin excretion rates, creatinine, and blood pressure Safety: Incidence of clinical endpoints, all-cause mortality, and safety	T40 mg (Micardis®) uptitrated to 80 mg Enalapril 10 mg uptitrated to 20 mg (A allowed as background therapy; only patients on T \pm concomitant A analyzed in SCS.)	T: 120 Enalapril: 130 (250 total) Analyzed in SCS: 82 T w/o con. A, 38 T with con. A
502.396 U06-1367-01 (VIVALDI)	To compare the effects of telmisartan 80 mg and valsartan 160 mg on proteinuria in hypertensive patients with type 2 diabetes and overt nephropathy after 1 year of treatment.	Randomized, double-blind, double dummy, forced titration, parallel-group comparison	Male and female patients with type 2 diabetes mellitus, hypertension (untreated SBP $>$ 130 mm Hg or DBP $>$ 80 mm Hg, or currently receiving antihypertensive medication), and overt nephropathy (serum creatinine \leq 265 μ mol/L and UPER \geq 900 mg/24 hr)	1 year	Primary: Change from baseline in UPER Secondary: 24-hr UAER, 24-hr urine sodium excretion, serum creatinine, CrCl, eGFR; ADMA levels, 8-iso-prostaglandin F2 α levels; high sensitive CRP; BP; time to a composite of a doubling of serum creatinine concentration, ESRD, or all-cause death Safety: AEs, PEs, laboratory parameters; ECG, and vital signs	T40 mg (Micardis®) uptitrated to 80 mg Valsartan 80 mg uptitrated to 160 mg (A allowed as background therapy; only patients on T \pm concomitant A analyzed in SCS.)	T: 443 Valsartan: 442 (885 total) Analyzed in SCS: 278 T w/o con. A, 165 T with con. A

* Study medication was in tablet form, administered orally once daily unless otherwise noted.

Trial No. / Report No. (Name)	Objectives	Trial Design	Patient Population	Treatment Duration	Key Endpoints	Treatment Groups*	Number of Subjects (total)
Phase IIIb/IV Trials with Telmisartan in Hypertensive Diabetics (by concomitant use of amlodipine)							
502.397 U07-3079 (AMADEO)	To show that telmisartan 80 mg is at least as effective and possibly superior to losartan 100 mg in reducing proteinuria after 1 year of treatment.	Randomized, double-blind, double-dummy, forced titration, parallel-group comparison	Male and female patients with type 2 diabetes mellitus, hypertension (untreated SBP >130 mm Hg or DBP >80 mm Hg, or currently receiving antihypertensive medication), and overt nephropathy (UPCR ≥700 mg/g and serum creatinine ≤265 μmol/L [female] or ≤283 μmol/L [male])	1 year	Primary: Change from baseline in UPCR Secondary: GFR, abbreviated MDRD; serum creatinine; macroalbuminuria; sodium excretion; UNACR; high sensitive CRP; serum aldosterone; composite of a doubling of serum creatinine concentration; ESRD, or all-cause death; composite of morbidity and mortality from cardiovascular causes; change over 8 wk in UPCR, UACR, and UNACR following discontinuation of study treatment (after 1 yr of treatment) Safety: AEs, PEs, laboratory parameters, and vital signs	T40 mg (Micardis®) uptitrated to 80 mg Losartan 50 mg uptitrated to 100 mg (A allowed as background therapy; only patients on T ± concomitant A analyzed in SCS.)	T: 419 Losartan: 441 (860 total) Analyzed in SCS: 247 T w/o con. A, 172 T with con. A

* Study medication was in tablet form, administered orally once daily unless otherwise noted.

Trial No. / Report No. (Name)	Objectives	Trial Design	Patient Population	Treatment Duration	Key Endpoints	Treatment Groups*	Number of Subjects (total)
Telmisartan Outcome Trial (subset of patients with and without hypertension as concomitant diagnosis, with and without concomitant use of DHP CCBs)							
502.373 U08-1821-01 (ONTARGET)	Compare the efficacy of telmisartan and the combination of telmisartan and ramipril to ramipril in preventing cardiovascular morbidity/mortality	Phase III, multicenter, double-blind, double-dummy, randomized	Male and female patients ≥55 years of age, with history of coronary artery disease, stroke, peripheral vascular disease, TIA, or diabetes mellitus type 1 or 2 with end-organ damage	3.5-5.5 years	Primary efficacy: Combined endpoint of cardiovascular mortality, stroke, acute myocardial infarction, and hospitalization for CHF Safety: SAEs other than outcome measures, AEs leading to discontinuation, laboratory, BP, PR, PE, ECG	T80 mg (Micardis®) Ramipril (R) 5 mg uptitrated to 10 mg T80 mg + R10 mg (Patients randomized only if tolerant of T40 mg + R5 mg uptitrated during 3-4-week run-in.) (Only patients on T or T+R with or without concomitant DHP CCBs analyzed in SCS.)	1487 non-hypertensive pts on T 7055 hypertensive pts on T 1448 non-hypertensive pts on T+R 7054 hypertensive pts on T+R

* Study medication was in tablet form, administered orally once daily unless otherwise noted.

9.3.2 APPENDIX 2: AEs from Pivotal Trial 1235.1

This appendix is a tabular listing of all AEs by treatment group for trial 1235.1. The total number (N) of patients in each treatment group is listed under each treatment group. For each AE, the

actual number of patients within each treatment group that had the AE is listed and is followed by the percentage of patients in that treatment group that had the particular AE in parentheses. The table of all AEs had to be separated into 4 separate tables. The first and second tables provide all AEs for 8 treatment groups (placebo, A2.5, A5, A10, T20, T40, T80 and T20 +2.5). The third and fourth tables provide all AEs for the remaining 8 treatment groups (T20+A5, T20+A10, T40 +A2.5, T40+A5, T40+A10, T80+A2.5, T80+A5, T80+A10).

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	Placebo	A2.5	A5	A10	T20	T40mg	T80	T20+ A2.5
N	46	48	137	124	42	129	132	44
Allergic reaction, Hypersensitivity	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	1 (2.3%)
Fever	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Infection	6 (13%)	2 (4.2%)	13 (9.5%)	13 (10.5%)	8 (19%)	7 (5.4%)	12 (9.1%)	5 (11.4%)
Abscess, Boil	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pneumonia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	1 (0.8%)	0 (0%)
Influenza, Flu-like Illness	0 (0%)	0 (0%)	2 (1.5%)	2 (1.6%)	0 (0%)	0 (0%)	0 (0%)	1 (2.3%)
URI, Sinusitis, Tonsillitis, Nasal Congestion, Sore Throat	6 (13%)	3 (6.3%)	8 (5.8%)	8 (6.5%)	8 (19%)	7 (5.4%)	13 (9.8%)	3 (6.8%)
Bronchitis, Pneumonia, Tracheitis	1 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	1 (0.8%)	0 (0%)
UTI	0 (0%)	0 (0%)	3 (2.2%)	1 (0.8%)	1 (2.4%)	0 (0%)	0 (0%)	0 (0%)
Pruritis	1 (2.2%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rash	1 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.6%)	2 (1.5%)	0 (0%)
Urticaria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
All Neoplasia	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Headache	5 (10.9%)	2 (4.2%)	13 (9.5%)	8 (6.5%)	4 (9.5%)	13 (10.1%)	5 (3.8%)	4 (9.1%)
Migraine	0 (0%)	0 (0%)	1 (0.7%)	1 (0.8%)	1 (2.4%)	1 (0.8%)	0 (0%)	0 (0%)
CAD, Myocardial Ischemia, (Including AMI)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Angina	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unstable Angina, ACS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chest Pain (Non-Anginal)	1 (2.2%)	1 (2.1%)	4 (2.9%)	1 (0.8%)	3 (7.1%)	2 (1.6%)	0 (0%)	1 (2.3%)
CHF, Pulmonary Edema	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-Pulmonary Edema, Fluid Retention, Fluid Overload	0 (0%)	1 (2.1%)	2 (1.5%)	25 (20.2%)	0 (0%)	1 (0.8%)	1 (0.8%)	1 (2.3%)
Edema of Face, Hands, Arms, OR Angioneutic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Angioneutic Edema	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypertensive Crisis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MI	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypertension, BP Increased	1 (2.2%)	2 (4.2%)	2 (1.5%)	0 (0%)	0 (0%)	1 (0.8%)	1 (0.8%)	0 (0%)
Low BP	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Orthostasis	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dehydration	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Palpitations	0 (0%)	1 (2.1%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Arrhythmia	0 (0%)	0 (0%)	2 (1.5%)	1 (0.8%)	0 (0%)	1 (0.8%)	1 (0.8%)	0 (0%)
Supra-Ventricular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Atrial Fibrillation /Flutter	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PVCs	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Conduction Disturbance	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
AV Block	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IVCD	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Tachycardia	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bradycardia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Pre-Syncope	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Syncope	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pericarditis, Effusion	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pulmonary Embolism	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diabetes, Glucose Intolerance, Hyperglycemia, Glycosuria	0 (0%)	1 (2.1%)	1 (0.7%)	0 (0%)	1 (2.4%)	0 (0%)	1 (0.8%)	0 (0%)
Gout, High Uric Acid	0 (0%)	2 (4.2%)	0 (0%)	0 (0%)	1 (2.4%)	1 (0.8%)	0 (0%)	0 (0%)
DVT	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CPK Increased	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.3%)
Low K+	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (2.3%)	0 (0%)
Low K+	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.6%)	0 (0%)	0 (0%)
CVA, TIA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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	Placebo	A2.5	A5	A10	T20	T40mg	T80	T20+ A2.5
N	46	48	137	124	42	129	132	44
TIA, cerebral ischemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Confusion, Delirium, Altered Mental Status	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Seizure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neuralgia, Neuritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Paresthesia, Hypoaesthesia	1 (2.2%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	1 (0.8%)	1 (0.8%)	0 (0%)
Paralysis, Paresis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Tremor, Shakiness, Trembling	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Depression	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.6%)	0 (0%)	0 (0%)
Anxiety, Nervousness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.4%)	2 (1.6%)	1 (0.8%)	0 (0%)
Insomnia, Sleep Disturbance, Abnormal Dreams	1 (2.2%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	2 (1.6%)	1 (0.8%)	1 (2.3%)
Dizziness, Light-Headedness	2 (4.3%)	0 (0%)	4 (2.9%)	0 (0%)	2 (4.8%)	2 (1.6%)	1 (0.8%)	2 (4.5%)
Emotional Mood Disturbance (Non-Depressive)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.4%)	2 (1.6%)	1 (0.8%)	0 (0%)
Asthenia, Fatigue, Malaise, Lethargy	0 (0%)	2 (4.2%)	3 (2.2%)	2 (1.6%)	1 (2.4%)	3 (2.3%)	5 (3.8%)	3 (6.8%)
Dysuria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Proteinuria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Polyuria	2 (4.3%)	1 (2.1%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Nocturia	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nephrolithiasis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Erectile Dysfunction	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Decreased Libido	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Anemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ecchymosis, Hematoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Bleeding	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
DOE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
COPD	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rales, Crackles	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Epistaxis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hemoptysis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cough	1 (2.2%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	2 (1.5%)	1 (2.3%)
Wheeze, Bronchospasm, Asthma	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (2.4%)	1 (0.8%)	0 (0%)	1 (2.3%)
Arthralgia, Arthritis	1 (2.2%)	0 (0%)	3 (2.2%)	3 (2.4%)	0 (0%)	3 (2.3%)	3 (2.3%)	1 (2.3%)
Cramps, Muscle Spasm	0 (0%)	0 (0%)	4 (2.9%)	1 (0.8%)	1 (2.4%)	2 (1.6%)	3 (2.3%)	1 (2.3%)
GOT, GPT, GGTP	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	1 (0.8%)	1 (0.8%)	0 (0%)
Constipation	0 (0%)	0 (0%)	1 (0.7%)	1 (0.8%)	0 (0%)	0 (0%)	2 (1.5%)	0 (0%)
Diarrhea, Colitis, Enteritis, Proctitis	1 (2.2%)	0 (0%)	2 (1.5%)	2 (1.6%)	1 (2.4%)	1 (0.8%)	5 (3.8%)	0 (0%)
Nausea	0 (0%)	0 (0%)	3 (2.2%)	1 (0.8%)	1 (2.4%)	0 (0%)	1 (0.8%)	0 (0%)
dyspepsia, Vomiting, Indigestion, Epigastric Pain, Gastroenteritis	0 (0%)	1 (2.1%)	0 (0%)	1 (0.8%)	1 (2.4%)	2 (1.6%)	0 (0%)	0 (0%)
Gastroenteritis	0 (0%)	1 (2.1%)	2 (1.5%)	1 (0.8%)	0 (0%)	0 (0%)	1 (0.8%)	1 (2.3%)
Reflux	0 (0%)	0 (0%)	1 (0.7%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Esophagitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gastritis, Duodenitis, Gastric Ulcer	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Abdominal Pain, Distension, Bloating, Spasm, IBS	1 (2.2%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	4 (3%)	0 (0%)
Flatulence	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
GI Bleed	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Choking	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Back Pain	0 (0%)	1 (2.1%)	5 (3.6%)	1 (0.8%)	1 (2.4%)	0 (0%)	2 (1.5%)	1 (2.3%)
Vertigo; Vestibular Dysfunction	1 (2.2%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tinnitus	1 (2.2%)	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)
Menstrual Irregularities, Dysmenorrhea	0 (0%)	0 (0%)	3 (2.2%)	3 (2.4%)	1 (2.4%)	2 (1.6%)	1 (0.8%)	3 (6.8%)
Injury	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Extremity Pain	2 (4.3%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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	T20 + A5	T20 + A10	T40 + A2.5	T40 + A5	T40 + A10	T80 + A2.5	T80 + A5	T80+A10
N	45	40	47	141	123	46	143	136
Allergic reaction, Hypersensitivity	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (2.2%)	1 (0.7%)	0 (0%)
Fever	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)
Infection	2 (4.4%)	4 (10%)	5 (10.6%)	13 (9.2%)	15 (12.2%)	7 (15.2%)	14 (9.8%)	17 (12.5%)
Abscess, Boil	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.4%)	0 (0%)
Pneumonia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Influenza, Flu-like Illness	0 (0%)	1 (2.5%)	2 (4.3%)	2 (1.4%)	1 (0.8%)	0 (0%)	4 (2.8%)	3 (2.2%)
URI, Sinusitis, Tonsillitis, Nasal Congestion, Sore Throat	2 (4.4%)	2 (5%)	3 (6.4%)	9 (6.4%)	11 (8.9%)	5 (10.9%)	8 (5.6%)	12 (8.8%)
Bronchitis, Pneumonia, Tracheitis	0 (0%)	0 (0%)	0 (0%)	2 (1.4%)	2 (1.6%)	1 (2.2%)	1 (0.7%)	1 (0.7%)
UTI	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (2.2%)	0 (0%)	1 (0.7%)
Pruritis	1 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rash	0 (0%)	1 (2.5%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	2 (1.4%)	1 (0.7%)
Urticaria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
All Neoplasia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)
Headache	4 (8.9%)	2 (5%)	3 (6.4%)	8 (5.7%)	6 (4.9%)	0 (0%)	6 (4.2%)	8 (5.9%)
Migraine	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	1 (0.8%)	0 (0%)	0 (0%)	1 (0.7%)
CAD, Myocardial Ischemia, (Including AMI)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)
Angina	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unstable Angina, ACS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chest Pain (Non-Anginal)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	1 (0.8%)	1 (2.2%)	2 (1.4%)	3 (2.2%)
CHF, Pulmonary Edema	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Non-Pulmonary Edema, Fluid Retention, Fluid Overload	2 (4.4%)	5 (12.5%)	1 (2.1%)	3 (2.1%)	13 (10.6%)	1 (2.2%)	4 (2.8%)	19 (14%)
Edema of Face, Hands, Arms, OR Angioneurotic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)
Angioneurotic Edema	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypertensive Crisis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
MI	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypertension, BP Increased	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)
Low BP	0 (0%)	1 (2.5%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	1 (0.7%)	2 (1.5%)
Orthostasis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)
Dehydration	1 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Palpitations	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	1 (0.7%)
Arrhythmia	1 (2.2%)	0 (0%)	1 (2.1%)	2 (1.4%)	4 (3.3%)	1 (2.2%)	0 (0%)	0 (0%)
Supra-Ventricular	1 (2.2%)	0 (0%)	1 (2.1%)	0 (0%)	1 (0.8%)	1 (2.2%)	0 (0%)	0 (0%)
Atrial Fibrillation /Flutter	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PVCs	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)
Conduction Disturbance	1 (2.2%)	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
AV Block	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IVCD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tachycardia	0 (0%)	0 (0%)	0 (0%)	2 (1.4%)	2 (1.6%)	0 (0%)	0 (0%)	0 (0%)
Bradycardia	1 (2.2%)	0 (0%)	1 (2.1%)	0 (0%)	1 (0.8%)	1 (2.2%)	0 (0%)	0 (0%)
Pre-Syncope	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Syncope	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	1 (2.2%)	0 (0%)	0 (0%)
Pericarditis, Effusion	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)
Pulmonary Embolism	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)
Diabetes, Glucose Intolerance, Hyperglycemia, Glycosuria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Gout, High Uric Acid	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)
DVT	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)
CPK Increased	1 (2.2%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Low K+	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Low K+	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CVA, TIA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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	T20 + A5	T20 + A10	T40 + A2.5	T40 + A5	T40 + A10	T80 + A2.5	T80 + A5	T80+A10
N	45	40	47	141	123	46	143	136
TIA, cerebral ischemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Confusion, Delirium, Altered Mental Status	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Seizure	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neuralgia, Neuritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.6%)	0 (0%)	0 (0%)	1 (0.7%)
Paresthesia, Hypoaesthesia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)
Paralysis, Paresis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Tremor, Shakiness, Trembling	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Depression	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.6%)	0 (0%)	1 (0.7%)	0 (0%)
Anxiety, Nervousness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)
Insomnia, Sleep Disturbance, Abnormal Dreams	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	1 (2.2%)	1 (0.7%)	0 (0%)
Irritability, Agitation, Stress, Restless	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dizziness, Light-Headedness	1 (2.2%)	1 (2.5%)	1 (2.1%)	7 (5%)	3 (2.4%)	2 (4.3%)	6 (4.2%)	2 (1.5%)
Emotional Mood Disturbance (Non-Depressive)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)
Asthenia, Fatigue, Malaise, Lethargy	0 (0%)	2 (5%)	0 (0%)	3 (2.1%)	1 (0.8%)	1 (2.2%)	2 (1.4%)	1 (0.7%)
Dysuria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	1 (2.2%)	0 (0%)	1 (0.7%)
Proteinuria	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Polyuria	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)
Nocturia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Nephrolithiasis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	1 (0.7%)
Erectile Dysfunction	2 (4.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.4%)	1 (0.7%)
Decreased Libido	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anemia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.4%)	1 (0.7%)
Ecchymosis, Hematoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bleeding	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)
DOE	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)
COPD	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rales, Crackles	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Epistaxis	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hemoptysis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cough	1 (2.2%)	0 (0%)	0 (0%)	1 (0.7%)	1 (0.8%)	1 (2.2%)	0 (0%)	1 (0.7%)
Wheeze, Bronchospasm, Asthma	1 (2.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Arthralgia, Arthritis	3 (6.7%)	0 (0%)	1 (2.1%)	2 (1.4%)	2 (1.6%)	0 (0%)	2 (1.4%)	3 (2.2%)
Cramps, Muscle Spasm	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.6%)	1 (2.2%)	0 (0%)	4 (2.9%)
GOT, GPT, GGTP	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)
Constipation	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)	2 (1.4%)	0 (0%)
Diarrhea, Colitis, Enteritis, Proctitis	0 (0%)	1 (2.5%)	1 (2.1%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	3 (2.2%)
Nausea	0 (0%)	1 (2.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	0 (0%)
dyspepsia, Vomiting, Indigestion, Epigastric Pain, Gastroenteritis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	1 (0.7%)	3 (2.2%)
Gastroenteritis	0 (0%)	1 (2.5%)	0 (0%)	1 (0.7%)	0 (0%)	1 (2.2%)	1 (0.7%)	1 (0.7%)
Reflux	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)
Esophagitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)
Gastritis, Duodenitis, Gastric Ulcer	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)	1 (0.7%)
Abdominal Pain, Distension, Bloating, Spasm, IBS	0 (0%)	2 (5%)	1 (2.1%)	3 (2.1%)	1 (0.8%)	2 (4.3%)	0 (0%)	3 (2.2%)
Flatulence	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)
GI Bleed	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Choking	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Back Pain	0 (0%)	1 (2.5%)	2 (4.3%)	4 (2.8%)	4 (3.3%)	1 (2.2%)	1 (0.7%)	3 (2.2%)
Vertigo, Vestibular Dysfunction	0 (0%)	0 (0%)	1 (2.1%)	1 (0.7%)	0 (0%)	0 (0%)	0 (0%)	2 (1.5%)
Tinnitus	0 (0%)	0 (0%)	1 (2.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Menstrual Irregularities, Dysmenorrhea	1 (2.2%)	0 (0%)	0 (0%)	1 (0.7%)	2 (1.6%)	1 (2.2%)	5 (3.5%)	2 (1.5%)
Injury	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Extremity Pain	0 (0%)	0 (0%)	0 (0%)	3 (2.1%)	2 (1.6%)	0 (0%)	0 (0%)	1 (0.7%)

9.3.3 Appendix 3: List of trials used for 4-month safety update

Trial No. / Report No.	Objectives	Trial Design	Patient Population	Treatment Duration	Key Endpoints	Treatment Groups*	Number of Subjects (total)
Multinational Double-Blind Trials							
1235.5 U09-1201-01	To demonstrate that the T40/A5 or T80/A5 FDC is superior to A5 and not inferior to A10 in reducing BP at 8 weeks and to demonstrate that the incidence of edema is lower for the pooled T40/A5 and T80/A5 groups than for the A10 group	Randomized, controlled, double-blind, non-responder study	Adult patients with essential hypertension and uncontrolled BP (DBP \geq 95 mmHg with treatment or \geq 100 mmHg untreated) who had DBP remaining \geq 90 mmHg after 6-week run-in treatment with open-label A5	Run-in: 6 weeks Double-blind: 8 weeks	Primary: Change from baseline in trough seated DBP, incidence of edema Secondary: Trough seated SBP; DBP and SBP control rates; DBP and SBP response; categorical BP Safety: AEs including edema, laboratory, PE, ECG	T40/A5 FDC T80/A5 FDC A5 (Norvasc®, over-encapsulated) A10 (Norvasc®, over-encapsulated)	277 277 267 276 (1097)

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Trial No. / Report No.	Objectives	Trial Design	Patient Population	Treatment Duration	Key Endpoints	Treatment Groups*	Number of Subjects (total)
1235.6 U09-1261-01	To demonstrate that the T40/A10 or T80/A10 FDC is superior to A10 in reducing BP at 8 weeks	Randomized, controlled, double-blind, non-responder study	Adult patients with essential hypertension and uncontrolled BP (DBP \geq 95 mmHg with treatment or \geq 100 mmHg untreated) who had DBP remaining \geq 90 mmHg after run-in treatment with open-label A5 (2 weeks) uptitrated to A10 (6 weeks)	Run-in: 8 weeks Double-blind: 8 weeks	<u>Primary:</u> Change from baseline in trough seated DBP <u>Secondary:</u> Trough seated SBP; DBP and SBP control rates; DBP and SBP response; categorical BP; incidence of edema Safety: AEs including edema, laboratory, PE, ECG	T40/A10 FDC T80/A10 FDC A10 (Norvasc®, over-encapsulated)	315 317 315 (947)

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Trial No. / Report No.	Objectives	Trial Design	Patient Population	Treatment Duration	Key Endpoints	Treatment Groups*	Number of Subjects (total)
Multinational Open-Label Extension Trials							
1235.7 N/A (Trial ongoing) [Protocol No. U07-1757]	To assess the efficacy and safety of the combination of telmisartan 40 or 80 mg + amlodipine 5 mg alone or in addition to other antihypertensive therapies during open-label treatment for at least 6 months	Open-label, response-driven titration	Male or female patients who completed Trial 1235.5 within the previous 14 days	Up to 34 weeks	<u>Primary:</u> DBP control rate (<90 mmHg at trough) <u>Secondary:</u> change from baseline in DBP and SBP, DBP and SBP response, categorical BP, proportions of patients requiring uptitration or additional therapy, time to additional therapy	T40 mg/A5 mg FDC, uptitrated to T80 mg/A5 mg after 4 or 8 weeks if DBP ≥90 mmHg Subsequent additional antihypertensive medication (except ARBs or DHP CCBs) was allowed if DBP ≥90 mmHg.	1012 planned, 975 assessed in SU [data cutoff date 13-Jan-2009]

Trial No. / Report No.	Objectives	Trial Design	Patient Population	Treatment Duration	Key Endpoints	Treatment Groups*	Number of Subjects (total)
1235.8 N/A (Trial ongoing) [Protocol No. U07-1807]	To assess the efficacy and safety of the combination of telmisartan 40 or 80 mg + amlodipine 10 mg alone or in addition to other antihypertensive therapies during open-label treatment for at least 6 months	Open-label, with a randomized forced titration (3:2 ratio) after 4 weeks followed by a response-driven titration after 8 weeks for all patients	Male or female patients who completed Trial 1235.6 within the previous 14 days	Up to 34 weeks	<u>Primary:</u> DBP control rate (<90 mmHg at trough) <u>Secondary:</u> change from baseline in DBP and SBP, DBP and SBP response, categorical BP, proportions of patients requiring uptitration or additional therapy, time to additional therapy Safety: AEs, laboratory, VS, ECG	T40 mg/A10 mg FDC, uptitrated to T80 mg/A10 mg after 8 weeks if DBP ≥90 mmHg T80 mg/A10 mg FDC (assigned by 3:2 randomization after 4-week initial treatment with T40/A10 FDC) Subsequent additional antihypertensive medication (except ARBs or DHP CCBs) was allowed if DBP ≥90 mmHg.	900 planned, 837 assessed in SU [data cutoff date 13-Jan-2009]
					Safety: AEs, laboratory, VS, ECG		

Trial No. / Report No.	Objectives	Trial Design	Patient Population	Treatment Duration	Key Endpoints	Treatment Groups*	Number of Subjects (total)
Double-Blind Trials Conducted in Japan							
1235.13 U09-3036-01	To demonstrate that telmisartan 40 mg plus amlodipine 5 mg FDC is superior to amlodipine 5 mg monotherapy in BP-lowering effect in patients with essential hypertension whose BP is not controlled with amlodipine 5 mg monotherapy	Multicenter, randomized, active-controlled, double-blind, parallel-group	Patients aged ≥ 20 years with DBP ≥ 95 and ≤ 114 mmHg and SBP ≥ 140 and ≤ 200 mmHg before 6-week run-in treatment with open-label A5, and DBP ≥ 90 and ≤ 114 mmHg and SBP ≤ 200 mmHg after run-in	Run-in: 6 weeks Double-blind: 8 weeks	Primary: Change from baseline in trough seated DBP Secondary: Trough seated SBP; DBP and SBP control rates; DBP and SBP response rates; categorical BP Safety: AEs, laboratory, postural changes in BP and PR, ECG	T40/A5 FDC (uptitrated from T20+A5 free combination after 2 weeks) A5 (over-encapsulated tablets) NOTE: FDC tablet formulation was slightly different from that used in the multinational trials.	269 262 (531)

Source: safety update

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1235.14 U08-3883-02	To demonstrate that telmisartan 40 mg plus amlodipine 5 mg FDC is superior to telmisartan 40 mg monotherapy in BP-lowering effect in patients with essential hypertension whose BP is not controlled with telmisartan 40 mg monotherapy	Multicenter, randomized, active-controlled, double-blind, parallel-group	Patients aged ≥ 20 years with DBP ≥ 95 and ≤ 114 mmHg and SBP ≥ 140 and ≤ 200 mmHg before 6-week run-in treatment with open-label T40 (up-titrated from T20 after 2 weeks), and DBP ≥ 90 and ≤ 114 mmHg and SBP ≤ 200 mmHg after	Run-in: 6 weeks Double-blind: 8 weeks	Primary: Change from baseline in trough seated DBP Secondary: Trough seated SBP; DBP and SBP control rates; DBP and SBP response rates; categorical BP Safety: AEs, laboratory, postural
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9.3.4 APPENDIX 4: EFFICACY BY REGION

US-4 (N=163)					
		A0	A2.5	A5	A10
T0	N				
	Adj mean (SE)	-9.3 (3.5)	-5.9 (3.1)	-8.8 (1.6)	-15.0 (1.7)
T20	N				
	Adj mean (SE)	-11.0 (2.8)	-14.9 (4.0)	-12.4 (3.5)	-11.3 (4.0)
	Diff vs. T				
	Adj mean (SE)		-3.9 (4.9)	-1.4 (4.5)	-11.2 (6.5)
	95% CI		(-5.7, 13.5)	(-7.4, 10.2)	(-1.8, 24.2)
	p-value		0.4260	0.7519	0.0899
	Diff vs. A				
	Adj mean (SE)		-9.0 (5.0)	-3.6 (3.8)	-0.4 (4.9)
	95% CI		(-18.9, 1.0)	(-11.0, 4.0)	(-9.3, 10.0)

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	p-value		0.0769	0.3520	0.9399
T40	N				
	Adj mean (SE)	-15.0 (1.9)	-12.4 (2.9)	-13.1 (1.7)	-17.9 (1.8)
	Diff vs. T				
	Adj mean (SE)		2.6 (3.5)	1.9 (2.5)	-2.9 (2.6)
	95% CI		(9.4, -4.3)	(6.9, -3.2)	(-2.3, 8.1)
	p-value		0.4620	0.4631	0.2687
T80	N				
	Adj mean (SE)	-14.5 (2.0)	-18.4 (3.4)	-17.7 (1.7)	-20.1 (1.6)
	Diff vs. T				
	Adj mean (SE)		-4.0 (4.0)	-3.2 (2.6)	-5.6 (2.6)
	95% CI		(-4.0, 11.8)	(-2.0, 8.5)	(-0.5, -10.7)
	p-value		0.3237	0.2209	0.0305
US-3 (N=239)	N				
	Adj mean (SE)		-12.5 (4.6)	-8.9 (2.3)	-5.1 (2.3)
	95% CI		(-3.4, -21.7)	(-4.3, -13.4)	(-0.5, -9.7)
	p-value		0.0075	0.0002	0.0294
		A0	A2.5	A5	A10
	T0	N			
	Adj mean (SE)	-3.8 (3.0)	-12.3 (3.2)	-9.0 (1.8)	-14.1 (8.9)
T20	N				
	Adj mean (SE)	-12.9 (3.2)	-21.5 (2.8)	-11.7 (3.4)	-17.0 (3.4)
	Diff vs. T				
	Adj mean (SE)		-8.6 (4.2)	1.2 (4.7)	-4.1 (4.7)

	95% CI p-value		(-0.3, -16.9) 0.0434	(-10.5, 8.0) 0.7919	(-5.1, 13.3) 0.3782
	Diff vs. A				
	Adj mean (SE) 95% CI p-value		-9.1 (4.2) (-0.8, -17.5) 0.0317	-2.7 (3.8) (-10.3, 4.8) 0.4786	-2.9 (3.9) (-10.6, 4.8) 0.4603
T40	N				
	Adj mean (SE)	-10.8 (1.2)	-13.8 (2.8)	-12.7 (1.7)	-15.8 (1.8)
	Diff vs. T				
	Adj mean (SE) 95% CI p-value		-3.1 (3.3) (-3.5, 9.6) 0.3580	-2.0 (2.5) (-3.0, 6.9) 0.4327	-5.0 (2.6) (-0.02, 10.1) 0.0513
	Diff vs. A				
	Adj mean (SE) 95% CI p-value		-1.5 (4.2) (-9.8, 6.9) 0.7280	-3.8 (2.5) (-8.6, 1.1) 0.1280	-1.6 (2.6) (-6.8, 3.5) 0.5290
T80	N				
	Adj mean (SE)	-12.6 (1.7)	-14.4 (3.0)	-13.9 (1.8)	-19.2 (1.8)
	Diff vs. T				
	Adj mean (SE) 95% CI p-value		-1.8 (3.4) (-4.9, 8.5) 0.5974	-1.2 (2.4) (-3.6, 6.1) 0.6116	-6.6 (2.4) (-1.8, -11.4) 0.0077
	Diff vs. A				
	Adj mean (SE) 95% CI p-value		-2.1 (4.3) (-10.6, 6.5) 0.6330	-4.9 (2.5) (-9.8, 0.03) 0.0514	-5.1 (2.6) (-10.2, 0.03) 0.0515
US-2 (N=247)					
		A0	A2.5	A5	A10
T0	N Adj mean (SE)	-3.4 (2.5)	-8.9 (2.6)	-11.6 (1.6)	-15.8 (1.7)

T20	N				
	Adj mean (SE)	-6.7 (3.3)	-17.8 (2.5)	-17.0 (2.5)	-18.9 (2.3)
	Diff vs. T				
	Adj mean (SE) 95% CI p-value		-11.1 (4.1) (-2.9, 19.2) 0.0081	-10.2 (4.2) (-2.0, -18.4) 0.0146	-12.1 (4.1) (-4.1, -20.2) 0.0032
	Diff vs. A				
T40	N				
	Adj mean (SE)	-15.1 (1.6)	-20.3 (2.8)	-15.9 (1.8)	-19.5 (1.6)
	Diff vs. T				
	Adj mean (SE) 95% CI p-value		-5.2 (3.2) (-1.1, 11.5) 0.1047	-0.9 (2.1) (-3.3, 5.1) 0.6791	-4.5 (2.2) (-0.1, -8.8) 0.0443
	Diff vs. A				
T80	N				
	Adj mean (SE)	-11.2 (1.6)	-13.1 (2.8)	-17.1 (1.4)	-17.5 (1.5)
	Diff vs. T				
	Adj mean (SE) 95% CI p-value		-1.9 (3.2) (-4.5, 8.3) 0.5612	-5.9 (2.2) (-1.7, -10.1) 0.0067	-6.3 (2.2) (-2.0, -10.7) 0.0047
	Diff vs. A				
T80	Adj mean (SE) 95% CI		-4.3 (3.8) (-11.8, 3.3)	-5.5 (2.2) (-1.2, -9.8)	-1.8 (2.3) (-6.2, 2.7)

	p-value		0.2673	0.0117	0.4430
US-1 (N=228)					
		A0	A2.5	A5	A10
T0	N				
	Adj mean (SE)	-4.0 (2.7)	-3.8 (2.5)	-15.5 (1.6)	-17.1 (1.7)
T20	N				
	Adj mean (SE)	-8.6 (2.7)	-17.4 (3.4)	-13.3 (2.7)	-19.1 (3.1)
	Diff vs. T				
	Adj mean (SE)		-8.8 (4.3)	-4.7 (3.8)	-10.5 (4.1)
	95% CI		(-0.2, -17.3)	(-2.7, 12.1)	(-2.5, -18.5)
	p-value		0.0443	0.2104	0.0106
	Diff vs. A				
	Adj mean (SE)		-13.6 (4.2)	-9.6 (3.7)	-2.0 (3.5)
	95% CI		(-5.3, -21.9)	(-2.4, -16.8)	(-8.8, 4.9)
	p-value		0.0014	0.0096	0.5734
T40	N				
	Adj mean (SE)	-12.0 (1.6)	-11.8 (2.7)	-16.0 (1.6)	-20.3 (1.7)
	Diff vs. T				
	Adj mean (SE)		0.2 (3.2)	-4.1 (2.3)	-8.4 (2.4)
	95% CI		(-6.4, 6.0)	(-0.4, 8.5)	(-3.6, -13.1)
	p-value		0.9458	0.0763	0.0006
	Diff vs. A				
	Adj mean (SE)		-8.0 (3.7)	-12.3 (3.0)	-3.2 (2.4)
	95% CI		(-0.7, -15.3)	(-6.4, 18.1)	(-7.9, 1.5)
	p-value		0.0310	<.0001	0.1777
T80	N				
	Adj mean (SE)	-11.9 (1.7)	-9.9 (2.9)	-20.5 (1.5)	-18.2 (1.7)
	Diff vs. T				
	Adj mean (SE)		2.0 (3.3)	-8.5 (2.3)	-6.3 (2.4)

	95% CI p-value		(-8.6, 4.6) 0.5446	(-3.9, -13.1) 0.0003	(-1.5, -11.7) 0.0101
	Diff vs. A				
	Adj mean (SE) 95% CI p-value		-6.2 (3.8) (-13.6, 4.4) 0.1078	-4.9 (2.2) (-9.3, -0.5) 0.0287	-1.1 (2.4) (-5.7, 3.5) 0.6386
S. Africa (N=210)					
		A0	A2.5	A5	A10
T0	N Adj mean (SE)	-5.3 (3.8)	-20.9 (3.3)	-16.8 (2.0)	-17.2 (2.4)
T20	N Adj mean (SE)	-22.6 (3.8)	-21.5 (3.5)	-20.2 (3.5)	-16.0 (3.5)
	Diff vs. T				
	Adj mean (SE) 95% CI p-value		1.12 (5.2) (-11.3, 9.1) 0.8278	2.5 (5.2) (-12.6, 7.7) 0.6352	6.7 (5.2) (-16.9, 3.5) 0.2000
	Diff vs. A				
	Adj mean (SE) 95% CI p-value		-0.6 (4.8) (-10.1, 8.9) 0.8980	-3.4 (4.0) (-11.3, 4.5) 0.3997	1.3 (4.3) (-7.1, 9.7) 0.7679
T40	N Adj mean (SE)	-12.7 (2.2)	-17.0 (3.3)	-18.9 (2.1)	-20.6 (2.3)
	Diff vs. T				
	Adj mean (SE) 95% CI p-value		-4.2 (4.4) (-4.1, 12.8) 0.3359	-6.2 (3.1) (-0.2, -12.2) 0.0440	-7.9 (3.1) (-1.7, -14.1) 0.0126
	Diff vs. A				
	Adj mean (SE) 95% CI p-value		3.9 (5.0) (-6.0, 13.8) 0.4333	-2.1 (2.9) (-7.9, 3.6) 0.4638	-3.4 (3.3) (-9.9, 3.1) 0.3006

T80	N Adj mean (SE)	-14.8 (2.1)	--17.1 (3.3)	-19.2 (2.0)	-22.3 (2.0)
	Diff vs. T				
	Adj mean (SE)		-2.3 (3.9)	--4.3 (2.9)	-7.5 (2.9)
	95% CI		(-5.4, 9.9)	(-1.9, 10.0)	(-2.4, 8.7)
	p-value		0.5610	0.1307	0.2604
	Diff vs. A				
	Adj mean (SE)		3.8 (4.6)	-2.4 (2.8)	-5.1 (3.1)
	95% CI		(-5.3, 12.9)	(-7.9, 3.1)	(-11.2, 1.3)
	p-value		0.4138	0.3923	0.1026
Mexico (N=169)					
		A0	A2.5	A5	A10
T0	N Adj mean (SE)	-14.5 (3.9)	-10.0 (3.6)	-12.3 (2.3)	-20.6 (2.3)
T20	N Adj mean (SE)	-14.1 (3.6)	-11.4 (3.6)	-14.4 (3.6)	-23.2 (4.4)
	Diff vs. T				
	Adj mean (SE)		2.7 (5.1)	-0.3 (5.1)	-9.1 (5.6)
	95% CI		(-12.8, 7.3)	(-12.8, 7.3)	(-2.1, 20.2)
	p-value		0.5893	0.5893	0.1104
	Diff vs. A				
	Adj mean (SE)		-1.4 (5.1)	-2.2 (4.2)	-2.6 (4.9)
	95% CI		(-11.4, 8.6)	(-10.5, 6.2)	(-12.4, 7.11)
	p-value		0.7795	0.6075	0.5957
T40	N Adj mean (SE)	-13.9 (2.1)	-16.8 (3.9)	-15.8 (2.3)	-20.7 (2.3)
	Diff vs. T				
	Adj mean (SE)		-2.9 (4.5)	-1.9 (3.0)	--6.8 (3.2)
	95% CI		(-5.9, 11.8)	(-4.1, 7.8)	(-0.3, -13.0)

	p-value		0.5120	0.5377	0.0334
	Diff vs. A				
	Adj mean (SE)		-6.9 (5.3)	-3.5 (3.1)	-0.1 (3.3)
	95% CI		(-17.3, 3.6)	(-9.6, 2.7)	(-6.5, 6.3)
	p-value		0.1963	0.2634	0.9792
T80	N				
	Adj mean (SE)	-14.3 (2.1)	-18.2 (3.6)	-15.4 (2.3)	-19.5 (2.3)
	Diff vs. T				
	Adj mean (SE)		-3.9 (4.1)	-1.1 (3.1)	-5.2 (3.1)
	95% CI		(-12.5, 3.8)	(-5.0, 7.1)	(-0.9, 11.4)
	p-value		0.2957	0.7288	0.0951
	Diff vs. A				
	Adj mean (SE)		-8.3 (5.1)	-3.1 (3.2)	1.1 (3.2)
	95% CI		(-18.2, 1.7)	(-9.5, 3.3)	(-5.4, 7.5)
	p-value		0.1037	0.3415	0.7463
Brazil (N=87)					
		A0	A2.5	A5	A10
T0	N				
	Adj mean (SE)	2.2 (4.2)	-7.2 (5.2)	-18.7 (2.6)	-20.8 (2.4)
T20	N				
	Adj mean (SE)	-19.6 (7.4)	-15.7 (4.2)	-21.8 (4.3)	-25.4 (5.2)
	Diff vs. T				
	Adj mean (SE)		3.9 (8.5)	-2.3 (8.7)	-4.6 (5.70)
	95% CI		(-20.7, 13.0)	(-15.0, 19.6)	(-16.0, 6.9)
	p-value		0.6496	0.7941	0.4274
	Diff vs. A				
	Adj mean (SE)		-8.5 (6.7)	-3.1 (5.1)	-5.9 (8.9)
	95% CI		(-21.9, 4.8)	(-13.2, 6.9)	(-12.0, 23.7)

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	p-value		0.2937	0.5365	0.5137
T40	N				
	Adj mean (SE)	-11.6 (2.8)	-21.4 (4.2)	-19.9 (2.4)	-23.3 (2.6)
	Diff vs. T				
	Adj mean (SE)		-9.7 (5.0)	-8.3 (3.7)	-11.7 (3.8)
	95% CI		(-0.3, 19.8)	(-0.9, -15.6)	(-4.2, -19.2)
	p-value		0.0567	0.0276	0.0028
T80	Diff vs. A				
	Adj mean (SE)		-14.2 (6.7)	-1.2 (3.6)	-2.5 (3.5)
	95% CI		(-27.5, -0.9)	(-8.3, 5.9)	(-9.6, 4.6)
	p-value		0.0367	0.7393	0.4058
T80	N				
	Adj mean (SE)	-18.0 (2.4)	-21.6 (4.3)	-18.5 (2.6)	20.2 (2.5)
	Diff vs. T				
	Adj mean (SE)		-3.7 (5.0)	-0.6 (3.6)	-2.5 (3.5)
T80	95% CI		(-6.4, 13.7)	(-6.5, 7.6)	(-4.4, 9.3)
	p-value		0.4678	0.8765	0.4816
T80	Diff vs. A				
	Adj mean (SE)		--14.5 (6.8)	0.2 (3.7)	0.4 (3.5)
T80	95% CI		(-28.1, -0.8)	(-7.1, 7.5)	(-6.5, 7.3)
	p-value		0.0381	0.9619	0.9002
Argentina (N=80)					
		A0	A2.5	A5	A10
T0	N				
	Adj mean (SE)	-13.4 (4.1)	-9.9 (4.1)	-15.2 (2.7)	-14.5 (2.6)
T20	N				
	Adj mean (SE)	-18.6 (4.1)	-17.9 (5.0)	-13.0 (5.2)	-29.8 (5.0)
T20	Diff vs. T				

	Adj mean (SE)		0.7 (6.5)	5.6 (4.4)	-11.2 (6.5)
	95% CI		(-13.7, 12.2)	(-18.9, 7.7)	(-1.8, 24.2)
	p-value		0.9112	0.4041	0.0899
	Diff vs. A				
	Adj mean (SE)		-8.0 (6.5)	2.2 (5.9)	-15.3 (5.7)
	95% CI		(-21.0, 5.1)	(-9.5, 13.9)	(-26.6, -4.0)
	p-value		0.2263	0.7065	0.0087
T40	N				
	Adj mean (SE)	-13.0 (2.4)	-26.6 (4.1)	-20.7 (2.7)	-26.4 (2.9)
	Diff vs. T				
	Adj mean (SE)		-13.6 (4.7)	-7.7 (3.6)	-13.4 (3.7)
	95% CI		(-4.2, -23.1)	(-0.6, -14.9)	(-5.9, -20.9)
	p-value		0.0054	0.0346	0.0007
	Diff vs. A				
	Adj mean (SE)		-16.7 (5.8)	-5.5 (3.8)	-11.9 (3.9)
	95% CI		(-28.3, -5.1)	(-13.1, 2.1)	(-19.7, -4.1)
	p-value		0.0053	0.1526	0.0032
T80	N				
	Adj mean (SE)	-16.3 (2.5)	-16.5 (4.10)	-23.5 (2.7)	-22.1 (2.7)
	Diff vs. T				
	Adj mean (SE)		-0.2 (4.8)	-7.2 (3.70)	--5.8 (3.7)
	95% CI		(-9.5, 9.9)	(-0.1, 14.5)	(-1.6, 13.2)
	p-value		0.9728	0.0540	0.1237
	Diff vs. A				
	Adj mean (SE)		-6.6 (9.9)	-8.3 (3.8)	-7.6 (3.7)
	95% CI		(-18.3, 5.1)	(-15.9, -0.7)	(-15.0, -0.3)
	p-value		0.2646	0.0333	0.0418

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22401	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	TELMISARTAN/AMLODIPINE FIXED DOSE COM TB
NDA-22401	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	TELMISARTAN/AMLODIPINE FIXED DOSE COM TB

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MELANIE J BLANK
09/09/2009