SCIENTIFIC DISCUSSION

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

1. Introduction

Inhibition of the renin-angiotensin system is a well proven approach to the treatment of arterial hypertension. It can be achieved by inhibiting the angiotensin-converting enzyme (ACE) that converts angiotensin I into its active form angiotensin II, or by blockade of angiotensin II (type AT_1) receptors.

AprovelKarvea is an oral formulation containing irbesartan, a selective antagonist of the AT_1 receptors. Two antihypertensive agents of the same class (angiotensin II receptor antagonist) have previously been authorised, losartan and valsartan.

2. Part II: Chemical and pharmaceutical aspects

Composition

The product is available in the form of tablets containing a dose of 75, 150 or 300 mg of irbesartan. Tablets containing each dosage are identified by a corresponding code. The quantitative and qualitative composition was adequately described.

The accelerated and long-term stability data demonstrated the suitability and compatibility of irbesartan with the packaging system (opaque blister pack in polyvinylchloride with a coating of heat sealed polyvinylidene chloride).

Clinical trials formulations

Both capsules and tablets were used in clinical trials. The trial dosage formulations including injectable and oral solutions and their method of manufacture were adequately described.

Data from three bioequivalence studies showed that irbesartan tablets and capsules used in the clinical trials were bioequivalent.

Development pharmaceutics

Irbesartan was successfully formulated into a stable, immediate release tablet. The excipients were selected on the basis of their functionality and compatibility with the active substance.

Irbesartan is a non-hygroscopic white or whitish crystalline powder with low solubility in water (< 0.1 mg/ml at 25°C). Although irbesartan solubility is low, solubility in the gastrointestinal tract is adequate.

The irbesartan bulk drug substance is well compressible and compactible.

Manufacture of the product

Tablets are manufactured by conventional pharmaceutical tabletting methods.

The manufacturing process for irbesartan was validated by the manufacture of seven batches (90 kg) at the commercial site in Evansville, USA. Based on the results from the validation studies, one lot was manufactured at full production scale (270 kg) in Evansville, USA. Additionally, three batches (125 kg) were manufactured at the commercial site in Ambares, France. Tablets of all three strengths manufactured at the USA and France sites were compressed without incident. All the tablets properties presented are satisfactory.

Control of starting materials

Active substance

Irbesartan is manufactured by Sanofi Chimie, Aramon, France; Bristol-Myers Squibb, Humacao, Puerto Rico; Orgamol, Switzerland and Swords, UK. Quality control and release of irbesartan takes place in the USA and in France. A Drug Master File was prepared in which the whole synthesis is

sufficiently described in the confidential part. The open part of the Drug Master File contains information to assure that the manufacture at the proposed commercial site is of high quality.

The proposed specifications and routine tests are sufficiently described in the dossier, in accordance with the established quality and backed up by the results presented in the batch analysis.

The profile of impurities has been established on the basis of an analysis of 16 industrial batches. The manufacture of irbesartan by the proposed commercial process contains trace levels of impurities. The results support the consistency of the manufacturing process, which allows irbesartan to be obtained with the established quality.

Degradation impurities were detected during the product development phase. They were present in batches used in toxicity and safety studies. These impurities have not been detected in batches produced by the industrial process.

Control tests on the finished product

The specifications proposed at release and at the end of shelf-life are appropriate to control the quality of the finished product.

The results of the analysis of 6 batches containing a dose of 75 mg, 8 batches containing a dose of 150 mg and 8 batches containing a dose of 300 mg manufactured in Evansville, USA and one batch of each dose manufactured in Ambares, France were submitted. All batches were found to be within the specifications.

Stability

Stability of the active substance

Seven batches were studied, three of which were from pilot scale production and four industrial scale. The analytical methods are correctly described and demonstrate stability.

Stress condition studies demonstrated that irbesartan is stable in various conditions.

Results of long term and accelerated studies showed that irbesartan is stable and does not require special handling or storage conditions.

Stability of the finished product

Long-term stability was studied in four batches of 75 mg irbesartan tablets, 3 batches of 150 mg and 4 batches of 300 mg all manufactured from five 90 kg batches produced in Evansville, USA. Results from batches stored for 18 months at 25°C ± 2°C/60% ± 5% RH, for 12 months at 30°C ± 2°C/60% ± 5% RH, and for six months at 40°C ± 2°C/75% ± 5% RH were presented. Results were also given for 30 days under light in both conditions.

These data showed that all tablets comply with the specifications proposed in all storage conditions, and support a proposed shelf-life of 24 months, packaged in blister packs stored at temperatures up to 30°C. Results of long-term stability studies of the finished productwere submitted after the marketing authorisation and supported a shelf-life of 36 months.

3. Part III: Toxicological and pharmacological aspects

All pivotal toxicokinetic studies were conducted in compliance with Good Laboratory Practice following Good Laboratory Practice and CPMP guidelines.

Pharmacodynamics

The pharmacodynamic effects of irbesartan were investigated *in vitro* and *in vivo* in various animals species, including rodents, rabbits, dogs and macaques. The macaque was used because of its more active basal renin angiotensin system. Saralasin (an antagonist of both AT_1 and AT_2 receptors) and losartan (a selective AT_1 receptor antagonist) were used as reference substances.

In an extensive battery of *in vitro* tests in several animal species, irbesartan showed a high affinity and selective antagonism to the angiotensin II subtype AT_1 receptor. The affinity of irbesartan for the AT_1 receptor was of the same order as that of saralasin, and approximately 10-fold higher than that of losartan (IC50 irbesartan 1nM, IC50 losartan 10 nM). Irbesartan had very low affinity for the AT_2 subtype, negligible affinity for various other neurotransmitter or endogenous peptide receptors, and did not inhibit renin or angiotensin-converting enzyme.

Tests both *in vitro* and *in vivo* in several animal species showed that irbesartan antagonizes angiotensin II-induced vasoconstrictor and pressor responses whereas in some experimental models it acted like a non-competitive antagonist.

Studies showed that irbesartan induces elevation of plasma renin and decrease of plasma aldosterone. No negative effects on renal function were shown.

Irbesartan inhibited the growth stimulating effect of angiotensin II on rat vascular smooth muscle cells more effectively than losartan.

Irbesartan produced a long-lasting hypotensive effect in hypertensive animals and also slightly reduced blood pressure in normotensive animals.

A fair correlation was found between individual plasma drug concentration and inhibition of the angiotensin-II pressor response, but the hypotensive effect did not correlate with plasma drug levels. Irbesartan did not show any agonist activity.

No untoward organ system effects were noticed with irbesartan at doses which effectively block AT_1 receptors.

Irbesartan was characterised as a nonpeptide orally effective potent and selective AT_1 antagonist with almost no pharmacological effect not related to AT_1 blockade. Animal studies do not currently support any indication other than hypertension.

Pharmacokinetics

Metabolism and disposition of irbesartan were investigated in mice, rats, rabbits and macaques.

Absorption

In all species, irbesartan was rapidly absorbed. Maximum plasma concentrations were reached within 0.5-6 hours. During repeated administration, steady state was achieved within 8 days. No significant accumulation was observed.

In both rats and macaques, the pharmacokinetics of irbesartan were characterised by a large volume of distribution, a low plasma clearance and a relatively long terminal half-life. AUC (area under the curve) and C_{max} (maximum plasma concentration) increased less than proportionally above 30 mg/kg. The absorption of irbesartan appeared to be nonlinear and saturable at high doses. Sufficient plasma concentrations were however reached in toxicity studies. Bioavailability in rats was low (10-20%). In macaques, absolute bioavailability was higher, 74% after 10 mg/kg oral dose, but variable, and was similar to that found in humans (61-82%).

Distribution in normal and pregnant animals

Irbesartan was widely distributed. No unusual retention of radioactivity in tissues other than liver and kidney was noted. Small amounts of radioactivity were transferred to rat and rabbit embryos or fetuses and also excreted in milk of lactating rats. In rats, enterohepatic circulation after oral dosing was 9-14 %.

Plasma protein binding was linear over the 0.01 and 50 mg/l range which includes therapeutic levels (92-96% in rats and macaques and 90-92% in humans). The binding was saturable at higher concentrations.

Biotransformation

Irbesartan was the main circulating active principle, although several minor active metabolites were formed. In plasma, unchanged irbesartan accounted in rat, macaque and rabbit for 67-95%, 51-67% and 14-68% respectively of the administered radioactivity. In mice, irbesartan accounted for only 3-12% of plasma radioactivity and the main circulating compound was a N-dealkyl derivative of irbesartan.

Irbesartan was metabolised by oxidation and glucuronidation. The overall pathways within different species yielded 18 different metabolites detected in bile, urine, faeces and also in small amounts in plasma. All metabolites identified in humans were detected in the different biological media, suggesting that animals in the toxicological studies were exposed to all human metabolites. The metabolic profile of irbesartan in rat and macaque is comparable to that in humans.

The cytochrome P450 2C9 isoform was mainly responsible for the oxidation of irbesartan. The lack of metabolism by CYP 2D6 provides strong evidence that irbesartan metabolism would not be subject to genetic polymorphism.

Excretion

The main elimination route in all animal species investigated was glucuronidation followed by excretion in the urine only in small amounts (up to 15% of excreted radioactivity in macaque).

In most species, irbesartan was mainly excreted in feces, with more than 80% of a radioactive dose recovered within 24-48 hours.

The pharmacokinetic studies are the weakest part of the preclinical dossier. Most quantitative pharmacokinetic parameters are not reliable due to lack of statistical power. However irbesartan was well defined in qualitative terms as a drug with good oral bioavailability (in macaques) and which does not accumulate. Identification of metabolites was adequately done, showing that no major metabolites are formed. Enterohepatic circulation of irbesartan was demonstrated in rats (10%) and macaques.

Rat and macaque proved to have similar pharmacokinetics as humans and these species were used for the major toxicology studies.

Toxicology

The toxicological effects of irbesartan were assessed using a standard battery of *in vitro* and *in vivo* studies. Since hydrochlorothiazide is a frequently co-administered drug in hypertension, several combination toxicity studies were also conducted.

The oral route was selected for the majority of the toxicological studies.

All batches of irbesartan used in the toxicological studies were fully characterised with regard to identity and purity and are considered representative of the drug product to be marketed for clinical use.

Single dose toxicity

The toxicity of irbesartan after single administration was investigated after oral, intravenous or intraperitoneal administration in rodents. These studies indicate a low acute toxicity of irbesartan.

Repeated dose toxicity

The main repeated oral dose toxicity studies were conducted in Sprague Dawley rat, macaque and mouse for up to 1 year using a wide range of doses up to 1000 mg/kg/day.

Irbesartan was well tolerated up to 500 mg/kg/day for 6 months in rats, and 1 year in macaques. Many of the observed effects were related to the pharmacodynamic activity of irbesartan, like dose-related decreases in blood pressure and hyperplasia of the juxtaglomerular apparatus (in rats at ≥ 90 mg/kg, in macaques ≥ 10 mg/kg), which has also been reported for other angiotensin II type AT_1 receptor inhibitors and angiotensin converting enzyme inhibitors.

Irbesartan caused slight changes in hematology (decreased hemoglobin, hematocrit and erythrocyte count) and blood chemistry (decreased total protein, increased urea, creatinine and potassium). These changes were not observed routinely at the lowest doses and were generally evident at the dose level of 90 mg/kg per day in rats and macaques.

In rats but not in macaques, irbesartan induced a dose-dependent increase in blood glucose. Irbesartan reduced heart weight in both species, an effect also observed with losartan.

Toxicokinetics data obtained during these studies confirmed that the exposure levels were adequate in rats and macaque. Based on mean plasma irbesartan $AUC_{0\text{-}24h}$ values, comparison of exposure observed at 500 mg/kg/day with that obtained in humans at the maximum dose of 300 mg/day gave an exposure ratio between 2.4-6.3 in rats and 16 in macaques.

Reproductive toxicity studies

Reproductive toxicity of irbesartan was studied in rats and rabbits following oral administration. Reproduction studies revealed that irbesartan, when given during gestation, causes slight development toxicity (hydroureter, subcutaneous edema) in rat fetus and increased incidence of abortions and post-implantation loss in rabbits at doses that induced maternal toxicity. When given during lactation, irbesartan induced a slight retardation in body weight gain of offspring. Similar effects were observed with other AT_1 receptor inhibitors and angiotensin converting enzyme inhibitors. As a precautionary measure, irbesartan should preferably not be used during first trimester of 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, irbesartan is contraindicated in the second and third trimesters of pregnancy. AprovelKarvea is contraindicated during lactation.

Genotoxic potential

The genotoxic potential of irbesartan as well as the combination of irbesartan and hydrochlorothiazide was studied in an adequate battery of *in vitro* and *in vivo* tests. No mutagenic or clastogenic effect was observed.

Carcinogenicity studies

The carcinogenic potential was assessed in two 104-week studies in mice and rats.

No carcinogenic potential was observed in either species given maximally tolerated doses (1000 mg/kg/day in mice and female rats or 500 mg/kg/day in male rats).

The AUC based exposure levels were over 4-fold higher in mice at 1000 mg/kg, over 2-fold higher at 500 mg/kg in rats, and over 20-fold higher at 1000 mg/kg (female rats) than that of humans at 300 mg/day.

Local tolerance

Irbesartan did not show any phototoxic or photoallergic reactions in the guinea pig. Irbesartan was not irritating to the eye or the skin in the rabbit.

Special toxicity studies

A combination study where pregnant rats were given irbesartan with hydrochlorothiazide during the organogenetic period showed similar effects as after administration of irbesartan alone.

Ecotoxicity and environmental risk assessment

The risk of an environmental impact from the use of irbesartan is of no concern.

4. Part IV: Clinical aspects

Clinical pharmacology

A clinical pharmacology program was completed in over 600 subjects, including healthy volunteers and patients with hypertension.

Pharmacodynamics

The pharmacodynamic profile of irbesartan in humans was established through single and multiple

dose studies.

In healthy volunteers, two randomised, single blind, placebo-controlled studies were carried out in order to evaluate the duration and level of inhibition of irbesartan on the effects of angiotensin II. Single doses of irbesartan of 5 mg to 300 mg dose-dependently inhibited the pressor and heart rate responses induced by exogenous angiotensin II. The peak inhibition was 84-100% at 75, 150 and 300 mg, with a peak inhibitory effect between 2 and 4 hours. The inhibition lasted for up to 24-36h at doses ≥ 50 mg.

In another study in salt depleted healthy subjects, irbesartan had a significant hypotensive effect. Mean arterial pressure (MAP) changes from pre-dosing levels were - 10.9 and -18.8 mm Hg at 25 and 50 mg, respectively.

Repeated administration in healthy subjects at high doses (up to 900 mg daily) induced a slight, non-significant decrease (-8.8/-8.5 mm Hg) from baseline in supine BP (blood pressure).

In patients with mild or moderate essential hypertension (DBP 95 to 110 mm Hg), treatment with irbesartan 100 mg and 300 mg once daily orally for up to 4 weeks decreased systolic blood pressure (SBP) and diastolic blood pressure (DBP) without altering heart rate. The effect was sustained over 24 hours. The trough to peak ratio was 0.99 for the 100 mg dose and 0.63 for the 300 mg dose. Irbesartan induced an expected dose dependent increase in both plasma angiotensin II and plasma renin activity. Excretion of aldosterone was significantly lower in the irbesartan groups than in the placebo groups. Urinary excretion of sodium, creatinine, potassium and chloride was not modified in the study using 300 mg of irbesartan.

Combination with 25 mg of hydrochlorothiazide was studied in patients with mild or moderate essential hypertension following the administration of 150 mg irbesartan over a 7 days period. Association of hydrochlorothiazide with irbesartan increased the plasma levels of angiotensin II and plasma renin more than irbesartan alone. The reduction in SBP and DBP was greater in the irbesartan-hydrochlorothiazide group than that produced by irbesartan-placebo group, the difference being statistically significant. The association of hydrochlorothiazide produced a greater excretion of sodium, potassium and chloride than in the group that received irbesartan alone. No differences were observed between groups in the excretion of creatinine and aldosterone.

Irbesartan did not affect glomerular filtration rate or effective renal blood flow, but transiently reduced renal vascular resistance in hypertensive patients.

Irbesartan also inhibited the renal effects of exogenous angiotensin II (i.e., increase in filtration fraction and renal vascular resistance, decrease in glomerular filtration rate and effective renal plasma flow, decrease in glomerular permselectivity and ultrafiltration coefficient, increase in glomerular transcapillary pressure gradient).

Irbesartan was confirmed as an orally active antagonist of the angiotensin II AT_1 receptors by blocking its effects, such as aldosterone secretion and vasoconstriction. No agonist activity was observed. It does not require biotransformation into an active form for its antihypertensive activity. Increases in plasma angiotensin II levels and renin activity are detected after administration of irbesartan following loss of negative feed-back mediated by AT_1 receptors. Plasma and urinary aldosterone levels are decreased.

Pharmacokinetics

The pharmacokinetics of irbesartan were studied after oral single and repeated doses.

The data showed that irbesartan is absorbed rapidly with C_{max} (maximum plasma concentration) achieved within 1 to 3.5 h. Plasma concentration of irbesartan increased linearly up to 600 mg dose level. Thereafter the absorption appeared to reach a plateau with increasing doses.

After 300 mg dose, the mean estimated bioavailability across several studies was 60-80% and not affected by food. Since the two lower strength tablets to be marketed (75 and 150 mg) are direct scale downs of the 300 mg formulation and have comparable *in vitro* dissolution profiles, the bioavailibility of all three strengths of the proposed commercial tablet formulation can be expected to be similar.

In the initial application, Irbesartan binding to serum proteins was 90-92% over the concentration range achieved with the proposed therapeutic doses. After the marketing authorization, the MAH

conducted a new *in vitro* study with a more specific method and a higher number of subject which showed that plasma protein binding is approximately 96% instead of 90%. This change was considered to have no impact on the clinical use of Irbesartan as its clinical safety and efficacy have been well established.

The apparent steady state volume of distribution is 53-93 l. Total body clearance is 157-176 ml/min with a renal clearance of 3-3.5 ml/min. Elimination half-life ranged from 11 to 15 h. During once daily repeated administration, steady state is achieved within 3 days and limited (< 20%) accumulation is observed.

The metabolic profile in humans is similar to that of rats and macaques. The cytochrome P450 isozyme, CYP2C9 is mainly responsible for the oxidation of irbesartan. Unchanged irbesartan is the main circulating compound accounting for 80% of total radioactivity following administration of radioactive irbesartan. Small amounts of several metabolites can also be detected in plasma (mainly irbesartan glucuronide up to 6% and the carboxylic acid derivative up to 9% of total radioactivity). Irbesartan and its metabolites are excreted by both biliary and renal routes. Following oral or intravenous administration, urinary and fecal recoveries were about 20-24% and 54-65%, respectively. Less than 2% of the administered dose of irbesartan was detected as intact drug in urine.

Irbesartan did not significantly affect the steady state pharmacokinetics of digoxin.

Both irbesartan and warfarin are metabolised by CYP2C9 indicating a possibility of metabolic interactions. *In vitro* studies indicated that warfarin inhibits metabolism of irbesartan in a dose-dependent manner (at concentrations of 10-100 μM), but this effect was not studied *in vivo*. Prothrombin time ratio values were not affected by concomitant administration of irbesartan and warfarin in healthy subjects, but this does not exclude the possibility for metabolic interactions with warfarin in clinical use.

The effect of other CYP2C9 inducers on the pharmacokinetics is not known.

The pharmacokinetics of irbesartan were not affected by co-administration of nifedipine or hydrochlorothiazide *in vivo.* The plasma concentration and elimination half-life were 20-25% higher in blacks, while C_{max} was comparable between blacks and whites.

After the marketing authorisation, two studies (one pharmacokinetic and one pharmacodynamic) have been conducted to test for a potential interaction between irbesartan and acenocoumarol (4 mg). Nevertheless, due to few reports of suspected drug interactions between irbesartan and any coumarin-like medication, and the low dose of acenocoumarol used in the pharmacodynamic study, no final conclusion can be currently decided.

No effect of irbesartan on the pharmacokinetics of simvastatin was shown in another post-authorisation study. Such interaction was theorically not expected based on metabolic profiles of irbesartan and HMGCoA-reductase inhibitors.

In elderly normotensive subjects (65-90 years) with normal renal and hepatic function, the plasma concentration AUC and C_{max} were 20% and 50% greater than those observed in younger subjects (18-40 years), while the elimination half-life was comparable.

In patients with mild to moderate cirrhosis, the pharmacokinetic parameters of irbesartan were not significantly altered. Studies were not performed in patients with severe hepatic impairment.

Pharmacokinetics of irbesartan were not significantly affected in patients with impaired renal function.

In hypertensive subjects, C_{max} and AUC of irbesartan were respectively 25% and 44% higher in women compared with men. However, following multiple dosing, men and women did not show differences in either accumulation or elimination half-life.

On the whole, the clinical pharmacokinetics program was well conducted and comprehensive. The results justify the intended use of the drug. Irbesartan is absorbed after oral administration, does not accumulate and no major active metabolites are formed. The blood pressure lowering effect is similar when the same total daily dose is given either once or twice daily. The relevance of the observed pharmacokinetic differences in relation to gender are not likely to be relevant.

Clinical experience

The clinical development program has been adequately conducted including 2500 patients with mild to moderate hypertension (DBP 95 to 110 mm Hg) and 121 patients with severe hypertension (DBP 115-130 mm Hg), treated with irbesartan. Aside from the two pilot dose finding studies and the long-term extensions, the duration of the studies ranged from 8 to 24 weeks. No studies on the effects of irbesartan on mortality/morbidity have been submitted.

Clinical experience on irbesartan relevant to the proposed indication is based on 16 studies:

Study reference number	Description	Duration of treatment	Number of patients
ACT1967	Pilot dose finding	6 days	86
CV131-001	Pilot dose finding	7 days	77
CV131-002	Pilot dose ranging	8 weeks	570
CV131-025	Dose ranging	10 weeks	319
CV131-050	Dose ranging	8 weeks	524
CV131-029	Placebo controlled	12 weeks	319
CV131-030	Placebo controlled	8 weeks	215
CV131-039	Placebocontrolled	8 weeks	178
CV131-038	Placebo and hydrochlorothiazide controlled	12 weeks	815
CV131-037	Placebo and hydrochlorothiazide controlled	8 weeks	683
CV131-040	Placebo and hydrochlorothiazide controlled	12 weeks	238
CV131-027	Atenolol controlled	24 weeks	231
CV131-028	Enalapril controlled	12 weeks	202
CV131-031	Amlodipine controlled (elderly)	24 weeks	188
CV131-032	Enalapril controlled in severe hypertension	12 weeks	182
CV131-033	Renal failure	12 weeks	100

These trials (excluding ACT1967, CV131-032, -033, -040) included a placebo lead-in phase of at least 4 weeks following withdrawal of previous antihypertensive medications to ensure stability of blood pressure and to assess baseline status.

The primary efficacy variable was the mean change from baseline in seated diastolic blood pressure (seDBP), with the exception of two pilot studies where it was supine DBP (CV131-001) or supine and standing DBP and SBP (ACT1967).

Secondary variables were: seated systolic blood pressure (seSBP), trough to peak ratio for the antihypertensive effect, the proportion of subjects who achieved normalised seDBP (< 90 mm Hg) at trough (24h post-dose), and changes in standing diastolic (stDBP) and systolic (stSBP) blood pressures.

Study subjects were monitored for the appearance of clinical adverse events and laboratory test abnormalities. Questionnaires were also used in order to evaluate health status. Blood samples for hematological and biochemical analyses were obtained prior to enrollment and randomization, and were repeated at least every 8 weeks throughout the studies. Creatine kinase levels were measured at baseline and periodically throughout the placebo-controlled trials. Creatine kinase was also measured in any subject with unexplained muscle pain. Heart rates were monitored in all studies. Ambulatory electrocardiographic monitoring was performed in a subset of patients at baseline, during the double-blind phase and during the withdrawal phase in study CV131-050. Electrocardiograms and chest X-rays were obtained at study entry and at completion. In several studies, funduscopic examinations were recorded at baseline and at the end of the study.

Uniform inclusion and exclusion criteria resulted in comparable subject populations among the individual placebo controlled studies in patients with mild to moderate hypertension. In general, subjects were in their early to mid-fifties (range 21-85 years), over 80% were white, and over 50% were male.

Dose-finding studies

The five dose-finding studies were all of similar design: randomised, double-blind, parallel, placebo controlled, in patients with mild to moderate essential arterial hypertension. The treatment phase was preceded by a period of 4-5 weeks with placebo.

The overall results indicate that irbesartan administered once daily at doses of 1-900 mg produces dose-dependent reduction in DBP and SBP with statistically significant reduction in SeDBP (versus placebo) with a 50 mg dose and a flattening from 300 mg to 900 mg. Testing over a wide dose range was possible with irbesartan because of the absence of dose-limiting side effects, even at doses associated with the apparent plateau of the antihypertensive effect.

Placebo controlled trials

Study CV131-029 and study CV131-030 were multicentre, randomised, double blind, placebo-controlled trials in patients with hypertension (DBP 95-110 mm Hg).

In study CV131-029, patients were randomised into three groups:

- 104 patients to irbesartan 75 mg once daily and increased dose to 150 once daily at 6 weeks if DBP > 90 mm Hg
- 98 patients to irbesartan 150 mg once daily and increased dose to 300 once daily at 6 weeks if DBP > 90 mm Hg
- 117 patients to placebo

Statistically significant reductions compared to placebo in both DPB and SBP were observed for trough and peak BP at week 12. At each time point, for each blood pressure parameter, the 150 mg dose regimen produced greater decreases than 75 mg irbesartan dose regimen. Of these who completed week 12 of double blind treatment, at least 50% of the subjects on each treatment group had DBP ≥ 90 mm Hg and were titrated to double their initial randomised dose. The greatest percentage (89%) were titrated in the placebo group and the smallest (53%) occurred in the irbesartan 150 mg dose regimen. 65 % of patients randomised to irbesartan 75 mg were titrated to 150 mg.

In study CV131-030, the primary objective was to determine the reduction in the mean 24-hour Ambulatory DBP from baseline to the end of 8 weeks of treatment in subjects with hypertension (DBP 95-110 mm Hg and a mean 24-hour Ambulatory DBP ≥ 85 mm Hg).

Patients were randomised into four groups:

- 55 patients to irbesartan 75 mg once daily
- 53 patients to irbesartan 150 mg once daily
- 57 patients to irbesartan 75 mg twice daily
- 44 patients to placebo

Statistically significant reductions compared to placebo in 24-hour Ambulatory DBP and SBP were observed at week 8. There was a larger reduction in the group administered 150 mg once daily. The 75 mg twice daily showed nearly identical results in the 24-hour Ambulatory DBP as compared to 150 mg once daily.

Considering the seven main placebo-controlled trials and using the placebo-subtracted trough blood pressure values, a decrease in the range of 8-10/5-6 mmHg and 8-13/5-8 mmHg were observed with irbesartan 150 mg and 300 mg respectively. A normalisation rate of seDBP (< 90 mmHg) was reached in 60% of the patients. The blood pressure normalisation rate at doses of ≤ 75 mg was not significantly different from placebo (20-25%). The blood pressure normalisation rate was significantly increased at doses of ≥ 150 mg.

The antihypertensive effect of irbesartan was evident after the first dose, increased substantially by 2 weeks and reached the maximum within 4-6 weeks. Trough to peak ratios were generally > 60% with 150 mg once daily. Ambulatory BP monitoring confirmed that similar effects were achieved whether irbesartan was administered in the morning or in the evening. The 150 mg dose reduced the mean 24h ambulatory BP consistently more than placebo. No blood pressure increases were observed after

withdrawal of irbesartan.

In summary, the documentation and further clarifications provided by the applicant support the 150 mg dosage as the usual recommended initial and maintenance dose. Although clinically and statistically significant reductions in BP were achieved with doses ≥ 75 mg, consistent antihypertensive effect was seen at ≥ 150 mg doses and were in better accordance with the ICH guideline on dose response information to support drug registration. Irbesartan had furthermore no dose related increases in adverse events across the therapeutic range (150 to 300 mg) including hypotension-related first dose effects.

Controlled studies with active comparators

Three randomised, double-blind, active controlled comparative studies with atenolol (CV131-027), amlodipine (CV131-031), enalapril (CV131-028) were conducted in patients with mild to moderate hypertension. One study (CV131-032) was conducted in patients with severe hypertension.

In study CV131-027, 231 patients were randomized to receive either irbesartan 75 mg or atenolol 50 mg once daily for 24 weeks. At week 6 the dose of the study was doubled if seDBP was = 90 mmHg. At week 12, or any time thereafter, the dose of the product was doubled (if not done earlier) for subjects with seDBP = 90 mmHg followed by addition of HCTZ 12.5 mg titrated to 25 mg as needed, and when needed, addition of sustained release nifedipine 20 mg once daily. The primary efficacy variable was the change from baseline in trough seDBP at week 12; changes were similar for both study groups(-12.3 mmHg in the irbesartan group and -11.6 mmHg in the atenolol group).

In study CV131-028, 202 patients were randomized to receive either irbesartan 75 mg or enalapril 10 mg once daily for 12 weeks. The doses were doubled at weeks 4 and 8 for subjects with seDBP = 90 mmHg. The primary efficacy endpoint, change from baseline in trough seDBP at week 12 was similar in both groups, -12.7 mmHg for irbesartan and -14 mmHg for enalapril.

In study CV131-031, 188 elderly patients were randomized to receive either irbesartan 75 mg or amlodipine 5 mg once daily for 24 weeks. The doses were doubled at weeks 6 or 12 or anytime thereafter to week 20 for subjects with seDBP was = 90 mmHg. After 12 weeks, additional open-label treatment with HCTZ (12.5 mg titrated to 25 mg) followed by atenolol (50 mg) once daily when needed was started to achieved se DBP < 90 mmHg. The primary efficacy endpoint, change from baseline in trough seDBP at week 12 was significantly larger in the amlodipine group (-14.9 mmHg) compared to the irbesartan group (-10.5 mmHg).

In study CV131-032, 182 patients were randomized with severe essential hypertension. It included a withdrawal period of at least 24 h for subjects receiving antihypertensive therapy and a placebo lead-in period lasting a maximum of 7 days followed by randomization in a 2:1 ratio to receive irbesartan 150 mg or enalapril 20 mg once daily for 12 weeks. The dose for both products was doubled for subjects 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/nifedipine/atenolol) was added if seDBP = 90 mmHg. The change from baseline in trough seDBP at week 12 (the primary efficacy outcome measure) was similar in both groups; irbesartan –29.6 mmHg and enalapril –30.5 mmHg.

At doses of 75 and 150 mg of irbesartan, efficacy was comparable to those of 50 and 100 mg of atenolol. At doses of 75, 150 mg and 300 mg of irbesartan, efficacy was comparable to those of 10, 20 and 40 mg of enalapril in subjects with mild to moderate and also in severe hypertension patients. In elderly subjects, BP responses were similar between amlodipine 5 mg and irbesartan 150 mg, but amlodipine 10 mg was more effective than irbesartan at 150 mg.

Irbesartan and hydrochlorothiazide

Studies CV131-037, CV131-038, CV131-039 and CV131-40 were multicentre, randomised, double blind and placebo controlled trials.

These indicated that combination of irbesartan and hydrochlorothiazide lead to further reductions in DBP and SBP than when the drugs were given separately.

Patients with hypertension and renal insufficiency

Study CV131-033 was a non-comparative study in patients with hypertension and severe renal

insufficiency. Results indicated that lower doses of irbesartan (75 mg) should be considered in patients undergoing haemodialysis.

Long-term efficacy data

The long-term open-label extension studies of the double-blind studies (CV131-002, -025, -027, - 028, -029, -031, -037, -038) confirmed sustained efficacy for more than 1 year.

Demographic subgroups

There were no significant differences in the antihypertensive effect of irbesartan between men and women, elderly (≥ 65 years) and younger subjects, and between subjects with baseline seDBP < or ≥ 100 mmHg.

Diminished BP responses were generally observed with black subjects when compared with whites. This has also been reported with other antihypertensive drugs inducing renin angiotensin system (RAS) antagonism (beta-blockers, angiotensin converting enzyme inhibitors, losartan). However, during long-term treatment of irbesartan with concomitant hydrochlorothiazide, BP responses in black subjects approached those of white subjects suggesting that irbesartan might be more effective in black subjects whose RAS is activated.

In the case of salt depleted patients, sodium and/or volume depletion should be corrected before initiation of treatment with irbesartan.

Although dose-adjustment is not usually necessary for the elderly, since this group of patients may be more sensitive, consideration should be given to initiate therapy with 75 mg in patients over 75 years of age.

Safety

The integrated summary of safety for irbesartan monotherapy and irbesartan/hydrochlorothiazide combination therapy is based on the analysis of the profile of clinical adverse events and laboratory abnormalities in 5849 subjects enrolled in 49 completed clinical studies. A total of 4925 subjects were exposed to irbesartan. Of these, over 900 were elderly over 65 years and 150 were over 75 years. Approximately 1300 hypertensive subjects were treated with irbesartan for over 6 months and 400 for over 1 year.

Dose response and placebo controlled monotherapy studies

The overall incidence of adverse events was 56.2% in irbesartan treated subjects and 56.5% in placebo treated subjects.

The most common adverse events in subjects receiving irbesartan were headache (12.3%), upper respiratory infection (8.5%), musculoskeletal pain (6.6 %), dizziness (4.9%) and fatigue (4.3%). These events occurred with a similar incidence in the placebo group except for headache, which occurred more frequently in subjects receiving placebo (16.7%). Musculoskeletal trauma and flushing were reported infrequently, but occurred significantly more often in the irbesartan than in the placebo group (1.9% vs. 0.5% and 0.6% vs. 0%, respectively). The incidence for hypotension and orthostatic hypotension was 0.4% in subjects treated with irbesartan and 0.2% in those treated with placebo.

The overall incidence of serious adverse events was 1.0% in irbesartan-treated subjects and 1.9% in placebo-treated subjects. Serious events occurred most commonly in the cardiovascular system (0.2% of subjects receiving irbesartan and 1.6% of subjects receiving placebo). The only serious adverse event occurring in more than 1 irbesartan treated subject was myocardial infarction which was reported in 2 (0.1%) irbesartan treated subjects and 1 (0.2%) placebo-subject.

The overall incidence of marked laboratory abnormalities was similar between the irbesartan and placebo treatment groups.

Irbesartan/hydrochlorothiazide studies

The overall incidence of adverse events was similar between the study groups: 59.1% in irbesartan/hydrochlorothiazide treated subjects, 58.2% in hydrochlorothiazide monotherapy, 56% in irbesartan monotherapy group and 53.4% in the placebo group.

The most common adverse events in subjects receiving irbesartan/hydrochlorothiazide were headache

(11%), dizziness (7.6%), fatigue (6.5%), musculoskeletal pain (6.5%) and upper respiratory infection (5.6%). These events occurred in a similar incidence in the placebo group except for headache, which occurred more frequently in subjects receiving placebo (16.1%), and fatigue, which had a significantly lower incidence in the placebo group (3%). The incidence of nausea/vomiting and fatigue was also significantly higher in irbesartan/hydrochlorothiazide treated subjects compared with placebo treated subjects. The reported incidences for orthostatic hypotension/dizziness were 1.6% in subjects receiving irbesartan/hydrochlorothiazide, 1% with irbesartan monotherapy, 0.8% in subjects receiving hydrochlorothiazide monotherapy and 0.4% in subjects receiving placebo.

The overall incidence of serious adverse events was similar between study groups: 1.3% in irbesartan/hydrochlorothiazide treated subjects, 1.2% in irbesartan monotherapy group, 1.8% in hydrochlorothiazide monotherapy and 0.4% in the placebo group. The only serious adverse event occurring in more than 1 irbesartan/hydrochlorothiazide treated subject was myocardial infarction which was reported in 2 (0.2%) irbesartan treated subjects and 1 (0.2%) placebo-subject.

The overall incidence of marked laboratory abnormalities was similar between study groups.

Active controlled studies

The overall incidence of adverse events was similar between the subjects receiving irbesartan monotherapy (60%) and active control (62.7%). The most common adverse events in subjects receiving irbesartan were headache (10.6%), fatigue (7.1%), dizziness (5.9%), and upper respiratory infection (5.9%). There were no significant differences in the incidence of these events between treatment groups. When looking at each study separately, adverse events occurred more frequently in the atenolol and amlodipine groups when compared with the irbesartan group. Irbesartan treated subjects experienced a slightly greater incidence of adverse events in study CV131-028 when compared with the enalapril group. However, in protocol CV131-032 in subjects with severe hypertension, the incidence of adverse events was considerably lower in the irbesartan group.

The overall incidence of serious adverse events was 4.7% in the irbesartan group and 3.2% in the active control group. Serious adverse events occuring in the renal/genitourinary system were the most common (1.4 % in subject receiving irbesartan and 0.8 % in subjects receiving placebo).

The overall incidence of marked laboratory abnormalities was similar between study groups.

Long-term open-label extension studies

The incidence of adverse events in 2176 subjects treated with irbesartan or irbesartan/hydrochlorothiazide was 56.2%. The most common adverse events were upper respiratory infection (9.6%), musculoskeletal pain (9.6 %) headache (8.3 %), fatigue (6.3%) and dizziness (5.6%).

Serious adverse events occurred in 4.6% of subjects treated with irbesartan or irbesartan/hydrochlorothiazide. The most frequently reported were myocardial infarction (0.7%), invasive cardiac procedure (0.5%) and orthopedic surgery (0.5%).

The most common laboratory abnormalities were increased leukocytes (3.7%), increased creatine kinase (1.6%), increased eosinophils (1.3%), increased blood urea nitrogen (1.3%) and increased triglycerides (1.3%).

Discontinuation and deaths

In the dose response and placebo controlled monotherapy studies, a total of 3.3% of irbesartan treated and 4.5% of placebo-treated subjects discontinued therapy because of adverse events during the double-blind therapy. The most common events leading to withdrawal of study drug were headache (0.6%), dizziness (0.3%) and general chest pain (0.3%). One subject receiving irbesartan died during the double-blind therapy. The cause of death was cardiorespiratory arrest and myocardial infarction.

In the irbesartan/hydrochlorothiazide studies, discontinuations due to adverse events were significantly less frequent in the irbesartan/hydrochlorothiazide combination group (3.6%) compared with the placebo group (6.8%). The most common events leading to withdrawal in subjects receiving irbesartan/hydrochlorothiazide were headache (0.7%) and dizziness (0.7%). One subject receiving irbesartan/hydrochlorothiazide died during the double-blind therapy due to myocardial infarction.

In the long-term open-label extension studies, the most common events contributing to study drug withdrawal were myocardial infarction (0.7%) and fatigue (0.6 %). A total of 3 subjects (0.1%)

receiving irbesartan died. The causes of death were hemorrhagic hypovolemic shock and Goodpasture's syndrome in subjects receiving irbesartan monotherapy and motor vehicle accident in a subject receiving irbesartan/hydrochlorothiazide combination therapy.

All deaths occurring in these trials were classified as unrelated to study medication.

A detailed description of every case of myocardial infarction during irbesartan therapy was provided. The following special warning was included in the Summary of Product Characteristics: "Excessive blood pressure decrease in patients with ischemic cardiopathy or ischemic cardiovascular disease could result in a myocardial infarction or stroke."

Additional analyses revealed that the incidence of adverse events in placebo-controlled studies was not affected by age, gender or race. There were no dose-related adverse events between 1 and 300 mg. Some events occurred more frequently in the > 300 mg groups, but none of these events were dose limiting.

First-dose effects for both the placebo controlled irbesartan monotherapy studies and the irbesartan/hydrochlorothiazide controlled combination studies were comparable between irbesartan and placebo. Orthostatic hypotension was reported in 3 (0.2%) subjects and syncope in one (0.1 %) subject receiving irbesartan monotherapy. None of the subjects receiving irbesartan/hydrochlorothiazide combination therapy experienced hypotension or syncope as a result of the first dose. Overall the incidence of hypotension or its symptomatic equivalent (orthostatic hypotension/dizziness, syncope, dizziness and vertigo) was low and similar for subjects treated with monotherapy, irbesartan/hydrochlorothiazide combination therapy or placebo.

The incidence of cough was low (range 0-4.5% in all subjects receiving irbesartan) and occurred similarly in subjects receiving irbesartan monotherapy, irbesartan/hydrochlorothiazide combination therapy or placebo.

An analysis of selected musculoskeletal adverse events (musculoskeletal pain, muscle ache, muscle cramp and myalgia) revealed no differences between subjects treated with irbesartan monotherapy, irbesartan/hydrochlorothiazide combination therapy or placebo. However in placebo-controlled monotherapy studies the incidence of musculoskeletal trauma was significantly higher in subjects receiving irbesartan compared with placebo (1.9% vs. 0.5%). These included events of sprains, strains, injury to fingers and torn ligaments. The differing types and causes of these traumas, the similar incidence of other musculoskeletal events in the irbesartan and placebo group and the lack of association of these events with dizziness or orthostatic dizziness suggest that the statistically significant higher incidence of musculoskeletal trauma in irbesartan-treated subjects is most likely spurious and of no clinical relevance.

The analysis of ECGs in 4 protocols (CV131-002, -025, -050, -057) and ambulatory ECG-monitoring (in protocol CV131-050 in a subset of subjects at selected study sites) showed no clinically significant changes between subjects receiving irbesartan or placebo or after irbesartan withdrawal.

In placebo-controled studies, no evidence of clinically important adverse interactions was observed between irbesartan monotherapy or irbesartan/hydrochlorothiazide combination therapy and concomitant medications including aspirin, acetaminophen, estrogen and ibuprofen.

In post-marketing experience, as with other angiotensin-II receptor antagonists, rare cases of hypersensitivity reactions (rash, urticaria, angioedema) have been reported. The following have also been reported very rarely during post-marketing surveillance: asthenia, diarrhoea, dizziness, dyspepsia, headache, hyperkalemia, myalgia, nausea, tachycardia, arthralgia, tinnitus, liver function abnormalities, including hepatitis and impaired renal function including isolated cases of renal failure in patients at risk. Cases of cough have been reported very rarely with irbesartan.

5. Overall conclusions and benefit/risk assessment

Overall benefit-risk assessment

Efficacy of irbesartan in long-term reduction of blood pressure in patients with essential hypertension (duration of the studies ranging from 8 to 24 weeks) has been demonstrated. The usual recommended

initial and maintenance dose of 150 mg once daily generally provides a better 24 hour blood pressure control than 75 mg. However, initiation of therapy with 75 mg could be considered, particularly in haemodialysed patients and in the elderly over 75 years.

At doses of 75 and 150 mg of irbesartan, efficacy was comparable to those of 50 and 100 mg of atenolol. At doses of 75, 150 mg and 300 mg, efficacy was comparable to those of 10, 20 and 40 mg of enalapril in subjects with mild to moderate, and also in severe hypertension patients. In elderly subjects, BP responses were similar between amlodipine 5 mg and irbesartan 150 mg, but amlodipine 10 mg was more effective and with a higher number of adverse effects.

In patients with blood pressure insufficiently controlled with 150 mg once daily of irbesartan, the dose can be increased to 300 mg, or other anti-hypertensive agents such hydrochlorothiazide, can be added.

The long-term effects of irbesartan on target organ damage in hypertension or on mortality are not yet known.

The toxicity studies raised no immediate concern regarding the safety of the product. Irbesartan is embryotoxic in rats with the kidney as major target organ. As precautionary measure, irbesartan should preferably not be used during first trimester of 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, irbesartan is contraindicated in the second and third trimesters of pregnancy. AprovelKarvea is contraindicated during lactation.

Irbesartan was generally well tolerated in the clinical studies. Its overall safety profile is comparable to other previously authorised AT_1 receptor antagonists. The overall incidence of adverse events in the irbesartan treatment groups is not different from the incidence in the placebo group. In most studies, there were no adverse events occurring more frequently after irbesartan than in the placebo group. In the placebo controlled monotherapy studies, 3.3% of irbesartan-treated subjects and 4.5% of placebo treated subjects discontinued the treatment.

Headache, dizziness and chest pain were the more common reasons for discontinuation in the irbesartan group but discontinuations due to headache and dizziness were less common in the irbesartan group than in the placebo group. Although the incidence was not high (0.7 %) considering the treated population, the most common serious adverse event in the irbesartan treatment groups was myocardial infarction.

Conclusions

AprovelKarvea is an oral formulation containing irbesartan, a new selective antagonist of the angiotensin II (type AT_1) receptor.

Efficacy and safety data support a favourable benefit-risk ratio for the treatment of essential hypertension.

The CPMP therefore recommends the granting of a Marketing Authorisation for this medicinal product.

6. New indication for the treatment of renal disease in patients with hypertension and type 2 diabetes mellitus as part of an antihypertensive drug regimen

Introduction

According to the US National Kidney Foundation, diabetes mellitus is the leading cause of End Stage Renal Disease (ESRD), accounting for 35% of new cases every year. The prevalence of diabetic renal disease in patients who have had type I or type II diabetes for at least 25 years has been reported as 48% and 57%, respectively. ESRD secondary to type II diabetes has become the single most common cause of renal replacement therapy throughout the Western world. Patients with advanced renal disease who require dialysis or renal transplantation have a poor survival prognosis. The annual mortality rate of patients with diabetic ESRD approaches 40%. Cardiovascular morbidity and mortality remain a significant medical problem in diabetic renal disease, and therapies to prevent or slow the renal complications of diabetes remain a priority in the management of these patients.

The pathogenesis and natural history of diabetic nephropathy is characterised by sequential and progressive abnormalities of renal function and of glomerular morphology. There is a highly predictable course in type I diabetes, which seems to be similar in type II diabetes, but is less well documented. The earliest clinical evidence occurs with the appearance of low but abnormal levels of albumin in the urine, termed microalbuminuria. Studies show that 5 to 10% of diabetic type II patients with microalbuminuria develop overt nephropathy each year. Without specific interventions, 20-50% of type II diabetic patients with sustained microalbuminuria progress over 5 to 10 years to clinical albuminuria. By 20 years after the onset of clinical albuminuria, about 20% of patients have progressed to ESRD.

Renal function before and after onset of microalbuminuria follows a typical course: early in diabetes, glomerular filtration rate (GFR) tends to be high (*i.e.,* hyperfiltration); during the phase of microalbuminuria, GFR is still within the normal range; and once clinical albuminuria occurs, the GFR falls over a period of several years at a rate that is highly variable between individuals.

Renal biopsy studies have shown characteristic changes of diabetic glomerulopathy in both type 1 and type II diabetic patients. The relationship between kidney lesions and microalbuminuria is less clear in type II than in type I diabetes. Only 30% of type II diabetic patients with microalbuminuria have typical diabetic glomerulopathy (Kimmelstiel Wilson's lesions), while 40% have more advanced tubulo-interstitial and/or vascular lesions and 30% have normal renal structure.

In 1984, Mogensen reported that microalbuminuria in type I and type II diabetic patients (microalbuminuria defined as 30 μg/ml–140 μg/ml) predicted the progression of renal disease and led to an overall excess mortality of 148% over a 9-year period in the latter patients. Even very small increases in albuminuria were shown to be quite significant. Apart from being a predictor of ESRD, microalbuminuria is also thought to be a predictor of cardiovascular complications and cardiovascular death. Several studies have demonstrated an increased mortality risk in type II diabetic patients with increasing levels of albuminuria.

Subtle abnormalities in blood pressure appear when microalbuminuria develops. Abnormal blood pressure is observed in type II diabetic patients at the earliest stages of the disease and worsens as the disease progresses. The prevalence of hypertension increases markedly when proteinuria, and more specifically elevated serum creatinine, is present. The prevalence of arterial hypertension, defined in a study published by Gall et al as ≥ 160/≥ 95 mmHg, increases with increasing albuminuria, being 48%, 68%, and 85% in patients with normoalbuminuria, microalbuminuria, and clinical albuminuria, respectively.

Reduction in blood pressure has been shown to have beneficial effects on mortality and morbidity. The UK Prospective Diabetes Study (UKPDS) showed that each 10 mmHg decrease in mean systolic blood pressure was associated with reductions in risk of 12% for any complication related to diabetes (95% confidence interval 10% to 14%, $p < 0.0001$), 15% for deaths related to diabetes (12% to 18%, $p < 0.0001$), 11% for myocardial infarction (7% to 14%, $p < 0.0001$), and 13% for microvascular complications (10% to 16%, $p < 0.0001$).

Angiotensin-converting enzyme inhibitors (ACE-Is) and AIIRAs have been shown to provide benefits in the treatment of incipient or overt type I diabetic nephropathy above and beyond that achieved simply due to blood pressure reduction alone. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends that blood pressure should be maintained < 130/85 mmHg in individuals with diabetes and < 125/75 mmHg when proteinuria is $\geq$1 g/24 hours.

Several studies have demonstrated a reno-protective effect of ACE-Is in type I diabetes. These blood pressure independent benefits seem to be mediated by the inhibition of the renin-angiotensin system. It is well known that the rate of progression of nephropathy in type II diabetes is similar to although more variable than that in type I diabetes. This variability may relate to the fact that type II diabetes is usually a disease of the elderly, so that renal changes from ageing are superimposed upon the changes from diabetes. At the time of the submission of this variation, there were no published studies with clinically definitive renal outcomes addressing the issue of renoprotection in type II diabetes.

Clinical aspects

The current submission is based on two large pivotal studies: IRMA 2 (IRbesartan MicroAlbuminuria in type 2 diabetes) and IDNT (Irbesartan Diabetic Nephropathy Trial), which included patient populations at two different stages of diabetic kidney disease within the continuum of the disease process, in order to evaluate the effect of intervention at two key periods of the chronological evolution of the disease. Both trials have been published in the same issue of the New England Journal of Medicine (September 20, 2001). A Glomerular Filtration Rate (GFR) sub-study and its extension were included in the IRMA 2 study.

In addition to these two pivotal trials, three other supportive small-scale trials studies have been conducted: Protocol CV131-047 was a pilot study for the IDNT study; the other two protocols (CV131-046 and CV131-093) were renal haemodynamic studies. None of these 3 studies provide any substantial efficacy or safety data, and hence will not be reviewed.

Appropriate GCP-compliance statements have been provided with all study reports.

IRMA 2

Study design and objectives

This was a multinational, multicentre, randomised, double-blind study comparing 2 doses of irbesartan versus placebo in a parallel group design. Following a 3-week single-blind placebo period, subjects were randomly allocated to one of three treatments: 150 mg irbesartan, 300 mg irbesartan, or placebo. Thereafter, subjects entered a 4-week titration period during which, for the first 2 weeks (Week 0 to Week 2), subjects allocated to both irbesartan treatment groups received only 75 mg daily of active medication. At the Week 2 Visit, all subjects receiving irbesartan had their daily dose titrated to 150 mg. At Week 4, subjects allocated to 150 mg irbesartan remained on the same daily dose (i.e., 150 mg) and those allocated to 300 mg irbesartan had their dose titrated to 300 mg daily. Subjects remained on this daily dosing regimen until Month 24 in the double-blind maintenance period. A post-study visit (Visit 10) occurred 1 week after the end-of-study visit (Month 24 or premature discontinuation). The total duration of treatment was 25 months, including 24 months of double-blind treatment.

Of the 611 subjects randomised in the main study, a subset of subjects (133) was selected for the *GFR sub-study and its extension* to have GFR and Extracellular Fluid Volume (ECV) assessments performed periodically while receiving treatment. At the same timepoints, blood plasma was frozen and sent to a central laboratory for measurements of pro-renin, active renin, and angiotensin II concentration. In the GFR sub-study extension, the subjects returned to the study centres once weekly for 4 weeks after all study medication and concomitant antihypertensive medications were discontinued at Visit 9 (Month 24). The effect of withdrawing the study drug and adjunctive antihypertensive medication on BP, microalbuminuria, and GFR were evaluated.

The primary objective of IRMA 2 was to evaluate the effects of irbesartan on progression to overt proteinuria, defined as urinary albumin excretion rate [AER] > 200 µg/minute and an increase of at least 30% from baseline, in hypertensive subjects with Type II diabetes mellitus and microalbuminuria.

Secondary objectives were to evaluate the change from baseline in:

- overnight urinary AER.
- estimated creatinine clearance using the Cockroft and Gault formula.
- von Willebrand factor (vWF), fibrinogen, factor VII (FVII), plasminogen activator inhibitor-1 (PAI_1), and lipid profile (total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and apolipoprotein) after 1 and 2 years of treatment.

The following additional objectives were established for the *GFR sub-study* and its *extension* conducted in a subset of subjects:

- changes from baseline in GFR after 3 months and 2 years of treatment, as well as ECV, pro-renin, active renin, and angiotensin II were secondary assessments in the GFR sub-study.
- changes in GFR after withdrawing study medication and any concomitant antihypertensive medications for 4 weeks, as well as blood pressure (BP) and urinary AER were secondary assessments in the GFR sub-study extension.

Diagnosis and inclusion/exclusion criteria

Subjects were males or nonlactating and nonpregnant females aged 30 - 70 with type II diabetes mellitus and seated systolic BP (SeSBP) > 135 mmHg and/or seated diastolic BP (SeDBP) > 85 mmHg which was not being treated, or if receiving antihypertensive medication, SeSBP ≤ 160 mmHg and/or SeDBP ≤ 90 mmHg; evidence of microalbuminuria defined as an urinary albumin excretion rate (AER) between 20 and 200 μg/minute on 2 of 3 timed overnight collections; serum creatinine ≤ 1.5 mg/dL in males and 1.1 mg/dL in females; serum potassium in the normal range (3.5-5.5 mmoles/l); Body Mass Index (BMI) ≤ 40 kg/m^2.

Type II diabetes was defined according to the standard ADA definition, as follows:

1. In case of diabetes not treated with insulin: hyperglycemia requiring treatment with an oral hypoglycemic agent, and/or fasting plasma glucose ≥ 140 mg/dl on two occasions, and/or fasting C peptide level exceeding the normal level of the local laboratory; or

1) In case of diabetes treated with insulin: time between diagnosis of type II diabetes and insulin use greater than 1 year, or fasting C peptide level exceeding the normal level of the local laboratory.

Exclusion criteria included:

- Age of onset of Type II diabetes mellitus < 20 years.
- Type 1 (insulin-dependent, juvenile onset) diabetes mellitus.
- Renal disease as follows (criteria changed by Amendment No. 3):
- Renal allograft.
- Known non-diabetic renal disease.
- Known renovascular occlusive disease affecting both kidneys or a solitary kidney.
- Systolic BP (SBP) > 200 mmHg; diastolic BP (DBP) > 120 mmHg.
- Absolute requirement for treatment with an ACE inhibitor, or angiotensin II receptor antagonist, or dihydropyridine calcium antagonist (e.g., amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, nitrendipine). Use of a non-dihydropyridine calcium antagonist (e.g., diltiazem, verapamil) was permitted.
- Unstable angina pectoris; recent myocardial infarction or coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty (< 3 months); recent stroke or transient ischaemic attack (< 3 months); symptomatic heart failure requiring medication; obstructive valvular heart disease or hypertrophic cardiomyopathy.
- Clinically important active or uncontrolled cardiac, hepatic, non-diabetic metabolic, neurological, pulmonary, or hematological disorder.
- Need for chronic (> 2 weeks) immunosuppressive therapy, including corticosteroids.
- Need for chronic (≥ 1 month) treatment with NSAIDs or aspirin (low-dose aspirin not exceeding 325 mg/day was permitted).

Study endpoints

The primary efficacy endpoint was the time-to-occurrence of clinical proteinuria and was reached if the clinical proteinuria criteria were observed at two successive evaluations. The primary analysis was

performed on the per-protocol population. The Mantel-Haenszel log-rank test was used to compare the outcome between each irbesartan dose group (150 mg and 300 mg) and placebo separately. The significance level was fixed at 2.5% according to Bonferroni adjustment procedure to maintain an overall two-sided significance level of 5%.

As a secondary analysis of the primary endpoint, the estimates of treatment effects (hazard ratios) on the amount of time free of clinical proteinuria were adjusted for prognostic factors. Adjusted estimates of the risk ratios were provided with 95% confidence intervals (CIs). The following prognostic factors at baseline were included in the Cox model as fixed covariates: gender, age, BMI, diabetes duration, use of insulin, hypertension duration, fundoscopic grade and AER at baseline. Mean arterial pressure (MAP) was added to the Cox model as a time-dependent covariate. Another Cox's model, including only AER at baseline as a covariate and MAP as a time-dependent covariate was tested as well. In addition, for some selected baseline covariates, risk ratios were presented by sub-groups.

Secondary efficacy endpoints**:** AER and estimated creatinine clearance were log-transformed before analysis. Treatment effect comparisons between treatment groups were performed on the absolute change from baseline using an ANOVA model for repeated measures including treatment groups as a factor, time as a repeated factor and a treatment-by-time interaction.

The study was designed to attain similar degrees of BP control within all 3 treatment groups. Given variable subject responses to changes in BP medications, the physician could use his/her clinical judgment to choose intervals between adjustments of antihypertensive medication dosage in order to achieve control. If the maximally titrated dose of study medication did not result in a reduction of BP to target levels, treatment with adjunctive antihypertensive therapy was permitted, except for treatment with the ACE inhibitors, dihydropyridine calcium antagonists (changed by Amendment No. 1) and angiotensin II antagonists. If despite titration to the maximum doses of tolerated study medication and adjunctive antihypertensive agents, the SeBP had not responded (defined as a SeSBP > 160 mmHg or SeDBP > 90 mmHg), the Investigator was to consult with the Sponsor's Trial Monitor or the Principal Investigator.

Efficacy results

A total of 608 patients were exposed to one of the three study treatments and 445 (73%) completed the 2-year study. Fewer patients discontinued the study in the irbesartan groups (34%, 27% and 20% in the placebo, irbesartan 150 mg and irbesartan 300 mg groups, respectively). The average exposure to study drug during the study was similar across all treatment groups: 206 subjects received placebo for an average of 561 days, 202 subjects received irbesartan 150 mg/day for an average of 599 days and 200 subjects received irbesartan 300 mg/day for an average of 641 days.

The majority of subjects were male (416/611, 68%), Caucasian (595/611, 97%), had a history of treatment for hypertension averaging 7 years prior to entering the study (59.9%) and were not using insulin prior to entering the study (65.3%). The average age of subjects in the study was 58 years. The average age of subjects at the time of diabetes diagnosis was approximately 49 years, with an average disease duration of approximately 10 years at study entry.

The proportion of exposed subjects who used concomitant medications during the double-blind period was similar across all treatment groups, the most commonly used being antidiabetic therapies (more than 90% of all subjects). Anti-hypertensive drugs, other than study medication, were used in 55% of patients including diuretics (24%), beta-blocking agents (35%) and calcium channel blockers non-dihydropyridine agents (24%).

The BP changes from baseline were similar among the three groups during the study. This is important since potential differences in blood pressure would impact the interpretation of the data. At the end of the study, the SeSBP/SeDBP mean values were comparable between treatment groups: 143.5/82.2, 143.5/82.4 and 141.6/83.4 mmHg in the placebo, irbesartan 150 and 300 mg/day groups, respectively and not statistically significant with respect to placebo.

Primary Analysis: Occurrence of Clinical Proteinuria

All randomised subjects who were evaluable for the primary efficacy endpoint were included. The primary analysis was planned to be performed with the per protocol data set, which excluded patients with major protocol violations. The analyses were also performed with an intention-to-treat (ITT) data set to test the robustness of the results. No substantial differences were observed between the *per* protocol and ITT results and so the latter, representing a larger dataset, are presented in this report.

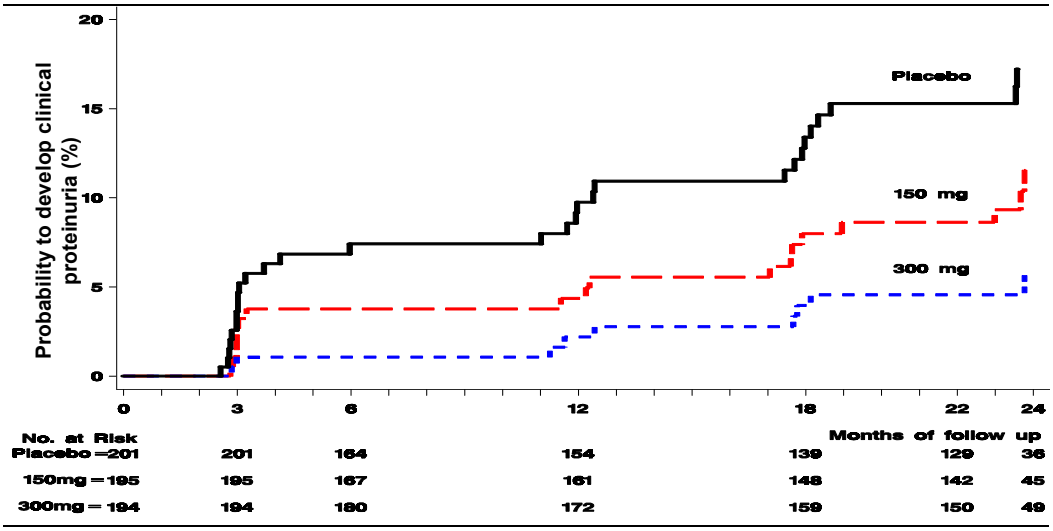
The results in Table 1 show that irbesartan 300 mg/day was significantly better than placebo by Month 24 in reducing the risk of developing clinical proteinuria (Relative Risk Reduction [RRR] = 70%, p = 0.0004). The RRR provided by the 150 mg/day dose was 39%, which did not reach statistical significance (RRR = 39%, p = 0.085).

Table 1:IRMA 2: Occurrence of Clinical Proteinuria - Irbesartan vs. Placebo ITT population

Number (%) of Subjects		**Relative Risk**		
Placebo N = 201	**Irbesartan 300mg N = 195**	**Estimate**	**95% Confidence Interval**	**P**
30 (14.9)	10 (5.2)	0.295	0.144, 0.606	0.0004
Placebo N = 201	**Irbesartan 150mg N = 195**			
30 (14.9)	19 (9.7)	0.607	0.341, 1.079	0.085

The figure below shows how Kaplan-Meier curves on the time to occurrence of overt proteinuria start to separate as early as 3 months after randomisation and continue to do so through month 24.

Figure 1: Time-to-Occurrence of Clinical Proteinuria - Kaplan-Meier Estimates ITT Population



The treatment effect of irbesartan compared to placebo on the main endpoint was independent of the baseline AER and of the BP-lowering effect of irbesartan at the two doses tested. The risk ratio, when adjusted for baseline AER and BP as time-dependent covariates using the Cox model, was slightly decreased with irbesartan 150 mg/day (RR unadjusted = 0.607; RR adjusted = 0.556) and similar with irbesartan 300 mg/day (RR unadjusted = 0.295; RR adjusted = 0.316).

When sub-populations were examined, the risk ratio was always below 1 for any stratum of sub-group, suggesting that there was no difference in treatment effect in any sub-group and no interaction between treatment group and sub-group population.

Regarding *secondary analyses*, the two doses of irbesartan significantly alter the change in AER during the 24 months of the study. Mean decreases from baseline of AER were observed in both

treatment groups at all time points compared with placebo, with the greatest decrease occurring in the higher dose group at Month 24 (-47.15 µg/min for irbesartan 300 mg/day group vs. -7.55 µg/min for placebo; p = 0.0001). The corresponding value in the irbesartan 150 mg/day group was -30.48 µg/min (p = 0.046 *vs.* placebo). A dose response increase in plasma renin activity, highest with irbesartan 300 mg, reinforces the dose response relationship.

One third of the subjects normalised their urinary AER in the irbesartan 300 mg/day group compared with 20% and 24% in the placebo and irbesartan 150 mg/day groups, respectively. Normalised urinary AER for this analysis was defined as the last value below 20 µg/min. This analysis, although not prospectively defined in this study, was undertaken to more clearly understand the effect of irbesartan.

Mean decreases from baseline were observed in estimated creatinine clearance for all treatment groups at all time points. By Month 24, the greatest decrease (-7.68%) was observed in the irbesartan 300 mg/day group, although there were no statistically significant differences between either irbesartan dose and placebo at any time point. During this period of follow-up, irbesartan did not alter the evolution of the estimated creatinine clearance compared with the evolution under placebo. It should be reminded that the control of blood pressure was equivalent in all three groups, thus reducing the potential for differentiation on renal function. There was a greater decline of estimated creatinine clearance during the first 3 months than during the rest of the study, possibly due to the relatively acute hemodynamic effect of anti-hypertensive treatments initiated after the run-in placebo period.

There was a loss of GFR in the *sub-study* that was more pronounced in the irbesartan 300 mg group, especially during the first three months of therapy, although this study was neither ideal nor powered to assess differences in the the evolution of GFR. This initial decline may be due to the haemodynamic effect of the antihypertensive treatment. After 4 weeks of withdrawal of both study treatment and all concomitant anti-hypertensive therapy, GFR increased (although the 95% CIs overlap) without reaching the baseline values.

Both doses of irbesartan reduced AER in the sub-study by the same magnitude as in the main study. Four weeks after withdrawal of antihypertensive therapy, AER increased to values close to the baseline, except in those patients treated with irbesartan 300mg/day whose AER values remained lower. These results are consistent with a possible non-haemodynamic action on renal structure, although given the small size of the sub-study, they do not constitute any definitive proof.

Safety results

Table 2 Summary of clinical adverse events (as reported) in exposed subjects during and up to 14 days post double-blind therapy.

Number of subjects	**Placebo N=206**		**Irbesartan 75/150 mg N=202**		**Irbesartan 75/300 mg N=200**		**Total Irbesartan N=402**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
with at least 1 AE	*141*	*(68.4)*	*129*	*(63.9)*	*149*	*(74.5)*	*278*	*(69.2)*
with at least 1 ADE	*27*	*(13.1)*	*25*	*(12.4)*	*21*	*(10.5)*	*46*	*(11.4)*
with at least 1 SAE	*47*	*(22.8)*	*32*	*(15.8)*	*30*	*(15.0)*	*62*	*(15.4)*
who died	4	(2.0)	3	(1.5)	*6*	*(3.0)*	*9*	*(2.3)*
who permanently discontinued study drug due to an AE	19	(9.2)	18	(8.9)	*11*	*(5.5)*	*29*	*(7.2)*

AE: adverse event; ADE: adverse drug experience; SAE: serious adverse event

A total of 17 subjects died during the study, of which: 1 never received study drug and died during the placebo-lead-in period, 5 received placebo, 2 received irbesartan 75 mg during the titration period (1 was randomised to irbesartan 150 mg and 1 was randomized to irbesartan 300 mg), 2 received irbesartan 150 mg, and 7 received irbesartan 300 mg. The relationship of one death (myocardial infarction, irbesartan 150 mg) to study medication was unknown whereas all the others were not considered related to study treatment according to the Investigator's assessment. The primary cause of death in 6 cases was cardiovascular (1 in the placebo group, 1 in the irbesartan 150 mg group, and 4 in the irbesartan 300 mg group); malignancy was the cause of death in 5 cases (1 in the placebo group, 2 in the irbesartan 150 mg group, and 2 in the irbesartan 300 mg group).

Of the 608 exposed subjects, 109 experienced SAEs during double-blind treatment; the frequency of occurrence was slightly higher in placebo-treated subjects (22.8%) compared to subjects treated with irbesartan 150 mg (15.8%) and irbesartan 300 mg (15.0%). The most frequently occurring SAEs were those associated with cardiovascular body system (8.3% in placebo-treated subjects and 6.2% in irbesartan-treated subjects). Adjudicated serious cardiovascular events occurred with similar frequency between placebo-treated subjects (8.7%) and irbesartan-treated subjects (6.0%). Myocardial infarction was the most frequently occurring event (<2% frequency in each treatment group); heart failure and pulmonary oedema were reported more frequently in the irbesartan treatment groups whereas non-fatal myocardial infarction and unstable or new-onset angina were reported more frequently in the placebo group. These results should be interpreted with caution because of the small number of events (1.0% to 2.0%).

The rate of discontinuation owing to AEs was 9.2% for placebo-treated subjects, 8.9% for irbesartan 150 mg-treated subjects and 5.5% for irbesartan 300 mg-treated subjects.

The most commonly occurring AEs across all treatment groups were associated with the following body systems: cardiovascular system, nervous system, musculoskeletal/connective tissue, general, gastrointestinal, and respiratory system. The single most common AE was musculoskeletal pain (9.7% in placebo-treated subjects and 11.4% in irbesartan-treated subjects). Subjects receiving irbesartan 300 mg tended to have a higher overall incidence of reported clinical AEs compared with placebo-treated subjects. Subjects in the irbesartan 150 mg group reported clinical AEs at a similar or less frequent rate than did subjects in the placebo group, except for diarrhoea and nausea/vomiting. Diarrhoea may be dose-related, whereas nausea/vomiting, however, does not appear to be dose-related. Subjects in the 300 mg irbesartan group had a more frequent occurrence of musculoskeletal pain, dizziness, diarrhea, pulmonary infection, urination abnormality, depression, vertigo, and sleep disturbance than did placebo-treated subjects.

The frequency of laboratory AEs was low and the occurrence was similar between placebo-treated subjects (10.7%) and irbesartan-treated subjects (8.7%). There were no trends observed in laboratory AEs in any treatment groups. The proportion of patients with low creatinine clearance was higher in the irbesartan 300 mg group compared to placebo (8.1% vs. 4.5%), as was the proportion of patients with high serum potassium (2.0% in the irbesartan 150 mg group vs. 0% in the other two groups). The mean change from baseline in serum potassium at Month 12 was statistically significant for the comparison of irbesartan 150 mg and placebo. At Month 12, mean values for serum potassium decreased in the placebo group (-0.15 mEq/L from a baseline mean of 4.68) and increased in the irbesartan 300 mg group (0.03 mEq/L from a baseline of 4.67). These changes were small and were expected with an angiotensin II receptor antagonist. Finally, statistically significant mean (±SD) changes from baseline were observed at Months 12 and 24 for haemoglobin when comparing the irbesartan 300 mg group.

Overall, there was no clinically significant variation in BP, HR or bodyweight in any treatment group. ECG abnormalities occurred with similar frequency across all treatment groups with the exception of PR and QRS, which occurred with greater frequency in the irbesartan 300 mg group, although it was not possible to establish causality for these abnormalities. QT changes were reported with similar frequency in the irbesartan and placebo groups.

IDNT study

Study design and objectives

This was a multinational, multicentre, randomised, double-blind, placebo- and active-controlled study in hypertensive subjects with diabetic nephropathy due to type II diabetes comparing irbesartan (up to 300 mg/day) after a titration period of 8 weeks, with placebo and amlodipine (up to 10 mg/day) after a similar titration period. The study phases were as follows:

Screening (Period A; up to 3 weeks): Renal function was determined by measuring serum creatinine and 24-hour urine protein and albumin excretion in subjects with hypertension in either an untreated subject, or one receiving antihypertensive medication. ACEI, AIIRAs and calcium channel blockers (CCBs) were to be discontinued for at least 10 days prior to collection of the first 24-hour urine. Although CCBs could not be started during the Screening or Enrollment Periods, if a subject was taking one at the time consent was signed, they could continue until randomisation subject to the investigator's judgement. Use of other antihypertensive medication was permitted.

Enrollment (Period B; 7 to 14 days): Subjects were enrolled if the screening serum creatinine was 1.0-3.0 mg/dl in women and 1.2-3.0 mg/dl in men, and their 24-hour protein excretion was ≥ 900 mg. If the Screening serum creatinine fell below the specified criteria, a subject could be entered if the creatinine clearance measured at the Screening visit was ≤ 80 ml/min in women and ≤ 90 ml/min in men. The difference between the Screening and Enrollment Period serum creatinines must not have been > than 25%. The maximum time permitted between the collection of the first 24-hour urine during Screening and the day of randomisation was 35 days.

Titration (Period C; 8 weeks): Subjects were randomised (1:1:1) to regimens of irbesartan or amlodipine or placebo, receiving once-daily in the morning initially at irbesartan 75 mg or amlodipine 2.5 mg or placebo (Level I). At the end of Week 2, the dose was increased to irbesartan 150 mg or amlodipine 5 mg or placebo once-daily in all subjects as tolerated (Level II regimen) and further increased to irbesartan 300 mg or amlodipine 10 mg or placebo once-daily at the end of Week 4 in all subjects as tolerated (Level III regimen). To allow for titration to the highest-tolerated dose, discontinuation of other antihypertensive medications was advisable and may have been required between randomization and Week 4. However, use of antihypertensive medication was permitted to maintain BP control, with the exception of ACEI, AIIRA, and CCBs. Additionally, a more rapid titration regimen, with an increase to Level II at Week 1 and Level III at Week 2 was allowed for subjects whose BP was difficult to control. Subjects who experienced symptoms of orthostatic hypotension or had a SeSBP < 120 mmHg were not titrated. Adjunctive antihypertensive medications were to be tapered or withdrawn to allow for titration to the highest dose of study drug tolerated. If symptoms persisted, subjects were to be "down-titrated". All subjects were to return at the end of 8 weeks to confirm that target blood pressure goals were reached (SeSBP ≤135 mmHg and SeDBP ≤ 85 mmHg, or for subjects with SeSBP > 145 mmHg at the Screening visit, the target decrease in SeSBP was at least 10 mmHg; the maximum allowable SeSBP was 160 mmHg).

Maintenance (Period D; 21-57 months): Subjects were seen every 3 months from the end of Month 3. Titration to the next level of study drug could occur at any time during the Maintenance Period in subjects who were not previously titrated to Level II or III study drug. Use of adjunctive antihypertensive agents was permitted throughout the trial (with the exception of ACEI, AIIRAs, and CCBs) to achieve target blood pressure. The same titration precautions were adopted as for Period C.

Objectives and endpoints

The primary *objectives* of this trial were:

- to determine whether irbesartan increases the time to the primary composite endpoint [doubling of serum creatinine, ESRD (defined as renal transplantation or need for dialysis or serum creatinine equal to or greater than 6.0 mg/dl) or death (all-cause mortality)] compared to placebo.
- to compare the safety and tolerance of irbesartan with placebo when administered long-term

The secondary objectives were:

- to determine whether irbesartan increases the time to the main composite endpoint compared to amlodipine;
- to determine whether irbesartan increases the time to a secondary cardiovascular composite endpoint (cardiovascular death, nonfatal myocardial infarction, hospitalisation for heart failure, permanent neurologic deficit attributed to stroke or above-the-ankle amputation) compared to placebo and amlodipine.
- To compare the safety and tolerance of irbesartan with amlodipine.

The tertiary objectives were:

- To determine whether irbesartan increases the time to a tertiary cardiovascular composite endpoint (cardiovascular death, nonfatal myocardial infarction, unplanned coronary artery revascularization procedure, heart failure requiring hospitalization or therapy with an ACEI or AIIRA, permanent neurologic deficit attributed to stroke, above-the-ankle or below-the ankle amputation or unplanned peripheral artery revascularization procedure) compared to placebo and amlodipine

The efficacy of irbesartan was evaluated using primary, secondary and tertiary outcome measures, defined as the time from randomisation until the first confirmed occurrence of any of the events of the primary, secondary and tertiary endpoints respectively.

Diagnosis and inclusion/exclusion criteria:

Patients included were men and women aged 30 to 70 with type II diabetes mellitus (as per IRMA 2), hypertension (defined as in the IRMA 2 study in an untreated subject, or receiving antihypertensive medication) and proteinuria (24-hour urine protein excretion ≥ 900 mg) were studied. The exclusion criteria were similar to those applied in the IRMA 2 study.

Statistical methods:

All randomised subjects were included in the efficacy analysis. Kaplan-Meier curves were generated for each of the 3 composite endpoints to show the estimated cumulative event rate over time for each treatment group. Irbesartan was compared with placebo or amlodipine with respect to the risk to event by the log-rank test, and the relative risk was estimated by Cox-proportional-hazards regression containing only a term for treatment. Additionally, Cox regression analyses were used to compare irbesartan with placebo adjusting for baseline characteristics or a time-dependent covariate, mean arterial blood pressure, separately. The same displays and analyses were generated for the individual components of the primary composite endpoint.

Results

A total of 1715 subjects were randomised (placebo: 569, irbesartan: 579, amlodipine 567) and 1699 received treatment, of which 1291 (76.0%) completed double-blind therapy and 408 (24.0%) discontinued prematurely with a similar incidence among the 3 treatment groups. The most common reasons for discontinuation were AEs and requiring therapy with prohibited medications.

The mean duration of double blind study treatment for each treatment group was 793 days for placebo, 815 days for irbesartan, and 773 days for amlodipine. The final daily dose of amlodipine was 10 mg in 85% of patients and 300 mg irbesartan in 83% of patients.

In general, there were no imbalances between the treatment groups in the various demographic and baseline characteristics deemed large enough to affect the efficacy comparisons. Overall, 66.5% of the subjects were male, 72.4% were Caucasian and only 27.1% of the subjects were aged 65 or more. Mean BMI was 30.8; the duration of diabetes was somewhat shorter in the amlodipine group (13.9 years) compared to placebo and irbesartan groups (15.0 and 15.5 years, respectively). Overall, 57.8% of the patients were using insulin treatment, 45.4% had a history of cardiovascular disease and 44.1% had prior ACE-I use. The mean serum creatinine was 1.68 mg/dl, estimated creatinine clearance 57.8

ml/min/1.73 sqm, and mean urinary protein excretion rate was 3005 mg/24 h. In the overall study population, the mean baseline SeSBP was 159 mmHg and SeDBP was 87 mmHg.

Regarding *concomitant medication* during the double-blind period, 70% of the subjects in placebo group received insulin therapy *vs.* 67.1% in the irbesartan group and 67.8% in the amlodipine group. As far as oral hypoglycemic agents are concerned, 39.8% in the placebo group, 42.8% in the irbesartan group, and 41.5% in the amlodipine group received sulfonylureas. Metformin was used by 28.6% of the placebo group, by 32.6% of the irbesartan group, and by 30.7% of the amlodipine group. Beta-blockers were most commonly used adjunctive antihypertensive agents (52% in the placebo group, 43.5% in the irbesartan group, and 40.6% in the amlodipine group); followed by alpha/beta adrenergic blockers agents (48.1% in the placebo, 43.2% in the irbesartan, and 41.5% in the amlodipine group). Many of the subjects received loop diuretics at the time of enrollment (41.2%, 43.3%, and 38.8% in the placebo, irbesartan, and amlodipine groups, respectively) and the percentages increased during the course of the study (71.9%, 67.2%, and 73.5% in the placebo, irbesartan, and amlodipine groups, respectively). The majority of subjects required two to four antihypertensive agents as concomitant treatment during the double-blind period to control blood pressure. Mean arterial pressure (MAP) was significantly higher by 2.9 mmHg in the placebo group ($p = 0.0001$) than in the two active treatment groups, which did not differ significantly in MAP results.

Efficacy

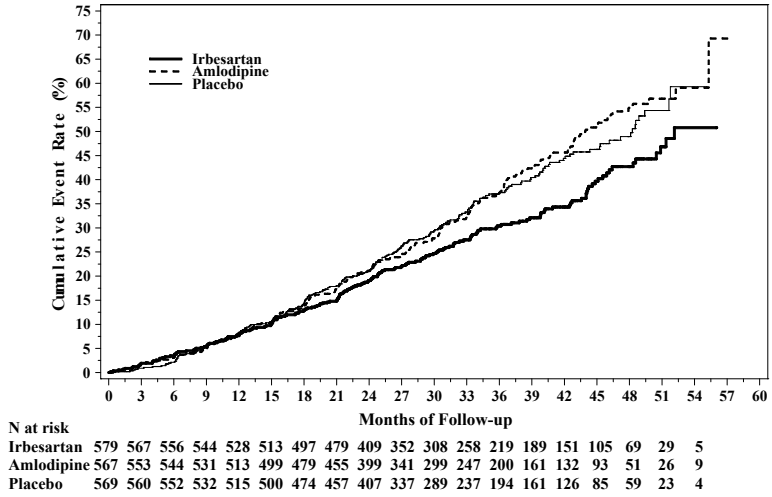
Patients in the irbesartan group demonstrated a 20% relative risk reduction in the primary endpoint *vs.* placebo ($p = 0.0234$) and a 23% relative risk reduction in the primary endpoint *vs.* amlodipine ($p = 0.0064$). Irbesartan was still significantly different from placebo and amlodipine after the disparity in blood pressure control was taken into account.

Table 3: IDNT: Primary Composite Endpoint

Event	**Number (%) of Subjects**			**% Relative Risk Reduction**	
	Irbesartan N = 579	**Placebo N = 569**	**Amlodipine N = 567**	**Irbesartan *vs.* placebo**	**Irbesartan *vs.* Amlodipine**
Primary Composite Renal Endpoint	189 (32.6)	222 (39.0)	233 (41.1)	20 p = 0.0234	23 p = 0.0064

The Kaplan-Meier curve of irbesartan shown below clearly separates from the amlodipine and placebo curves as early as 15 months and continues to diverge during the course of the study whereas the amlodipine and placebo curves cannot be differentiated

Figure 2: Time to Occurrence of Primary Composite Endpoint: Kaplan-Meier Estimates



The total occurrence of the individual outcomes during the complete course of the study is summarised below (Table 4).

Table 4: IDNT: Total Occurrence of Renal Events and Deaths

Occurrence[a] of:	Number (%) of Subjects			Relative Risk Reduction			
	Irbesartan N = 579	Placebo N = 569	Amlodipine N = 567	Irbesartan *vs.* placebo		Irbesartan *vs.* Amlodipine	
				RR (95% CI)	p	RR (95% CI)	p
Death (all causes)	87 (15.0)	93 (16.3)	83 (14.6)	0.92 (0.69-1.23)	0.5683	1.04 (0.77-1.40)	0.8083
Doubling of Serum Creatinine	98 (16.9)	135 (23.7)	144 (25.4)	0.67 (0.52-0.87)	0.0027	0.63 (0.49-0.81)	0.0003
ESRD	82 (14.2)	101 (17.8)	104 (18.3)	0.77 (0.57-1.03)	0.0731	0.77 (0.57-1.03)	0.0746
ESRD or Death	151 (26.1)	169 (29.7)	162 (28.6)	0.85 (0.68-1.05)	0.1331	0.90 (0.72-1.13)	0.3648
ESRD or Doubling of Serum Creatinine	125 (21.6)	158 (27.8)	179 (31.6)	0.74 (0.59-0.94)	0.0116	0.66 (0.53-0.83)	0.0003

[a] The individual components do not represent a breakdown of the combined primary endpoint but rather the total number of subjects experiencing an event during the course of the study.

Irbesartan caused a non-statistically significant 23% relative risk reduction in ESRD compared with either placebo (p = 0.0731) or amlodipine (p = 0.0746). Given the similarity of the results of both comparisons, a *post-hoc* analysis of irbesartan *vs.* pooled placebo and amlodipine groups was performed leading to a statistically significant result (p = 0.0422). This analysis is not felt to be appropriate and is therefore not reviewed here.

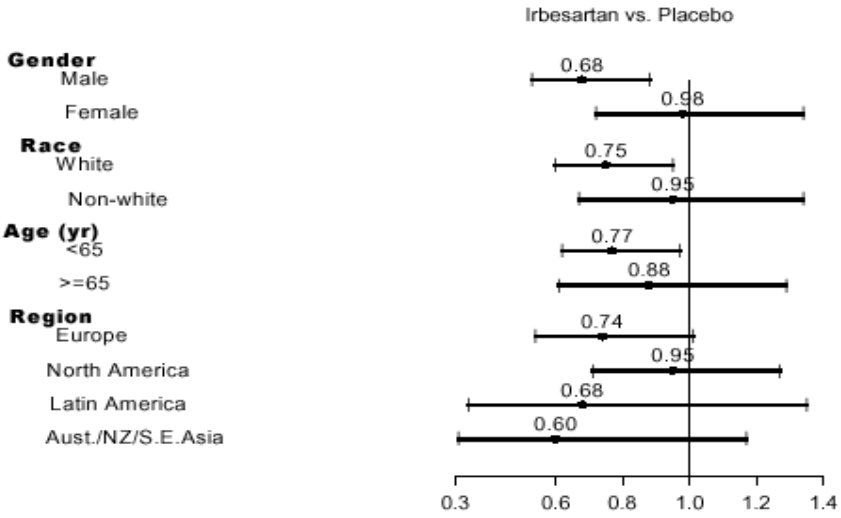
There was no difference in all cause mortality across the three groups, although the study was not powered to show a difference on mortality alone. The inclusion of all-cause mortality in the composite endpoint was considered necessary to ensure that the effect observed was not undermined by a potentially harmful effect on mortality. The results do not indicate an adverse effect of irbesartan on mortality.

All comparisons show statistically significant differences only when doubling of serum creatinine is included in the outcome. The significant decrease in time to doubling of serum creatinine was supported by additional analyses. The yearly rate of change of serum creatinine and creatinine clearance were statistically significantly lower ($p<0.05$) in the irbesartan group than in both the other groups. Urine protein and albumin excretion were similar in all 3 groups at baseline but a statistically greater ($p<0.001$) reduction was observed only in the irbesartan group, despite larger numbers of patients being removed from the placebo and amlodipine arms when they reached a renal endpoint. These data confirm a positive effect of irbesartan on renal function.

Cox regression models adjusting individually for baseline prognostic factors were used to assess the relative risks for 17 *a priori* baseline prognostic factors that predict the primary composite endpoint and assess consistency of treatment effects across sub-populations. Based on these analyses, the relative risk for the primary composite endpoint for patients treated with irbesartan compared with placebo controls is lower for males than females (0.79; CI: 0.65-0.96) and relatively lower for whites than non-whites (0.81; CI: 0.67-0.98). The relative risk also increases for every unit increase in age, unit increase in duration of diabetes, unit increase in seated MAP, unit increase in serum creatinine, unit increase in AER and unit increase in protein excretion rate.

Sub-groups were also identified (e.g., < 65 years and ≥ 65 years) and the relative risk of treatment with irbesartan compared with placebo determined using Cox regression models (see figure below).

Figure 3.1: Primary Efficacy Outcome: Relative Risk with 95% Confidence Intervals within Subgroups



With respect to the female subgroup, the relative risk was lower for males (0.68; CI: 0.53-0.88] than females (0.98 [CI: 0.72-1.34]). The number of subjects was small to detect a significant difference between treatment groups and the confidence interval for relative risks were wide. No clinically meaningful imbalance was observed in baseline characteristics or concomitant medication usage in the male and female subgroups. With respect to geographical region, the relative risk was lower for Europeans (0.74 [CI: 0.54-1.01] than for North Americans (0.95 [CI: 0.71-1.27]). Among all-randomised patients in the North American region, 47% were non-white, 51% had a history of cardiovascular disease and 58% prior use of ACE-I, all higher than the corresponding percentages for European patients (6%, 43% and 35%, respectively). These differences might have contributed to the higher incidence of the renal composite endpoint observed in the North American region.

As for the secondary cardiovascular endpoint, there were no significant differences among any of the groups with respect to the composite cardiovascular endpoint or any of its components. Cardiovascular death rates were also similar across the groups as was time to death from cardiovascular disease. The only differences were observed in the incidence of non-fatal MI and stroke (lower for amlodipine) and hospitalisation for heart failure (lower for irbesartan). These findings are based on inappropriately powered *post hoc* analysis and should be interpreted with caution.

Similarly, there was no statistically significant relative risk reduction in the tertiary cardiovascular composite endpoint for irbesartan *vs.* placebo or amlodipine.

Other changes in efficacy measures *can be summarised as follows:*

- irbesartan demonstrated a significant reduction in the annual rate of increase in serum creatinine as compared with placebo ($p = 0.004$) and amlodipine ($p = 0.013$).
- irbesartan demonstrated a significant reduction in the annual rate of decline in creatinine clearance compared with placebo and amlodipine.
- Mean changes from baseline in serum creatinine and creatinine clearance, albumin excretion rate and protein excretion rate showed trends in favour of irbesartan. The results should be viewed with caution due to small numbers of patients in the late timepoint analyses.

- Triglycerides tended to increase from baseline on irbesartan (statistically significant at Month 12 but not at months 24, 36, and 48). Urine urea nitrogen excretion rate tended to decline from baseline with time, but generally less so for irbesartan than for placebo.

The decrease from baseline in each of the *blood pressure* parameters in either position was statistically significantly greater for irbesartan than for placebo ($p \leq 0.049$). However, the differences between irbesartan and amlodipine in mean change for the blood pressure parameters ($p \geq 0.120$) were not statistically significant. There were no significant differences in change in heart rates when irbesartan was compared to either placebo or amlodipine.

Safety

The overall summary of clinical AEs, adverse drug experiences, (ADE), serious adverse events (SAE), and deaths in terms reported by the Investigators is shown below. Of the 1699 treated subjects, 1082 (63.7%) experienced SAEs.The frequencies of the most common (≥ 1%) SAEs and cardiovascular events by adjudicated terms, during and up to 14 days post double-blind therapy, by body system and treatment group were similar across the treatment groups. With the exception of ADEs (most frequently reported in the amlodipine group), there were no clear differences between the treatment groups.

Table 5. Summary of Clinical Adverse Events (as Reported) During and Up to 14 Days Post Double-Blind Therapy by Treatment Group

	Number (%) of Subjects		
Event	**Placebo N = 563**	**Irbesartan N = 577**	**Amlodipine N = 559**
AE, total (% of subjects)	524 (93.1)	540 (93.6)	526 (94.1)
ADE[a]	225 (40.0)	266 (46.1)	285 (51.0)
SAE[a]	326 (57.9)	326 (56.5)	317 (56.7)
Death[b]	90 (16.0)	86 (14.9)	79 (14.1)

[a] Subset of total AEs: subject may be represented in more than one category
[b] During and post double-blind therapy

Discontinuations due to adverse events occurred at a similar rate in the groups: placebo 6.4%, irbesartan 7.5% and amlodipine 7.9%, and, with the exception of oedema (highest frequency in the amlodipine groups), the AEs did not lead to any differences between the groups as regards treatment discontinuation.

Regarding *deaths*, a total of 255 subjects died during and post double blind therapy; 90 (16.0%) in the placebo group, 86 (14.9%) in the irbesartan group, and 79 (14.1%) in the amlodipine group. The incidence and causes are similar in the 3 treatment groups. There were 130 deaths adjudicated to the cardiovascular system (49 irbesartan, 41 placebo, and 40 amlodipine) and 76 deaths in the General body system (26 placebo, 26 amlodipine and 24 irbesartan). In addition, 8 randomised subjects died but never received study medication. The most frequent adjudicated cause of death in the cardiovascular system was sudden death (5.3% placebo, 5.0% irbesartan and 4.1% amlodipine), followed by MI (1.9% irbesartan, 1.4% amlodipine, and 1.1% placebo) and invasive cardiac procedure (1.2% irbesartan, 0.9% amlodipine, and 0.7% placebo).

Fewer subjects experienced a hypertensive crisis in the amlodipine group (1 subject with amlodipine 10 mg) compared to the placebo (7 subjects) and irbesartan groups (7 subjects with irbesartan 300 mg). All seven of the hypertensive crises in the irbesartan group were assessed as unrelated to study

drug and five such cases were assessed as severe. Only one of the cases in the placebo group was graded severe.

A total of seven subjects (4 placebo and 3 irbesartan) experienced a hypoglycemic coma or symptoms, or diabetic coma or complication during and up to 14 days post double-blind therapy. Regarding the irbesartan-exposed subjects, two patients experienced a hypoglycemic coma and one experienced hypoglycemic symptoms. These cases were assessed as unrelated to study drug.

Anaemia was reported slightly more frequently in the irbesartan group, heart failure tended to occur more frequently in the amlodipine group and pulmonary congestion was less frequent in the irbesartan group. Conversely, myocardial infarction tended to occur less frequently in the amlodipine group.

The only treatment-emergent *laboratory AE* with a clearly higher incidence in the irbesartan group was high serum potassium: 9.4% with placebo, 8.1% with amlodipine and 23.2% with irbesartan. Sixteen subjects with persistent hyperkalemia were discontinued due to persistent hyperkalemia: 11 with irbesartan, 3with amlodipine, and 2with placebo.

One hundred and seven (18.6%) irbesartan subjects met the marked abnormality criteria (>6 mEq/l) for high potassium values, compared to 34 (6.2%) amlodipine subjects, and 34 (6.0%) placebo subjects. The data were reanalysed using a more clinically relevant cut-off (> 5.5 mEq/l) following a request from CPMP. The results showed a high frequency of mild transient elevations in serum potassium and in IDNT a large relative risk reduction was observed in subjects who developed mild hyperkalemia, although these results should be regarded with caution. These laboratory findings lacked clinical significance given that few patients discontinued therapy or required intervention due to mild hyperkalemia.

Discussion

The MAH has conducted two studies to support this indication: IRMA 2 included patients with early renal damage whereas IDNT included patients with more advanced renal impairment. As hypertension itself can be a risk factor for the renal disease, comparability between the groups of treatment both at baseline and at the end of the study was ensured. Although the recommended target levels of blood pressure for the target population were higher than those currently recommended at the time the pivotal studies were performed, this should not impact the results of either study as long as the blood pressure levels attained were comparable accross the treatment groups.

It is generally believed that interference in the renin-angiotensin system with ACEIs slows the progression of renal disease in patients with type 1 diabetes, making an ACE-I the preferable comparator instead of a calcium channel blocker. However, direct proof that they decrease the rate of progression of renal damage in hypertensive patients with type 2 diabetes is not available, and consequenly, the clinical trials necessarily included a placebo arm. A further comparator arm is included in the IDNT study, namely amlodipine, to assess whether any improvement is related to the renin-angiotensin system interference and not just to normalisation of blood pressure.

Although the recommended posology in the SPC (initial dose 150 mg, maintenance dose 300 mg per day) is not in line with the titration scheme used in both studies (two step titration from 75mg to 150mg followed by 300mg), no major safety concerns are anticipated based on the data provided. In addition, the proposed dosing regimen is expected to facilitate patient compliance.

- **IRMA 2**

Considering the Note for Guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP/EWP/1080), the study objectives and endpoints are appropriate. Progression of microalbuminuria to macroalbuminuria is an "intermediate" endpoint that should preferably be supported by at least 24-month data indicating a favourable evolution of glomerular filtration (GFR). Both in absolute and relative terms, the risk reduction in time to occurrence of clinical proteinuria with

the 300 mg dose is statistically significant and appears sustained after 4 weeks of treatment cessation, despite the lack of a favourable evolution of GFR compared to placebo, even if it is acknowledged that IRMA-2 was neither optimal nor powered to demonstrate a beneficial effect on GFR due to the study design and the relatively short follow-up (indeed, GFR was only assessed in the GFR substudy). This lack of positive effect of irbesartan on GFR has been reflected in section 5.1 of the SPC. In fact, a "rebound effect" on GFR and creatinine clearance was observed as both tended to decrease more during irbesartan than placebo treatment, especially during the initial 3 months of treatment. It must be noted, however, that previous studies suggest that the faster initial decline in GFR (or creatinine clearance) is due to a functional (haemodynamic) effect of anti-hypertensive treatment and is reversible, while the sustained slower decline reflects the beneficial effect on progression of diabetic nephropathy. In any case, the results with regard to GFR change were not statistically significantly different between irbesartan and placebo in this trial.

As stated previously, a change in GFR is considered a harder endpoint than a delay in the progression to clinical albuminuria. However, in view of the patients' early-stage disease, the slow course of the nephropathy over the short period of two years, and the haemodynamic effect of the antihypertensive treatment, it would be difficult to distinguish differences in GFR changes between groups at this early stage of the disease. The alternative use of kidney biopsies to analyse renal integrity is not very feasible. Thus, a significant delay in the more surrogate endpoint "progression to macroalbuminuria" is considered clinically relevant despite the absence of a positive effect on GFR. In this respect, the results of the IDNT trial provide reassurance since irbesartan was not found to have deleterious effects on the kidney.

The demographic and disease characteristics were adequately balanced between the groups. Subgroup analyses have shown that the non-significant imbalance in some specific baseline characteristics (duration of diabetes, prior insulin use or prior antihypertensive medication) cannot explain the differences in the primary efficacy outcome as observed in the IRMA2 trial. Similarly, supplementary analyses with regard to proportion of patients achieving target BP level in the treatment groups does not suggest any clinically significant differences.

The *safety profile* of irbesartan (150 mg or 300 mg) in the population of patients with hypertension and incipient diabetic type 2 nephropathy is acceptable and does not greatly differ from the one observed in general hypertension. The risk of hyperkalemia in this patient population with elevated BP and early diabetic nephropathy appears low. Only dizziness and diarrhoea were clearly more frequent during irbesartan 300 mg compared to placebo. These findings are already reflected in section 4.8 of the SPC.

Regarding the possibility of interaction between oral antidiabetic treatments (metformin, sulfonylureas and thiazolidinediones) and irbesartan, although no proper drug-drug interaction studies have been performed, potentially and clinically relevant interactions between antidiabetic drugs (either metabolised through the CYP2C9/other isoenzime pathways or not metabolised) and irbesartan are not anticipated. In addition, data provided on glycemic control and other related adverse events are reassuring regarding the safety profile of the drug in diabetic populations.

- **IDNT study**

The general design of the trial is appropriate and the composite endpoint of doubling of serum creatinine, progression to end-stage renal disease (ESRD) and all-cause mortality acceptable, although the study was not powered to detect differences in the individual subcomponents. Time to doubling of serum creatinine and the evolution of chronic renal failure defined as the need for maintenance dialysis or transplantation or sustained increase in plasma creatinine (>250 µmol/l) are considered hard endpoints in this population. In the current study, ESRD was defined as initiation of dialysis, renal transplantation, or a serum creatinine of 6.0 mg/dl (530 µmol/l) or above. The addition of all-cause mortality to the primary endpoint is justified since the analysis of renal disease progression in this group of patients can be confounded by premature cardiovascular deaths.

The primary composite endpoint was statistically significantly in favour of irbesartan over placebo and amlodipine. The overall level of risk reduction in the composite endpoint can be considered clinically significant despite the fact that the result was driven mainly by the doubling of serum creatinine component. A drawback is that the difference vs. neither placebo nor amlodipine was statistically significant with regard to reaching the ESRD endpoint, but the trend in the right and expected direction is acknowledged. No trends were observed for all-cause mortality. The aim to achieve similar BP control in the 3 treatment groups failed since decreases from baseline in both SeSBP and SeDBP were statistically significantly higher in the irbesartan group compared to placebo, but not compared to amlodipine. Nonetheless, given the statistically significant risk reduction (primary efficacy composite endpoint) compared to both amlodipine and placebo, this is not considered to have an impact on validity of the results

Post-hoc subgroup analyses showing an apparent lack of efficacy in females, non-white subjects and in North American centres as well as weaker efficacy in elderly patients. Although the trial was not powered to observe treatment benefits in subgroup populations and subgroup analyses must be regarded with great caution, these findings are a cause for concern casting doubt on the robustness of the results. It is well known that blacks (or Afro-Americans) generally have low renin hypertension and consequently respond less well than whites to treatments that act through renin angiotensin system inhibition. The results in females, based on a substantial number of subjects, are of greater concern since no apparent explanation is available. As a result, appropriate warning statements have been included in section 4.4 of the SPC and a summary of the actual findings in these subgroups has been included in section 5.1.

The secondary and tertiary objectives of the study are overly ambitious considering the size of the study and the length of follow-up. No statistically significant differences were observed between the 3 treatment groups. A lack of difference in cardiovascular events with respect to “placebo” (which in fact consists of active antihypertensive treatment based on diuretics and alpha and beta blockers) is not surprising since both groups are presumably equally "protected" by adequate hypertension control. However, a trend in favour of amlodipine in the secondary cardiovascular endpoint (i.e. more CV events with irbesartan, especially in females) raises the question whether the renal benefit observed with irbesartan is not counterbalanced by a lower decrease in cardiovascular risk compared to other treatment alternatives, particularly ACEIs. With regard to this observation, the applicant has rightly indicated that subjects treated with irbesartan had a longer follow-up on study drug than subjects treated with amlodipine, since irbesartan significantly delayed the development of the primary outcome. This introduces observational bias in the cardiovascular endpoint comparison in favour of amlodipine. Nonetheless, this lack of benefit in terms of CV events has been mentioned in the SPC

To conclude, a global renal benefit has been shown in patients with advanced renal disease, even if no cardiovascular benefit has been demonstrated in the studied population. Thus, it would appear unreasonable not to allow the treatment with irbesartan due to theoretical considerations on CV risk.

Regarding the *safety* profile of irbesartan, there was no indication of an increased incidence of hypoglycaemic complications in the irbesartan group compared to placebo. The frequency of hypertensive crisis was also similar between groups. The frequency of anaemia marked abnormality of decreased Hb was slightly higher in the irbesartan group compared to placebo, but the review of cases of severe anaemia does not suggest a causal relationship. Dizziness, orthostatic dizziness and orthostatic hypotension in both IDNT and IRMA 2 studies were more frequently reported in the irbesartan group but were of little clinical significance, mild or moderate in intensity and did not require any action to be taken. Regarding dyspepsia and diarrhoea, both occurred more often in the irbesartan group. However there was only one discontinuation for that reason.

The very high frequency of hyperkalaemia was an obvious concern**.** The data on the safety profile of patients with hyperkalemia are reassuring. There is a high frequency of mild transient elevations of serum potassium above 5.5 mEq/l in these patients, and in IDNT a large relative risk reduction was observed in subjects who developed mild hyperkalemia although, these results should be regarded with caution since they arise further to subgroup analyses. Moreover, the data presented show a lack of clinical significance of these laboratory findings, given that few patients discontinued therapy or

required intervention due to mild hyperkalemia. Despite the reassuring data, it is recognised that AIIRAs can cause elevations of serum potassium through a combination of decreasing serum aldosterone and a reduction in GFR, and that this risk is related to the characteristic of the population being treated, with a high risk among patients with advanced renal disease. This fact highlights the importance of monitoring serum potassium in all patients treated with irbesartan, but especially in type 2 diabetic patients with proteinuria. A warning regarding hyperkalaemia in patients with overt proteinuria due to diabetic renal disease as well as a recommendation for adequate frequent monitoring has been included in section 4.4 of the SPC.

In conclusion, the safety profile of the drug in the proposed indication is acceptable.

7. Post authorisation: safety updates

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 Karvea is contra-indicated in the second and third trimesters of pregnancy. As a preacuationary measure, Karvea should not be used during the first trimester of pregnancy. If pregnancy is diagnosed, Karvea 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 Karvea 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.

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

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk profile of Karvea was favourable in the treatment of essential hypertension and renal disease in patients with hypertension and type II diabetis mellitus as part of an antihypertensive drug regimen.