SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures which have been finalised before 1 November 2004. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

The application is a new combination of two previously known active substances in the combinations 150 mg/12.5 mg and 300 mg/12.5 mg of irbesartan and hydrochlorothiazide (HCTZ).

Marketing authorisations have previously been granted to irbesartan 150 mg and 300 mg tablets through the centralised procedure. Irbesartan is a non-peptide long lasting competitive antagonist of the AT_1-type angiotensin II receptor (AIIRA), active through oral administration. HCTZ is a well-known thiazide diuretic.

The rationale for the doses submitted in this application are related to the second-line strategy proposed for the combination. The dose of 150 mg/12.5 mg is proposed as an alternative to the titration to 300 mg of irbesartan in subjects not adequately controlled by 150 mg irbesartan or hydrochlorothiazide alone. Similarly, the dose of 300 mg/12.5 mg is proposed as an additional useful step for the subjects not adequately controlled by the combination 150 mg/12.5 mg or by 300 mg monotherapy.

2. Part II: Chemical, pharmaceutical and biological aspects

Uncoated tablets

Composition

The medicinal product is available in the form of tablets with doses of 150 mg/12.5 mg and 300 mg/12.5 mg of irbesartan/HCTZ. The qualitative and quantitative composition is adequately described. No overage of the active substances is used. For some excipients, variable amounts are proposed depending on the potency of the active substances.

The medicinal product is packaged in opaque blister package made of polyvinyl chloride coated with white opaque polyvinylidene chloride, and heat sealed to aluminium foil backing.

Clinical trial formula

Clinical studies were performed with 12.5 mg, 25 mg, 50 mg, 75 mg, or 100 mg irbesartan capsules; 75 mg, 150 mg and 300 mg irbesartan tablets; and 6.25 mg, 12.5 mg, or 25 mg HCTZ tablets. All formulations were adequately described. The compositions of irbesartan tablets were the ones previously authorised.

In support of this application, two studies were conducted to demonstrate bioequivalence of the proposed commercial tablets with the clinical dosage forms. Dissolution results on irbesartan/HCTZ 150 mg/12.5 mg and 300 mg/12.5 mg tablets, irbesartan 75 mg and 100 mg capsules, and HCTZ 12.5 mg tablets used in the bioequivalence studies were also presented. Bioequivalence between both formulations was shown in both studies.

Development pharmaceutics

The development of the commercial formulation was satisfactory detailed.

Irbesartan, was successfully formulated with HCTZ into a stable, immediate release tablet. The commercial tablets were shown to be equivalent to the individual clinical irbesartan capsules and HCTZ tablets.

Development of irbesartan/HCTZ tablets closely followed the development of the single entity irbesartan tablets, in terms of both formulation and process. Different prototype formulations were developed which led to the commercial formulation. Excipients were selected based on their contributions to product stability.

The irbesartan/HCTZ formulation differs qualitatively from that of the approved irbesartan formulation by the exclusion of poloxamer, and the inclusion of red and yellow iron oxides, in order to impart a peach colour to distinguish them from the white single entity tablets.

Studies were performed to evaluate the effects of excipients or different processing conditions on powder and tablet properties, including dissolution.

In-process controls

During the manufacturing process, the dried granulation is tested for moisture content, and the tablets are tested for hardness and uniformity of mass.

Process validation

The process was validated by the manufacture of two 90 kg batches of the 150 mg/12.5 mg combination, three 90 kg batches of the 300/12.5 mg combination, and one 270 kg batch 150/12.5 mg combination in Evansville. In addition, two pilot scale batches (35 kg) of the 150/12.5 mg potency combination were manufactured in New Brunswick. Granulation was tested for particle size distribution, bulk density, tap density and flow. The finished tablets were tested for potency, uniformity of content, dissolution, gauge, hardness, friability, weight, and disintegration. The results showed that the tablets were within the proposed specifications and that the manufacturing process is adequately controlled.

Control of Starting Materials

Irbesartan

The routine controls are supported by the scientific documentation. The proposed specifications are consistent with the established quality and supported by the batch analysis data. Test methods were updated to correspond to the current Ph.Eur.

Scientific data presented in the dossier were acceptable. Irbesartan presents only positional isomerism. The isomers due to alternative location of substitutes in the phenyl rings are controlled during the manufacturing process.

The process description presented in the open and restricted part of the DMF is adequate. The results obtained on 14 batches from different manufacturers showed that all batches comply the specifications of the irbesartan drug substance.

HCTZ

The manufacturing process was adequately described. The quality of the starting material is well established, adequately controlled and complies with the specifications of the current Ph.Eur.

Scientific data presented in the dossier were acceptable. The specifications for impurities were adequately described and, although within the established of the Ph. Eur., could be tightened, on the basis of the results presented of the batch analysis. Results from an analysis evaluating the possible reduction of the impurity limits were submitted and a tightened specification agreed.

The results of the analysis for three batches showed that the batches comply with the specifications proposed.

Other

All excipients used in the manufacture of tablets comply with the specification of Ph. Eur. or of other Member State Pharmacopoeias. Specifications and control methods of packaging material are acceptable.

Control tests on intermediate products

Not applicable

Control tests on the finished product

The specifications for release and shelf life of the finished product, as well as the specifications for the active substances, are acceptable. The limits defined for impurities/degradation products have been tightened and different specifications for degradation products at release and shelf-life have been established.

Stability

Active substance

Irbesartan

8 batches were studied, of which 3 were from pilot scale production and 5 from industrial scale. The control methods were correctly described and demonstrated stability. 12 months long-term stability data for commercial-scale lots are now available as well as the stability results of pilot-scale lots up to 4 years. The re-test period when stored in double polyethylene bags placed in cardboard containers is 3 years.

HCTZ

Stability studies were conducted on 13 batches manufactured between 1983 and 1995. Stability data of 5 years are available for 9 batches, 4 years for one batch, 3 years for 1 batch and 2 years for 2 batches. Results showed that the specifications of HCTZ are met. HCTZ is known to be stable.

(1) Finished product

Stability data of 18 months (8°C, 30°C, 25°C/60% RH), 12 months (30°C/60% RH), 6 months (40°C/75% RH) and 3 months (50°C) were available at the time of submission for three 150 mg/12.5 mg tablet batches with different packaging materials including the package for marketing. An updated stability report presents 24-months data which support the proposed shelf-life of 24 months when stored at temperature up to 30°C.

Stability data were available at the time of submission for one 300 mg/12.5 mg batch in HDPE bottles and clear blisters up to 6 months (8°C, 50°C, 25°C/60% RH; 30°C/60% RH; 40°C/75% RH), for 2 batches in clear blister and one batch in HDPE bottle with desiccant for 3 months. An updated stability report presents 12-months data on one batch and 6-months data on two other batches.

The batches meet the specifications proposed, except one batch of 300 mg/12.5 mg tablets packaged in clear blister for which the upper specification for a degradation product/total impurities was exceeded under storage conditions of 45°C/75%RH.

For the 300 mg/12.5 mg strength, no results were presented for the marketing packaging material neither for the minimum period of 6 months as set out in the CPMP ICH stability guideline implemented in January 1998. Results from stability studies will be submitted for the first three batches of the 300 mg/12.5 mg strength tablets made at the commercial scale and packaged in the commercial blister opaque package.

Results from additional stability studies showed that tablet qualities were not affected by the freeze/thaw cycle and two different light sources.

Bioequivalence

A capsule formulation of irbesartan and a tablet formulation of HCTZ were used in the core efficacy and safety trials. Two separate 2-way, crossover studies (**study CV131-054**, **study CV131-100**) were conducted. Both strengths of irbesartan/HCTZ combination tablet formulations are bioequivalent to the clinical irbesartan capsules and HCTZ tablet formulations.

Film-coated tablets

Composition

The medicinal product is presented also as film coated tablets containing 150/12.5 mg and 300/12.5 mg of irbesartan and hydrochlorothiazide respectively as active ingredients. Other ingredients include lactose monohydrate as diluent, microcrystalline cellulose as diluent and binder, hypromellose as binder, croscarmellose sodium as disintergrant, silicon dioxide as glidant and magnesium stearate as lubricant. The film coating consists of a commercially available film coating material containg lactose monohydrate, hypromellose, titanium dioxide, macrogol 3000 and yellow and red iron/ferric oxides (Opadry II pink 32F24503) and carnauba wax as a polishing agent.
The product is packaged in the same packaging as the approved formulation.

Active substance

The manufacturing method and the specifications of the active substances remain the same as the ones used for the uncoated tablets.

Other ingredients

Except for Hypromellose, Opadry II pink 32F24503 and Carnauba wax, all other excipients are already used in the currently approved formulation. The excipients comply with Eur. Ph. Requirements and Opadry II pink is controlled according to an in house monograph, which employs simple identification procedures derived from compedial methods, which are specific to the ingredients to be identified.
There are two potential specified risk materials used in the proposed formulation: lactose monohydrate in the film coating and magnesium stearate. A TSE certificate of suitability has been provided together with a confirmation from the manufacturer of lactose monohydrate that it is derived from milk from healthy animals in the same conditions as the one collected for human consumption in accordance with the CPMP "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products". Magnesium stearate is of vegetable origin.
The packaging materials are the same as for the uncoated tablets

Product development and finished product

The new formulation of irbesartan/hydrochlorothiazide film coated tablets has been developed in order to mask the bitterness of the drug substances by applying a film coating to the tablet that does not change its dissolution profile. In addition, some minor changes have been in the formulation. Among them is the replacement of pregelatinized maize starch and poloxamer with hypromellose and the decrease in the size of the tablet keeping the shape similar to that of the currently marketed tablets and change of the code number engraved on the tablet

The manufacturing process is a standard wet granulation method and remains unchanged except for the addition of a final coating step.
In process control data from testing at various points during manufacturing showed consistent results, which complied with the specifications and show no significant variation between or within batches. Process validation results from two batches on the critical parameters affecting the granulation, tableting and coating process confirm that the manufacturing method is robust and reproducible and yields product with the same quality characteristics as the currently approved one.

Product specification

The specifications and analytical procedures for the proposed irbesartan film-coated tablets are the same as those for the currently approved product, with the exception of (i) appearance, which differs by an engraved digit code number, (ii) the addition of an identification test for the fim coating coloring agent, titanium dioxide and iron oxides (red/yellow) and (iii) the minor revision of the sample preparation procedure for the assay/degradants test .

Additional validation testing has been performed for some of the analytical procedures (identification, assay, degradation products and dissolution testing) due to the quantitative and qualitative changes of the excipients in the product formulation. The results confirm the lack of interference of the excipients used with the active substances and prove that the analytical meethods employed are suitable for the evaluation and release testing of the product.
Product specifications are justified by the results of the long-term stability studies and batch analysis data from four batches for eachcombination, manufactured using the same method and equipment as the proposed commercial ones. No new degradation products have been observed neither were any of the known degradants observed at higher levels than in the already approved formulation.

Stability of the Product

Three batches for each of the combinations packaged in the packaging intended for marketing have been placed in stability studies in accordance with ICH guidelines. Test results good stability at 40°C/75% RH, 30°C/60% RH and 25°C/60% RH. No significant attribute was noted for any batch.
As suggested from the stability studies results the proposed shelf life under the conditions specified in the SPC is acceptable. The stability studies for the proposed formulation will however continue for up to 36 months

Discussion on chemical, pharmaceutical and biological aspects

The addition of the coating step and the changes in the excipients have been adequately described and validated. The obtained stability results show no different trends form the coated formulation and justify the proposed shelf life under the specified in the SPC conditions.

3. Part III: Toxico-pharmacological aspects

Preclinical studies were carried out with the active substances in combination to identify potential interactions. These studies include:

- One pharmacodynamic study in spontaneously hypertensive rats
- One pharmacodynamic study in normotensive rats and monkeys
- Single oral toxicity studies in mice and rats
- Repeated oral doses toxicity studies over six months in rats and monkeys
- One reproduction toxicity study (teratogenesis) in rats
- Battery of genotoxicity tests *in vitro* and *in vivo*

Pharmacodynamics

Irbesartan

The pharmacodynamics of irbesartan are well known. Its effects were investigated *in vitro* and *in vivo* in various animal species including rodents, rabbits, dogs and monkeys. Irbesartan showed a high affinity and selective antagonism of the angiotensin II subtype AT_1 receptor.

HCTZ

The pharmacodynamics of HCTZ are well known. It reduces blood pressure in volume dependent and in salt-induced hypertension, as well as in renin-dependent hypertensive rat models.

Irbesartan and HCTZ

The combination of irbesartan/HCTZ was studied in normotensive rats and monkeys, and in spontaneously hypertensive rats. Data in normotensive rats and monkeys were obtained from 6-month toxicity studies carried out with irbesartan/HCTZ at doses of 10/10 and 90/90 mg/kg/day. The lower dose of 10 mg/kg of irbesartan corresponds to the maximum antihypertensive effect in most models of hypertension.

In the 6-month study of normotensive rats, the combination of irbesartan/HCTZ at doses of 10/10 and 90/90 mg/kg/day reduced systolic arterial pressure (SAP) with a dose-related effect, and with a tendency to a time-related effect between 15 and 24 weeks. After 6 months of treatment, the combination of irbesartan/HCTZ at 90/90 mg/kg caused a greater reduction of SAP with respect to irbesartan alone at 90 mg/kg. The combination 90/90 mg/kg/day was not consistently more effective in lowering SAP than irbesartan alone.

In normotensive monkeys, only the effect of the combination 90/90 mg/kg/day on SAP was statistically significant at the end of the 6-month oral study. Coadministration of irbesartan/HCTZ at a dose of 90/90 mg/kg provided a greater reduction in SAP than irbesartan alone at 90 mg/kg. Compared to the components, the effect was additive.

In spontaneously hypertensive rats, irbesartan was administered in a wide range of pharmacologically active doses (up to 13 mg/kg/day) with HCTZ (10 mg/kg). Oral administration at 13/10 mg/kg for three days led to a maximum antihypertensive effect from days 1 to 3. This antihypertensive effect was significantly higher than that observed at the equivalent dose of irbesartan administered alone on days 1 and 2. Administration of irbesartan produced decreases in mean arterial pressure, which were not dose-dependent on day 1 and 2. However, dose-dependency was demonstrated on day 3.

The studies with the association were considered well designed although some did not comply with GLP. Although the additive antihypertensive effect of the combination was convincingly demonstrated only in spontaneously hypertensive rats, the doses selected and the ratio of doses of irbesartan and HCTZ were considered adequate.

Pharmacokinetics

Pharmacokinetic data for each component were obtained from the toxicokinetic data in the 6-month studies carried out in rats and monkeys with the irbesartan/HCTZ association at doses of 10/10 mg/kg and 90/90/mg/kg/day.

Irbesartan

The pharmacokinetics of irbesartan are well known in the animal species studied (rats and monkeys). Irbesartan is completely and rapidly absorbed after oral administration. Bioavailability is low in rats because of the extensive first hepatic pass. In monkeys, bioavailability is above 60%. Irbesartan and its metabolites are quickly distributed in most organs and tissues, including intrauterine tissue, and are excreted in milk. The ratio of tissue/plasma concentrations (as measured by radioactivity) is less than one for most tissues.

The main compound in plasma is the unchanged active substance. In animals, the main elimination route is N-glycosidation, followed by biliary excretion, and finally faecal excretion. All metabolites detected in humans are observed in the animal species studied.

CYP2C9 is the most important enzyme in the oxidative metabolism of irbesartan. *In vitro* studies showed significant inhibition of the formation of oxidised metabolites of irbesartan with known substrates inhibiting CYP2C9 (warfarine, tolbutamide, sulphaphenazol and nifedipine). Results of *in vivo* studies, however, indicated a lack of significant interaction between irbesartan and warfarine or nifedipine.

HCTZ

The main pharmacokinetic parameters of HCTZ were obtained from humans. HCTZ is absorbed rapidly with a bioavailability of around 60% after oral administration. Plasma levels and urinary excretion of HCTZ are dose proportional. HCTZ accumulates in erythrocytes and does not significantly bind to plasma proteins. It passes the placental barrier and is excreted in milk. The substance is slightly metabolised in rats, monkeys, and almost completely excreted in humans as an unchanged substance in urine. Urinary excretion is around 50-70% of the administered dose.

Irbesartan/HCTZ

Both in rats and monkeys, plasma concentrations and T_{max} of irbesartan following oral administration of irbesartan/HCTZ at a dose of 90/90 mg/kg/day, or irbesartan alone at a dose of 90 mg/kg/day were comparable, suggesting that HCTZ does not alter the availability and the exposure of irbesartan.

However, a pharmacokinetic interaction was observed in rats and macaques when HCTZ was given in combination with irbesartan (90/90 mg/kg/day). Plasma concentrations of HCTZ were consistently higher when HCTZ was given with irbesartan. Exposure to HCTZ increased by 60 % in macaques and 86 % in rats with the administration of the irbesartan/HCTZ combination (90/90 mg/kg/day) compared to HCTZ alone (90 mg/kg/day). The mechanism whereby irbesartan increases plasma levels of HCTZ is not clearly established. However, this increase does not represent a safety concern because the interaction was not observed in man and HCTZ AUCs in animals are approximately 100 times higher than human AUCs at the therapeutic dose.

Pharmacokinetic data in animals for the separate species were scant but it must be taken into account that both substances are used in therapy for humans and that toxicokinetic trials considered as sufficient were carried out with the association of irbesartan/HCTZ. All metabolites detected in

humans were observed in various biological fluids in the different species studied.

Toxicology

The toxicity profiles for both compounds administered separately were well described.

Single dose toxicity

Irbesartan/HCTZ combination up to maximum doses of 2,000/4,000 mg/kg in mice or 3,000/500 mg/kg in rats did not show any indication of toxicological interaction.

Repeated dose toxicity

In a six-month repeated dose toxicity study in rats, the drug-related changes were decreased SAP, slight decreases in haemoglobin and erythrocyte count, serum cholesterol and triglycerides, decreased heart weight, decreased liver weight in males, hypertrophy/hyperplasia of the juxtaglomerular apparatus, and a reduced incidence of progressive nephropathy. These were observed in the irbesartan (90 mg/kg) and in the combination (10/10 and 90/90 mg/kg) groups and were attributable to irbesartan. However, in the 26-week toxicology study in rats with irbesartan alone, irbesartan 90 mg/kg/day did not cause hyperplasia/hypertrophy of the juxtaglomerular apparatus. The company further discussed the discrepancies in this well-known response affecting the renin angiotensin system. It was agreed that these observations have no safety implications for humans as they seem to be class-specific (described also for irbesartan alone and other AGII antagonists such as losartan).

In the toxicological studies, the ratio of the doses of irbesartan/HCTZ was different from the ratio of the recommended therapeutic dosage. At the time the studies were initiated, the ratio of irbesartan/HCTZ to be used for the clinical dosage form was not yet established. The doses for the toxicological studies with irbesartan/HCTZ combination were selected to detect additive or potentiated toxicological effects when the two drugs were co-administered. The most appropriate dose for irbesartan was decided first and thereafter, the most appropriate dose of HCTZ was added.

Most of the treatment-related changes observed after repeated oral administration of irbesartan alone were generally evident in both rats and macaques at 90 mg/kg/day. This dose was 15-times the maximum human dose of 300 mg/day and corresponds to an exposure to irbesartan at least equal to that observed in humans. It was considered useful for identifying potential toxicological interactions between the two without undue risk of mortality. The 1/1 ratio was selected to allow for the maximal exposure to the two drugs when coadministered and maximises the chances of identifying any interactions between the two drugs. This 1/1 ratio represents a conservative approach. Use of clinical ratios (12/1 and 24/1) would have resulted in HCTZ doses of only 7.5 or 3.75 mg/kg/day. Based on the fact that HCTZ is well tolerated in animals, it was decided that administration of HCTZ at 90 mg/kg/day would maximise the chances of observing a toxicological interaction.

Digestive tract lesions (stomach discoloration, ulcers and necrosis) were observed in rats with the irbesartan 90 mg/kg/day, HCTZ 90 mg/kg/day and combination (10/10 mg/kg/day and 90/90 mg/kg/day) groups. These findings were not observed previously in studies with irbesartan alone at these dose levels. Relevant differences in the conduct of the studies may have accounted for the differences in the gastric lesions findings. These findings were further discussed by the company and the clarifications were considered acceptable.

In a six-month oral toxicity study in macaques, drug-related changes were mild-to-moderate decreases in blood pressure and juxtaglomerular hypertrophy/hyperplasia. These changes were attributable to irbesartan. Changes seen only at 90/90 mg/kg/day of the combination were decreases in haemoglobin, erythrocytes and serum sodium, moderate increase in serum urea nitrogen and mild to moderate increase in serum creatinine.

Reproduction studies

No specific fertility studies were carried out with the irbesartan/HCTZ combination as neither irbesartan nor HCTZ have revealed evidence of adverse effects on fertility when administered separately. Although another angiotensin-II antagonist (losartan) alone did not impair female fertility in rats, it did so following coadministration with HCTZ (the dose of HCTZ was smaller than that used in irbesartan studies). This change was not attributable to maternal toxicity. Therefore the company also submitted a review of all available evidence of the effect of HCTZ on fertility. No adverse effects

on fertility were reported in mice and rats of either sex with HCTZ at dose levels of up to 100 mg/kg/day and 4 mg/kg/day, respectively. Fertility studies with four fixed combinations medicinal products containing HCTZ with bisoprolol, losartan, metoprolol and reserpine showed that with the exception of losartan there were no adverse effects on fertility with these combination products. No toxicological effects on the gonads were observed in rats and macaques with irbesartan/HCTZ combination.

Irbesartan administered during pregnancy has been shown to produce slight and reversible toxicity in rat foetuses, an increase in the incidence of resorptions in rabbits and a slight delay in weight gain of offspring during lactation.

Irbesartan was shown to produce no teratogenic effects. Likewise, HCTZ was tested in teratology studies in mice and rats and failed to demonstrate any adverse effects on the developing foetus. The teratogenic effects of irbesartan and HCTZ were studied when administered together or separately, to pregnant rats at doses of up to 150/150 mg/kg/day. This study revealed only slight maternal toxicity characterised by a reduction in the body weight gain together with a slight reduction in the weight of the foetuses within the group receiving the combination at a dosage level of 150/150 mg/kg. No other treatment-related effects were observed during gestation or at necropsy. No teratogenic effects were detected.

Justification provided for not carrying out toxicity studies in non-rodent species was considered acceptable. Because only very low doses of medicinal products interacting with the renin angiotensin system in combination would be tolerated, rabbits have seldom been used to evaluate their potential teratogenic effect.

The reproduction studies did not reveal any additional potential toxicity with the irbesartan/HCTZ combination. Nonetheless this combination is contraindicated during pregnancy and breast-feeding.

Genotoxicity studies

Irbesartan alone gave negative results in a battery of *in vitro* and *in vivo* tests. HCTZ gave ambiguous evidence of *in vitro* genotoxicity.

HCTZ brought about gene mutations in mouse lymphoma cells and increased sister chromatid exchange in Chinese hamster cells with negative results in other tests. The potential genotoxicity of the irbesartan/HCTZ combination was studied in three *in vitro* tests (Ames test, gene mutations in Chinese hamster cells and cytogenetic study in human lymphocytes) together with an *in vivo* test (Micronucleus in the mouse). The proportion was 1/1 irbesartan/HCTZ to allow the maximum exposure to both medicines at very high concentrations, close to the cytotoxicity threshold in the *in vitro* tests, and at doses up to 2,000/2,000 mg/kg in the *in vivo* Micronucleus test. Results did not indicate genotoxic effects of the combination.

Although some experimental models have reported evidence of genotoxicity and carcinogenicity with HCTZ, there is no evidence of such effect in humans.

Carcinogenicity studies

No carcinogenic effects were reported in mice and rats receiving irbesartan at doses which represent a ratio of exposure to irbesartan ranging from 3.6 to 25 compared to humans receiving the maximum dose of 300 mg/day.

Equivocal evidence for carcinogenic effects was reported with HCTZ in rodent carcinogenicity studies: male mice given high doses (i.e. approximately 600 mg/kg/day) of HCTZ for 2 years had a slight increase in liver tumours. There was no evidence of an increase in tumours in female mice or rats of either sex given HCTZ for 2 years. HCTZ has been extensively used as a diuretic and antihypertensive agent since 1957 at doses higher than that to be used in the irbesartan/HCTZ combination and despite the equivocal nonclinical findings, there has been no evidence of carcinogenicity in humans.

No specific carcinogenicity study has been carried out with the irbesartan/HCTZ combination. There were no carcinogenic effects with either compound when administered alone, and the results of 6-month studies in rats and macaques with the combination showed no significant toxicological interactions and no preneoplastic lesions suggesting a carcinogenic effect which were not seen with

either drug alone. The conduct of a specific carcinogenicity study with irbesartan and HCTZ in combination would have therefore provided no additional information useful to the safety evaluation of the two drugs.

Other studies

No phototoxicity or photoallergy has been observed with irbesartan.

Ecotoxicity/Environmental risk assessment

The use of irbesartan/HCTZ combination is not considered to have hazardous effects on the environment.

4. Part IV: Clinical aspects

The clinical development program included a total of over 2500 patients with mild to moderate hypertension treated with irbesartan and HCTZ in combination, including over 600 elderly patients and 121 patients with severe hypertension. Aside from the long term extensions, the duration of the studies ranged from 8 to 24 weeks. Studies with the combination in other special populations (patients with renal or hepatic impaired function) were not performed.

Human pharmacology

The pharmacodynamics and pharmacokinetics of both irbesartan and HCTZ are well known. Therefore only a very limited clinical pharmacology program involving 115 subjects in four studies was conducted.

Pharmacodynamics

The pharmacodynamic profile of irbesartan in humans has been established through single and multiple-dose studies both in healthy volunteers and hypertensive patients. These studies confirmed the blockade of angiotensin II receptors as the mechanism of action of irbesartan.

HCTZ is a well known diuretic, widely used as antihypertensive agent that increases sodium, chloride, water and potassium excretion, and produces a mild but progressive volume contraction and secondary activation of the renin angiotensin system (RAS). The blood pressure lowering effects require several weeks to reach a maximum.

One pharmacodynamic study evaluated the association of irbesartan and HCTZ (**Study CV131-005**). In this study, 25 mg HCTZ was administered to patients with mild to moderate hypertension for 7 days following the administration of 150 mg irbesartan over a 7 day period. The plasma levels of AII and PRA increased more with irbesratan/HCTZ than with irbesartan alone. The reductions in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were greater in the irbesartan/HCTZ group than in irbesartan/placebo group; the difference was statistically significant.

Pharmacokinetics

Study CV131-005 was a randomised, double-blind, placebo-controlled trial in patients with mild to moderate essential hypertension (seated DBP 95 to 110 mmHg) to compare the pharmacokinetics of irbesartan when coadministered with HCTZ vs. when administered alone.

36 subjects were randomised to receive either irbesartan 150 mg for 7 days then irbesartan 150 mg and HCTZ 25 mg for 7 days, or irbesartan 150 mg for 7 days then irbesartan 150 mg and placebo for 7 days.

There were no significant differences in C_{max}, T_{max} and AUC of irbesartan following irbesartan and HCTZ for 7 days as compared to irbesartan and placebo for 7 days, when compared to the first 7 days of treatment in which each treatment group received only irbesartan.

Study CV131-123 was a 2-way crossover study to evaluate the effect of irbesartan on the pharmacokinetics of HCTZ. Twenty healthy subjects (11 males and 9 females) were enrolled and 19 completed the study. Each subject received a single 12.5 mg tablet of HCTZ or a 300/12.5 mg irbesartan/HCTZ combination tablet according to a randomisation schedule. All parameters were within limits of bioequivalence.

Coadministration of irbesartan and HCTZ produced the expected pharmacodynamic effects and demonstrated that the agents have additive antihypertensive effects. Concomitant administration of HCTZ and irbesartan has no effect on the pharmacokinetics of either drug.

Study CV131-069 was a single centre, open label, single dose, cross-over study to investigate the effect of food on the oral bioavailability of a irbesartan/HCTZ combination tablet. 16 healthy male volunteers received a single irbesartan/HCTZ (150 mg/12.5 mg) combination tablet under either fasted or fed conditions.

When the combination was given with food, a statistically significant prolongation of T_{max} was observed for irbesartan. A decrease in C_{max} and a prolongation of T_{max} was observed for HCTZ when the combination was given with food.

The prolongation of T_{max} for irbesartan or T_{max} and C_{max} for HCTZ will not probably have clinical relevance in a multiple dose posology since the AUC does not change.

Study CV131-054 was a single dose, open label, 2-way crossover study to assess the bioequivalence of the combination tablet of irbesartan/HCTZ (150 mg/12.5 mg) compared to the individual irbesartan 150 mg capsule and HCTZ 12.5 mg tablet used in the clinical studies. 37 healthy male volunteers were randomised to receive a single 150 mg dose of irbesartan and a 12.5 mg dose of HCTZ either as a combination tablet or as individual formulations following a 10 h fast on two separate occasions.

The 90% confidence intervals (CI) for AUC and C_{max} of the combination are within the accepted limits for bioequivalence. No statistically significant differences were found in the median T_{max} values of either irbesartan or HCTZ between the combination tablets and the reference.

Study CV131-100 was a single dose, open label, 2-way crossover study to assess the bioequivalence of the intended commercial combination tablet of irbesartan/HCTZ (300 mg/12.5 mg) compared to the individual components, irbesartan (3x100 mg capsule) and HCTZ 12.5 mg tablet used in the clinical studies.

The 90% confidence intervals for AUC and C_{max} of the combination are within the accepted limits for bioequivalence. No statistically significant differences were found in the median T_{max} values of either irbesartan or HCTZ between the combination tablets and the reference. However, the T_{max} for HCTZ was higher for the combination tablet in comparison to the reference formulation.

Clinical experience

Efficacy

Placebo-controlled studies

All placebo-controlled studies were multicentre, randomised, double-blind in patients with mild-to moderate hypertension

Study CV131-037 was a 4x4 factorial (16 cell) trial of multiple doses of irbesartan and HCTZ. The aim of the study was to assess the dose-relationship in blood pressure reduction following 8 weeks administration of combinations of irbesartan and HCTZ. The primary efficacy endpoint was the change from baseline in trough DBP.

683 patients were randomised for 8 weeks to receive once daily treatment with one of the different fixed doses of the combination of irbesartan (37.5 mg, 100 mg, 300 mg or placebo matching irbesartan) and HCTZ (6.25 mg, 12.5 mg, 25 mg or placebo matching HCTZ).

The proportion of subjects with normalised DBP increased as a function of dose for the combination therapy, the irbesartan monotherapy and the HCTZ monotherapy groups. In patients with irbesartan 100 mg/HCTZ 12.5 mg treatment, seDBP was reduced by 11.9 mmHg and normalised in 61 % of patients, while in patients with irbesartan 300 mg treatment seDBP was reduced by 10.2 mmHg and normalised in 49 % of patients. However, in patients receiving irbesartan 300mg/HCTZ 12.5 mg, seDBP reduction was the highest, 15.0 mmHg and it normalised in 65 % of the patients. Placebo-adjusted trough-to-peak ratios for seDBP were over 0.67 in combination regimens with HCTZ 12.5 mg and lowest in irbesartan monotherapy groups, e.g. 0.54 in patients receiving irbesartan 37.5 mg and 0.55 in patients receiving irbesartan 300 mg. The study had approximately 40 patients per cell, and was not powered to assess individual cells vs one another or vs placebo. The fact that the global

statistical test was positive ($p < 0.001$) indicates that at least one combination dose produced larger BP reduction than either its components.

Study CV131-038 was a 12-week study to compare two combinations of irbesartan/HCTZ (75 mg/l2.5 mg and 150 mg/12.5 mg) with their individual components and with placebo in 819 patients.

The primary endpoint (change from baseline of trough seDBP at week 12) showed statistically significant reductions over placebo in all active treatment groups. The combination treatment demonstrated statistically significant reductions compared to its component treatment ($p < 0.01$). Only the combination doses produced blood pressure normalisations that differed statistically significantly from that of placebo ($p<0.01$).

Irbesartan 150 mg/HCTZ 12.5 mg combination produced a placebo-adjusted, mean trough seDBP reduction of 2.3 mmHg greater than irbesartan 150 mg and 3.8 mmHg greater than HCTZ 12.5 mg (combination vs. components, $p < 0.01$).

Study CV131-039 randomised 178 patients to receive once daily combination of irbesartan 75 mg/HCTZ 12.5 mg, irbesartan 150 mg/HCTZ 12.5 mg or placebo. The primary efficacy endpoint was the reduction in the mean 24-hour ambulatory diastolic blood pressure (ADBP) from baseline to the end of the 8 weeks period.

Results showed statistically significant reductions ($p<0.01$) in the mean 24 hour ADBP and ASBP daytime, in the trough 24th hour ADBP and ASBP and in the trough office seDBP and seSBP for both irbesartan/HCTZ groups compared with placebo.

Add-on studies

Study CV131-040 was a multicentre, randomised, double-blind, and placebo controlled study in 238 hypertensive patients not adequately controlled (DBP 93-110 mmHg) after receiving HCTZ 25 mg once daily for 4 weeks.

Results showed statistically significantly greater reductions in trough and peak DBP and SBP at week 12 with irbesartan/HCTZ compared to placebo/HCTZ.

Study CV131-025 was a multicentre, randomised, double-blind, placebo controlled study in patients with mild to moderate hypertension (DBP 95-110 mmHg). 319 patients were randomised for 8 weeks to receive once daily treatment of irbesartan 100 mg, 200 mg, 300 mg or placebo. After 8 weeks, patients with seDBP = 90 mmHg were given, in addition to blinded study medication, HCTZ 12.5 mg for additional 2 weeks. The primary efficacy endpoint was a change from baseline in trough DBP at week 8 of double-blind treatment.

The proportion of subjects with normalisation of seDBP at week 8 to < 90 mmHg showed a 44%, 41% and 60% response, respectively, with irbesartan 100 mg, 200 mg and 300 mg. Placebo response was 23%. In addition, in the subjects who were not well controlled at week 8, the addition of HCTZ 12.5 mg normalised, at week 10, 14% (6/42) of the subjects already treated with placebo, 27% (8/30) of those treated with irbesartan 100 mg, 30% (10/33) of those treated with irbesartan 200 mg and 57% (12/21) of those treated with irbesartan 300 mg. However, the number of the patients in this period was too low (21 patients in the group of irbesartan 300 mg) and the duration of the treatment too short (2 weeks) to draw valid conclusions.

Conclusions on placebo controlled studies

Irbesartan 300 mg/HCTZ 12.5 mg, irbesartan 150 mg/HCTZ 12.5 mg and irbesartan 75 mg/HCTZ 12.5 mg combination doses were shown to be significantly more effective than either component alone. The placebo-subtracted, mean trough blood pressure reduction achieved with irbesartan 150 mg/HCTZ 12.5 mg was 12.9-18.0/6.9-9.6 mmHg (CV131-038, CV131-039). With this combination dose, blood pressure was normalised (seDBP <90 mmHg) in 56-69 % of the patients. With irbesartan 150 mg, only 39 % of the patients achieved normalisation. The trough-to-peak ratio for seDBP was 0.68 with irbesartan 150 mg/HCTZ 12.5 mg combination treatment and 0.64 with irbesartan 150 mg treatment.

Irbesartan 300 mg/HCTZ 12.5 mg produced reductions of 15.9/15.0 mmHg in trough blood pressure compared with reductions of 14.9/10.2 mmHg in the irbesartan 300 mg group and 8.9/6.2mmHg in the

HCTZ 12.5 mg group (reductions of 2.3/3.5 mmHg in the placebo group). However, only 43 patients received the dose of irbesartan 300mg/HCTZ 12.5 mg in a randomised, double-blind, placebo-controlled study (CV131-037) and there was no statistically significant evidence of its superiority to its components or to the lower combination dose of irbesartan 150 mg/HCTZ 12.5 mg.

The effect of adding irbesartan or HCTZ to patients not adequately controlled by either component alone was studied in trials CV131-025 and CV131-040. When HCTZ 12.5 mg was given in an open label setting as an adjunctive treatment to patients not adequately controlled by irbesartan 300 mg alone (seDBP = 90 mmHg), further decreases in the mean trough blood pressure were noticed. However, only 21 patients received irbesartan 300 mg followed by additional HCTZ 12.5 mg and, therefore, these results are only suggestive (CV131-025).

Active controlled studies

All active controlled studies were multicentre, randomised, and double-blind trials.

Study CV 131-032 was an enalapril controlled study in subjects with severe hypertension (DBP 115-130 mmHg). 182 patients were randomised to receive irbesartan 150 mg or enalapril 20 mg once daily for 12 weeks.

The primary objective was to assess the change from baseline in trough DBP. The doses were doubled for patients with seDBP = 106 mmHg at the end of week 1 or seDBP = 90 mmHg at the end of week 2. Thereafter, at each study visit, adjunctive open-label antihypertensive therapy (HCTZ 25 mg, followed by a long-acting nifedipine 30 mg titrated to 60 mg and/or atenolol 50 mg titrated to 100 mg) was added if seDBP was = 90 mmHg. Approximately 85 % of patients in both treatment groups were titrated to the second level (irbesartan 300 mg or enalapril 40 mg) plus HCTZ 25 mg by week 12, and most were receiving other adjunctive medications as well.

Results showed that there was no statistically significant difference between irbesartan and enalapril regimens. The percentage of patients on irbesartan in need of triple antihypertensive therapy was 58% while 68% of the patients randomised to enalapril required such additional treatment.

This study was not considered supportive to the demonstration of added benefit of 300 mg/12.5 mg versus 300 mg, because the dose of HCTZ was 25 mg.

Study CV131-041 was conducted in elderly patients (=65 years) with mild to moderate essential hypertension (seDBP 90-110 mmHg). 234 patients were randomised for a treatment duration of 8 weeks (with 24 weeks in the extension study) to receive either losartan 50 mg or irbesartan 75 mg or irbesartan 150 mg (N=79), each in combination with open label HCTZ 12.5 mg, once daily for 24 weeks.

The primary efficacy variable was the change from baseline in trough seDBP at week 8 of treatment.

Results showed that at week 8 there were no statistically significant differences between groups. At week 24, no statistically significant differences were observed.

At the end of the study (week 24), adjunctive nifedipine (predominantly 20 mg daily) was used by 29% of the losartan/HCTZ group, 28% of the irbesartan/HCTZ 75/12.5 group, and 19% of the irbesartan/HCTZ 150/12.5 mg group. The incremental systolic/diastolic blood pressure reductions amounted to 4-7/5-6 mmHg when nifedipine was added to irbesartan/HCTZ and 10/5 mmHg when it was added to losartan/HCTZ. A few subjects received add-on atenolol.

Study CV131-042 was conducted in patients with severe essential hypertension (seDBP 115-130 mmHg). 207 patients were randomised for a duration of treatment of 12 weeks to receive once-daily oral regimen of irbesartan 75 mg/HCTZ 12.5 mg, irbesartan 150 mg/HCTZ 12.5mg or losartan 50 mg/HCTZ 12.5 mg.

The primary efficacy variable was the change from baseline in trough seDBP at week 12 of treatment. HCTZ was dispensed open-label. Patients who had seDBP = 106 mmHg at the end of the 1 week of double-blind study medication, or seDBP = 90 mmHg at the end of 2 weeks had their initial regimen dose doubled to irbesartan 150 mg/HCTZ 25 mg, irbesartan 300 mg/HCTZ 25 mg or losartan 100 mg/HCTZ 25 mg. Thereafter, at each study visit (week 2, 4, 6, 8 and 10) the patients with seDBP = 90 mmHg had an adjunctive open-label antihypertensive therapy (long-acting nifedipine 30 mg titrated to 60 mg and/or atenolol 50 mg titrated to 100 mg) added as needed to normalised seDBP.

Results showed that at week 12 there were no statistically significant differences between groups. However, the demographic characteristics were slightly different between irbesartan and losartan group. Losartan group presented a higher baseline seDBP and a lower age, and more women than men.

The proportion of patients requiring addition of nifedipine and/or atenolol was lowest in the irbesartan 150 mg/HCTZ group (71% vs. 87% for irbesartan 75 mg, 90% for losartan 50 mg/HCTZ). The proportion of patients in whom DBP was controlled without doubling the initial dose was 8% for irbesartan 150 mg/HCTZ and 0% for irbesartan 75 mg/HCTZ and losartan 50 mg/HCTZ. However, this difference was not statistically significant.

At week 12, most patients were receiving adjunctive medication. Approximately equal numbers of subjects were receiving nifedipine or nifedipine plus atenolol, and a few (approx. 7%) of subjects were receiving add-on atenolol only. Nifedipine 30-60 mg resulted in substantial further BP reductions of 10-18/9-12 mmHg when added to irbesartan/HCTZ, and 14/10 mmHg when added to losartan/HCTZ

Study CV131-064 was a multicentre, randomised, double-blind, active controlled study in 193patients with mild-to-moderate hypertension to compare irbesartan 75 mg and losartan 50mg during 8 weeks treatment period. Both agents could be uptitrated in case of insufficient response to 150 mg and100 mg, respectively. The primary efficacy endpoint was the change in trough seDBP. After the 8 weeks blinded phase, patients who had seDPB = 90mmHg were randomised on open label basis to either irbesartan 300mg or irbesartan 150mg+HCTZ 12.5mg.

54 patients randomised to the open treatment phase completed the study. 29 subjects in the irbesartan 75-150 mg group and 25 subjects in the losartan 50-100 mg group did not achieve a trough seDBP < 90 mmHg after 8 weeks of treatment. These patients were re-randomised to receive open label treatment for 4 weeks with either irbesartan monotherapy 300 mg or irbesartan 150 mg/HCTZ 12.5 mg. The seDBP was reduced in both groups by approximately 10mmHg. The differences in the change of trough seSBP or in the number of responders were not significant between the groups either. A dose increase during the first 8 weeks was necessary in 46% and 44% of irbesartan and losartan treated patients, respectively. Therefore for patients not adequately controlled by irbesartan 150 mg, the two alternative next steps, 150 mg/12.5 mg combination or continued monotherapy at an increased dose of 300 mg of irbesartan, provide comparable efficacy. A marginal incremental efficacy of the combination irbesartan/HCTZ 150 mg/12.5 mg over irbesartan 300 mg alone was observed. The benefit of a back titration of irbesartan before adding HCTZ would be a less than optimal strategy for non-responders.

The small sample size and small number of patients/centre prevents any firm conclusions. However, it is interesting to note that irbesartan 150mg+HCTZ 12.5mg seems to be at least as effective as irbesartan 300mg.

Compared with 300 mg and 100/12.5 mg and 200/12.5 mg, a moderate further decrease in blood pressure is observed at 300/12.5 mg.

Study CV131-077 compared irbesartan and amlodipine based regimens in patients with mild-to-moderate hypertension. Patients received either irbesartan 150 mg or amlodipine 5 mg once daily. If trough seDBP was >90 mmHg at week 4, the dosage of study medication was doubled. At the end of week 8, if trough seDBP was still >90 mmHg, open-label HCTZ 12.5 mg was added for the remaining 4 weeks. Subjects whose seDBP was >90 mmHg at week 8 but who had not undergone titration at week 4 also received add-on HCTZ 12.5 mg.

At the end of week 12, add-on HCTZ was taken by 31/67 irbesartan patients (46%) and 28/72 amlodipine patients (39%), of whom 27 and 22 were receiving irbesartan 300 mg and amlodipine 10 mg, respectively. From week 8 to week 12, in subjects who received add-on HCTZ the incremental decrease in seDBP was 7.3 mmHg in the irbesartan group and 3.6 mmHg in the amlodipine group. At the same time point, the overall normalisation rate with the regimen, including irbesartan/HCTZ 300/12.5 mg, was similar to that seen with a regimen including the combination of amlodipine 10 mg and HCTZ 12.5 mg: 64% and 68%, respectively.

In patients not normalised on irbesartan 300 mg alone, the additional normalisation provided by add-on HCTZ 12.5 mg was observed in 15/27 patients (55%).

The proportion of non-responders to irbesartan 300 mg who responded to add-on HCTZ 12.5 mg was substantial in this small study.

Study CV131-031 included 20 patients receiving HCTZ in addition to amlodipine 10 mg. 11 (55%) were normalised at 1 month. Twenty-seven (27) patients received HCTZ in addition to irbesartan 150 mg, of whom 12 (44%) were normalised at 1 month. 2 patients were not controlled by 75 and 300 mg of irbesartan and were normalised after adding HCTZ. The number of patients who received HCTZ were too low to demonstrate the benefit of 300 mg/12.5 mg versus irbesartan 300 mg in this study.

Study CV131-027 compared irbesartan at doses up to 150 mg with atenolol at doses up to 100 mg followed by the addition of open-label HCTZ 12.5 mg in non-responders. The proportion of non-responders to irbesartan 150 mg who responded to add-on HCTZ 12.5 mg was 37 %.

Conclusion on active controlled studies

In active-controlled studies, irbesartan 75mg/HCTZ 12.5 mg and irbesartan 150 mg/HCTZ 12.5 mg combinations were at least as effective as the losartan 50 mg/HCTZ 12.5 mg combination dose in the treatment of elderly patients with mild-to-moderate hypertension (CV 131-041). In the treatment of severe hypertension (seDBP 115-130 mmHg), irbesartan 75 mg/HCTZ 12.5 mg and irbesartan 150 mg/HCTZ 12.5 mg combinations were as effective as the losartan 50 mg/HCTZ 12.5 mg combination (CV131-042). In the treatment of severe hypertension the regimen starting with irbesartan 150 mg, gave comparable results with enalapril 20 mg (CV131-032).

The incremental antihypertensive efficacy after adding beta-adrenergic antagonists or long-acting calcium channel blockers to irbesartan/HCTZ were addressed in two controlled studies, several long-term extension studies, and a third controlled study in which most subjects first received irbesartan plus HCTZ. These studies include approximately 200 subjects on irbesartan/HCTZ who received atenolol, and approximately 300 subjects who received add-on nifedipine.

The usefulness of adding a third treatment was assessed for patients who received add-on nifedipine and/or atenolol for BP control after 1 month. In the long-term extension combination studies, the dose of HCTZ was 25 mg, which is not the dose in the combination tablet, and in the long-term extension monotherapy the number of the patients was low. The evidence was not sufficient to recommend particular medicinal products to be added when the BP is not controlled with irbesartan/HCTZ . The fact that the antihypertensive effect of combination of irbesartan and HCTZ (not necessarily at the doses of irbesartan 300 mg/12.5 mg and irbesartan 150 mg/12.5 mg) may be increased with the concomitant use of other antihypertensive agents is already mentioned in section 4.5 Interactions with other medicinal products of the Summary of Product Characteristics.

Long- term extensions, open label studies

Ten double blind studies were followed by open label long-term extensions. In seven studies (CV131-002, CV131-025, CV131-027, CV131-028, CV131-029, CV131-01, CV131-050), subjects completing the double-blind period had the option of enrolling in an open label treatment with irbesartan plus HCTZ and adjunctive treatment, if needed. One study in patients with severe hypertension (controlled with enalapril) was also conducted. No studies on the effects of irbesartan/HCTZ in special populations (renal and hepatic impairment) were conducted.

A total of 1542 patients entered the long-term open label phase of irbesartan/HCTZ combination therapy studies. The patient population included 293 elderly (>65 years) and 50 very elderly (>75 years). Of the 1542 patients entering the extensions, 195 patients received irbesartan/HCTZ and at least one adjunctive medication at any time during the extensions. Of the 1231 subjects seen at month 12, 11% were receiving further adjunctive medication, predominantly atenolol and long-acting nifedipine.

All subjects received initially open label irbesartan/HCTZ or irbesartan once daily. If BP was not controlled, the initial dose of irbesartan/HCTZ or irbesartan could be increased; in the irbesartan monotherapy extensions, HCTZ was added next. Thereafter, once daily nifedipine or atenolol were added to achieve BP control. In two double-blind, randomised placebo-controlled trials, HCTZ was added in non responders to irbesartan monotherapy. The double blind phase of study CV131-032 compared 2 titration schemes with irbesartan and enalapril in severely hypertensive subjects and was

followed by an open-label irbesartan phase where HCTZ could be added.

Regarding normalisation rates in studies allowing titration to irbesartan 300 mg, 83% of 821 patients seen at month 12 had a normalised seDBP. Of these normalised subjects, 62% were on irbesartan monotherapy and an additional 23% were on irbesartan/HCTZ only.

From the patients randomised to the main studies with fixed irbesartan/HCTZ combinations (CV131-037 and CV131-038), 67% and 78%, respectively, were recruited in the open label extension phases. Nine hundred out of 1098 patients completed the one year extension. Compared to the pre-treatment baseline, the mean change of seDBP ranged between -14.2mmHg and -15.7 mmHg at visits month 12. The corresponding range for seDBP was -19.l mmHg to 20.7 mmHg. Sixty two percent of patients achieved a clinically significant blood pressure reduction with irbesartan 150 mg/HCTZ 12.5 or less. However, it should be noted that 11.4% of the patients had irbesartan 300mg/HCTZ 25mg and 11.8% of the patients had additional antihypertensive treatment.

Safety

A total of 3164 subjects were enrolled in the completed irbesartan/hydrochlorothiazide clinical trials. Of them, 2746 subjects were exposed to irbesartan and HCTZ in combination including 96 irbesartan treated subjects in the clinical pharmacology studies, 2650 irbesartan/HCTZ treated subjects in the clinical/efficacy studies, and additional 1202 subjects who received irbesartan/HCTZ for the first time in the long term, open label extension studies. 620 subjects were elderly subjects. 1542 patients (296 elderly) were exposed for more than 6 months, and 968 subjects (178 elderly) for at least 1 year. In double-blind, placebo-controlled studies, 994 patients received an irbesartan/HCTZ combination. A combination dose of irbesartan 150 mg/HCTZ 12.5 mg or more was received by 1770 patients. The exposure time was at least 6 months for 897 patients and one year or more for 288 patients. 938 patients received doses of irbesartan 300 mg/HCTZ 12.5 mg or more. The exposure time to this dose was at least 6 months for 523 patients and at least one year for 111 patients.

Various subgroups were represented in studies. These included 1049 women, 620 elderly (> 65 years), 98 very elderly (> 75 years), 351 blacks and 259 patients in "other" racial groups.

Placebo-controlled trials (CV131-037, CV131-038, CV131-039)

The frequency of all adverse events (AE) was similar or slightly higher with irbesartan/HCTZ (59%) than with irbesartan alone (56%), HCTZ alone (58%) or placebo (53%). The AE were not related to the dose of irbesartan/HCTZ combination. However, the incidence of three AE differed statistically significantly with irbesartan/HCTZ vs placebo: headache (11.0% vs 16.1%), fatigue, (6.5% vs 3%) and nausea/vomiting (3.2% vs 0.4%). The most frequently reported AE in subjects receiving irbesartan/HCTZ combination therapy occurred in the nervous (21.5%), respiratory (15.4%), general (14.0%), gastrointestinal (13.35%), muskuloskeletal/connective tissue (12.2%) and cardiovascular (10.0%) systems.

In the placebo controlled monotherapy studies, 3.6% of irbesartan/HCTZ treated subjects, 3% of irbesartan, 4.5% of HCTZ and 6.8% of placebo treated subjects discontinued. Headache (0.7%), dizziness (0.7%), and rash (0.6%) were the more common reasons for discontinuation in the irbesartan/HCTZ group.

Add-on studies

In studies CV 131-040 and CV 131-025, there was some evidence that the addition of HCTZ or irbesartan to high dose of irbesartan or HCTZ produced a small increase in AE. Headache, dizziness, fatigue and nausea were the most common AE in patients receiving combination treatment (CV131-040). However, the events were mild and did not cause discontinuation of drug therapy.

Active controlled trials

In the three active-controlled studies (CV13I-041, CV131-042, CV131-032), the overall incidences of AE were similar with irbesartan/HCTZ treatment compared with losartan/HCTZ treatment.

Long term extensions

The AE profile of patients treated with irbesartan/HCTZ in the long-term extensions was similar to that seen during the blinded controlled study periods. One case of lymphoma was reported in which a

causal relationship with irbesartan or irbesartan/HCTZ could not be excluded with certainty. This issue will be addressed in forthcoming PSURs.

Discontinuations and deaths

Discontinuations of study drug treatment for AE occurred in 3.6 % of the patients with irbesartan/HCTZ treatment, in 3.0 % of the patients with irbesartan treatment, in 4.5 % of the patients with HCTZ treatment and in 6.8 % of the patients randomised to placebo treatment in placebo-controlled monotherapy short-term trials. The difference in favour of irbesartan/HCTZ over placebo was statistically significant (p=0.023). The most common reasons for discontinuing treatment were cardiovascular events, fatigue, headache, dizziness, and rash.

In the active controlled trials, the discontinuation rate for irbesartan/HCTZ was 3.9% compared with 7.5% for the losartan combination. The discontinuation rate during long term therapy was somewhat higher (7.7%) because the exposure was about three times longer than that during double-blind studies.

A total of 11 deaths occurred in hypertension studies, 9 on irbesartan/HCTZ or irbesartan and 2 on control group (including long-term extensions). 4 deaths occurred in the short-term phases of placebo-controlled and active-controlled trials. All deaths were sudden or cardiac deaths, and considered unrelated to study drug treatment. The 7 deaths which occurred in the open-label long-term extensions, were also considered unrelated to irbesartan/HCTZ treatment.

Serious adverse events

The incidence of serious AE (SAE) was low, 1.3 % in patients treated with irbesartan/HCTZ, 1.2 % in patients treated with HCTZ and 0.4 % in patients treated with placebo. None of the SAE was attributed to study drug.

There seemed to be a trend towards more cardiovascular AE with irbesartan/HCTZ and the active comparators for serious cardiovascular AE-related withdrawals. The 395 subjects receiving irbesartan/HCTZ in the active-controlled studies experienced 54 (13.7%) cardiovascular AE, and 5 subjects (1.3%) SAE. The 200 subjects receiving active comparator/HCTZ experienced 27 (13.5%) cardiovascular AE, but there were no SAE. The SAE in the irbesartan/HCTZ treated patients included atrial rhythm disturbance, angina pectoris (history of CHD), syncope (history of aortic stenosis), myocardial infarction in a patient with CHD, and sudden death. All SAE were considered to be unrelated to study medication by the investigator or both by the investigator and the company. Four of the 5 subjects were withdrawn from study due to the SAE.

The causality assessment in the case of syncope may be debated because the severity of aortic stenosis was unknown. Special precaution should be however paid in patients with aortic stenosis, because vasodilatation induced by irbesartan may lead to syncope in a patient with clinically important stenosis.

The occasional serious cardiovascular AE reported in the irbesartan/HCTZ group are not unexpected for this patient population with underlying cardiovascular disease. The overall incidence is low and no more than one event of a specific type occurred. Cardiovascular safety data will be updated in forthcoming PSURs.

Laboratory changes

Laboratory tests did not reveal frequent marked abnormalities in placebo-controlled studies. Moreover, the observed marked laboratory abnormalities occurred at similar rates with irbesartan/HCTZ and placebo. In placebo-controlled studies, the mean changes from the baseline in laboratory analyses showed expected dose-related changes with HCTZ, i.e., decreases in sodium and potassium, and increases in blood urea nitrogen, uric acid, glucose, cholesterol and triglycerides. When HCTZ was given in combination with irbesartan, there was a statistically significant decrease (at week 8) in mean plasma potassium and sodium and blood haemoglobin concentrations as well as a statistically significant increase in plasma BUN and uric acid concentrations. However, compared to HCTZ alone, the changes in plasma potassium, glucose and cholesterol tended to be slightly blunted in patients treated with irbesartan/HCTZ combination.

Four patients had marked hyponatremia during the blinded phases of the controlled studies. The reported cases of hyponatremia (and concomitant hypokalaemia) can be attributed to HCTZ. None of the electrolyte abnormalities were severe or symptomatic.

A review of clinical data revealed 21 subjects with CK levels that met marked abnormality criteria (>4x pre-treatment) while receiving irbesartan/HCTZ therapy. The review did not suggest an apparent association with irbesartan/HCTZ or an interaction with other concomitant medications, including statins.

5. Overall conclusions and benefit/risk assessment

Quality

The pharmaceutical and chemical part of the dossier is acceptable.

Preclinical safety

Studies with the combination of irbesartan and HCTZ are considered well designed although some did not comply with GLP. Although the additive antihypertensive effect of the combination was convincingly demonstrated only in spontaneously hypertensive rats, the doses selected and the ratio of doses of irbesartan and HCTZ were considered adequate.

The pharmacokinetic data in animals for the separate species are scant but it must be taken into account that both substances are used in therapy for humans and that sufficient toxicokinetic trials were carried out with the association of irbesartan/HCTZ.

The results of the pre-clinical safety assessment of the studies with irbesartan and HCTZ in combination did not show relevant toxicological interactions between these two drugs.

The reproduction studies did not reveal any additional potential toxicity with the irbesartan/HCTZ combination. Nonetheless this combination is contraindicated during pregnancy and breast-feeding.

Although some experimental models reported ambiguous evidence of genotoxicity and carcinogenicity with HCTZ, there is no evidence of such effects in humans.

Clinical efficacy

In three placebo-controlled double-blind studies (CV131-037, CV131-038, CV131-40) different combination doses of irbesartan (37.5 mg - 300 mg) and HCTZ (6.25 mg-25 mg) were administered once daily to patients with mild-to-moderate hypertension for 8-12 weeks. In general, there was a tendency to achieve more pronounced blood pressure reductions with increased doses of each drug. It was shown that a significantly greater reduction in blood pressure with the combination tablets vs. their components was achieved with irbesartan 150 mg/HCTZ 12.5 mg and irbesartan 300 mg/HCTZ 12.5 mg.

The two combinations of irbesartan/HCTZ (150/12.5 and 300/12.5 mg) have not been compared in a head-to-head study. However, the dose-response relationship regarding BP decrease with irbesartan alone is retained with the combination according to data combined from several studies.

During the oral explanation, the applicant presented an overview of data which support the efficacy of both combinations (150/12.5 and 300/12.5 mg) as compared to their components. The CPMP also considered that both combinations may facilitate flexibility in treatment.

In active-controlled studies, irbesartan 75mg/HCTZ 12.5 mg and irbesartan 150 mg/HCTZ 12.5 mg combinations were at least as effective as the losartan 50 mg/HCTZ 12.5 mg combination dose in the treatment of elderly patients with mild-to-moderate hypertension. In the treatment of severe hypertension, irbesartan 75 mg/HCTZ 12.5 mg and irbesartan 150 mg/HCTZ 12.5 mg combinations were as effective as the losartan 50 mg/HCTZ 12.5 mg combination. In severe hypertensive patients the regimen starting with irbesartan 150 mg gave comparable results with enalapril 20 mg.

Clinical safety

In the clinical development program, 1770 subjects were exposed to 150/12.5 mg or above, with nearly 900 exposed for 6 months and 288 for at least 1 year. At the 300/12.5 mg dose level or above, 938 subjects were exposed, with 523 exposed for at least 6 months and 111 for at least 1 year. Over 400 elderly subjects received doses of at least 150/12.5 mg and over 200 received 300/12.5 or more.

The overall program did not raise any safety concern, whatever the dose or the duration of treatment. The incidence of SAE was low and consistent with the population under investigation. No deaths were attributed to the combination. In double-blind studies, SAE occurred with similar frequencies in irbesartan/HCTZ treated subjects, in monotherapy-treated subjects and in placebo-treated subjects.

Dose-related laboratory changes with HCTZ were evident in major trials, i.e. decreases in sodium and potassium and increases in BUN, uric acid, glucose, cholesterol and triglycerides. Irbesartan tended to ameliorate the HCTZ related changes in plasma glucose and cholesterol, and the hypokalemic and hyperuricemic effects of HCTZ 12.5 mg were most evenly balanced by the 150 mg and 300 mg doses of irbesartan.

Irbesartan/HCTZ was generally well tolerated. The frequency of all AE was similar with irbesartan/HCTZ (59%) than with irbesartan alone (56%), HCTZ alone (58%) or placebo (53%). However, the incidence of three AE differed statistically significantly with irbesartan/HCTZ vs placebo: headache (11.0% vs 16.1%), fatigue (6.5% vs 3%) and nausea/vomiting (3.2% vs 0.4%). Orthostatic dizziness or hypotension occurred in 1.6 % of the patients with irbesartan/HCTZ treatment, in 1.0 % with irbesartan treatment, in 0.8 % with HCTZ treatment and 0.4 % with placebo treatment.

Benefit/risk assessment

The benefit/risk assessment for the fixed combinations of irbesartan 150 mg/HCTZ 12.5 mg and irbesartan 300 mg/HCTZ 12.5 mg is considered favourable. Marketing authorisation is recommended.

6. Post authorisation: safety updates

Pregnancy
Thiazides cross the placental barrier and appear in cord blood. They may cause decreased placental perfusion and foetal electrolyte disturbances. Cases of neonatal thrombocytopenia and foetal or neonatal jaundice have been reported with maternal thiazide therapy. Since CoAprovel contains HCTZ, it is not recommended during the first trimester of pregnancy. A switch to a suitable alternative treatment should be carried out in advance of a planned pregnancy.

In the second and third trimesters, substances that act directly on the renin-angiotensin-system can cause foetal or neonatal renal failure, foetal skull hypoplasia and even foetal death, therefore CoAprovel is contra-indicated in the second and third trimesters of pregnancy. If pregnancy is diagnosed, CoAprovel should be discontinued as soon as possible and foetal skull and renal function should be checked with echography if, inadvertently, the treatment has been taken for a long period.

Interaction with other medicinal products
Cases of potential interaction with *lithium* have been reported. The combination of lithium and CoAprovel is not recommended. If the combination proves necessary, careful monitoring of serum lithium levels is recommended during concomitant use.

As with ACE inhibitors, concomitant use of AIIRAs and *NSAIDs* may lead to an increased risk of worsening of renal function, including possible acute renal failure, and an increase in serum potassium, especially in patients with poor pre-existing renal function. The combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring renal function after initiation of concomitant therapy, and periodically thereafter.

Adequate monitoring of *serum potassium* in patients at risk is recommended

Side effects
Cases of cough and dysgeusia have been reported very rarely with irbesartan.

7. Post authorisation: new irbesartan 300 mg/HCTZ 25 mg dose

7.1 Introduction

The current approved posology includes irbesartan 150 mg/HCTZ 12.5 mg and 300/12.5mg doses. The MAH applied to amend the Posology section of the SPC and PL to include a 300/25 mg dose (2x150mg/12.5mg) as a treatment alternative if hypertensive patients are uncontrolled on lower doses or monotherapy.

Rationale

Current treatment guidelines on hypertension outline a "titration to full dose before adding new drugs" strategy as one recommended way of getting hypertensive patients to target. Keeping patients on well-tolerated combinations is therefore of great importance, since adding a third drug from another therapeutic class, on top of an existing dual combination, will inevitably increase the pharmacodynamic complexity, with possible drug-drug interactions as a result.

In addition to these clinical recommendations, it is also important to consider the actual prescribing pattern of HCTZ with or without irbesartan. Nowadays, the most prescribed dose of HCTZ is 25 mg. Due to the common use of this dose it is important to provide guidance in the SmPC as to the safety and efficacy of combining irbesartan 300 mg and HCTZ 25 mg.

7.2 Clinical aspects

Six clinical trials have been conducted to provide efficacy and safety data on the 300/25 mg combination: 3 controlled parallel group studies (CV131-032, CV131-037 and CV131-042) and 3 open label studies (Combo LT, Mono LT and a study by Coca *et al*).

Further to a request from CHMP regarding the incremental efficacy of the proposed 300/25 mg dose over the existing 300/12.5mg dose and possible titration recommendations, the MAH has submitted the results of trial CV131052, which was not included in the initial variation application. Although the primary endpoint was not BP lowering efficacy, the results of the trial provide important additional information.

Methods

- Controlled Parallel Group Studies

Study CV131-037 was a randomised, double-blind, placebo controlled, 4x4 factorial (16 cell) trial in subjects with mild to moderate essential hypertension (SeDBP 95mm - 110 mm Hg) to assess the dose response efficacy and safety/tolerability of irbesartan and HCTZ mono and combination treatments during an 8-week follow up. Following a 4 to 5-week single-blind placebo lead-in period, 687 subjects were randomised to receive one of 16 different doses of the combination of irbesartan (37.5, 100 and 300 mg or placebo matching irbesartan) and HCTZ (6.25, 12.5 and 25 mg or placebo matching HCTZ) during 8 weeks of double-blind, parallel-group treatment. Subjects completing the double-blind portion were eligible for enrollment into an optional long-term open-label extension period. The study included ~ 40 subjects/cell. The main *inclusion criteria* were consenting males and females with no child-bearing potential, aged 18 years or greater, with mild to moderate essential hypertension (SeDBP 95-110 mmHg). The main *endpoint* was the change from baseline in trough seated diastolic blood pressure (SeDBP) at week 8 of double blind treatment. Secondary endpoints were the effects on serum potassium and fasting lipid concentrations.

Study CV131-042 was a multicentre double-blind, randomised, controlled parallel group trial in patients with severe hypertension (SeDBP 115-130 mm Hg) to compare the efficacy and safety of irbesartan + HCTZ with losartan + HCTZ. After a maximum of 7 days lead-in, patients were randomised 1:1:1 to receive either irbesartan 75 mg + open label HCTZ 12.5 mg (N=67), irbesartan 150 mg + open label HCTZ 12.5 mg (N=72) or losartan 50 mg + open label 12.5 mg HCTZ (N=68).

The doses were doubled after 1 week to irbesartan/HCTZ 150/25 mg, 300/25 mg or losartan 100/25 mg, respectively, if SeDBP ≥106 mm Hg, or after 2 weeks if SeDBP >90 mm Hg. Patients were followed up for 12 weeks. Open-label adjunctive treatment was allowed if patients did not reach treatment goals after maximum doses of treatment drugs. The *primary endpoint* measurement was trough SeDBP after 12 weeks. Secondary endpoints included SeSBP at 12 weeks, SeDBP and SeSBP after 2 weeks, the number of patients reaching treatment goals (SeDBP < 90 mm Hg), and SeHR at 12 weeks and finally to ascertain the safety and tolerability of the studied combinations during the 12 weeks. Blood and urine samples were collected for analysis (Haemoglobin, creatinine, BUN, glucose, potassium and uric acid).

Study CV131-032 was a randomised, double-blind parallel group, active-controlled study in patients with severe hypertension (SeDBP 115-130 mm Hg) investigating the efficacy of an irbesartan-based regimen vs an enalapril-based regimen. The *primary endpoint* was to compare the reduction in trough SeDBP from baseline following 12 weeks of a once-daily oral regimen beginning with irbesartan 150 mg vs a regimen beginning with enalapril 20 mg. Placebo lead-in ranged from 1-7 days. Subjects were randomised 2 irbesartan:1 enalapril. Subjects with SeDBP > 105 mm Hg at week 1 or > 90 at week 2 received a double dose of irbesartan or enalapril (300 mg and 40 mg, respectively). Subjects with SeDBP > 90 mm Hg at week 4, 6, 8 or 10 were given additional 25 mg HCTZ. If still uncontrolled, additional medication was allowed (nifedipine and atenolol). Secondary endpoints were SeSBP at week 12, standing SBP and DBP at 12 weeks, trough SeSBP and SeDBP at week 4, peak BP at 1 day, 4 weeks and 12 weeks, the proportion of normalised patients (SeDBP < 90 mm Hg and/or decrease >10 mm Hg in SeDBP), the proportions of patients controlled or responding (>10 mm Hg SeDBP) in those receiveing monotherapy, study medication + HCTZ 25 mg or triple therapy at week 12, and the safety and tolerability after 12 weeks of treatment with the irbesartan and enalapril regimens.

- *Study CV131052*

A multi-centre, randomised, double blind trial comparing the structural and functional CV efficacy and safety of an irbesartan-based regimen with an atenolol-based regimen. The primary objective was to compare the change in left ventricular mass index (LVMI) from baseline in hypertensive patients with left ventricular hypertrophy (LVH) after 24 and 48 weeks of irbesartan 150 mg once daily (electively titrated to 300 mg, 300/12.5 HCTZ, 300/25 HCTZ, 300/25HCTZ + adjunctive medication) versus an atenolol-based regimen. Eligible patients were those with LVMI >131 (men) and >100 g/m^2 (women) and SeDBP of 90-115 mm Hg.

- Open-Label Studies

The *Mono LT study* was an integrated pooled analysis of open-label long-term follow up trials of 7 double-blind, randomised placebo or active controlled trials (CV131-002 ,025, 027, 028, 029, 031 and 050 LT). Although the trials were conducted separately, data have been integrated and presented in a single report due to the population similarity. A total of 1,545 of the 2,053 subjects included in the double-blind randomised trials were included in the open label extensions.
Patients were started at 75 or 150 mg irbesartan directly after the double-blind treatment period and titrated to 300 mg. If normalised BP (<140/90mm Hg) was not achieved with irbesartan 300 mg alone, adjunctive medication with HCTZ (12.5, 25 and 50 mg/day) was added (all trials except CV131-028). If patients were still uncontrolled, amlodipine, nifedipine and atenolol as adjunctive medication were allowed. The *primary objective* was to ascertain the safety and tolerability of irbesartan during long-term administration. The secondary endpoints were to ascertain the safety and tolerability of irbesartan in combination with adjunctive medication and to monitor the long term efficacy of irbesartan-based regimens in subjects with hypertension.

The *Combo LT study* was a long-term open-label follow up of 1,098 patients completing two randomised, double-blind trials (CV131-037, 038) of irbesartan alone, HCTZ alone, irbesartan/HCTZ combinations, or placebo) in which the tolerability and efficacy of the combination of irbesartan and HCTZ was assessed. Patients received 1 year of open-label therapy starting with irbesartan 75 mg/HCTZ 12.5 mg once daily. If target BP (<140/<90 mm Hg) was not achieved, the dose was titrated sequentially at 2- to 4-week intervals to irbesartan 150 mg/HCTZ 12.5 mg, then (at 12 weeks) to irbesartan 300 mg/HCTZ 25 mg. If necessary, adjunctive therapies were added.

The study by *Coca et al* was a single-arm, open-label trial in hypertensive Caucasian patients aged 45-78 years (mean 60.4±7.2) recruited consecutively from the outpatient hypertension clinics of 3 reference hospitals in Spain. Patients had previously treated and uncontrolled essential hypertension (clinic BP ≥140/90 mmHg) with high doses of a single antihypertensive drug or with low-dose combination therapy for more than 2 months. After a 1-week wash-out period, 57 patients (28 males and 29 females) with a mean daytime-BP higher than 135/85 mm Hg were treated with irbesartan 300/HCTZ 25 once daily for 12 weeks. BP was monitored at the end of the wash-out period and during the last week of treatment. BP changes were assessed by 24-hour ambulatory blood pressure monitoring (ABPM) during normal daily activity (daytime period) and sleep (night time period).

Results

Efficacy

Study CV131-037

Larger mean reductions from baseline in both SeDBP and SeSBP were observed with increasing doses of the combination treatment. The proportion of subjects normalised increased as a function of dose for the combination therapy and for the irbesartan and HCTZ monotherapy groups (from 16% with placebo to 68% with irbesartan 300 mg/HCTZ 25 mg). The response rate ranged from 24% to 80% in the placebo and irbesartan 100 mg/HCTZ 25 mg groups respectively, as seen in the table below.

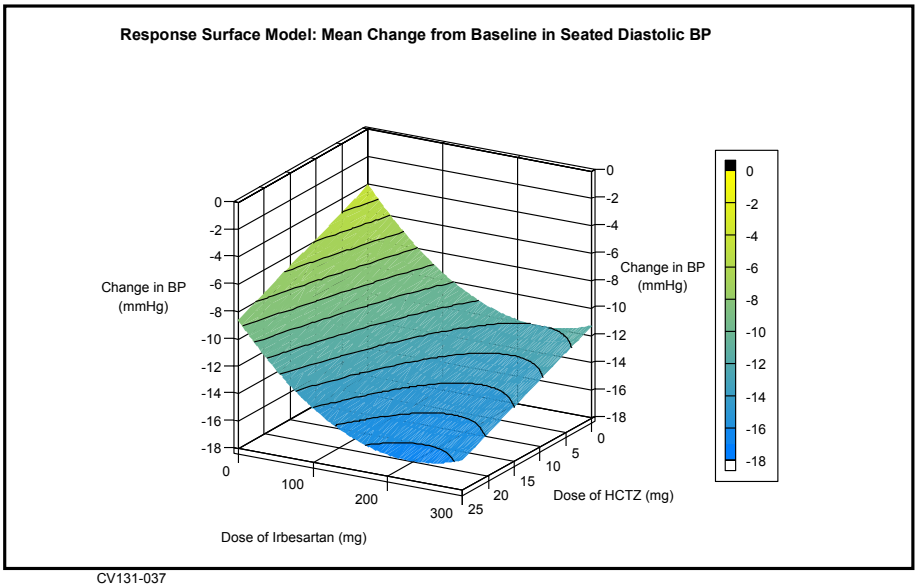
Table 1 Mean change from baseline in trough BPs and therapeutic response at Week 8

	Placebo	**Irbesartan 37.5 mg**	**Irbesartan 100 mg**	**Irbesartan 300 mg**
Placebo				
N	38	40	36	43
SeDBP (mmHg)	-3.5	-7.1	-9.1	-10.2
SeSBP (mmHg)	-2.3	-7.5	-11.1	-14.9
Normalised (%)	16	25	42	49
Responders (%)	24	35	50	58
HCTZ 6.25 mg				
N	39	39	41	38
SeDBP (mmHg)	-5.1	-8.1	-10.0	-13.2
SeSBP (mmHg)	-4.6	-10.2	-11.9	-17.2
Normalised (%)	31	33	49	58
Responders (%)	36	44	63	71
HCTZ 12.5 mg				
N	39	39	38	43
SeDBP (mmHg)	-6.2	-9.0	-11.9	-15.0
SeSBP (mmHg)	-8.9	-14.7	-14.9	-15.9
Normalised (%)	31	46	61	65
Responders (%)	38	54	68	79
HCTZ 25 mg				
N	36	40	40	41
SeDBP (mmHg)	-8.3	-11.7	-13.8	-14.4
SeSBP (mmHg)	-11.5	-16.8	-21.5	-23.1
Normalised (%)	47	60	65	68
Responders (%)	53	65	80	76

The absolute trough SBP and DBP reductions from baseline for the 300/25 mg combination were 23.1 and 14.4 mm Hg, respectively. The corresponding values for the 100/12.5 mg combination were 14.9 and 11.9 mm Hg, respectively. The additional SeSBP reduction of 300/25 mg compared with 300/12.5 mg was 7.2 mm Hg, while the decrease in DBP was virtually similar between the two groups.

However, the response surface model analysis of predicted change in SeDBP at week 8 shown below, predicted additive effects of irbesartan + HCTZ. Predicted BP effect at each combination dose of HCTZ (range 0-25 mg) and irbesartan (range 0-300 mg) can be interpolated from the graph, showing a direct relationship between BP decrease and combination dose. The response surface model for trough Se SBP showed a similar pattern.

Figure 1 Response Surface Model in SeDBP at week 8 derived from study CV131-037



In patients receiving the 300/25 mg an additional SeSBP reduction was observed compared with patients receiving 300/12.5 mg. Nonetheless, the proportions of normalised patients and responders are similar in 300/12.5 and 300/25 mg dose regimen (65-79% and 68-76% respectively) and the only difference found between both doses is a SBP decrease of -7.1 mmHg obtained with 300/25 mg regimen.

Although the response surface model predicts an incremental SeSBP and SeDBP decrease from 300/12.5 mg to 300/25 mg, the observed (as opposed to predicted) mean reduction in DBP was similar for both combinations.

Study CV131-042

There were no significant differences among the groups in the baseline characteristics, although there was a slight imbalance in gender and elderly age categories for baseline demographics.

All 3 treatment regimens reduced SeDPB by 29-31 mmHg and SeSBP by 44-45 mmHg after 12 weeks. The BP reduction was greatest in the high dose irbesartan/HCTZ group, but the differences among the groups were not significant. The proportions of normalised patients were 63%, 72% and 74% for the losartan/HCTZ, irbesartan 75 mg/HCTZ group and irbesartan 150 mg/HCTZ groups, respectively. The differences in normalised patients at week 12 were not statistically significant. Almost all of the subjects in each group were classified as total responders at week 12.

Table 2 Mean Changes (se) from Baseline in trough BP and therapeutic response at week 12

Efficacy variable	**Losartan 50 mg /HCTZ N=59**	**Irbesartan 75 mg /HCTZ N=58**	**Irbesartan 150 mg /HCTZ N=62**	**Overall p-value**
SeDBP (mmHg)				
Baseline mean (SD)	118.6 (3.1)	118.6 (3.0)	118.5 (2.9)	
Mean change from baseline (se)	-29.2 (1.0)	-31.1 (1.0)	-31.4 (1.0)	0.23
Difference vs losartan (95% CI)	-	-1.9 (-4.7,0.9)	-2.3 (-5.0,0.5)	
SeSBP (mmHg)				

Baseline mean (SD) Mean change from baseline (se) Difference vs losartan (95% CI)	179.5 (17.0) -44.8 (1.8) -	182.3(14.9.0) -44.7 (1.9) 0.1 (-5.0,5.2)	179.6 (19.1) -45.6 (1.8) -0.8 (-5.8,4.2)	0.93
Normalised (%) Rel. benefit vs losartan (95% CI) p-value vs losartan **Responders (%)**	37 (63%) 57 (97%)	42 (72%) 1.17 (0.81,1.67) 0.41 58 (100%)	46 (74%) 1.36 (0.94,1.97) 0.10 60 (97%)	

Means are adjusted means obtained from ANCOVA models with terms for treatment, site and baseline
Normalised = trough SeDBP<90mm Hg
Total responder = Normalised, or reduction in trough SeDBP≥10mm Hg
Relative benefit = proportion of responders on ibesartan/proportion of responders on losartan, stratified by sites

Of the patients who received higher doses of irbesartan and HCTZ (up to 300/25 mg respectively), 29% did not need any adjuvant medication. In the low dose irbesartan/HCTZ regimen (doses up to 150 mg irbesartan and 25 mg HCTZ) only 14% managed without adjuvant medication. The need for adjuvant medication was even greater in the losartan/HCTZ group (only 10% of the subjects without adjunctive medication). Titration to 300/25 mg irbesartan/HCTZ was necessary between week 1 and week 2 in 57% of subjects receiving initial 150/12.5 mg irbesartan/HCTZ, resulting in a further 7.0/5.2 mmHg SeSBP/SeDBP reduction. After 12 weeks only 5 of 62 subjects (8%) were still on the original 150/12.5 mg irbesartan/HCTZ while 57 patients received 300/25 mg irbesartan/HCTZ either alone or with adjuvant medication

Table 6.3 Summary of Titration Categories at Week 12 for Randomized Subjects

Titration Category	Losartan 50 mg/HCTZ N=59	Irbesartan 75 mg/HCTZ N=58	Irbesartan 150 mg/HCTZ N=62
Low study medication dosage with HCTZ 12.5 mg	0 (0%)	0 (0%)	5 (8%)
High study medication dosage with HCTZ 25 mg	6 (10%)	8 (14%)	13 (21%)
High study medication dosage with HCTZ 25 mg and atenolol	4 (7%)	5 (9%)	4 (6%)
High study medication dosage with HCTZ 25 mg and nifedipine	26 (44%)	27 (47%)	14 (23%)
High study medication dosage with HCTZ 25 mg, atenolol and nifedipine	22 (37%)	18 (31%)	26 (42%)
Other	1 (2%)	0 (0%)	0 (0%)

CV131-042
Source: Appendix 6.3
Reference: Supplemental Table S.6.3
Note: N = number of subjects with an efficacy assessment at Week 12.
Low dosages of study medication were 75 mg irbesartan, 150 irbesartan and 50 mg losartan
High dosages of study medication were 150 mg irbesartan, 300 irbesartan and 100 mg losartan

Assuming that at the end of the trial all patients were well controlled and that up-tritation stopped when adequate control was reached, it would appear that 94 out of 120 patients (considering the 2 irbesartan treated arms of the study together) were not controlled with the combination proposed (i.e. they needed additional drugs). Of the 26 that were controlled with irbesartan/HCTZ, none were controlled with 75/12.5, 5 were controlled with 150/12.5, 8 were controlled with 150/25 and 13 with 300/25. It is confirmed that 300/25 is more useful than 150/12.5. It would be useful to know if the same result could have been obtained with 300/12.5, which is the currently approved combination and which was surprisingly not included in the up-titration schedule.

Study CV131-032

There were no statistically significant differences in baseline demographic characteristics or BP between the two treatment groups. There was no significant difference between the enalapril and the irbesartan-based regimens in mean SeDBP change from baseline at week 12 (29.6 vs 30.5 mmHg for irbesartan and enalapril respectively). The SeSBP reductions were 40.1 and 39.3 mm Hg respectively. The proportion of subjects normalised after 12 weeks did not differ significantly between the groups (59% vs. 57% for the irbesartan and enalapril groups). However, subjects tended to achieve normalisation earlier with the irbesartan regimen. Peak SeSBP reductions at 12 weeks were 47.2 mm Hg (irbesartan) and 44.5 mm Hg (enalapril).

Analysis of Trough BP at week 12

Efficacy variable	Irbesartan N=103	Enalapril N=62	p-value
Trough SeDBP (mmHg) Mean change from baseline (se) Difference vs enalapril (95% CI)	 -29.6 (0.8) 0.9 (-1.6,3.3)	 -30.5 (1.0)	 0.48
Trough SeSBP (mmHg) Mean change from baseline (se) Difference vs enalapril (95% CI)	 -40.1 (1.4) -0.8	 -39.3 (1.9)	 NA[a]
Therapeutic Response Normalised (%) Rel. benefit vs enalapril (95% CI) Difference vs enalapril	 59% 1.0 (0.8,1.3)	 57%	 0.97

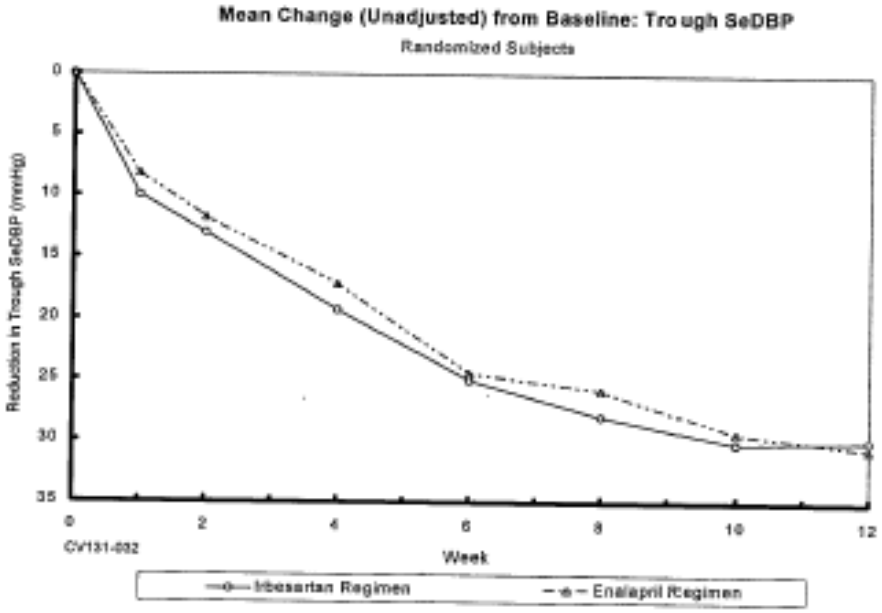
a: A comparison of the treatment groups with regards to SeSBP was not tested because of a significant treatment-by-baseline interaction

Means are adjusted means obtained from ANCOVA models with terms for treatment, site and baseline

Normalised = trough SeDBP<90mm Hg

Total responder = Normalised, or reduction in trough SeDBP≥10mm Hg

Relative benefit = proportion of responders on ibesartan/proportion of responders on enalapril, stratified by sites



The SeSBP and SeDBP at week 2, 4 and 12 are presented in the table below.

Treatment Effect (SeSBP/SeDBP) at 2, 4 and 12 Weeks

SeSBP/SeDBP mm Hg	Baseline	Week 2	Week 4	Week 12
Irbesartan group	175/119	163/106	151/100	135/89
Enalapril group	178/119	167/107	158/102	137/89

Titration categories at week 12 are presented in table below. At week 2, none of the subjects received irbesartan in combination with HCTZ. Between week 2 and week 4, 57 patients (52%) of the subjects in the irbesartan arm received the combination of irbesartan 300mg + HCTZ 25 mg. At 12 weeks only 9 patients were still on irbesartan monotherapy (8.8%). Twenty-five patients (24.3%) received irbesartan + HCTZ 25 mg.

Table 6.4.1 Summary of Titration by Treatment Group at Week 12 for Randomized Subjects

Titration Category	Irbesartan N (%)	Enalapril N (%)
Monotherapy - irbesartan 150 mg or enalapril 20 mg	4 (3.9%)	0 (0%)
Monotherapy - irbesartan 300 mg or enalapril 40 mg	5 (4.9%)	4 (7.1%)
Combination therapy: addition of HCTZ only	25 (24.3%)	10 (17.9%)
Combination therapy: addition of nifedipine or atenolol - no HCTZ	9 (8.7%)	4 (7.1%)
Combination therapy: addition of HCTZ and (nifedipine or atenolol)	60 (58.3%)	38 (67.9%)
Total	103 (100%)	56 (100%)

CV131-032

Source: Appendices 6.0A, 6.4.1A, and 6.4.1B

Reference: Supplemental Table S.6.4.1

Note: N = Number of subjects in the titration category.
The Week 12 titration category was determined from start and stop prescription information on or after the Week 10 visit.

An irbesartan-based regimen with a starting dose of 150 mg titrated to 300 mg, 300/25 mg and adjunctive medication proved to be as effective in lowering BP as an enalapril-based regimen. The irbesartan-based regimen appears safe and well tolerated. The addition of 25 mg HCTZ to irbesartan provided incremental SeSBP and SeDBP BP reductions.

It can be concluded that the 300/25 combination is more useful than irbesartan monotherapy in lowering BP. Unfortunately, the 300/12.5 titration step was not included in the study and, therefore, no comparative data between the the 300/25 mg and the 300/12.5 mg doses has been obtained.

Study CV131-052

The results of the primary endpoint will not be discussed, but rather the incremental BP effects observed in the subset of patients who added 12.5 mg HCTZ to either 300/12.5 irbesartan/HCTZ (n = 22) or 100/12.5 mg atenolol/HCTZ (n = 16). Table 2 provides a detailed analysis to describe BP responses with “high”/12.5 mg HCTZ and “high”/25 mg HCTZ, where “high” represents either irbesartan 300 mg or atenolol 100 mg. The addition of 25 mg HCTZ to 300 mg irbesartan led to a 24.0/13.3 mmHg reduction in SeSBP and SeDBP whereas the 300/12.5 resulted in a 10.7/5.0 mmHg reduction.

The normalisation rate for SeDBP < 90 mmHg and for SeSBP <140 and SeDBP < 90 mmHg was reached by additional 32% and 18% respectively after the first visit on 300/25 mg irbesartan/HCTZ.

Table 2: Incremental BP lowering with 300/25 mg over 300/12.5 mg combination of irbesartan/HCTZ

Summary of Incremental BP Changes in CV131052

Variable	Group	N	Untreated Baseline	Last Visit on "high"/12.5	First Visit on "high"/25	Incremental Effect of Adding HCTZ 12.5mg
			Mean (SD)	Mean (SD)	Mean (SD)	Mean Change (95% CI)
SeDBP	Irbe 300	22	107.0 (6.2)	102.0 (7.0)	93.7 (9.4)	-8.3 (-11.2, -5.3)
	Aten 100	16	109.5 (5.3)	94.6 (8.5)	94.0 (9.2)	-0.6 (-4.0, +2.8)
SeSBP	Irbe 300	22	173.3 (15.0)	162.6 (20.2)	149.3 (22.1)	-13.3 (-18.1, -8.5)
	Aten 100	16	170.0 (19.1)	156.1 (18.3)	155.2 (19.4)	-0.9 (-6.6, +4.8)

pgm: wwbdm/clin/proj/cv/131/052lt/dev/stats/bpincrem.sas

Notes: "Untreated Baseline" = Measurements at end of placebo lead-in period.

"Last Visit on "high"/12.5 = Measurements at end of treatment with HCTZ 12.5mg combined with either irbesartan 300mg or atenolol 100mg.

"First Visit on "high"/25 = Measurement after first interval of treatment with HCTZ 25mg combined with either irbesartan 300mg or atenolol 100mg.

Both treatment groups (irbesartan and atenolol) showed statistically significant reductions from baseline in SeSBP and SeDBP. The mean reduction was similar in both groups at week 48, although the reduction was slightly higher in the irbesartan group.

The primary endpoint of this trial was not the incremental BP effect of the titration but the results obtained are considered of use. Patients not controlled (22) with the 300/12.5 combination were titrated to 300/25. An incremental BP lowering effect was observed for both SBP and DBP (13.3 and 8.3 mm Hg, respectively). After receiving the higher dose (300/25 mg), an additional 32% (7/22) of the uncontrolled patients achieved SeDBP < 90 mmHg, and 18% (4/22) were controlled with respect to SeSBP and SeDBP (<140/<90 mmHg).

Study Mono LT (CV131-002 ,025, 027, 028, 029, 031 and 050 LT)

In this open label long term study, 170 patients were titrated from 300/12.5 to 300/25 mg irbesartan/HCTZ. The average follow-up on the higher combination dose from the last visit on 300/12.5 mg was 132 days.

Systolic and diastolic BP reductions (placebo baseline) after 1 month of treatment on 300/25mg were -20.5 and -13.0 mm Hg, respectively and were well maintained for the average of 5 months of treatment duration. The incremental systolic and diastolic BP lowering after 1 month of the higher dose combination 300/25mg was -8.3 and -4.8 mmHg, respectively. At last observation carried forward (LOCF) the incremental BP lowering effect was well maintained. Compared to the last visit on 300/12.5mg, the incremental BP lowering for 300/25mg was -7.8 mm Hg and -4.2 mm Hg for SeSBP and SeDBP respectively. (See table 3)

Table 3: Summary of Incremental BP Changes in LT Monotherapy Studies After addition of HCTZ 12.5mg to Irbesartan/HCTZ 300/12.5mg

Months on 300/25	Variable	N	Untreated Baseline Mean (SD)	Last visit on '300/12.5' Mean (SD)	Followup on '300/25' Mean (SD)	Incremental Effect of Adding HCTZ 12.5mg Mean Change (95% CI)
1	SeDBP	160	102.7 (4.3)	94.6 (6.5)	89.7 (8.1)	-4.8 (-5.8, -3.9)
	SeSBP	160	160.9 (15.6)	148.7 (12.7)	140.4 (13.6)	-8.3 (-10.0, -6.6)
LOCF	SeDBP	170	102.6 (4.3)	94.2 (6.6)	90.0 (9.0)	-4.2 (-5.3, -3.1)
	SeSBP	170	160.6 (15.5)	148.3 (12.7)	140.5 (14.5)	-7.8 (-9.7, -5.9)

pgm: wwbdm/clin/proj/cv/131/031/dev/stats/monocom1.sas

Notes: "Untreated Baseline" = Measurements at end of placebo lead-in period.

"Last visit on '300/12.5' = Measurements at end of treatment with Irbe/HCTZ 300/12.5mg.

"Followup on '300/25' = Measurement after one month and at end of treatment with Irbe/HCTZ 300/25mg.

"LOCF" = Last Observation on 300/25 without adjunctive medication.

The incremental control rates (defined by both SeSBP < 140 mmHg and SeDBP < 90 mmHg) on the high dose combination 300/25mg in subjects previously uncontrolled on 300/12.5, are shown in Table 4. Both systolic and diastolic BP control rates were substantially improved |(33%) after 1 month of treatment with the higher dose and were maintained at LOCF after almost 5 months of treatment (Tables 4 and 4a), thus demonstrating long term effectiveness.

Table 4: Number (Percent) of Patients with Blood Pressure Control Before and After Incremental Addition of HCTZ 12.5mg

Response Category	300/12.5 Last visit	300/25 Month 1	300/25 LOCF
N	170	160	170
SeDBP<90	37 (21.8)	84 (52.5)	71 (41.8)
SeSBP<140 & SeDBP<90	3 (1.8)	56 (35.0)	48 (28.2)

pgm: wwbdm/clin/proj/cv/131/031/dev/stats/monocom1.sas

"LOCF" = Last Observation on 300/25 without adjunctive medication.

Table 4a: Days On Irbesartan/HCTZ 300/25

Statistic	Month 1	LOCF
N	160	170
Mean Days	27	132
SD	7.4	144.3
Q1-Q3	27-30	28-222

pgm: wwbdm/clin/proj/cv/131/031/dev/stats/monocom1.sas

"LOCF" = Last Observation on 300/25 without adjunctive medication.

Q1=25th percentile; Q3=75th percentile.

Study CV131-037,038 LT (Combo LT)

Mean SeSBP and SeDBP from months 2 to 12 are presented in the table below.

Blood Pressure Reduction Throughout the Study Period

	Mean Trough Se SBP (mmHg)	**Mean Trough Se DBP (mmHg)**	**N**
Month 2	-19.1	-14.2	941
Month 6	-20.7	-15.7	948
Month 12	-20.6	-15.6	898

Normalisation rates (trough SeDBP <90 mm Hg) ranged from 75-85% and total responder rates (normalised or ≥ 10 mm Hg trough SeDBP reduction) ranged from 81-91%, while target BP was achieved in 65-75% of patients.

At least 87% of the patients were receiving irbesartan/HCTZ alone. The distribution of dose regimens during open-label therapy is shown in the table below.

Treatment Regimens at 2, 6 and 12 Months

Dose Regimen	Month 2	Month 6	Month 12
Irbesartan 75 mg / HCTZ 12.5 mg	504 (54%)	474 (50%)	430 (48%)
Irbesartan 150 / HCTZ 12.5 mg	316 (34%)	228 (24%)	209 (23%)
Irbesartan 300mg / HCTZ 25 mg	74 (8%)	110 (12%)	102 (11%)
Irbesartan / HCTZ + Adjunct	21 (3%)	93 (10%)	106 (12%)

The specific incremental BP lowering effect of 300/25 mg irbesartan/HCTZ compared with 150/12.5 mg is shown in the table below. The *post-hoc* data presented in the table are derived only from subjects titrated from 150/12.5 to 300/25 without adjunctive medication.Values in the table correspond to the last visit on 150/12.5 mg combination and first visit after dose titration to 300/25 mg irbesartan/HCTZ. The mean time between the 2 visits was 23 days. From last visit 150/12.5 mg to first visit with 300/25 mg irbesartan/HCTZ the control rate increased dramatically from 2% to 48%.

Incremental SeSBP of Irbesartan/HCTZ 300/25 mg compared with 150/12.5 mg

All Subjects (Long-Term) Titrated from 150/12.5mg(Irbesartan/HCTZ) to 300/25mg (Irbesartan/HCTZ)

SeSBP (mmHg)

Visit	N	Baseline Mean (SD)	During (300/25)** Treatment Mean (SD)	Change from Baseline Mean (SD)
Baseline (ST)	226	157.82 (13.70)		
Baseline* (LT) (150/12.5)	226	146.84 (12.25)		
First Visit** (300/25mg)	226		138.77 (12.88)	-8.07 (13.09)

* Visit at which titration from 150/12.5mg to 300/25mg (Irbesartan/HCTZ) was started
** Visit following the first titrated dose of 300/25mg (Irbesartan/HCTZ)

Incremental SeDBP of Irbesartan/HCTZ 300/25 mg compared with 150/12.5 mg

All Subjects (Long-Term) Titrated from 150/12.5mg (Irbesartan/HCTZ) to 300/25mg(Irbesartan/HCTZ)

SeDBP (mmHg)

Visit	N	Baseline Mean (SD)	During (300/25)** Treatment Mean (SD)	Change from Baseline Mean (SD)
Baseline (ST)	226	102.52 (4.54)		
Baseline* (LT) (150/12.5 mg)	226	95.90 (5.84)		
First Visit** (300/25 mg)	226		90.35 (7.78)	-5.55 (7.21)

* Visit at which titration from 150/12.5mg to 300/25mg (Irbesartan/HCTZ) was started
** Visit following the first titrated dose of 300/25mg (Irbesartan/HCTZ)

The incremental efficacy of irbesartan/HCTZ 300/25 mg titrated directly from irbesartan/HCTZ 150/12.5 mg is 8.07 and 5.55 mm Hg, respectively for SeSBP and SeDBP.

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The different BP reductions are presented in the table below.

Ambulatory 24 h SBP and DBP Reduction

SBP (mmHg)		DBP (mmHg)	
Peak Reduction	25.2	Peak Reduction	14.7
Trough Reduction	22.3	Trough Reduction	12.3
24 h Reduction	22.7	24 h Reduction	13.2
Trough/Peak	0.92	Trough/Peak	0.84

A significant reduction in the average values of clinic BP was observed (from 169.4±9.0 to 143.1±11.1 mm Hg, $p<0.0001$ for SBP and from 101.4±5.2 to 86.7±6.7 mm Hg, ($p< 0.0001$) for DBP after treatment in all of 57 patients. Likewise, average values of both 24-h SBP and 24-h DBP were significantly reduced (from 146.0±11.0 to 123.3±13.3 mm Hg, $p<0.001$ for 24-h SBP; and from 89.8±8.2 to 76.5±9.4 mm Hg, $p< 0.001$ for 24-h DBP).

The response rate (BP lowering > 5 mm Hg of either 24h-SBP or 24h-DBP average values) was 94.7% and the control rate (daytime BP< 135/85 mm Hg) was 68.4%.

Clinical safety

Patient exposure

The safety of irbesartan has been extensively studied studied in doses up to 900 mg, in 19 completed clinical studies with a total of 2,746 subjects. Different population subgroups were represented across the various dose groups, including 1049 women, 620 elderly (>65 years) including 98 very elderly (> 75 years) subjects, 351 blacks and 259 subjects in "other" racial groups. In the LT protocols, 2306 subjects were treated for ≥ 6 months (including > 300 elderly subjects) and 2129 subjects for ≥ 1 year. These data were submitted in 1997 in the original irbesartan/HCTZ marketing authorisation application (MAA). Since the first marketing approval of irbesartan/HCTZ in the US 30 September 1997 exposure to irbesartan/HCTZ is estimated at 3,483,744 patient-treatment years.

This summary will focus on the 300/25 mg irbesartan/HCTZ combination patients. In addition, further to a request from CHMP, a detailed comparative analysis (300/12.5 vs 300/25) focussing on the incidence of dizziness and potassium changes over time has been submitted by the MAH.

The total exposure to the newly proposed 300/25 mg irbesartan/HCTZ combination is approximately 650 patients; 406 patients exposed in the 2 long-term follow up studies, and 85, 41, 61 and 22 patients exposed in the CV131-032, CV131-037, CV131-042 and CV131-052 randomised controlled trials, respectively. In the Coca *et al*. publication, all 57 patients received 300/25 mg of irbesartan/HCTZ. All subjects in all studies were monitored for the occurrence of adverse events (AEs) and laboratory test abnormalities. AEs were classified by ICD codes. The relationship of each AE to study drug according to the investigator's blinded opinion was also recorded. Mean changes in selected laboratory parameters including electrolytes and the risk factors of fasting glucose and lipids were also assessed.

Adverse events

The frequency of all AE regardless of attribution was similar or slightly higher with irbesartan/HCTZ (59%) than with irbesartan alone (56%), HCTZ alone (58%) or placebo (53%). AEs in the cardiovascular and gastrointestinal systems were more common in the combination and HCTZ groups, whereas nervous system events were more common in the combination and placebo groups. As outlined in the individual study reports, no relationship between irbesartan/HCTZ dose and AE frequency was seen. The most common AEs reported from placebo-controlled Irbesartan/HCTZ trials are shown below.

CV131-037

The mean duration of exposure was 55 days. The overall incidence of AEs did not appear to correlate with the dose of either agent; indeed, the highest AE rates tended to occur in the subjects receiving placebo or the lowest doses. There were no differences in the incidence of serious AE (SAE) or treatment discontinuations between different combinations and doses. None of the 11 SAEs reported was considered related to study drug. Two out of the 22 patients who discontinued received 300/25 mg irbesartan/HCTZ. A few events (dizziness and dyspepsia/heartburn, and perhaps diarrhoea) showed a trend by dose, but the small numbers are hard to interpret.

There was an increased frequency of dizziness in the 300/25 mg group (9 vs 3 on 300/12.5 mg and 5 on 37.5 mg /HCTZ 6.25 and 37.5/25 mg respectively). This is illustrated in Table 5a below.

Table 5a: Number (Percent) of Subjects with Events Termed Dizziness During the 8-Week Double-Blind Period

Dose	Placebo	Irbesartan 37.5mg	Irbesartan 100mg	Irbesartan 300mg	Total
Placebo	3 (6.8)	1 (2.4)	3 (7.3)	3 (7.0)	10 (5.9)
HCTZ 6.25mg	3 (6.8)	5 (11.4)	2 (4.5)	4 (10.0)	14 (8.1)
HCTZ 12.5mg	2 (5.0)	3 (6.7)	3 (7.0)	3 (6.8)	11 (6.4)
HCTZ 25mg	3 (7.7)	5 (12.2)	3 (6.8)	9 (20.0)	20 (11.8)
Total	11 (6.6)	14 (8.1)	11 (6.4)	19 (11.0)	55 (8.1)

CV131-037
Source: Appendices 7.5.1A-P
Reference: Supplemental Table S.7.5.1B

It is of importance to note that the various doses of irbesartan (0-300 mg) or HCTZ (0-25 mg) or their combinations were administered to subjects after a 4-5 week placebo lead in. Since the antihypertensive effect is more pronounced in the high dose cells, it is not unexpected that some subjects experienced dizziness when switched directly from placebo to 300/25 mg, which lowers SBP in the range of 20-24 mm Hg. This abrupt initiation of a high dose combination is clearly not recommended in the posology section of the SPC.

There were no increases in potassium-related laboratory AE during the 8 weeks of the trial in the combination group compared to either of the monotherapy groups.

CV131-032

Sixty-six (54.5%) patients in the irbesartan group and 39 (63.9%) in the enalapril group experienced an AE. Respiratory side effects (cough, etc) are more prevalent in the enalapril group. The distribution of treatment-emergent AE according to body system is presented in the table below.

Treatment-Emergent Adverse Events (CV131-032)

	N(%)	
Primary Term	Irbesartan (N=121)	Enalapril (N=61)
Headache	21 (17.4)	12 (19.7)
Musculoskeletal Pain	12 (9.9)	5 (8.2)
Dizziness	11 (9.1)	11 (18.0)
Pharyngitis	7 (5.8)	1 (1.6)
Influenza	7 (5.8)	1 (1.6)
Fatigue	6 (5.0)	3 (4.9)
Upper Respiratory Infection	5 (4.1)	7 (11.5)
Edema	5 (4.1)	2 (3.3)
Somnolence	5 (4.1)	0

Rhinitis	4 (3.3)	3 (4.9)
Sinus Abnormality	4 (3.3)	0
Hypotension	4 (3.3)	0
Cough	3 (2.5)	8 (13.1)
Chest Pain	3 (2.5)	3 (4.9)
Muscle Cramp	3 (2.5)	3 (4.9)
Dyspepsia/Heartburn	3 (2.5)	2 (3.3)

There were 7 (5.8%) discontinuations due to AE in the irbesartan regimen group, one of which was considered related to study drug (irbesartan 150 mg monotherapy), and 3 (4.9%) in the enalapril group, all of which were considered related to study drug.

CV131-042
There was no clear dose response related increase in treatment emergent AE for the 2 different (low/high dose) irbesartan/HCTZ regimens. There were 9 discontinuations of which 3 were considered to have a possible relationship to treatment (1 losartan/HCTZ 50/12.5 mg, 1 losartan/HCTZ/nifedipine 100/25/30 mg and 1 irbesartan/HCTZ/atenolol 300/12.5/50 mg).

CV131052
The exposure to irbesartan/HCTZ 300/25 was between 18 and 36 weeks in this trial. In general, the irbesartan-based regimen proved to be safe and well tolerated compared to an atenolol-based regimen. Adverse Drug Experience (ADE) frequency was lower in the irbesartan group. The irbesartan regimen was less prone to cause AEs related to hypotension, such as dizziness, orthostatic dizziness, hypotension and syncope. There were no reports of dizziness or orthostatic dizziness from patients receiving 300/25 mg irbesartan/HCTZ. There was no investigator identified laboratory AE related to either hyper- or hypokalemia in the irbesartan group during the 48 weeks of follow up. There were 2 marked abnormalities (MA) in potassium levels.

Table 6a: Number of Patients with Events of Interest

EVENTS	Irbe (N=56)	Aten (N=57)
Dizziness	3	12
orthostatic dizziness	3	0
hypotension	0	1
syncope	0	0
lab AE: decr K+	0	2
lab AE: incr K+	0	0
lab MA: decr K+	2	0
lab MA: incr K+	1	1

Mono LT
The number of treatment-emergent AE from the Mono LT study report, sorted by dose of the combination, are presented in the table below.

Treatment Emergent AEs Sorted by Dose in Monotherapy Extension Trial

	Irbesartan 75-100 mg/HCTZ 12.5 mg	Irbesartan 150-225 mg/ HCTZ 12.5 mg	Irbesartan 300 mg / HCTZ 12.5 mg	Irbesartan 300 mg / HCTZ 25 mg
Mean Duration of Exposure (Days)	198	175.7	133.2	224.3
Total Subjects With at Least One AE	46 (50%)	48 (40.3%)	143 (41.9%)	101 (47.6%)

The mean exposure of all patients receiving 300/25 mg irbesartan/HCTZ was 224 days; 170 patients were titrated from 300/12.5 to 300/25 mg, of which 116 have been observed for at least 6 months. Of

those treated with the combination in the range 150-300/12.5 mg, 137 patients have been observed for 6 months or more.

The AE rates by dose in the monotherapy LT extension protocols suggest that irbesartan monotherapy and irbesartan/HCTZ were associated with similar rates of AEs, whereas subjects receiving adjunctive medication had higher rates of AEs (albeit with longer mean exposure). Considering the well-known limitations in trying to assess dose-response relationships in optional titration designs, the overall long-term data do not suggest any important increase in the risk of AEs with the combination vs monotherapy, nor with higher doses of the irbesartan/HCTZ combination.

Only 18 subjects treated with combination irbesartan/HCTZ doses ranging 150-300/12.5-25mg discontinued from the open label monotherapy extension study due to AEs. The proportion of subjects who discontinued due to AEs in the lower HCTZ dose combinations (150 to 300mg/12.5mg HCTZ) was slightly lower than in the 300/25mg combination group. The most common AEs reported were musculoskeletal pain, respiratory infection and headache, all typical AEs of hypertension clinical studies. There was no difference in the incidence of discontinuations due to events potentially linked to hypotension or metabolic/electrolyte imbalance

With the overall low number of events and no difference between groups it is impossible to draw any conclusions regarding dose relationship. But, in summary, long term exposure to high-dose irbesartan /HCTZ did not cause more discontinuations or SAEs than in lower HCTZ dose groups (150-300/12.5mg).

The overall incidence of MAs was low and there were no increases in potassium-related MAs with the irbesartan/HCTZ regimen compared with irbesartan monotherapy (1.3 vs 1.2 % respectively). A total of 6 MAs of hypokalemia were reported in the irbesartan/HCTZ group during an exposure of 543 patient years. MAs in BUN, creatinine, glucose fasting, potassium, triglicerides and creatine kinase occurred in greater than 1 % in all of the doses used in this long term extension. There is a trend to increased creatinine and BUN in high HCTZ combination, which is expected

COMBO LT
The extent of exposure and the incidence of AEs sorted by dose are presented in Table 8a.

Table 8a: Extent of Exposure and Overall Incidence of Treatment-Emergent Adverse Events During the Combo Long-Term, by Dose

	Irbesartan 75 mg / HCTZ 12.5 mg N=1091	Irbesartan 150-225 mg / HCTZ 12.5 mg N=574	Irbesartan 300 mg / HCTZ 12.5 mg N=58	Irbesartan 300 mg / HCTZ 25 mg N=273
Mean Duration of Exposure (days)	177	148	113	231
Total Subject/Years	529	233	18	173
Total Subjects with at Least One Event (%)	485 (44.5)	291 (50.7)	27 (46.6)	182 (66.7)

Source: Integrated Study Report: Protocols CV131037 and CV131038; Open Label Irbesartan with Hydrochlorothiazide; September 24, 1997 Tabl 7.5.1B / and 7.1B-modified

Table 8b presents selected AEs potentially linked to hypotension, including dizziness. The same table lists selected clinical AEs potentially related to metabolic and/or electrolyte imbalance.

Table 8b: Combo Long-Term: Treatment Emergent Adverse Events of Interest By Dose

Event	DOSE CATEGORY		
	150-225/12.5 N=574	300/12.5 N=58	300/25 N=273
	N (%)	N (%)	N (%)
Events potentially Related to Hypotension			
Orthostatic Hypotension	0	0	0
Hypotension	0	0	1 (0.4)
Syncope	2 (0.3)	0	2 (0.7)
Orthostatic Dizziness	9 (1.6)	0	6 (2.2)
Dizziness	21 (3.7)	5 (8.6)	19 (7.0)
Vertigo	1 (0.2)	2 (0.6)	5 (2.4)
Events potentially Related to Metabolic and Electrolyte Imbalance			
Arrhythmia or Conduction Disturbance (any)	9 (1.5)	2 (3.4)	7 (2.6)
Muscle Pain/Cramp/ Ache (any)	57 (9.9)	5 (7.0)	30 (10.9)
Numbness	6 (1.0)	0	6 (2.2)
Paresthesia	5 (0.9)	0	2 (0.7)
Weakness	6 (1.0)	0	3 (1.1)
Fatigue	23 (4.0)	4 (6.9)	20 (7.3)

Source: Integrated Study Report: protocols CV131002, -025, -027, -028, -029, -031, -050 Open-Label Irbesartan Table S 7.5.1A Treatment Emergent Adverse Events by dose

There was no orthostatic hypotension reported for these dose categories and only 1 case of hypotension. Syncope was reported in 2 cases on 150-225/12.5 mg and in 2 cases on 300/25mg. Orthostatic dizziness and dizziness were reported slightly more often with the higher dose combination. All cases of orthostatic dizziness were mild. In 4 subjects orthostatic dizziness appeared to be temporarily related to dose increase; in 3 subjects it occurred within 1-7 days following the increase of irbesartan/HCTZ from 150/12.5 to 300/25mg, and in 1 case it occurred when atenolol 25mg was added to irbesartan /HCTZ 300/25mg.

Dizziness was more frequent in the 300/25mg group than in the 150-225/12.5mg group, but the incidence was similar in the 300/12.5 mg group. Overall, dizziness was mild and resolved during observation and most subjects continued in the study.

Clinical laboratory safety evaluations were obtained at initiation of the open label therapy, every 4 months, at month 12 or at discontinuation. Additionally, electrolytes, BUN and creatinine were obtained following upward titration of combination doses. There was very limited experience available for patients on 300/12.5 mg. The number of lab tests available and the subjects who experienced at least 1 MA potentially related to metabolic/electrolyte imbalance are presented by dose in Table 8d.

Table 8d: Combo Long-Term: Marked Abnormalities per Dose Number (Percent) of Subjects Experiencing at least 1 MA

Lab test	DOSE CATEGORY					
	150-225/12.5		300/12.5		300/25	
Low Potassium	[a]N =518	3 (0.6)	N=46	1(2.2)	N=255	7 (2.7)
High Potassium	N=518	5(1)	N=46	0	N=255	0
Creatinine High	N=440	4 (0.9)	N=42	1 (2.4)	N=212	6 (2.8)
BUN High	N=518	6 (1.2)	N=42	1 (2.4)	N=255	5 (2.0)
Urea High	N=79	8 (10.1)			N=43	5 (11.6)
Fasting Glucose High	N=404	3 (0.7)			N=240	3 (1.3)
Trigliceride Fasting High	N=404	3 (0.7)			N=61	4 (6.6)
Cholesterol High	N=404	0			N=239	1 (0.4)

[a] Number with evaluable test

source Integrated Study Report -037-038 Table S 7.6.1B

Three patients experienced low potassium in the 150-225/12.5 dose category, 1 patient in 300/12.5 and 7 patients in 300/25mg group. As expected, there was a trend towards higher incidence at higher doses of the combination. However, a lower incidence of hyperkalemia with HCTZ 25 mg was observed. Similarly, slightly more subjects had low potassium Laboratory Adverse Event reported by investigators.

In conclusion long term treatment with the combination irbesartan/HCTZ in the dose ranges of 150-300/12.5-25mg was well tolerated and safe. There was a trend to somewhat more dizziness in the higher dose groups but this did not appear to be related to the titration step from 300/12.5 to 300/25mg.

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The following AEs were reported: dizziness (7%), Nausea (3.5%) and palpitation (1.7%). The rate of AE is in line with that expected from antihypertensive treatment with "sartans" and/or HCTZ.There were no discontinuations due to AEs, nor were there any SAEs or deaths. Study follow-up was 12 weeks (84 days).

Other Laboratory findings
The mean changes from baseline in laboratory analytes reflect the known effects of each component of the combination. Dose-related changes with HCTZ were evident in the major trials, ie, decreases in sodium and potassium, increases in BUN, uric acid, glucose, cholesterol and triglycerides. Of note, irbesartan tended to ameliorate the HCTZ dose-related changes in plasma potassium, glucose and cholesterol. These results suggest that irbesartan/HCTZ doses up to 300/25 mg do not dramatically change the potassium homeostasis due to the ameliorating effect of irbesartan.
In general, there were no differences between irbesartan monotherapy and irbesartan/HCTZ combinations to endocrine/metabolic, haematopoetic, hepatic, musculoskeletal and renal analytes except a higher frequency of hypokalemia (2.2% vs 0.2%). However, irbesartan monotherapy resulted in a higher frequency of hyperkalemia (0.4% vs 0.2%).

Discussion

Efficacy
The absolute SeSBP and SeDBP reduction of irbesartan/HCTZ 300/25 vs. untreated baseline in mild to moderate patients appears to be approximately 21-24 and 13-16 mm Hg respectively. Data from 276 irbesartan/HCTZ treated patients are available to directly compare the efficacy of 300/25mg combination with the already approved 300/12.5mg combination, either in the parallel cell short term comparison trial (84 patients) or in long term elective titration studies - including 170 patients from

long term open label extension and 22 patients from study *CV131-052.* In all these trials the SeSBP reduction was more pronounced in patients receiving 300/25 mg, with the incremental efficacy ranging from 7.2 to 13.3 mm Hg with respect to those receiving 300/12.5 mg.

In all trials except the CV131037 trial SeDBP reduction was greater in patients receiving 300/25 mg than in those treated with 300/12.5 mg. The magnitude of this effect was 4.2 to 8.3 mm Hg. In trial CV131037, the DBP, the rate of normalised patients and the rate of "responders" were similar for both combinations. The DBP response surface model predicts less SBP reduction (4.7mmHg) but predicts a reduction of the DBP of 2.3mmHg. Although such small reductions are likely to translate, in epidemiological terms, into improvements in morbi/mortality, the real issue is the number of patients uncontrollable with 300/12.5 who would be controlled with 300/25.

In fact the only blinded evidence available on non-responders to 300/12.5 titrated to 300/25 comes from study CV131-052, whose primary endpoint was the change in LVMI from baseline in hypertensive patients with LVH. An incremental BP lowering effect was observed both on SBP and DBP (13.3 and 8.3 mm Hg, respectively). However, it should be taken into account that the number of patients titrated was rather small (22) and that the design of the study was not to determine the BP lowering effect of the combination. The proportion of patients normalised (32%) is in line with the rate obtained in the MONO LT open label study (31%). Thus, the data submitted are sufficient to conclude that there is an incremental lowering effect for the titration step, especially for the SBP, and that it translates into the normalisation of some, probably not many, patients. These findings have been included in section 5.1 of the SPC.

Safety
In general terms, there is a trend toward a higher frequency of some AE with the higher dose combinations, although the overall incidence was low, the severity mild and it did not cause more discontinuations. In some studies, notably the matrix study CV131037, dizziness was more frequently reported in the 300/25 group compared with lower doses. This was not unexpected given that some subjects switched directly from placebo to 300/25 mg, which lowers SBP in the range of 20-24 mm Hg. This abrupt initiation of a high dose combination is not recommended in the Posology section of the SPC.

With regard to the potassium abnormalities, the higher doses of the combination lead to increases renal parameters and low potassium, usually seen when HCTZ was increased from 12.5 to 25mg; these abnormalities were mild and reversible. It is well known that the dose dependent side effects of HCTZ (particularly electrolyte disturbances) may increase when titrating the HCTZ. This is clearly reflected in section 4.8 of the SPC.

Thus, from the safety point of view, for a patient uncontrolled on 300/12.5, the titration to 300/25 appears reasonable, but an increase in the dose-related effects of the HCTZ is to be expected.

7.3 Conclusion

The new 300/25 dose will control BP in some patients, probably not many, who are not adequately controlled with 300/12.5, despite the modest additional BP reduction obtained by increasing the HCTZ to 25 mg. For such patients for whom the safety/tolerability profile is still acceptable, the new dosage will be preferable to adding/substituting their existing therapy drugs of a different therapeutic class. Nonetheless, it should be emphasised that the proportion of patients not controlled by the already approved 300/12.5 mg likely to be controlled by the new 300/25 mg combination is not high, and the prescriber may directly consider alternative therapeutic approaches to increasing the dose of the HCTZ diuretic.