# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number** 20-818

## CLINICAL REVIEW(S)

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JAN 30 1998

# Cardio Renal Drug Product
# NDA Submission 20-818
# Valsartan-Hydrochlorothiazide
# Clinical Safety Review

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| **NDA #: 20-818** | **NDA Volumes: 1.1 - 1. 88** |
| **Drug Name: Valsartan/Hydrochlorothiazide** | **Sponsor: Novartis Pharmaceuticals Corporation** |
| **Type of Document: CANDA** | **Correspondence Date: March 28, 1997** |
| **Date Received: April 23, 1997** | **Date Completed: October 30, 1997** |
| **Medical Reviewer: Safety : A. O. Williams** | |

CC: NDA 20-818
HFD-110
HFD-110 / CCooley / AWilliams / SChun
HFD-110 / KBonjiovanni

## 1.0. Materials Utilized in Review

### 1.1 Materials from NDA: NDA 20-818

NDA submissions reviewed included conventional study reports for a total of 11 clinical studies including 1 placebo-controlled, 3 active controlled, and 7 uncontrolled trials. The CANDA submitted consisted of one CD-ROM, and several volumes of supporting documents. The CD-ROM contained all the clinical studies, biopharmaceutical studies, narratives for deaths, and listings of premature withdrawals for adverse events in protocols 19 and 301. The data for analyses of the uncontrolled studies in protocols 11, 20, 24, 28, and 31E were not submitted separately, but were merged with those of the controlled studies in the electronic submission. The clinical development programs for valsartan, and valsartan plus HCTZ were undertaken under NDA No. 20-665,

Some of these submissions were utilized in the current review and references were made in particular to valsartan monotherapy (NDA No. 20-665), and Hydrochlorothiazide [(NDA 11-793 (Esidrix)], both of which are in DIOVAN HCT, the trial drug.

### 1.2 Related Reviews, Consults, etc. for the NDA

NDAs for several AII receptor antagonist monotherapy, combination with HCTZ, and other combination products have been previously reviewed by the Cardio-Renal Division. None of these have been utilized in this review except the approved NDA 20-665 for valsartan monotherapy.

### 1.3 Other resources

A literature search was conducted in the NLM database to look for publications involving clinical trials of valsartan combined with HCTZ, and for related subjects (Section 5.2.3 and Appendix 1).

## 2.0 Background

This section provides an integrated outline for both safety and efficacy assessment, and also gives a brief overview of the two components of DIOVAN-HCT, the combination-trial drug, Valsartan and Hydrochlorothiazide.

### Outline for safety and efficacy assessment

The majority of the trials in the NDA under review (20-818) is in support of the valsartan monotherapy program in Phase III. There is, therefore, no true Phase II study for DIOVAN-HCT. Protocol 301 is the pivotal, multifactorial study for efficacy of DIOVAN-HCT, and this is considered adequate both for review, and also for application of NDA approval. During the Phase III study, 3 additional biopharmaceutical trials were conducted to verify bioavailability and bioequivalence of the final market image (FMI) of the fixed dose combination with the individual components of the drug administered in the clinical trials (Protocols 302 and 303). Out of the 8 phase III clinical trials reported in this NDA, one trial assessed the safety and tolerability of valsartan in hypertensive patients with volume depletion, using triamterene to induce volume depletion (Protocol 24). In this trial, where a special subpopulation was exposed to the drug, valsartan was administered as a single dose. and as a result, efficacy of the combination drug could not be assesed. Two trials were carried out comparing valsartan monotherapy to inactive control in a double blind fashion, and HCTZ was added in an open fashion for additional blood pressure control (Protocols 20 and 28). Data from these 2 trials were utilized and contributed to analysis of safety but not to efficacy. The only placebo-controlled, randomized, double-blind, pivotal trial was Protocol 301, whereas the active controlled trial was Protocol 19. There were 3 extension studies (Protocols 11E, 28E, and 31E) of controlled valsartan monotherapy trials in which HCTZ was added in an open label fashion which provided supportive evidence for evaluating long

term efficacy. All the eight trials contributed towards assessment of safety and tolerability, and their summaries form the basis of this safety review.

**Valsartan**

Valsartan is an orally active, specific competitive angiotensin II antagonist at the level of the $AT_1$ receptor subtype. The combination of ACE inhibitors with diuretics (usually HCTZ) is used frequently in clinical practice for the control of hypertension since this combination usually produces additive effects in lowering diastolic blood pressure. The present drug under review, a combination of valsartan and HCTZ, falls under this category. Because valsartan acts on the renin-angiotensin system, the combination of HCTZ with valsartan may therefore be expected to have additional effects in lowering blood pressure. The renin-angiotensin system (RAS) plays a fundamental role in the maintenance and regulation of extracellular fluid volume and blood pressure. This effect on the regulation of extracellular cluid volume coupled with similar diuretic effect of HCTZ makes this combination a potent regulator of ECF. Therefore, volume depleted patients on this therapy will need to be careful while taking this antihypertensive drug. Renin is secreted by the kidney in response to a decrease in circulating volume and blood pressure, and cleaves the substrate angiotensinogen to form the inactive decapeptide angiotensin I.

By the action of angiotensin converting enzyme (ACE), angiotensin I is converted to the active octapeptide angiotensin II which interacts with cellular receptors inducing vascular constriction, the release of catecholamines from the adrenal medulla and prejunctional nerve endings. It also promotes aldosterone secretion and sodium reabsorption. In addition, angiotensin II inhibits renin release, thus providing a negative feedback to the system. The RAS can be inhibited both by blocking the effects of ACE and renin, or by preventing the interaction of angiotensin II with cellular receptors. Two main subtypes of angiotensin II receptor have been described, $AT_1$ and $AT_2$. The $AT_1$ receptor appears to mediate all of the above mentioned actions of angiotensin II. Since ACE inhibitors have been shown to be effective and safe in the treatment of hypertension and congestive heart failure, angiotensin II receptor antagonists should have the potential in the same clinical indications, as well as an adequate safety profile. Moreover, angiotensin II receptor antagonists do not interfere with kinase II (ACE) responsible for the degradation of bradykinin. Bradykinin has been implicated in the pathogenesis of cough and angioneurotic edema, and until recently, both events have been considered to be class-specific side-effects of ACE inhibitor therapy. However, angioedema has been reported as adverse events with AII antagonists including losartan and valsartan. Blockade of angiotensin II receptors represents a specific means of blocking the RAS, and this approach produces effective antihypertensive agents with reduced frequency of some of the side effects of ACE inhibitors.

**Hydrochlorothiazide**

Hydrochlorothiazide (HCTZ), a thiazide diuretic with a well known safety and efficacy profile, is commonly used as monotherapy or in combination with other agents in the treatment of hypertension. HCTZ inhibits $Na^+$ reabsorption from the renal distal convoluted tubule, thereby potentiating water excretion, resulting in a reduction of intravascular fluid volume. HCTZ serum levels peak at 4 hours post-dose with a duration of action of 6-12 hours. In effect, HCTZ causes the urinary excretion of Na+ and water, leading to a compensatory induction of the renal-angiotensin-system (RAS) that modulates blood pressure. Therefore the addition of any drug which blocks the RAS (ACE inhibitors, AII antagonists, renin antagonists) would cause a potentiation of the antihypertensive effects of HCTZ. The usual dosage range of HCTZ as recommended by the National Institutes of Health is 12.5 mg to 25 mg/day *[( J Hyperten 1 (Suppl2 384-386 1983); (See Section 2.4.5)].(Appendix 1).*

## 2.1 Indication

Patients with essential hypertension who did not adequately respond to treatment with low-dose valsartan monotherapy and required an addition of HCTZ for control of hypertension. The groups of subjects enrolled for the controlled trials were representative of the patient populations who would most likely benefit from an increase in the dose of valsartan or the addition of a diuretic to a lower dose of valsartan. The dose regimens of valsartan were chosen because previous trials had shown 80 mg and 160 mg dose levels to be safe and effective in the treatment of essential hypertension (NDA 20-665). Hydrochlorothiazide is effective in doses of 12.5 to 100 mg once daily. The dose regimens of hydrochlorothiazide were chosen because they were the commonly used doses for the treatment of hypertension. To minimize dose-independent side effects, combination therapy is only indicated after a patient has failed to achieve the desired antihypertensive effect with valsartan monotherapy.

## 2.2 Important information from related NDAs and pharmacologically related agents

See Valsartan Review (NDA 20-665), and Physician's Desk Reference for a complete discussion of HCTZ efficacy and safety.

## 2.3 Administrative History

Any amendment to trials that seemed appropriate as the trial progressed was agreed upon between the principal investigator and the Ciba MTS/CTS. The amendments were submittedto the ERB/IRB for written approval and then made a formal part of the protocol, before implementation. The expedited review procedure for an amendment was only appropriate if minor changes were made in the protocol. The written signed approval from the ERB/IRB referred specifically to the investigator and to the protocol number and title. None of the amendments impacted the results of the studies. (Appendix 2).

## 2.4 Proposed labeling

The controlled trials and the open label extensions evaluated both efficacy and safety of adding HCTZ in doses of 12.5mg and 25 mg to valsartan 80 mg in identified hypertensive patients not adequately responding to valsartan 80 mg monotherapy. This combination therapy was also compared to increasing the dose of valsartan to 160 mg once daily. The objectives of the label are to show efficacy and safety of the combination of HCTZ 12.5 or 25 mg plus valsartan 80 mg once daily compared to valsartan 80 mg and 160 mg once daily; and also to show efficacy and safety of valsartan 160 mg once daily compared to 80 mg once daily in essential hypertensive patients not adequately responding to valsartan 80 mg. The recommended starting dose of valsartan is 80 mg once daily when used as monotherapy in patients who are not volume depleted. Valsartan may however be used over a dose range of 80 mg to 320 mg daily, administered once-a-day, but the adverse event rate relating to dizziness was significantly increased in patients treated with 320mg compared to those treated with a dose range of 10mg to 160mg (NDA 20-665). Hydrochlorothiazide is effective in the control of hypertension in doses of 12.5mg to 100 mg once daily. To minimize dose-independent side effects, combination therapy is only indicated after a patient has failed to achieve the desired antihypertensive effect with monotherapy.

### 2.4.1 Dose-response relationships-Valsartan and HCTZ and clinical outcomes

The dose regimens of valsartan were chosen based on previous data derived from Phase II trials which showed 80 mg and 160 mg were safe and effective in the treatment of essential hypertension (NDA 20-665). Based on those data 80 mg of drug was adopted as the recommended starting dose. The dose regimens of hydrochlorothiazide were chosen because they were the commonly used doses for the treatment of hypertension. A dose-related trend was observed for dizziness in the valsartan/HCTZ dose groups. The incidence of dizziness (also reported by the sponsors as lightheadedness) gradually increased as the dose of one or

both of the components increased (Section 8.2). In contrast, no dose related trends were observed for any of the other adverse experience (Section 8.2). The side effects in the sponsor's proposed label (see WARNINGS) of valsartan alone were apparently independent of dose.
The side effects of hydrochlorothiazide are a mixture of dose-dependent phenomena (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former being much more common than the latter. Therapy with any combination of valsartan and hydrochlorothiazide may be associated with both sets of dose-independent side effects, but regimens in which valsartan was combined with low doses of hydrochlorothiazide produced reduced effects on serum potassium. In controlled clinical trials of Diovan HCT, the average change in serum potassium was minimal in subjects who received Diovan HCT 80/12.5 mg or 160/12.5 mg, whereas the subjects who received Diovan HCT 80/25 mg or 160/25 mg experienced greater reduction in the levels of their serum potassium, similar to that experienced by subjects receiving the same dose of hydrochlorothiazide monotherapy. The possible relationships between hypokalemia alone and or dehydration to muscle weakness, muscle fatigue, and muscle pain, reported as adverse events were not analysed in depth, but was observed in one patient prematurely discontinued from the trial.

### 2.4.2 Pregnancy
Female patients of childbearing age should be apprised of consequences of second- and third-trimester drug exposure, particularly drugs that act on the renin-angiotensin system. They should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that had been limited to the first trimester. The patients should be advised to report pregnancies to their physicians as soon as possible.

### 2.4.3 Fetal/Neonatal Morbidity and Mortality
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. When pregnancy is detected, Diovan HCT should be discontinued as soon as possible.

### 2.4.4 Hypotension
A patient receiving Diovan HCT should be cautioned that lightheadedness or dizziness can occur, especially during the early days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Diovan HCT should be discontinued until the physician has been consulted.

### 2.4.5 Special populations
There were one study on special populations with the combined therapy. This was on volume depleted subjects (Protocol 24). The information on Valsartan monotherapy, with particular reference to patients with hepatic and renal impairment, and renal artery stenosis, can be assumed to apply to those on combined therapy since there are no reasons to suspect that the low dose of HCTZ will make a difference. This assumption can be partly justified by the pk data which shows that Valsartan reduces the systemic bioavailability of HCTZ by about 31% (Section 6). However, there are no studies on patients with severe impairment of renal function (creatinine clearance < 10mL/min) or patients undergoing dialysis, and it is not known whether valsartan is removed by hemodialysis. In the case of severe renal disease, dosing of the Diovan HCT should be carried out with care, particularly as thiazide diuretics are elimionated by the kidneys (see *Impaired renal function* and DOSAGE AND ADMINISTRATION).

*Volume depleted subjects :* All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope (Section 8.2).

*Impaired Hepatic Function:* As the majority of valsartan is eliminated in the bile, patients with mild to moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering valsartan to these patients.

*Impaired Renal Function:* As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), 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. Valsartan would be expected to behave similarly.

*Renal Artery Stenosis:* In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

### 2.4.6 Drug interaction

The only pharmacokinetic trial (Protocol 07), that examined the interaction of valsartan and HCTZ did not show any significant decrease in the bioavailability of valsartan. However, valsartan significantly decreased the bioavailability of HCTZ (AUC decreased by 31%). The pharmacodynamic effect of this interaction on blood pressure has not been determined. This effect may be relevant to the significant advantage enjoyed by subjects on combined therapy compared to monotherapy with particular reference to serum potassium levels (Section 8.1.6). This pharmacokinetic interaction did not seem to affect the clinical use of HCTZ in combination with valsartan as shown by analyses of safety data (Appendix 5, page 93).

## 2.5 Foreign Marketing History

There is no history of foreign marketing since the combination of valsartan and hydrochlorothiazide is neither approved nor currently marketed anywhere.

## 2.6 Miscellaneous Background

From the safety perspective, and considering the two controlled studies (Protocols 19 and 301), at least three pharmacologically significant features may be relevant to the combination therapy. These include possible relationships of drug to angioedema, and drug effects on alertness and respiration.

### 2.6.1 Angioedema

Although no patient was specifically reported by the sponsor as experiencing angioedema there were reports of edema affecting the face (4), and eye (1), in addition to peripheral or dependent edema in a few subjects. Some of these may be consistent with angioedema. However, these were not specifically categorized as angioedema by the investigators. Two (0.2%) patients in the valsartan/HCTZ, 3 (0.2%) patients in the valsartan, 1 (0.9%) patient in the ACEI/HCTZ, 1 (0.3%) patient in the Other, and 1 (1.1%) patient in the placebo treatment group experienced facial edema. Only one patient in the placebo treatment group was reported to have facial edema and considered to be trial drug-related by the sponsor. One patient in the valsartan treatment group (0.1%) with eye edema was considered not to be trial drug related by the sponsor but no other etiology was ascribed to this finding. During the placebo-controlled studies, and also during the open label periods 49 adverse events were classified as edema in the combined trial datasets. Edema affected different parts

of the body in subjects that received the combination therapy (Section 8.2 ) and some subjects were discontinued prematurely from the trial, albeit not on the basis of angioedema (Appendix Tables 3-5). Post marketing experience with Valsartan and Losartan has shown that angioedema is an adverse event in patients taking AII antagonists, similar to reports with ACE inhibitors.

### 2.6.2 Respiratory effects

Since angiotensin II receptor antagonists do not appear to interfere with the bradykinin mechanism, the risk of bradykinin mediated adverse effects, particularly cough may be significantly reduced compared to ACE inhibitors. In the controlled trials, coughing of all types occurred in 2.9% of patients receiving valsartan/HCTZ, 2.9% of patients receiving valsartan, 2.5% of patients receiving HCTZ, and 0.0% of patients receiving placebo. There was no statistically significant difference among the treatment groups in the incidence of coughing. The criteria laid down for drug-related "cough" and for "coughing" due to all other etiologies may be difficult to distinguish in the absence of microbiological evidence of respiratory infection. However, the data analysed in this review and the conclusions derived are based on the assumption that these two categories of cough were clinically distinguishable from one another. Therapy with valsartan/HCTZ would appear to pose little risk of causing symptoms of respiratory tract irritation above that caused by the individual agents alone. In the controlled trials, other respiratory symptoms such as bronchitis, rhinitis, sinusitis, pharyngitis, laryngitis, and symptoms of upper respiratory tract infection occurred at similar rates among the treatment groups (Section 8.2.5).

### 2.6.3 Effect on alertness

No specific studies have been performed to evaluate the effects of valsartan/HCTZ on alertness including driving performance or the ability to operate machinery. Although there are no data on the drug effect on alertness, episodes of dizziness may affect alertness, albeit temporarily. It would therefore be appropriate to caution patients about the possibility of dizziness during the first few weeks of exposure to DIOVAN-HCT since symptoms referable to the central nervous system usually occurred during the first few weeks of DIOVAN-HCT treatment when blood pressure fell from elevated levels. Dizziness was one of the most frequent adverse events in this study occurring in about 18% of all adverse events in the controlled and uncontrolled trials.

## 3.0 Chemistry, Manufacturing, and Controls

See Chemistry Review.

## 4.0 Animal Pharmacology

See Pharmacology review by Dr E. Barry. The review of this section is based on the sponsor's animal pharmacology review. The three major findings that the reviewer considers may be relevant to clinical safety are hematological parameters, renal function, and mutagenicity/ teratogenicity. There is considerasble data and information on safety with Valsartan monotherapy, and also on HCTZ monotherapy.

### 4.1 Hematological effects in animal studies

Treatment-related findings in animal toxicity studies were mainly related to exaggerated pharmacological effects of valsartan and/or HCTZ. The abnormalities consisted of reduction in red cell parameters, alterations in ionic and water concentrations in the body, hypertrophy of the juxtaglomerular apparatus, and renal tubular changes. Red cell parameters were reduced because of the effect of valsartan on the production of erythropoietin in the kidney via the renin-angiotensin-system and lacis cells of the juxtaglomerular apparatus.

### 4.2 Renal effects in animal studies

CGP 63172 is a 16:5 wt:wt combination of CGP 48933 (valsartan, marketed angiotensin II antagonist) and hydrochlorothiazide (HCTZ, a diuretic), which is being developed as an antihypertensive agent. Increased urine volume, decreased urinary specific gravity, increased water consumption, and alterations in blood and urine electrolytes were related to the pharmacological effects of valsartan (increased sodium excretion due to decreased aldosterone secretion) and HCTZ (decreased renal reabsorption of sodium). Hypertrophy of the juxtaglomerular cells and smooth muscle cells of the afferent glomerular arterioles reflects an increase in renin production, which is a typical response to angiotensin II antagonists. This occurs via a reduced availability of angiotensin II for feedback mechanism following blockage of the $AT_1$-receptor by the angiotensin II antagonist. Renal tubular and associated changes, including increased blood urea and creatinine, were attributed to decreased renal perfusion, renal ischemia and hypoxia following the chronic hypotensive effect of valsartan. In addition, the nephropathic effects of HCTZ may have contributed to these renal changes. The marmoset was a much more sensitive species in which there was an approximate 10-fold potentiation of blood pressure reduction with the combination (CGP 63172) compared to valsartan alone. HCTZ alone had no effect on blood pressure of marmosets. On the other hand, the effects of CGP 63172 in hypertensive humans were additive.

### 4.3 Teratogenic and mutagenic effects in animal studies

CGP 63172 was evaluated for toxicity in the rat and marmoset for up to 6 months and for teratogeniciy (Segment II studies) in the mouse, rat, and rabbit. In the Segment II studies with CGP 63172 in the mouse, rat, and rabbit, there was no evidence of teratogenicity; however, fetotoxicity associated with maternal toxicity was observed in the rat and rabbit. In the Segment I study with valsartan alone, there was no effect on fertility or reproductive performance in the rat. In the perinatal and postnatal reproductive study with valsartan alone (Segment III study in the rat), there was a slight reduction in pup survival and development in the presence of maternal toxicity.

Considering that the use of CGP 63172 will not be extended beyond the first trimester of pregnancy, the reproductive toxicity profile of CGP 63172 supports its use in humans. (See warning label in Section 9). "In mouse and rat studies, there was no clear evidence of carcinogenicity with valsartan or HCTZ". There was no evidence of mutagenicity with valsartan. For HCTZ, there was no evidence of mutagenicity based on Ciba-Geigy studies and an unlikely in vivo mutagenicity based on National Toxicology Program (NTP) studies. Therefore, carcinogenicity and mutagenicity studies with CGP 63172 were not considered necessary.

Based on these studies, CGP 63172 was considered safe for use in humans. However, as a preventive measure, one of the exclusion criteria stipulated that female patients should either be post-menopausal for one year, surgically sterilized, or should be using two effective forms of contraception (i.e., barrier method with spermicide or IUD), and had to have a negative serum pregnancy test at the beginning and throughout the duration of the trial (See Pharmacology reviews in NDAs 20-818 and 20-665).

### 4.4 Pharmacokinetics

Based on preclinical safety and human pharmacokinetic studies, there is no indication of any adverse drug interaction between valsartan and HCTZ. The NDA 20-665 for valsartan contains the results of extensive human pharmacology trials with this compound, as do NDA 11-793 and NDA 20-033 for hydrochlorothiazide formulation and capsule respectively. Thus, the clinical pharmacology trials using the combination focused on issues of drug interactions between the two components, bioavailability, bioequivalence, and dose response (Section 6 and Biopharm review).

## 5.0 Description of Clinical Data Sources

### 5.1.1 Study type, design, and subject enumeration

Table 1 summarizes all the studies included in the safety database.

**Table 1: Summary of all clinical trials**

| Protocol | NTs | Design | Valsartan (HCTZ) | All treatments | Comments |
|---|---|---|---|---|---|
| | | | | | All treatments given to all enrolled subjects in placebo-controlled, active-controlled and uncontrolled studies, includes open-label and controlled phases of studies. Total = 3065 subjects |
| **Placebo-Controlled** | | | | | |
| 301<br>NDA20-818<br>vol 1.29 | 1 | R,DB,PC<br>P,MD,MF | 378 | 867 | |
| **Active controlled** | | | | | |
| 19<br>NDA20-665;<br>NDA 20-818<br>vol 1.159 | 1 | R,DB,AC,P<br>,SD | 352 | 703 | |
| Controlled Subtotal | 2 | | 730 | 1570 | |
| NDA<br>20-818<br>11E<br>20<br>24<br>28<br>31E | 5 | DB,R,PC<br>FD,P,<br>*OL | 573 | 1495 | • Uncontrolled trials<br>• Protocol 11 Extension consisted of an open-label 98 week phase in which patients took valsartan monotherapy and could have HCTZ added on for blood pressure control if needed. An amendment to the protocol allowed patients who had been receiving valsartan/HCTZ for at least one year at the time of the amendment to continue for another year on the combination. These phases are summarized under 'Protocol 11 Extension' which incorporates 3 years of data.<br>• Protocol 28 consisted of a double-blind core portion which was 52 weeks in duration. Patients could have open-label HCTZ added on for blood pressure control if needed. An amendment to the protocol allowed patients who had been receiving valsartan/HCTZ for at least one year at the time of the amendment to continue for another year on the combination. These phases are summarized under 'Protocol 28' and incorporates 2 years of data.<br>• Three trials, Protocols 20, 24, and 28 were controlled for valsartan monotherapy but were not controlled for valsartan/HCTZ. Protocols 20 and 28 allowed HCTZ to be added in an open-label fashion onto the double-blind regimen as needed for blood pressure control.<br>• Protocol 24 was a single-dose three-way crossover trial on a background of label hydrochlorothiazide/a miloride (Moduretic®).<br>• Protocol 31E consisted of an open label 98 week phase of controlled valsartan monotherapy trials in which HCTZ was added in an open label fashi |
| | 7 | | 1,303 | 3,065 | Combined subtotal for clinical trials |
| 7, 302, 303 | 3 | | 86 | 86 | **Biopharmaceutic Trials** |
| | 10 | | **1,389** | **3,151** | **Total** |

[a] R = randomized, DB = double-blind, PC = placebo-controlled, P = parallel, MD = multiple dose, MF = multifactorial, AC = active-control, SD = single dose, FD = fixed dose, *OL = open label following-double blind.; NT=Number of trials.F=Factorial.

Figures 1 and 2 illustrate the study design in Protocols 301 and 19, respectively .

**Figure 1: Schematic study design diagram - Protocol 301**

| Period | Washout | Placebo Run-in/ Washout | Double-blind treatment<br>Randomization<br>⇓ |
|---|---|---|---|
| Visit | 0 | 1 | 2 3 4 5 |
| Week | -6 | -4 | 0 2 4 8 |
| Duration | | 2-4 weeks | 8 weeks |
| Treatment | | placebo | valsartan 80 mg po od/placebo |
| | | | valsartan 160 mg po od/placebo |
| | | | HCTZ 12.5 mg po od/placebo |
| | | | HCTZ 25 mg po od/placebo |
| | | | valsartan 80 mg/HCTZ 12.5 mg po od |
| | | | valsartan 80 mg/HCTZ 25 mg po od |
| | | | valsartan 160 mg/HCTZ 12.5 mg po od |
| | | | valsartan 160 mg/HCTZ 25 mg po od |
| | | | Placebo |

**Figure 2: Schematic study design diagram-Protocol 19**

| Period | Washout | Single-blind placebo run-in | Single-blind valsartan run-in | Double-blind treatment | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| | | Randomization | | | | | |
| | | | | ⇓ | | | |
| | | | | Valsartan 80 mg | | | |
| | | | | Valsartan 160 mg | | | |
| | | Placebo | valsartan | Valsartan 80 mg/12.5 mg HCTZ | | | |
| | | 2 Weeks | 4 Weeks | Valsartan 80 mg/25 mg HCTZ | | | |
| Visit | | 1 | 2 | 3 | 4 | 5 | 6 |
| Week | | -6 | -4 | 0 | 2 | 4 | 8 |

Protocol 301 was a multicenter, placebo-controlled, double-blind, randomized, multifactorial trial. The purpose of this pivotal trial was to confirm the efficacy of valsartan/HCTZ in a population of patients with essential hypertension and to demonstrate the contribution of the components to the efficacy of the combination. Eligible patients were randomized to once daily treatment with either placebo, valsartan 80mg or 160mg, HCTZ 12.5mg or 25mg, or valsartan/HCTZ 80/12.5mg 160/12.5mg or 160/25mg for 8 weeks. The combination drug was administered as a free combination of the individual components (Figure 1).

Protocol 19 was a multicenter, active controlled, double-blind, randomized, parallel group trial in which hypertensive patients [mean sitting diastolic blood pressure (MSDBP) $\geq$ 95 and $\leq$ 120 mmHg] who had been completely withdrawn from their previous antihypertensive medication for at least 2 weeks, received single-blind valsartan 80 mg once daily for 4 weeks following a 2 week single-blind placebo run-in period. After 4 weeks of treatment with valsartan 80 mg, those patients whose MSDBP was not adequately controlled (MSDBP $\geq$ 95 and $\leq$ 115 mmHg) were randomized to one of 4 double-blind treatment groups: 1) Valsartan 80 mg once daily, 2) Valsartan 160 mg once daily, 3) Valsartan 80 mg/HCTZ 12.5 mg once daily, 4) Valsartan 80 mg/HCTZ 25 mg once daily (Figure 2).

Three additional trials, Protocols 20, 24, and 28, were controlled for valsartan monotherapy but were not controlled for valsartan/HCTZ. Protocols 20 and 28 allowed HCTZ to be added in an open-label fashion onto the double-blind regimen as needed for blood pressure control. Protocol 24 was a single-dose three-way crossover trial on a background of open-label hydrochlorothiazide/amiloride.

In protocol 19, four weeks of treatment was considered sufficient to demonstrate whether or not monotherapy would be effective. During the 8 week double-blind treatment period, patients received either valsartan 80 mg, valsartan 160 mg, valsartan 80 mg/ hydrochlorothiazide 12.5 mg, or valsartan 80 mg/hydrochlorothiazide 25 mg. This period was considered sufficiently long enough to demonstrate an anti-hypertensive effect. For protocol 301 The diagnosis of mild to moderate hypertension was confirmed during the 2 - 4 week antihypertensive medication washout/single-blind placebo run-in period, whereas the 4 week single-blind valsartan treatment period was used to identify patients who were not adequately controlled by low-dose valsartan therapy (80 mg od).

- Protocol 11 Extension consisted of an open-label, 98 week phase in which patients took valsartan monotherapy and could have HCTZ added on for blood pressure control if needed. An amendment to the protocol allowed patients who had been receiving valsartan/HCTZ for at least one year at the time of the amendment to continue for another year on the combination. These phases are summarized under 'Protocol 11 Extension' which incorporates 3 years of data.
- Protocol 28 consisted of a double-blind core portion which was 52 weeks in duration. Patients could have open-label HCTZ added on for blood pressure control if needed. An amendment to the protocol allowed patients who had been receiving valsartan/HCTZ for at least one year at the time of the amendment to continue for another year on the combination. These phases are summarized under 'Protocol 28' and incorporates 2 years of data.
- Three trials, Protocols 20, 24, and 28 were controlled for valsartan monotherapy but were not controlled for valsartan/HCTZ. Protocols 20 and 28 allowed HCTZ to be added in an open-label fashion onto the double-blind regimen as needed for blood pressure control. Protocol 24 was a single-dose three-way crossover trial on a background of label hydrochlorothiazide/amiloride (Moduretic®).
- Protocol 31 Extension consisted of an open label 98 week phase of controlled valsartan monotherapy trials in which HCTZ was added in an open label fashion

The distribution of subjects by treatment groups is presented below in Tables 2-3, and the investigational plan for protocol 301 is presented in Table 4.

**Table 2: Randomized patients by treatment group - Protocol 301**

| Number of patients | Placebo | V80 | V160 | H12.5 | H25 | V80/H12.5 | V160/H12.5 | V80/H25 | V160/H25 | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Enrolled | - | - | - | - | - | - | - | - | - | 997 |
| Randomized | 94 | 99 | 99 | 100 | 100 | 96 | 97 | 92 | 94 | 871 |
| Completed | 83 | 90 | 89 | 81 | 90 | 95 | 91 | 86 | 87 | 792 |
| **Discontinued prematurely during double-blind period** | | | | | | | | | | |
| Total | 11 | 9 | 10 | 19 | 10 | 1 | 6 | 6 | 7 | 79 |
| For adverse experience | 4 | 3 | 6 | 8 | 3 | 1 | 3 | 6 | 7 | 41 |
| Abnormal lab value | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| For unsatisfactory therapeutic response | 2 | 3 | 1 | 2 | 1 | 0 | 0 | 0 | 0 | 9 |
| Other | 5 | 3 | 3 | 9 | 6 | 0 | 3 | 0 | 0 | 29 |
| Safety analyses | | | | | | | | | | |
| Adverse experiences | 93 | 99 | 97 | 100 | 100 | 96 | 96 | 92 | 94 | 867*** |
| Laboratory tests | 91 | 98 | 96 | 98 | 99 | 96 | 94 | 90 | 92 | 854 |

Note: P=Placebo, V80=Valsartan 80, V160=Valsartan 160, H12.5=HCTZ 12.5, and H25=HCTZ 25.*Six randomized, prematurely discontinued patients had no post-randomization measurements. **Seventeen prematurely discontinued patients who stopped taking trial drug between Visit 4 and the scheduled Visit 5, per the protocol, had blood pressure measurements at Visit 5 and were therefore included in the Visit 5 analysis. ***Four patients were lost to follow-up after the randomization visit and were excluded for adverse experience evaluation.

**Table 3: Randomized patients by treatment group - Protocol 19**

| Number of Patients | Valsartan 80 mg | Valsartan 160 mg | Valsartan 80/HCTZ 12.5mg | Valsartan 80/HCTZ 25mg | Total |
|---|---|---|---|---|---|
| Enrolled (Visit 1) | - | - | - | - | 1038 |
| Valsartan run-in (Visit 2) | - | - | - | - | 908 |
| Randomized (Visit 3) | 183 | 172 | 176 | 177 | 708 |
| Completed (Visit 6) | 157 | 153 | 158 | 163 | 631 |
| Discontinued prematurely during double-blind period | 26 | 19 | 18 | 14 | 77 |
| For adverse experience | 6 | 7 | 5 | 4 | 22 |
| For abnormal laboratory value | 2 | 0 | 0 | 0 | 2 |
| For unsatisfactory therapeutic response | 6 | 4 | 6 | 3 | 19 |
| Other | 12 | 8 | 7 | 7 | 34 |
| **Safety analyses** | | | | | |
| Adverse experience evaluation[a] | 179 | 172 | 176 | 176 | 703 |
| Laboratory tests[c] | 174 | 168 | 174 | 175 | 691 |

**Table 4: Schedule of investigations - Protocol 301**

| Period | Washout | Single-Blind Placebo Run-in/ Washout | Double-Blind Treatment Randomization | | | |
|---|---|---|---|---|---|---|
| Visit | 0 | 1 | 2 | 3 | 4 | 5 |
| Week | -6 | -4 | 0 | 2 | 4 | 8 |
| Informed Consent | X | | | | | |
| Discontinue Anti-hypertensive Medications | X | | | | | |
| Complete History | | X | | | | |
| Complete Physical Exam | | X | | | | |
| Interim/Final Physical Exam | | | X | X | X | X |
| 12-Lead EKG | | X | | | | |
| Chest X-ray | | X | | | | |
| CBC, Chemistry, Urinalysis | | X | X | | | X |
| Serum Electrolytes only | | | | X | X | |
| Serum Pregnancy Tests | | X | X | | X | X |
| Adverse Experience | | | X | X | X | X |
| Concomitant Medications | | X | X | X | X | X |
| Collect Unused Medications | | | X | X | X | X |
| Dispense Single-Blind Placebo | | X | | | | |
| Dispense Double-Blind Trial Medications | | | X | X | X | |
| Termination Sheet | | | | | | X |

### 5.1.1 Enumeration of subjects/patients - Protocols 19 and 301

The method for enumeration was considered adequate for all the trials. Tables 2 and 3 show how all the subjects randomized in Protocols 19 (708) and 301 (871), were accounted for. A total of 41 patients were discontinued for adverse events in Protocol 301, and 24 patients (22 and 2) were discontinued for clinical and laboratory adverse events, respectively, in Protocol 19. The listings of patients prematurely discontinued in all clinical trials are presented in Appendix Tables 3 - 15. Other reasons for discontinuations are discussed in section 8.1.5.

### Protocol violations - Protocol 301

All centers were monitored during the course of the trial for compliance with the protocol. Eight patients were discontinued for protocol violations. Four patients had clinically significant laboratory abnormalities, one patient became pregnant during the course of the trial, one patient stopped taking trial medication and started taking an unacceptable medication without the investigator's knowledge, one patient was randomized in error having not met the randomization blood pressure criteria, and one patient was noncompliant with trial medication. The most common protocol violation was patients taking prohibited medications.

### 5.1.2 Demographics

Demographic data for placebo-controlled and extension studies are presented in Tables 5-10. The distribution of subjects by age, sex, weight, and height for protocols 19 and 301 is presented in Tables 5-9, and for protocols 11, 20, 24, 28 and 31 Extension in Table 10.

5.1.2.1

Subjects enrolled in controlled trials were male and female outpatients, aged 21 to 80 years inclusive, and diagnosed with essential hypertension. The majority of the patients were white (83.9%) and the other ethnic groups including blacks constituted 16.1%. The percentage of men and women who participated in the trials were 59.2% and 40.8%, respectively. The mean age of the population was 56.5 years (± 12.3 range 20-91 years), 31.0% of the population was ≥ 65 years, and 6.1% of the population was ≥ 75 years. The mean weight was 86.2 kg (±19.2, range 41-199 kg). Mean duration of hypertension (HTN) was 8.5 years (±8.3).

**Table 5: Demographics - Protocols 19 and 301**

| | Treatment Group | | | |
|---|---|---|---|---|
| Patient | Valsartan/ HCTZ N (%) | Valsartan N (%) | HCTZ N (%) | Placebo N (%) |
| Total | 730 (100) | 547 (100) | 200 (100) | 93 (100) |
| **Sex** | | | | |
| Male | 454 (62.2) | 345 (63.1) | 113 (56.5) | 58 (62.4) |
| Female | 276 (37.8) | 202 (36.9) | 87 (43.5) | 35 (37.6) |
| **Race** | | | | |
| White | 533 (73.0) | 401 (73.3) | 143 (71.5) | 70 (75.3) |
| Black | 100 (13.7) | 78 (14.3) | 33 (16.5) | 13 (14.0) |
| Other | 97 (13.3) | 68 (12.4) | 24 (12.0) | 10 (10.8) |
| **Age (years)** | | | | |
| Mean | 52.9 | 52.6 | 52.1 | 51.8 |
| STD | 11.0 | 10.5 | 11.2 | 10.3 |
| Range | 26-86 | 23-77 | 24-80 | 22-74 |
| **Weight (kg)[1]** | | | | |
| Mean | 91.0 | 90.9 | 89.1 | 89.4 |
| STD | 18.5 | 19.2 | 19.2 | 18.6 |
| Range | 48-165 | 46-166 | 47-160 | 51-130 |
| **Duration of Htn.[2]** | | | | |
| Mean | 9.1 | 8.9 | 8.0 | 8.0 |
| STD | 8.7 | 8.4 | 7.1 | 8.0 |
| Range | 0-53 | 0-45 | 0-35 | 0-45 |

[1] - Weight not available for 1 patient in the valsartan/HCTZ treatment group and 1 patient in the valsartan treatment group and 1 patient in the HCTZ t reatment group. [2] - Duration of hypertension(yr) not available for 3 patients in the valsartan treatment group.

**Table 6: Distribution by sex, race and by treatment groups - 19**

| Protocol 19 Double-blind treatment group | Number of patients | Sex | | Race | | |
|---|---|---|---|---|---|---|
| | | Male | Female | White | Black | Other |
| Valsartan 80 mg | 183 | 116 (63%) | 67 (37%) | 131 72%) | 28 (15%) | 24 (13%) |
| Valsartan 160 mg | 172 | 109 (63%) | 63 (37%) | 124(72%) | 23 (13%) | 25 (15%) |
| Valsartan 80 mg/ HCTZ 12.5 mg | 176 | 117 (66%) | 59 (34%) | 121(69%) | 29 (16%) | 26 (15%) |
| Valsartan 80 mg/ HCTZ 25 mg | 177 | 124 (70%) | 53 (30%) | 125(71%) | 26 (15%) | 26 (15%) |
| Total | 708 | 466 (66%) | 242 (34%) | 501(71%) | 106 (15%) | 101 (14%) |

**Table 7: Distribution by age, weight, height and by treatment groups - 19**

| Protocol 19 Double-blind treatment group | Age (years) | | Weight (pounds) | | Height (inches) | |
|---|---|---|---|---|---|---|
| | N | Mean (±S.D.) | N | Mean (±S.D.) | N | Mean (±S.D.) |
| Valsartan 80 mg | 183 | 52.86 (±10.42) | 182 | 198.66 (±42.24) | 183 | 67.21 (±3.96) |
| Valsartan 160 mg | 172 | 52.53 (±10.87) | 172 | 199.47 (±41.06) | 172 | 67.59 (±3.80) |
| Valsartan 80 mg/ HCTZ 12.5 mg | 176 | 53.02 (±10.70) | 176 | 200.88 (±39.56) | 175 | 67.75 (±4.09) |
| Valsartan 80 mg/ HCTZ 25 mg | 177 | 54.27 (±10.45) | 176 | 201.55 (±39.65) | 177 | 68.11 (±4.11) |
| Total | 708 | 53.17 (±10.60) | 706 | 200.13 (±40.58) | 707 | 67.66 (±4.00) |

N:Number of randomized patients with available values for this variable.
*:Patients 222/5148/Gann and 717/5504/Schmitz did not have a Visit 1 weight measurement, and patient 4/5003/Cole did not have a Visit 1 height measurement. *Patients' age ranged from 23 to 78 years old with a mean age of 53 years old.

**Table 8: Distribution by sex, race and treatment groups - 301**

| Treatment group | Number of patients | Sex | | Race | | |
|---|---|---|---|---|---|---|
| | | Male | Female | White | Black | Other |
| Placebo | 94 | 58 (62%) | 36 (38%) | 70 (74%) | 14 (15%) | 10 (11%) |
| Valsartan 80 mg | 99 | 63 (64%) | 36 (36%) | 75 (76%) | 15 (15%) | 9 (9%) |
| Valsartan 160 mg | 99 | 61 (62%) | 38 (38%) | 75 (76%) | 13 (13%) | 11 (11%) |
| HCTZ 12.5 mg | 100 | 58 (58%) | 42 (42%) | 66 (66%) | 22 (22%) | 12 (12%) |
| HCTZ 25 mg | 100 | 55 (55%) | 45 (45%) | 77 (77%) | 11 (11%) | 12 (12%) |
| Valsartan 80mg/HCTZ 2.5mg | 96 | 58 (60%) | 38 (40%) | 69 (72%) | 12 (13%) | 15 (16%) |
| Valsartan 160mg/HCTZ .5mg | 97 | 58 (60%) | 39 (40%) | 78 (80%) | 11 (11%) | 8 (8%) |
| Valsartan 80mg/HCTZ 25mg | 92 | 47 (51%) | 45 (49%) | 72 (78%) | 9 (10%) | 11 (12%) |
| Valsartan 160mg/HCTZ 5mg | 94 | 51 (54%) | 43 (46%) | 68 (72%) | 15 (16%) | 11 (12%) |
| Total | 871 | 509(58%) | 362(42%) | 650 (75%) | 122 (14%) | 99 (11%) |

**Table 9:Distribution by age, weight, height and by treatment groups - 301**

| Treatment group | Number of patients | Mean (±S.D) | | |
|---|---|---|---|---|
| | | Age (years) | Weight at Visit 1 (pounds) | Height (inches) |
| Placebo | 94 | 52 (±10.4) | 196.9 (±40.82) | 67.6 (±4.05) |
| Valsartan 80 mg | 99 | 52 (±10.2) | 202.6 (±41.24) | 67.8 (±3.66) |
| Valsartan 160 mg | 99 | 52 (±10.5) | 204.0 (±46.56) | 68.0 (±4.11) |
| HCTZ 12.5 mg | 100 | 52 (±11.4) | 198.2 (±41.75) | 67.6 (±4.34) |
| HCTZ 25 mg | 100 | 52 (±11.0) | 194.6 (±42.80) | 67.3 (±3.94) |
| Valsartan 80mg/HCTZ 12.5mg | 96 | 52 (±11.9) | 198.2 (±39.71) | 67.3 (±3.69) |
| Valsartan 160mg/HCTZ 2.5mg | 97 | 53 (±11.3) | 201.2 (±41.58) | 67.6 (±4.09) |
| Valsartan 80mg/HCTZ 25mg | 92 | 51 (±11.2) | 202.1 (±42.17) | 67.5 (±3.92) |
| Valsartan 160mg/HCTZ 25mg | 94 | 53 (±11.2) | 198.1 (±44.29) | 67.7 (±4.04) |
| Total | 871 | 52 (±11.0) | 199.6 (±42.28) | 67.6 (±3.98) |
| Note:One randomized patient in the HCTZ 25 mg group has missing body weight measurement at Visit 1. | | | | |

**Table 10: Demographics -Open-label studies-Protocols 11, 20, 24, 28/31**

| Patient Data | Treatment | | | | |
|---|---|---|---|---|---|
| | Valsartan / HCTZ N (%) | Valsartan N (%) | HCTZ N (%) | ACEI / HCTZ N (%) | Other N (%) |
| Total patients | 573 (100) | 1198 (100) | 40 (100) | 111 (100) | 297 (100) |
| **Sex** | | | | | |
| Male | 362 (63.2) | 713 (59.5) | 14 (35.0) | 47 (42.3) | 133 (44.8) |
| Female | 211 (36.8) | 485 (40.5) | 26 (65.0) | 64 (57.7) | 164 (55.2) |
| **Race** | | | | | |
| White | 540 (94.2) | 1138 (95.0) | 38 (95.0) | 107 (96.4) | 287 (96.6) |
| Black | 16 (2.8) | 33 (2.8) | 0 (0.0) | 2 (1.8) | 4 (1.3) |
| Other | 17 (3.0) | 27 (2.3) | 2 (5.0) | 2 (1.8) | 6 (2.0) |
| **Age (years)** | | | | | |
| Mean | 58.4 | 58.9 | 65.5 | 68.2 | 67.0 |
| STD | 12.3 | 12.6 | 10.0 | 9.7 | 10.1 |
| Range | 25-88 | 20-91 | 34-85 | 34-88 | 29-88 |
| **Weight (kg)** | | | | | |
| Mean | 86.7 | 83.8 | 71.5 | 71.7 | 72.7 |
| STD | 19.2 | 19.1 | 12.6 | 12.3 | 12.4 |
| Range | 41-158 | 41-199 | 51-106 | 46-114 | 41-114 |
| **DurationHtn.**[1] | | | | | |
| Mean (yr) | 9.1 | 8.4 | 7.3 | 8.3 | 7.0 |
| STD | 8.5 | 8.3 | 6.9 | 7.1 | 7.7 |
| Range | 0-48 | 0-71 | 0-23 | 0-31 | 0-43 |

[1] - Duration of hypertension not available for 1 patient in the valsartan/HCTZ and 2 patients on valsartan.

**5.1.3 Extent of Exposure (dose/duration) and analyses of doses administered**
Out of the overall total of 3,151 subjects who participated in all the trials (Table 1), 86 were healthy subjects, and 1,303 hypertensive patients were exposed to valsartan/HCTZ. Of the 1,303 hypertensive patients exposed to the combination therapy, 365 (28%) patients received it for at least 6 months, and 170 (13%) patients received the drug for at least 12 months (Table 11).

**Table 11: All Subjects exposed to Valsartan/HCTZ**

| Protocol # | Patients exposed to V/HCTZ | Number of Pts exposed ≥ 6 months | Number of Pts exposed ≥ 12 months |
|---|---|---|---|
| 19 | 352 | - | - |
| 301 | 378 | - | - |
| 11E | 196 | 148 | 122 |
| 20 | 20 | - | - |
| 24 | 35 | - | - |
| 28 | 125 | 84 | 46 |
| 31E | 197 | 133 | 2 |
| Total | 1303 | 365 (28%) | 170 (13%) |

**5.1.3 Duration of exposure - Protocol 19**
The mean durations among the four treatment groups were comparable for both the valsartan 80 mg run-in period and the double-blind treatment period (Table 13). The duration on trial drug for each patient during the valsartan 80 mg run-in period was defined as the number of days from the Visit 2 date to the randomization (Visit 3) date. The duration on trial drug for each patient during the double-blind period was defined as the number of days from the randomization date to the last known medication date (inclusive). If the last known medication date was missing, then the last visit date was used. The mean total duration (days) on trial drug in all the trials is presented by treatment groups in Tables 12 - 14. Duration on trial drug in single-blind (27-28 days), and double-blind periods ( 51-54 days) is presented in Tables 13-14.

**5.1.3 Duration of exposures - Protocol 301**
The mean duration among the nine treatment groups in the pivotal trial was comparable (Table 12). The duration on trial drug for each patient during the double-blind period was defined as the number of days between the randomization date to the last known medication date (inclusive). If the last known medication date was missing, then the last visit date was used. Summaries for the duration on trial drug in double-blind period (50 - 57 days).

**Table 12: Mean total duration (days) on drug-Protocol 301**

| Treatment Group | Number of Patients | Mean Duration (Days) |
|---|---|---|
| Valsartan 80 mg | 99 | 54 |
| Valsartan 160 mg | 99 | 53 |
| HCTZ 12.5 mg | 100 | 50 |
| HCTZ 25 mg | 100 | 54 |
| Valsartan 80 mg/HCTZ 12.5 g | 96 | 57 |
| Valsartan160mg/HCTZ 12.5 g | 92 | 54 |
| Valsartan 80 mg/HCTZ 25 mg | 97 | 55 |
| Valsartan 160 mg/HCTZ 25 mg | 94 | 53 |
| Placebo | 94 | 53 |

**Table 13: Mean total duration (days) on trial drug - 19**

| Double-blind treatment group | Number of patients | Mean (days) | |
|---|---|---|---|
| | | Valsartan 80 mg, run-in period | Double-blind treatment period |
| Valsartan 80 mg | 183 | 28.05 | 51.51 |
| Valsartan 160 mg | 172 | 27.85 | 53.35 |
| Valsartan 80 mg/HCTZ 12.5 mg | 176 | 28.10 | 53.23 |
| Valsartan 80 mg/HCTZ 25 mg | 177 | 27.86 | 53.62 |

**Table 14: Duration of exposure all trials - 11, 19, 20, 24, 28, 31, 301**

| Duration of Exposure | Treatment | | | | | |
|---|---|---|---|---|---|---|
| | Valsartan/HCTZ N (%) | Valsartan N (%) | HCTZ N (%) | ACEI / HCTZ N (%) | Other N (%) | Placebo N (%) |
| ≥ 1 day | 1303 (100) | 1745 (100) | 240(100) | 111 (100) | 297 (100) | 93 (100) |
| ≥ 30 days | 1177(90.3) | 1565 (89.7) | 185(77.1) | 56 (50.5) | 249(83.8) | 87 (93.5) |
| ≥ 180 days | 365 (28.0) | 572 (32.8) | 0 (0.0) | 40 (36.0) | 97 (32.7) | 0 (0.0) |
| ≥ 330 days | 259 (19.9) | 459 (26.3) | 0 (0.0) | 21 (18.9) | 78 (26.3) | 0 (0.0) |
| ≥ 365 days | 170 (13.0) | 287 (16.4) | 0 (0.0) | 20 (18.0) | 31 (10.4) | 0 (0.0) |
| ≥640 days | 115 (8.8) | 109 (6.2) | 0 (0.0) | 12(10.8) | 0 (0.0) | 0 (0.0) |
| ≥730 days | 67 (5.1) | 27 (1.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

## 5.2. Secondary Source Data

### 5.2.1 Other studies

Not applicable in this review.

### 5.2.2 Post-Marketing Experience

There is no post-marketing experience for the combination product Diovan-HCTZ.

### 5.2.3 Literature

Literature search of the on-line catalog of NLM revealed at least 35 references on several aspects of Valsartan. The reviewer was unable to find any reference relating to trials of the combination of Valsartan and HCTZ in the NLM data base. However, there was one reference, albeit not directly related, that compared the incidence of cough between Valsartan and lisinopril and hydrochlorothiazide (*Benz J , Oshrain C , Henry D , Avery C , Chiang YT, Gatlin M. Valsartan, a new angiotensin II receptor antagonist: a double blind study comparing the incidence of cough with lisinopril and hydrochlorothiazide. J Clin Pharmacol 1997 ; 37: 101-107).* This publication was not reviewed in detail (Appendix 2). The results of the study on Valsartan/HCTZ are summarized in the medical review of NDA 20-665.

## 5.3 Adequacy of Clinical Experience

Development programs for antihypertensive combination agents are usually sized to provide data that can be interpreted for minimum level of safety. For all the trials (two controlled studies in Protocols 19 and 301, and the uncontrolled studies in Protocols 11E, 20, 24, 28 and 31E), a total of 1,303 patients were exposed to the combined drug. Of these, 365 had exposure of at least 6 months, and 170 had exposure of more than 12 months. This is considered to be adequate clinical experience in an unselected adult population for this class of drugs (Tables 11 and 14). However, there was no clinical experience in the pediatric age group and in severely hypertensive patients.The combination therapy is intended for life long

treatment of hypertension, particularly in subjects identified not to be responding adequately to valsartan monotherapy. The length of exposure in all the trials is several times the length of exposure obtained in the clinical development program.

**5.4 Data quality and completeness**

Study reports were provided for all pertinent clinical studies. The quality and completeness of the present safety analysis is enhanced by the review of previous clinical trials of Valsartan monotherapy (NDA 20-665). Data from all the completed trials derived from seven trials in hypertensive patients have been electronically merged into a master safety database. The combined dataset form the primary focus of the safety analysis. Safety data from three biopharmaceutic trials in healthy subjects were not pooled due to the small numbers of subjects in the trials. The NDA for valsartan (NDA 20-665) contains the results of extensive human pharmacology trials with this compound, as does the NDA for hydrochlorothiazide (NDA 11-793). The data from these 3 biopharmaceutical trials are also considered to be adequate because they focused on issues of drug interactions between the two components, bioavailability, bioequivalence, and dose response (See Dr Fadiran's review and Section 6).

**6.0 Human pharmacokinetic considerations**

Four clinical pharmacology trials were completed using the combination drug. The only pharmacokinetic trial carried out showed that Hydrochlorothiazide (HCTZ) did not affect the pharmacokinetics of valsartan. In contrast, Valsartan reduced the systemic availability of HCTZ by about 31%. However, given the wide therapeutic range for HCTZ in the controlled study, this change was not considered to be clinically significant in respect of safety, and presumably on efficacy (See Dr Chun's review). The pharmacokinetic trial investigated the possibility of drug interaction after a single dose (Protocol 07). Two trials (Protocols 302 and 303) examined bioavailability and bioequivalence with respect to different dose combinations and different formulations. The dose response of the combination of valsartan and HCTZ was investigated in a placebo-controlled, multifactorial trial (Protocol 301). The two bioavailability /bioequivalence trials showed that the 160/12.5 mg valsartan/HCTZ Fixed Market Image (FMI) was bioequivalent to the coadministered individual components, and the 80/12.5 mg valsartan/HCTZ FMI was bioequivalent to the coadministered individual components. In contrast, 160/12.5mg valsartan/HCTZ FMI was not bioequivalent, using the regulatory bioequivalence criteria (C.I. 80-125) to the coadministered individual components. The sponsors do not intend to market the 160/25mg formulation. The NDA for valsartan (NDA 20,665) contains the results of extensive human pharmacology trials with this compound, as does the NDA for hydrochlorothiazide (NDA 11-793).

**7.0 Integrated review of Efficacy** See Dr Chun's review.

**8.0 Integrated review of safety**

**8.1 Data sets analyzed for safety**

For protocol 19, all randomized patients who had baseline (pre-dose measurements at -4 wks), and post-baseline evaluations were included in the safety analyses (Table 15). The development program for valsartan and hydrochlorothiazide enrolled 1038 patients into the single-blind placebo run-in phase at week -6. Of those enrolled, 908 patients entered the valsartan 80 mg run-in phase at week week -4. Of the 908, 708 (78%) patients were randomized at week 0 into the double-blind treatment period, and 631 patients completed the trial (Table 15). Of the 77 patients discontinued, 24 patients were discontinued for clinical and laboratory safety adverse events (For listing of patients See Appendix Tables 3, 7 and 8)

**Table 15: Completers analysed for safety - Protocol 19**

| Number of patients | Valsartan 80 mg | Valsartan 160 mg | Valsartan 80mg /HCTZ 12.5mg | Valsartan 80 mg /HCTZ 25 mg | Total |
|---|---|---|---|---|---|
| Enrolled (Visit 1) | - | - | - | - | 1038 |
| Valsartan run-in (Visit 2) | - | - | - | - | 908 |
| Randomized (Visit 3) | 183 | 172 | 176 | 177 | 708 |
| Completed (Visit 6) | 157 | 153 | 158 | 163 | 631 |

For protocol 301, 997 patients were enrolled into the single-blind placebo run-in phase at week -4. Of those enrolled, 871 were randomized to the different treatment groups, and 792 completed the trial (Table 16). Of the 79 patients discontinued 41 patients were for clinical safety adverse events whereas there were no discontinuations for laboratory safety issues (For listing of patients see Appendix Tables 3 -6). The distribution of subjects and the completers in the open-label extension studies is presented in Table 17.

**Table 16: Completers analysed for safety - Protocol 301**

| Number of patients | P | V80 | V160 | H12.5 | H25 | V80/ H12.5 | V160/ H12.5 | V80/ H25 | V160/ H25 | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Enrolled | - | - | - | - | - | - | - | - | - | 997 |
| Randomized | 94 | 99 | 99 | 100 | 100 | 96 | 97 | 92 | 94 | 871 |
| Completed | 83 | 90 | 89 | 81 | 90 | 95 | 91 | 86 | 87 | 792 |

P=Placebo, V80=Valsartan 80mg, V160=Valsartan 160mg, H12.5=HCTZ 12.5mg, and H25=HCTZ25mg

**Table 17: Completers analysed for safety during open-label extension studies**

| Double-blind Treatment Group Extension Studies | | | | | | |
|---|---|---|---|---|---|---|
| Number of Patients | Placebo | V (80mg) | V (80mg) | V (160mg) | V (320mg) | Total |
| Entered the Extension | 71 | 70 | 75 | 77 | 83 | 376 |
| Treated with Valsartan alone | 33 | 41 | 28 | 42 | 35 | 179 |
| Treated with Valsartan + HCTZ | 38 | 29 | 47 | 35 | 48 | 197 |
| Completed Extension | 57 | 49 | 59 | 62 | 64 | 291 |
| Pts Discontinued prematurely | | | | | | |
| Adverse Experience | 5 | 6 | 8 | 3 | 8 | *30 |
| Abnormal Lab. Value | 0 | 0 | 0 | 0 | 0 | 0 |
| Unsatisfactory Response | 2 | 6 | 3 | 4 | 3 | 18 |
| Others | 7 | 9 | 5 | 8 | 8 | 37 |
| Total | 14 | 21 | 16 | 15 | 19 | 85 |
| In Safety Analyses | | | | | | |
| Adverse Experience evaluation | 71 | 70 | 75 | 76 | 83 | 375 |
| Laboratory Evaluation | 71 | 68 | 74 | 74 | 83 | 370 |
| V=Valsartan. | | | | | | |

* All the 30 patients (15 males and 15 females, 28 Whites, 1 black , and 1 other ) discontinued prematurely during the extension period, had Valsartan 160mg as the last treatment. Ten out of these 30 patients also took HCTZ. The duration on the drugs during the open-label extension studies varied from 6 to 293 days (Appendix Table 3). No subjects were prematurely discontinued for abnormal laboratory values during the extension studies.

**Criteria for safety and tolerability**
Valsartan and hydrochlorothiazide combination was to be considered safe and well tolerated if there were no clinically significant trends observed in the analysis of the safety variables.

**8.1.0. Background and methodology for safety review**
The background information and criteria for this safety review will be described under two headings: clinical and laboratory events.

**8.1.0.1 Clinical**
Safety and tolerability were evaluated at each visit during the trial using direct examination, questioning the patient, and laboratory tests and analyses. For all safety and tolerability measurements, summary statistics and patients listings were provided. No rigorous statistical analyses were performed on clinical adverse events except on laboratory data, particularly serum potassium. The period of safety analyses corresponded to the active treatment periods including the double-blind period in order to reduce bias in the assessment of anti-hypertensive effect and safety of the medications under study. Patients were observed specifically for changes or trends in significant physical findings, blood pressure, pulse rate, and adverse experiences. Safety and tolerability were assessed through changes or trends in adverse experiences, orthostatic changes in blood pressure, body weight, physical and clinical laboratory examinations. Special attention was paid to neurological and other cardiovascular adverse effects, and changes in clinical laboratory data. These evaluations were compared with baseline status among treatment groups for all randomized patients. For all the safety and tolerability measurements, summary statistics or patient listings were evaluated.

**8.1.0.2 Safety monitoring and tolerability evaluations**
For efficacy, patients were judged to exhibit a clinically significant postural decrease in blood pressure, when blood pressure measured from sitting to standing after two minutes, showed a decrease of $\geq$ 20 mmHg in systolic blood pressure and/or a decrease of $\geq$ 10 mmHg in diastolic blood pressure and was accompanied by symptoms of cerebral hypoperfusion (e.g., lightheadedness, dizziness, pre-syncope, syncope, etc.). If these conditions were met, "orthostatic hypotension" was recorded on the case report form as an adverse experience. The number of patients who experienced orthostatic blood pressure changes was recorded at each visit. Patients who reported having a dry cough that persisted for $\geq$ 3 consecutive days were considered to have a "dry cough" which was recorded on the case report form as an adverse experience. A productive cough or one associated with an etiology other than ACE inhibitor, was considered as"coughing" and was also recorded on the case report form as an adverse experience. This distinction between these two types of cough appears blurred and may have been difficult to separate in the absence of confirmatory evidence of pulmonary or upper respiratory infections.

**8.1.0.3 Physical examination**
Physical examinations were performed at all visits and significant findings were recorded. Significant findings not present at initial visits were recorded by the investigator. Any significant finding was also recorded in the "Adverse Experience" section of the CRF if it constituted a medical problem. Significant physical findings were therefore included in the overall incidence of adverse experiences.
Physical examination results were listed by treatment group, center, and patient. Significant findings that constitute medical problems were recorded as adverse experiences on the case report form. For screening purposes, a 12-lead ECG was performed at Visit 1 (- week 4), and a standard PA and lateral chest X-ray was performed within two weeks of - 4 weeks, unless a normal chest X-ray had been performed within the last year, and the results of that X-ray were used. ECGs were not performed during or at the end of the trial to monitor

possible effects of drug-induced cardiac changes, including the possible effects of serum potassium alterations on ECGs.

### 8.1.0.4 Laboratory

Clinical laboratory evaluations consisting of complete blood chemistry, hematology and urinalysis were performed at weeks -4, 0 and 8, following a 12 hour fast (Table 4). Serum electrolyte levels were performed at weeks 2 and 4 and serum pregnancy tests were performed at weeks -4, 0, 4, and 8 for women of childbearing potential. Specimens were analyzed by a central laboratory. . The laboratory data was forwarded to Ciba where it was reviewed for safety purposes. A clinically significant change was defined as one that was outside the normal range as specified by as well as the predefined percent change from baseline range. Laboratory results that were outside the normal range were reported immediately by telephone to the investigator and faxed to Ciba. All patients with laboratory tests containing clinically significant abnormal values were to be followed regularly until the values returned to within normal ranges or until a valid reason other than drug-related adverse experience was identified.

### 8.1.0.5 Clinical laboratory results

Laboratory data which met predefined percent change from baseline criteria were compared among treatment groups for all randomized patients. Summary statistics for changes from baseline in laboratory values during the double-blind treatment period are tabulated in Section 8.1.6. The number of patients with shifts in laboratory results from baseline to terminal values are also tabulated separately. In addition, clinical laboratory results are tabulated according to the number of patients with specified percent changes from baseline for specified laboratory tests (Tables 34-37).

### 8.1.1 Deaths

For each death reported by the sponsor, the narratives were verified and compared with the case report forms. There was a deliberate attempt to search for indications of drug relatedness of the immediate cause of death or associated pathological conditions. Table 18 lists the deaths in patients treated with Valsartan HCTZ, and the narratives describing events surrounding these deaths can be found in Appendix Table 1. None of the deaths reported can be attributed to the drugs as immediate or remote causes of death.

**Table 18: Deaths - Protocols 11E, 28E and 28**

| Center/Patient No/Protocol | Age/Sex/Race | Drug/Dose (mg) | Cause of Death | Duration of Therapy (days) |
|---|---|---|---|---|
| 012/509/11E1 | 62/M/W | V80/HCTZ12.5 | Arteriosclerotic Heart Disease | 68 |
| 757/1031/28E | 71/M/OTH | V80/HCTZ12.5 | Post-Cholecystectomy | 555 |
| 1082/62/28 | 68/M /W | V80/HCTZ25 | Coronary Artery Disease-Heart Failure | 2 |

### 8.1.2. Other serious adverse experiences

Frequency tabulations for symptoms-groups by international medical nomenclature (IMN) term and IMN body system were made for incidence of adverse experiences delineated for all randomized patients. There was no attempt in this review to validate the sponsor's claim whether the adverse experiences were drug related or not. The sponsor identified serious adverse events as those that were either fatal, life-threatening, permanently disabling, resulted in or prolonged hospitalization, cancerous, resulted in or associated with congenital

anomaly, or overdose of study drug. For the double-blind studies, (Protocols 19 and 301) a total of 166 (10.51%) patients out of 1579 randomized patients were discontinued out of which 65 (4.1%) patients were discontinued for significant adverse events and therefore did not complete the trials (Tables 15-16). The ratio of patients discontinued for adverse events to other reasons is 65:101 (about 39% versus 61%).
These serious adverse experiences will be discussed under Review of Systems. The lists of patients with serious adverse events prematurely discontinued in all the trials are presented in Appendix Tables 3 -15.

### 8.1.3. Dropouts and "Other Significant Adverse Events"

Withdrawals were characterized by the primary associated event identified by the sponsor. The similarity between the profile of withdrawals in valsartan monotherapy and the combination did not justify recharacterization of the causes for withdrawal. Sixtyfive patients out of a total of 1,303 patients randomized to valsartan HCTZ were discontinued due to adverse experiences whether or not trial drug related. Overall, the incidence of premature termination was lowest in the valsartan/HCTZ treatment group followed by valsartan, and placebo treatment groups. A slightly higher incidence of premature discontinuation was observed for the HCTZ treatment groups. This difference is most likely due to an increased percent of patients in the HCTZ treatment group discontinuing treatment for adverse experience and "other" reasons (primarily patient does not meet protocol criteria and patient withdrew consent) compared to the other treatment groups. Both the combination and monotherapy groups were comparable to placebo and demonstrated a lower incidence of discontinuation compared to the HCTZ groups (Section 8.1.5).

In Protocol 301, a total of 126 out of 997 enrolled patients were discontinued prematurely during the single-blind placebo run-in period. Of the 873 randomized patients, 206 patients were discontinued prematurely during the single-blind valsartan run-in period, and of the remaining 677 patients, 79 patients were discontinued prematurely during the double-blind period leaving a total of 573 patients in the uncontrolled trials (Table 19).

**Table 19: Patients discontinued during the controlled and extension studies**

| Protocol Number | Total number Enrolled | Subjects discontinued | Subjects discontinued for AEs |
|---|---|---|---|
| 301 | 997 | 79 (double-blinded D-B) | 41 (double-blind) |
| 19 | 1038 | 77 (double-blind) | 22 (double-blind) |
| 11E First year | 399 | 146 | 46 |
| 11E 2nd Year | 253 | 122 | 4 |
| 11E 3rd Year | 73 | 8 | 5 |
| 31E | 376 | 85 | 30 |
| 20 | 211 | 20 | 11 |
| 24 | 60 | 0 | 0 |
| 28 | 545 | 121 | 66 |
| 28E | 69 | 10 | 7 |
| Total | 4021 (100%) | 1124 (28%) | 275 ( 24.5%) |

In protocol 19, out of 703 patients who received double-blind treatment, 31 (4.4 %) patients reported serious adverse experiences and/or discontinued prematurely from the trial for an adverse experience or laboratory abnormality. Ten (1.4%) patients were treated with valsartan 80 mg, nine (1.3%) patients were treated with valsartan 160 mg, seven (1.0%) patients were treated with valsartan 80 mg and HCTZ 12.5 mg, and five (0.7 %) patients were treated with valsartan 80 mg and HCTZ 25 mg. Twenty-eight (4.0%) of the 703 patients, randomized to double-blind treatment, were considered to be so severe that they

required intervention . The listings of subjects discontinued prematurely by protocol can be found in Appendix Tables 3 -15. The principal reasons for premature discontinuations in the double blind trials are summarized in Table 20 below.

**Table 20 : Summary of principal reasons for premature termination by treatment groups - 19 and 301.**

| Principal Reasons | Treatment | | | | | |
|---|---|---|---|---|---|---|
| | Valsartan/HCTZ N (%) | Valsartan (N%) | HCTZ N (%) | ACEI/HCTZ N (%) | Other (N%) | Placebo (N%) |
| Total Patients | 1303 (100) | 1745 (100) | 240 (100) | 111 (100) | 297 (100) | 93(100) |
| Adverse Experience | 64 (4.9) | 111 (6.4) | 12 (5.0) | 11 (9.9) | 31 (10.4) | 4(4.3) |
| Abnormal Laboratory Value | 1 (0.1) | 7 (0.4) | 0 (0.0) | 1 (0.9) | 1 (0.3) | 0(0.0) |
| Unsatisfactory Therapeutic Effect | 78 (6.0) | 35 (2.0) | 3 (1.2) | 4 (3.6) | 0 (0.0) | 2(2.2) |
| Death | 3 (0.2) | 5 (0.3) | 0 (0.0) | 0 (0.0) | 2 (0.7) | 0(0.0) |
| "Other" | 103 (7.9) | 136 (7.8) | 19(7.9) | 3 (2.7) | 12 (4.0) | 4(4.3) |
| Total | 248 (19.0) | 295 (16.9) | 34(14.2) | 19 (17.1) | 46 (15.5) | 10(10.8) |

Protocols included: 11 Extension, 19, 20, 24, 28, 31 Extension and 301. The term "other" in the column "Principal reason" includes administrative problems, lost to follow-up, patient withdrew consent, patient non-compliance, or patient does not meet protocol criteria. Of those enrolled, 908 patients entered into the valsartan 80 mg run-in phase at Visit 2.

### 8.1.3.1 Overall profile of Dropouts/withdrawals

The overall incidence and profile of dropouts in the combined trial datasets is presented in Table 20 and in Section 8.1.5. There were 3 patients randomized to HCTZ alone who were discontinued for serious adverse events in Protocol 301. They were classified as not meeting the requirements of the protocol because the events were observed on week 2 (Table 21). The list of all discontinued subjects with adverse events treated with HCTZ alone is presented in Appendix Table 5.

**Table 21: Discontinuations associated with HCTZ alone-Protocol 301**

| Protocol | Patient number | Sex | Age | Last Visit | Medical Problem | Drug (mg) | Discontinued | Serious |
|---|---|---|---|---|---|---|---|---|
| 301 | 448/3402 | M | 66 | 3 | Hemiplegia | HCTZ 25 | Yes | Yes |
| 301 | 241/3218 | M | - | 3 | Elevated Liver Enzymes | HCTZ 25 | Yes | Yes |
| 301 | 390/3350 | M | 58 | 3 | Hyperbilirubinemia (3.4) | HCTZ 12.5 | Yes | Yes |

### 8.1.3.2 Adverse events associated with dropouts

There were no clinically significant adverse events associated with dropouts except headaches and dizziness. The principal reasons for premature termination and dropouts in the double blind trials are presented in Appendix Table 3. No deaths were reported in the controlled trials attributable directly to the combined drug.

### 8.1.3.3 Other significant adverse events

There were no other clinically significant adverse events reported, and no clinically significant trends were observed upon review of the adverse experiences considered trial drug related by sex, age, and race in Protocol 301.

**Analysis of withdrawals by race, sex and by treatment groups**
To evaluate if there is a pattern in the treatment groups of subjects discontinued, regardless of reasons for discontinuation, a slightly increased number of males compared to females was observed, and more blacks assigned to the placebo group, classified as withdrawals were in fact lost to follow up or withdrew consent because of adverse events. There is an exceess of blacks (61% ) compared to whites (39%), among those who withdrew in the placebo group. The significance of this excess of black patients withdrawing is not known. However, this does not seem to affect the analysis of the safety data. The causes of withdrawal among whites was lack of therapeutic effect in 3 subjects, and 2 withdrew consent because of adverse events. Overall there is an excess of males ( 62% ) compared to females (38%) of all the subjects discontinued from randomization to the end of the double-blind controlled studies. (Table 22)

**Table 22 : Discontinuations by sex and race - 19/301**

| Protocol | Treatment group at randomization (Total) | Male | Female | White | Black | Others |
|---|---|---|---|---|---|---|
| 301 | Placebo (94) | 6 | 7 | 5 | 8 | 0 |
| 301 and 19 | V80 (282) | 37 | 28 | 49 | 8 | 9 |
| 301 and 19 | V160 (271) | 44 | 27 | 42 | 19 | 14 |
| Subtotal Plcbo/ Monotherapy | | 87 | 62 | 96 | 35 | 23 |
| 301 and 19 | V80+12.5HCTZ (272) | 28 | 16 | 33 | 8 | 3 |
| | V80+25HCTZ (269) | 24 | 16 | 34 | 1 | 4 |
| | V160+12.5HCTZ (97) | 10 | 4 | 12 | 2 | 0 |
| | V160+25HCTZ (94) | 5 | 7 | 11 | 0 | 1 |
| Subtotal Combination | | 67 | 33 | 90 | 11 | 8 |
| Total | | 154 | 95 | 186 | 46 | 31 |

**8.1.4 Other search strategies**
Not applicable
**8.1.5 Adverse event incidence Tables**
Comparison of frequencies of trial drug-related adverse events versus all adverse experiences showed more adverse events with trial drug related events with patients on combination therapy compared to valsartan monotherapy ($p<0.001$) (Table 23).

**Table 23: Trial drug-related versus all adverse experiences - 19/301**

| | Valsartan/ HCTZ N (%) | Valsartan N (%) | HCTZ N (%) | Placebo N (%) |
|---|---|---|---|---|
| Total Patients | 730 (100) | 547 (100) | 200 (100) | 93 (100) |
| Total Patients With AEs | 388 (53.2) | 277 (50.6) | 109 (54.5) | 48 (51.6) |
| With Trial Drug-Related Reactions | 160 (21.9)[1] | 74 (13.5) | 41 (20.5) | 17 (18.3) |

[1] - Statistically significantly different compared to valsartan ($p<0.001$)

The overall percentage of patients in the controlled trials reporting severe adverse experiences was lowest in the valsartan treatment group. Severe adverse experiences were reported by 3.3% of patients receiving valsartan, 5.1% of patients receiving valsartan/HCTZ, 5.5% of patients receiving HCTZ, and 8.6% of patients receiving placebo. Headache was reported as severe more frequently in the placebo treatment group (3.2%) than in the active treatment groups (1.1% - 1.5%). The remaining incidence rates for severe occurrences of the five most frequently reported adverse experiences in the valsartan/HCTZ treatment group were comparable to the incidence rates in the other treatment groups.
In the combined tral datasets and in the individual controlled studies, the incidence of adverse events with frequencies > 2% , shows similar trends to those that are not drug related, except for headache in the placebo group which is statistically significantly different from subjects receiving Valsartan/HCTZ. The dizziness in the combination therapy group was due to HCTZ at the higher dose of 25 mg. The incidence of dizziness was lowest in the valsartan treatment group. The incidence of fatigue reported as trial drug-related was greatest in the HCTZ and valsartan/HCTZ treatment groups (Tables 24 and 25).

**Table 24: Incidence of the most frequently reported (> 2% in the valsartan/HCTZ group) adverse experience, by dose.19 and 301**

| | Valsartan/HCTZ | | | | Valsartan | | HCTZ | | Placebo |
|---|---|---|---|---|---|---|---|---|---|
| | 80/12.5 | 80/25 | 160/12.5 | 160/25 | 80 | 160 | 12.5 | 25 | - |
| Total Patients | 272 (100) | 268 (100) | 96 (100) | 94 (100) | 278 (100) | 269 (100) | 100 (100) | 100 (100) | 93 (100) |
| Total Patients with AEs | 145 (53.3) | 139 (51.9) | 51 53.1) | 53 (56.4) | 147 (52.9) | 130 (48.3) | 55 (55.0) | 54 (54.0) | 48 (51.6) |
| AEs N (%) | | | | | | | | | |
| Headache | 28 (10.3) | 31( 11.6) | 11 (11.5) | 9 (9.6) | 33 11.9) | 21 (7.8) | 17 (17.0) | 11(11.0) | 16(17.2) |
| Dizziness | 17 (6.3) | 21 (7.8) | 11(11.5) | 15(16.0) | 6 (2.2) | 8 (3.0) | 9 (9.0) | 6 (6.0) | 6 (6.5) |
| Fatigue | 12 (4.4) | 11 (4.1) | 8 (8.5) | 6 (6.0) | 9 (3.2) | 6 (2.2) | 6 (6.0) | 5 (5.0) | 1 (1.1) |
| Sinusitis | 7 (2.6) | 10 (3.7) | 2 (2.1) | 4 (4.3) | 5 (1.8) | 7 (2.6) | 4 (4.0) | 2 (2.0) | 3 (3.2) |
| Pharyngitis | 5 (1.8) | 10 (3.7) | 4 (4.2) | 3 (3.2) | 5 (1.8) | 5 (1.9) | 1 (1.0) | 2 (2.0) | 1 (1.1) |
| Upper R.T.I. | 11 (4.0) | 7 (2.6) | 3 (3.1) | 1 (1.1) | 16(5.8) | 12 (4.5) | 3 (3.0) | 4 (4.0) | 2 (2.2) |
| Coughing | 9 (3.3) | 8 (3.0) | 2 (2.1) | 2 (2.1) | 11(4.0) | 5 (1.9) | 3 (3.0) | 2 (2.0) | 0 (0.0) |
| Pain Back | 5 (1.8) | 5 (1.9) | 6 (6.3) | 4 (4.3) | 6 (2.2) | 9 (3.3) | 3 (3.0) | 2 (2.0) | 3 (3.2) |
| Pain Chest | 9 (3.3) | 6 (2.2) | 1 (1.0) | 2 (2.1) | 4 (1.4) | 7 (2.6) | 2 (2.0) | 0 (0.0) | 1 (1.1) |
| Diarrhea | 8 (2.9) | 4 (1.5) | 4 (4.2) | 2 (2.1) | 7 (2.5) | 13 (4.8) | 1 (1.0) | 3 (3.0) | 0 (0.0) |
| Infection Viral | 9 (3.3) | 7 (2.6) | 0 (0.0) | 2 (2.1) | 14 5.0) | 8 (3.0) | 6 (6.0) | 2 (2.0) | 1 (1.1) |

**Table 25: Adverse experiences in > 2% in the valsartan/HCTZ group, and corresponding incidence of premature discontinuation 11, 19, 20, 24, 28, 31 301.**

| | Valsartan/HCTZ N (%) | | Valsartan N (%) | | HCTZ N (%) | |
|---|---|---|---|---|---|---|
| | Overall Incidence | Premature Discont. | Overall Incidence | Premature Discont. | Overall Incidence | Premature Discont. |
| Total Patients | 1303 (100) | | 1745 (100) | | 240 (100) | |
| With AE | 777 (59.6) | 65 (5.0) | 1044 (59.8) | 109 (6.2) | 114 (47.5) | 11 (4.6) |
| **Adverse Experiences** | | | | | | |
| Headache | 108 (8.3) | 7 (0.5) | 197 (11.3) | 13 (0.7) | 28 (11.7) | 4 (1.7) |
| Dizziness | 99 (7.6) | 9 (0.7) | 84 (4.8) | 10 (0.6) | 15 (6.3) | 4 (1.7) |
| URTI | 83 (6.4) | 0 (0.0) | 118 (6.8) | 1 (0.1) | 7 (2.9) | 0 (0.0) |
| Infection Viral | 78 (6.0) | 0 (0.0) | 103 (5.9) | 0 (0.0) | 10 (4.2) | 0 (0.0) |
| Coughing | 58 (4.5) | 2 (0.2) | 84 (4.8) | 7 (0.4) | 5 (2.1) | 1 (0.4) |
| Fatigue | 56 (4.3) | 6 (0.5) | 57 (3.3) | 7 (0.4) | 11 (4.6) | 2 (0.8) |
| Sinusitis | 53 (4.1) | 0 (0.0) | 89 (5.1) | 0 (0.0) | 6 (2.5) | 0 (0.0) |
| Pain Back | 40 (3.1) | 1 (0.1) | 77 (4.4) | 4 (0.2) | 5 (2.1) | 0 (0.0) |
| Diarrhea | 39 (3.0) | 4 (0.3) | 74 (4.2) | 6 (0.3) | 4 (1.7) | 0 (0.0) |
| Pharyngitis | 39 (3.0) | 0 (0.0) | 54 (3.1) | 0 (0.0) | 3 (1.2) | 0 (0.0) |
| Pain Chest | 39 (3.0) | 5 (0.4) | 32 (1.8) | 6 (0.3) | 2 (0.8) | 1 (0.4) |
| Dyspepsia | 36 (2.8) | 1 (0.1) | 50 (2.9) | 3 (0.2) | 5 (2.1) | 0 (0.0) |
| Arthralgia | 31 (2.4) | 1 (0.1) | 70 (4.0) | 2 (0.1) | 2 (0.8) | 0 (0.0) |
| Nausea | 29 (2.2) | 4 (0.3) | 38 (2.2) | 2 (0.1) | 4 (1.7) | 1 (0.4) |
| Pain Leg | 29 (2.2) | 1 (0.1) | 24 (1.4) | 3 (0.2) | 2 (0.8) | 0 (0.0) |
| UTI | 29 (2.2) | 0 (0.0) | 36 (2.1) | 0 (0.0) | 5 (2.1) | 0 (0.0) |
| Rhinitis | 26 (2.0) | 0 (0.0) | 39 (2.2) | 1 (0.1) | 8 (3.3) | 0 (0.0) |

### Adverse experiences

The incidence of adverse experiences was 20.5% in the valsartan/HCTZ treatment group, 18.6% in the valsartan treatment group, 21.2% in the Other treatment group, 17.5% in the HCTZ treatment group, 17.1% in the ACEI/HCTZ treatment group, and 18.3% in the placebo treatment group. There are no statistically significant differences between the incidences of adverse experiences between patients treated with the combined drug compared to either placebo, valsartan, and HCTZ monotherapies. Adverse events were reviewed on case report forms for deaths and withdrawals.

In Protocol 19, a total of 354 /703 (50.4 %) raandomized patients had adverse experiences, regardless of relationship to trial drug. A similar proportion of patients in each treatment group reported adverse experiences. The most frequently reported adverse experience in all treatment groups was headache, reported by a similar proportion of patients in each treatment group . The incidence of headache was significantly higher in the placebo group compared to the groups on combination drugs, using a >2% as threshold (Tables 24 and 25). The most frequently reported adverse experiences, whether or not trial drug-related, in valsartan/HCTZ treated patients appear to be evenly distributed by sex, race, and age.

**Effects of Age, sex, and race on adverse events regardless of relationship to trial drug**

Tabulation of frequencies of adverse experiences by age, sex, and race were analysed to evaluate the potential for the trial drug to cause different adverse effects in male versus female patients, subjects below and above 65 years, and whites versus blacks and others (Tables 26 - 29).

**Adverse experiences considered trial drug-related**

Comparative data of the most frequently occuring drug related adverse events ( > 2 % ) in treated patients show similarities in incidence rates of common adverse events. A summary of adverse experiences in decreasing order of frequency, whether or not trial drug related, is presented in Table 30. None of the severe serious adverse experiences were reported with a frequency of ≥ 3% in any of the treatment groups, nor were any clinically meaningful patterns observed in the proportion of patients reporting severe adverse experiences. Similarly, none of the severe serious adverse events were reported with a frequency > 2% in the combined trial data sets.

The Treatment Emergent Signs and Symptoms system for adverse experiences data management was used in the trials. With this system, pre-existing adverse experiences were not counted as occurring during the treatment period unless their degree of severity worsened and/or a new onset date was recorded. Adverse experiences noted as "unlikely" related to trial drug were not counted as being drug related and were considered to be inter current illnesses. An adverse experience was counted as trial drug related when the investigator considered the drug relationship to be possible, probable, or highly probable. The incidence of most frequently reported adverse experiences by treatment groups regardless of drug exposure in Protocols 19 and 301 is presented in Tables 26 -29. In the analysis of long-term exposure, no new adverse experiences were observed with valsartan/HCTZ compared to those observed during trials of shorter duration. In addition, generally the incidence of adverse experiences did not increase as the length of time on treatment increased.

Dizziness was the adverse experience reported with the highest incidence among patients in the combination treatment groups. There was a dose related increase in the incidence among the combination groups (valsartan 160 mg/HCTZ 25 mg (16%), valsartan 160 mg/HCTZ 12.5 mg (12%), valsartan 80 mg/HCTZ 25 mg (11%) and valsartan 80mg/HCTZ 12.5mg (8%). Only three reported cases were considered severe (one case each in the placebo, valsartan 160 mg/HCTZ 12.5 mg and valsartan 80 mg/HCTZ 25 mg groups). The investigators considered the majority of incidences of dizziness to be trial drug related.

Headache was the second adverse experience reported with the highest incidence among patients in the combination treatment groups. Headache occurred in a higher percentage of placebo (17.2%) and HCTZ 12.5 mg (17.0%) patients than in any of the other treatment groups (8-13%), and there was no apparent increase related to dose. Headache is a common adverse event seen in hypertension trials, and has been reported with a similar incidence in previous monotherapy trials.

**Adverse experiences considered unrelated to trial**
**Effects of Age, sex, and race on adverse experiences**

**Age:** Adverse experiences are summarized by age (< 65 years and ≥ 65 years) in order to evaluate the potential for the trial drug to cause different adverse effects in young and elderly patients. The most frequent adverse experiences whether or not related to trial drug, are presented by age in Table 26. A similar proportion of patients ≥ 65 years of age reported adverse experiences as compared to patients < 65 years of age in all treatment groups. In the valsartan 80 mg/HCTZ 12.5 mg treatment group a slightly higher percent of patients ≥ 65 years of age reported adverse experiences as compared to patients < 65 years of age. These

results should be interpreted with caution due to the relatively small number of elderly patients. Of the 703 patients analyzed for safety (protocol 19), the majority of patients (590/703, or 84 %) were < 65 years of age as compared to those ≥ 65 years of age (113/703, or 16 %). Headache was the most frequently reported adverse experience regardless of age, except in patients ≥ 65 years of age in the valsartan 160 mg treatment group where sinusitis was the most frequently reported adverse experience. Diarrhea and upper respiratory infections were reported more often in patients < 65 years of age in all treatment groups (Table 26).

**Sex:** Adverse experiences were also summarized by sex in order to evaluate the potential for the trial drug to cause different adverse effects in males and females. The most frequent adverse experiences whether or not related to trial drug, are presented by sex in Table 27. A larger proportion of female patients reported adverse experiences, regardless of relationship to trial drug, compared to male patients. In all treatment groups, headache was the most frequently reported adverse experience, with a slightly higher percentage of females reporting headache than males. The remaining adverse experiences did not follow a consistent pattern of occurrence.

**Table 26: Most frequently reported adverse experiences by age - 19**

| | Valsartan 80 mg | | Valsartan 160 mg | | Valsartan 80 mg/ HCTZ 12.5 mg | | Valsartan 80 mg/ HCTZ 25 mg | |
|---|---|---|---|---|---|---|---|---|
| | <65 N (%) | ≥65 N (%) | <65 N (%) | ≥65 N (%) | <65 N (%) | ≥65 N (%) | <65 N (%) | ≥65 N (%) |
| Total patients: | 152 (100) | 27 (100) | 146 (100) | 26 (100) | 151 (100) | 25 (100) | 141 (100) | 35 (100) |
| With AEs: | 76 (50.0) | 14(51.9) | 74 50.7) | 12 (46.2) | 75 (49.7) | 14 (56.0) | 72 (51.1) | 17 (48.6) |
| Headache | 17(11.2) | 3(11.1) | 12(8.2) | 1(3.8) | 12(7.9) | 4(16.0) | 20(14.2) | 3(8.6) |
| UpperR.T.I. | 12(7.9) | 1(3.7) | 9(6.2) | 0(0.0) | 7(4.6) | 0(0.0) | 4(2.8) | 0(0.0) |
| Infection viral | 8(5.3) | 1(3.7) | 5(3.4) | 1(3.8) | 7(4.6) | 0(0.0) | 1(0.7) | 0(0.0) |
| Diarrhea | 3(2.0) | 1(3.7) | 8(5.5) | 0(0.0) | 6(4.0) | 0(0.0) | 4(2.8) | 0(0.0) |
| Rhinitis | 8(5.3) | 2(7.4) | 1(0.7) | 0(0.0) | 5(3.3) | 0(0.0) | 3(2.1) | 1(2.9) |
| Sinusitis | 4(2.6) | 0(0.0) | 5(3.4) | 2(7.7) | 3(2.0) | 0(0.0) | 9(6.4) | 0(0.0) |
| Dizziness | 4(2.6) | 0(0.0) | 6(4.1) | 0(0.0) | 7(4.6) | 2(8.0) | 9(6.4) | 2(5.7) |
| Coughing | 6(3.9) | 1(3.7) | 3(2.1) | 0(0.0) | 5(3.3) | 2(8.0) | 4(2.8) | 1(2.9) |
| Fatigue | 4(2.6) | 0(0.0) | 2(1.4) | 1(3.8) | 5(3.3) | 1(4.0) | 4(2.8) | 3(8.6) |

**Race:** Adverse experiences were analyzed by race (white, black, and other) in order to evaluate the potential for the trial drug to cause different adverse effects in patients of different races. Headache was the most frequently reported adverse experiences in each racial group, with a relatively higher proportion of white and black patients reporting this adverse experience. The most frequent adverse experiences whether or not related to trial drug are presented by race in Tables 28-29. Of the 703 patients in protocol 19 analyzed for safety, the majority [(497/703 (71%)] of patients were white as compared to black patients [(105/703 (15%)] and patients of other races [(101/703 (14%)]. However, in all the treatment groups, a lower proportion of patients of other races reported adverse experiences compared to white and black patients. Although these results should be interpreted with caution due to the unequal distribution of patients in each of the racial groups, the 3 fold increase in the frequency of headache among blacks on valsartan monotherapy compared to whites may be significant.when compared to the almost equal frequency of headache observed among both races on Valsartan/HCTZ25. However, more headaches were reported in blacks (20%) on valsartan/HCTZ 12.5mg compared to whites (7.4%), and an almost equal proportion between both races on the other dose regimens. Statistically, the

small number of black patients and of "other" races enrolled into the trial prohibits the comparison of individual experiences among each race. However, no statistically significant increase was observed in the incidence rate of adverse experiences among the racial groups.

**Table 27: Most frequently reported adverse experiences by sex - 19**

| | Valsartan 80 mg | | Valsartan 160 mg | | Valsartan 80 mg/ HCT 12.5 mg | | Valsartan 80 mg/ HCT 12.5 mg | |
|---|---|---|---|---|---|---|---|---|
| | Male N (%) | Female N (%) | Male N (%) | Female N (%) | Male N (%) | Female N (%) | Male N (%) | Female N (%) |
| Total patients: | 113 (100) | 66 (100) | 109 (100) | 63 (100) | 117 100) | 59 (100) | 123 (100) | 53 (100) |
| With AEs: | 52 (46.0) | 38 (57.6) | 53 (48.6) | 33 (52.3) | 53 (45.3) | 36 (61.0) | 62 (50.4) | 27 (50.9) |
| Headache | 10(8.8) | 10(15.2) | 7(6.4) | 6(9.5) | 9(7.7) | 7(11.9) | 15(12.2) | 8(15.1) |
| URTI | 8(7.1) | 5(7.6) | 7(6.4) | 2(3.2) | 5(4.3) | 2(3.4) | 3(2.4) | 1(1.9) |
| Infection viral | 6(5.3) | 3(4.5) | 4(3.7) | 2(2.3) | 3(2.6) | 4(6.8) | 3(2.4) | 1(1.9) |
| Diarrhea | 4 (3.5) | 0(0.0) | 4(3.7) | 4(6.3) | 5(4.3) | 1(1.7) | 1(0.8) | 3(5.7) |
| Rhinitis | 8(7.1) | 2(3.0) | 1(0.9) | 0(0.0) | 3(2.6) | 2(3.4) | 3(2.4) | 1(1.9) |
| Sinusitis | 2(1.80 | 2(3.0) | 4(3.7) | 3(4.8) | 0(0) | 3(5.1) | 8(6.5) | 1(1.9) |
| Dizziness | 3(2.7) | 1(1.5) | 2(1.8) | 4(6.3) | 7(6.0) | 2(3.4) | 8(6.5) | 3(5.7) |
| Coughing | 3(2.7) | 4(6.1) | 3(2.8) | 0(0) | 3(2.6) | 4(6.8) | 3(2.4) | 2(3.8) |
| Fatigue | 2 (1.8) | 2 (3.0) | 1 (0.9) | 2(3.2) | 3(2.6) | 3(5.1) | 5(4.1) | 2(3.8) |

**Table 28: Most frequently reported adverse experiences by race-19**

| | Valsartan 80 mg | | | Valsartan 160 mg | | |
|---|---|---|---|---|---|---|
| | White N (%) | black N (%) | other N (%) | White N (%) | black N (%) | other N (%) |
| Total patient | 127 (100) | 28 (100) | 24 (100) | 124 (100) | 23 (100) | 25 (100) |
| With AEs | 72 (56.7) | 14 (50.0) | 4 (16.7) | 68 (54.8) | 15 (65.2) | 3 (12.0) |
| Headache | 16(12.6) | 4(14.3) | 0(0.0) | 9(7.3) | 3(13.0) | 1(4.0) |
| Upper R.T.Infection | 10(7.9) | 3(10.7) | 0(0.0) | 9(7.3) | 0(.0) | 0(0.0) |
| Infection viral | 5(3.9) | 2(7.1) | 2(8.3) | 5(4.0) | 1(4.3) | 0(0.0) |
| Diarrhea | 4(3.1) | 0(.0) | 0(0.0) | 8(6.5) | 0(.0) | 0(0.0) |
| Rhinitis | 8(6.3) | 1(3.6) | 1(4.2) | 0(0.0) | 1(4.3) | 0(0.0) |
| Sinusitis | 4(3.1) | 0(.0) | 0(0.0) | 5(4.0) | 2(8.7) | 0(0.0) |
| Dizziness | 4(3.1) | 0(.0) | 0(0.0) | 3(2.4) | 2(8.7) | 1(4.0) |
| Coughing | 6(4.7) | 1(3.6) | 0(0.0) | 3(2.4) | 0(.0) | 0(0.0) |
| Fatigue | 3(2.4) | 1(3.6) | 0(0.0) | 3(2.4) | 0(.0) | 0(0.0) |

**Table 29: Most frequently reported adverse experiences by race-19**

| | Valsartan 80mg/HCTZ 12.5mg | | | Valsartan 160mg/HCTZ 25mg | | |
|---|---|---|---|---|---|---|
| | White N (%) | Black N (%) | Other N (%) | White N (%) | Black N (%) | Other N (%) |
| Total patient | 121 (100) | 29 (100) | 26 (100) | 125 (100) | 25 (100) | 26 (100) |
| With AEs | 63 (52.1) | 17 (58.6) | 9 (34.6) | 69 (55.2) | 12 (48.0) | 8 (30.8) |
| Headache | 9(7.4) | 6(20.7) | 1(3.8) | 18(14.4) | 3(12.0) | 2(7.7) |
| Upper resp tract infection | 4(3.3) | 1(3.4) | 2(7.7) | 3(2.4) | 1(4.0) | 0(0.0) |
| Infection viral | 5)4.1) | 0(0.0) | 2(7.7) | 3(2.4) | 1(4.0) | 0(0.0) |
| Diarrhea | 6(5.0) | 0(0.0) | 0(0.0) | 4(3.2) | 0(0.0) | 0(0.0) |
| Rhinitis | 3(2.5) | 2(6.9) | 0(0.0) | 2(1.6) | 2(8.0) | 0(0.0) |
| Sinusitis | 3(2.5) | 0(0.0) | 0(0.0) | 7(5.6) | 2(8.0) | 0(0.0) |
| Dizziness | 7(5.8) | 1(3.4) | 1(3.8) | 9(7.2) | 1(4.0) | 1(3.8) |
| Coughing | 6(5.0) | 1(3.4) | 0(0.0) | 3(2.4) | 2(8.0) | 0(0.0) |
| Fatigue | 5(4.1) | 1(3.4) | 0(0.0) | 6(4.8) | 0(0.0) | 1(3.8) |

The severity of adverse experiences was assessed as mild, moderate, or severe. Adverse experiences by severity are presented in Table 30.

**Table 30: Descending order of frequency and severity of the 5 most frequently reported AEs in Protocols 19/301**

| | Valsartan/ HCTZ N (%) | Valsartan N (%) | HCTZ N (%) | Placebo N (%) |
|---|---|---|---|---|
| Total Patients | 730 (100) | 547 (100) | 200 (100) | 93 (100) |
| Total Patients With AEs | 388 (53.2) | 277 (50.6) | 109 (54.5) | 48 (51.6) |
| Headache | | | | |
| Mild | 50 (6.8) | 26 (4.8) | 17 (8.5) | 9 (9.7) |
| Moderate | 20 (2.7) | 22 (4.0) | 8 (4.0) | 4 (4.3) |
| Severe | 9 (1.2) | 6 (1.1) | 3 (1.5) | 3 (3.2) |
| Dizziness | | | | |
| Mild | 45 (6.2) | 10 (1.8) | 11 (5.5) | 5 (5.4) |
| Moderate | 16 (2.2) | 4 (0.7) | 4 (2.0) | 0 (0.0) |
| Severe | 3 (0.4) | 0 (0.0) | 0 (0.0) | 1 (1.1) |
| Fatigue | | | | |
| Mild | 27 (3.7) | 11 (2.0) | 8 (4.0) | 0 (0.0) |
| Moderate | 5 (0.7) | 3 (0.5) | 3 (1.5) | 1 (1.1) |
| Severe | 2 (0.3) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Sinusitis | | | | |
| Mild | 13 (1.8) | 7 (1.3) | 4 (2.0) | 1 (1.1) |
| Moderate | 10 (1.4) | 4 (0.7) | 2 (1.0) | 2 (2.2) |
| Severe | 0 (0.0) | 1 (0.2) | 0 (0.0) | 0 (0.0) |
| Pharyngitis | | | | |
| Mild | 17 (2.3) | 10 (1.8) | 3 (1.5) | 0 (0.0) |
| Moderate | 5 (0.7) | 0 (0.0) | 0 (0.0) | 1 (1.1) |
| Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |