Assessment report

Edarbi

azilsartan medoxomil

Procedure No.: EMEA/H/C/002293

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

Abbreviation or Term	Definition
2-EH	2-Ethylhexanoic acid
ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
ADH	alcohol dehydrogenase
AEMPS	Agencia Espanola de Medicamentos y Productos Sanitarios
AI	angiotensin I
AII	angiotensin II
ALP	alkaline phosphatase
ARB	angiotensin II receptor blocker
AT1	angiotensin II type 1 receptor
AT2	angiotensin II type 2 receptor
AUC	area under the plasma concentration-time curve
$AUC_{(0-24)}$	area under the plasma concentration-time curve from time 0 to 24 hours
AUC(0-tau)	area under the plasma concentration-time curve from time 0 to tau
$AUC_{(0-tlqc)}$	area under the plasma concentration-time curve from time 0 to time of last quantifiable concentration
BfArM	Federal Institute for Drugs and Medical Devices
BMI	body mass index
BUN	blood urea nitrogen
Caco-2	colorectal adenocarcinoma-2
CCB	calcium-channel blocker
cGFR	calculated glomerular filtration rate
CHO	Chinese hamster lung
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CK	creatine phosphokinase
CLD	chlorthalidone
CL/F	apparent oral clearance
CPN	chronic progressive nephropathy
Cmax	maximum observed plasma concentration
CYP	cytochrome P-450
DBP	diastolic blood pressure
DOCA	deoxycorticosterone acetate
ECG	electrocardiogram
ESRD	end-stage renal disease
FAS	full analysis set
FDC	fixed-dose combination
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GRAS	generally recognized as safe
Hct	hematocrit
HCTZ	hydrochlorothiazide
Hgb	hemoglobin

IC50	50% inhibitory concentration
ID50	50% response inhibition
IRS-1	insulin receptor substrate 1
IV	intravenous
LC/MS/MS	liquid chromatography tandem mass spectrometry
LLOQ	lower limit of quantitation
LOCF	last observation carried forward
LS	least squares
MAA	Marketing Application Authorisation
MACE	major adverse cardiovascular event
MC	methylcellulose
MEB	Medicines Evaluation Board
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory
OL	open-label
Papp	permeability co-efficient
P-gp	P-glycoprotein
QTc	corrected QT interval
RAAS	renin-angiotensin-aldosterone system
RBC	Red Blood Cell
SAE	serious adverse event
SBP	systolic blood pressure
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
SMQ	standard MedDRA query
SOC	system organ class
T1/2	terminal elimination half-life
TAK-491	azilsartan medoxomil
TAK-491F	TAK-491 salt free form, also known as T-1302593
TAK-491	U-3 impurity of TAK-491
TAK-563	active moiety of TAK-491, azilsartan
TAK-563 M-I	metabolite of TAK-536 formed by decarboxylation
TAK-563 M-II	metabolite of TAK-536 formed by O-dealkylation
TEAE	treatment-emergent adverse event
TGRD	Takeda Global Research & Development Centre (Europe) Ltd.
TRAE	treatment-related adverse event
UDS	unscheduled DNA synthesis
ULN	upper limit of normal
UTI	urinary tract infection

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Takeda Global Research and Development Centre (Europe) Ltd. submitted on 29 September 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Edarbi, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 February 2010.

The applicant applied for the following indication treatment of essential hypertension in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/106/2010) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance azilsartan medoxomil contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice/Protocol Assistance

The applicant did not seek scientific advice at the CHMP.

Licensing status

Azilsartan medoxomil has been given a Marketing Authorisation in the USA and in Mexico on 25 February 2011 and 30 May 2011 respectively.

A new application was filed in the following countries: Switzerland and Canada.

1.2 Manufacturers

Manufacturer(s) responsible for batch release

Takeda Ireland Ltd.

Bray Business Park

Kilruddery

Co Wicklow

Ireland

1.3 Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Alar Irs**

- The application was received by the EMA on 29 September 2010.
- The procedure started on 20 October 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 07 January 2011 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 January 2011.
- During the meeting on 14-17 February 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 February 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 May 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 04 July 2011.
- During the CHMP meeting on 18-21 July 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 August 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 05 and 15 September 2011.
- During the meeting on 19-22 September 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Edarbi on 22 September 2011.

2 Scientific discussion

2.1 Introduction

Problem statement

Using a threshold of 140/90 mmHg, about 40% of the adult population in many EU countries have raised blood pressure although the proportion increases with age. Hypertension may often be inadequately treated and is a contributory factor in cardiovascular diseases which account for considerable proportion of all deaths and hospital bed days.

In most hypertensive patients, pharmacological intervention becomes necessary if blood pressure lowering is to be substantial and sustainable. Available evidence demonstrates firmly that a sustained reduction in blood pressure by drugs reduces the incidence of stroke, coronary heart disease and overall mortality. For an individual at any age, the greater the cardiovascular risk the greater the potential to benefit from treatment.

Most individuals who suffer raised blood pressure (around 95%) have essential (or primary) hypertension with no identifiable cause. Around 5% of individuals with raised blood pressure have secondary hypertension, where renal disease, pulmonary disease, endocrine complications, or other diseases underlie raised blood pressure.

For a long time, hypertension guidelines focused on blood pressure values as the only or main variables determining the need and the type of treatment. The more recent CHMP guidance on "Clinical investigation of medicinal products in the treatment of hypertension" (CPMP/EWP/238/95 Rev. 3) emphasizes that diagnosis and management of hypertension should be related to quantification of total cardiovascular risk. This concept is based on the fact that only a small fraction of the hypertensive population has an elevation of blood pressure alone, with the great majority exhibiting additional cardiovascular risk factors, with a relationship between the severity of the blood pressure elevation and that of alterations in glucose and lipid metabolism. Some evidence is available that in high risk individuals thresholds and goals for antihypertensive treatment, as well as other treatment strategies, should be different from those to be implemented in lower risk individuals.

Several classes of antihypertensive medicines are available. However, sooner or later, most of the patients end up using combination therapy, as monotherapy is unable to control their blood pressure. A need for new well tolerated potent antihypertensive agents is therefore undisputed.

About the product

TAK-491 (azilsartan medoxomil) is the prodrug of the active moiety, TAK-536 (azilsartan), a potent and selective antagonist of angiotensin II (AII) type 1 (AT1) receptors (an AII receptor blocker, or ARB). After oral administration, TAK-491 is rapidly converted to TAK-536 by ester hydrolysis in the gut and/or during the process of absorption. TAK-536 has high affinity for AT1 receptors and is >10,000-fold more selective for AT1 receptors compared with AII type 2 (AT2) receptors in vitro.

TAK-491 reduced blood pressure in animal models of hypertension after acute and repeat oral dosing. Non-clinical results demonstrate that TAK-536 has a much slower dissociation from AT1 receptors than the other AT1 antagonists (olmesartan, telmisartan, valsartan, and irbesartan).

The Applicant is seeking a Marketing Authorisation for TAK-491 tablets (20, 40, and 80 mg) for the once-daily treatment of essential hypertension in adults, either as monotherapy or in combination with other antihypertensive agents.

The recommended starting dose is 40 mg taken once daily and this dose may be increased to a maximum of 80 mg once daily for patients whose blood pressure is not adequately controlled at the lower dose. A 20 mg dose once daily can be considered as a starting dose for patients at risk of hypotension.

The primary objective of the TAK-491 development programme was to develop a more effective ARB compared with those currently approved with a safety profile similar to that of available therapies.

Type of Application and aspects on development

This Marketing Authorisation application is a full, stand alone application in accordance with Directive 2001/83/EC Article 8 (3).

The development programme of azilsartan medoxomil complies with the CHMP guidance on "Clinical investigation of medicinal products in the treatment of hypertension" (CPMP/EWP/238/95 Rev. 3).

A Paediatric Investigation Plan (P/106/2010) and a waiver for children aged below 6 months of age have been agreed for azilsartan medoxomil with the PDCO. A deferral to complete the PIP has been granted until April 2021. During the evaluation, a modification of the Paediatric Investigation Plan (P/39/2011) and of the waiver now for children below 1 year of age was agreed for azilsartan medoxomil with the PDCO.

Scientific advice from national competent authorities was obtained on several occasions during the development of the drug. Regulatory consultations have been undertaken with agencies in Europe including the Medical Products Agency in Sweden (September 2008) and the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (October 2008) during the early stages of the phase 3 programme. More recently, advice was sought from the Federal Institute for Drugs and Medical Devices (BfArM) in Germany (November 2009), the Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS) in Spain (December 2009), and the Medicines Evaluation Board (MEB) in the Netherlands (January 2010).

2.2 Quality aspects

2.2.1 Introduction

The product is presented as a tablet containing 20 mg, 40 mg, and 80 mg of azilsartan medoxomil (as potasium). Other ingredients are: mannitol (E 421), fumaric acid (E 297), sodium hydroxide, hydroxypropylcellulose (E 463), croscarmellose sodium, cellulose, microcrystalline (E 460) and magnesium stearate (E 572)

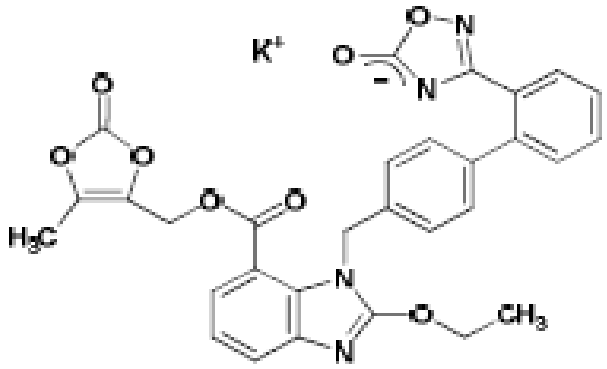
The tablets are packed in aluminum blisters packs integrated with desiccant.

2.2.2 Active Substance

Manufacture

Azilsartan medoxomil which has the chemical names (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)biphenyl-4-yl]methyl}-1H-benzimidazole-7-carboxylate monopotassium salt and 1H-Benzimidazole-7-carboxylic acid,1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-yl]methyl]-2-ethoxy-,(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, potassium salt is a white crystalline powder which is practically insoluble in water, freely soluble in methanol, dimethylsulfoxide and dimethylformamide, soluble in acetic acid, slightly soluble in acetone and acetonitrile and very slightly soluble in tetrahydrofuran and 1-octanol.

The chemical structure of the active substance is:



Azilsartan medoxomil does not contain chiral center and one stable anhydrous form has been detected.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC or Ultraperformance liquid chromatography (UPLC)), heavy metals, related substances (HPLC or UPLC). water, assay (HPLC,), particle size and (HPLC).

The specifications reflect all relevant quality attributes and were found to be adequate to control the quality of the active substance.

Batch analysis data of active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability studies were carried on 3 batches under ICH conditions (up to 24 months at 25°C/60% RH and satisfactory 6 months results at 40°C/75% RH can be accepted) stored in polyethylene bags, tied with a plastic tie. Parameters studied were: appearance, identification, related substances, water,assay, particle size and microbiology examination.

A photostability study was performed according with ICH guidelines.

The proposed retest period is justified based on the stability results.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions are explained. The compatibility of the active substance with excipients was evaluated. This resulted in the current formulation which was also used for the phase 3 clinical studies.

The goal of formulation development was to develop an orally available, robust immediate release formulation with good stability and dissolution characteristics. With consideration to the desired final market presentation, a tablet dosage form was preferred over other pharmaceutical forms. The formulation factors which may impact product quality were identified and classified. Each was assessed for its potential impact on quality attributes of the finished product.

Commercial formulations are the same as phase 3 formulations except for tablet debossing.

All excipients used comply with the current requirements specified either in the Ph.Eur. The chosen excipients are: mannitol (diluents), fumaric acid (pH control), sodium hydroxide (pH control), hydroxypropyl cellulose (binder), croscarmellose sodium (disintegrant), mycrocystalline cellulose (compressing aid), and magnesium stearate (lubricant)

The proposed commercial container closure system for the product intended for marketing are aluminium blisters containing forming film integrated with desiccant and aluminium lidding. Stability studies showed that the selected blister components provide adequate product protection and are compatible with the dosage form.

Adventitious agents

Magnesium stearate is the only excipient of potential animal origin used in the manufacture, it is certified that the magnesium stearate is of plant origin only.

Manufacture of the product

The manufacturing process has been adequately validated by a number of studies for the major steps of the manufacturing process in three commercial batches.

The batch analysis data show that the tablets can be manufactured reproducibly according to the agreed finished product specification, which is suitable for control of this oral preparation

Product specification

The product specification includes tests for appearance, identity (UV, HPLC or UPLC), related substances (HPLC or UPLC), assay (HPLC, or UPLC), dissolution, and uniformity of dosage units (HPLC or UPLC)

The test and limits of the release and shelf life specification for the finished product are appropriate to control the quality of this medicinal product for the intended purpose.

Batch data are provided for pilot and production batches and indicate satisfactory uniformity as well as compliance with the specification.

Stability of the product

The stability of the product in three pilot batches of all strengths in the proposed commercial packages has been evaluated in a series of studies performed under conditions representing both short-term stress (40°C/75%RH) for 6 months and long-term storage (25°C/60%RH and 30°C/65% RH) for 24 months. Additional studies performed under severe stress conditions and photostability were also performed on one selected batch.

The following parameters were tested: appearance, assay (HPLC, or UPLC), related substances (HPLC or UPLC), dissolution, moisture content, hardness, friability and microbiological examination.

On the basis of the stability data available, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

2.2.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3 Non-clinical aspects

2.3.1 Introduction

To support the chronic use of azilsartan medoxomil in humans, non-clinical safety studies have been conducted on TAK-491 (azilsartan medoxomil), TAK-536 (azilsartan), TAK-536-MII and the impurity TAK-491 U-3. The Applicant conducted a very comprehensive non-clinical development programme beyond regulatory requirements. This programme is in general agreement with the applicable scientific guidelines.

All main non-clinical toxicity studies were conducted in compliance with GLP. In addition, non-GLP studies were conducted too but were not considered to compromise the scientific integrity or affect the experimental results.

2.3.2 Pharmacology

The pharmacology programme consisted of 29 studies and was considered to be adequate. The overall results of these studies are reported below.

Primary pharmacodynamic studies

Primary pharmacodynamic in vitro

The results of the *in vitro* receptor binding studies clearly demonstrated that TAK-536 is a highly potent, selective and competitive antagonist of the angiotensin II type 1 receptor. Although full dissociation kinetics were not investigated, results of a washout study reveal that TAK-536 slowly

dissociates of the AT1 receptor when compared to the clinically used AT1 receptor blockers, suggesting that the duration of action of TAK-536 may be longer lasting than other AT1 receptor blockers. This effect was also observed in rats. The results of the indirect kinetic experiments (washout experiments) clearly showed that azilsartan slowly dissociates from the AT1 receptor and that this dissociation is significantly slower compared to the other ARBs tested. In addition, results of additional studies confirmed that azilsartan is an inverse agonist of the AT1 receptor.

In contrast to TAK-536, its metabolites showed weak binding affinity for the AT1 receptor, indicating that it is unlikely that these metabolites may contribute to the pharmacological functions of TAK-491.

TAK-536 potently and selectively inhibited angiotensin II-induced vasoconstriction of isolated rabbit aortic preparations.

Primary pharmacodynamics *in vivo*

The *in vivo* studies performed clearly demonstrated the antihypertensive effects of TAK-491 and TAK-536. In various hypertensive models in rats (angiotensin II-induced hypertensive, spontaneously hypertensive, renal hypertensive and salt-dependent hypertensive rats models) and dogs (renal hypertensive dogs model) oral administration of TAK-491 and TAK-536 significantly reduced blood pressure in a dose dependent manner without producing reflex tachycardia during treatment or rebound hypertension after termination of treatment. At doses ≥ 0.1 mg/kg, antihypertensive effects persisted up to 24 hours. The potency and duration of the antihypertensive effects tended to increase with repeated dosing compared to single administration.

In normotensive rats, TAK-536 increased renin concentrations but had no effect on blood pressure or aldosterone levels. However, pre-treatment of normotensive rats with TAK-536 inhibited angiotensin II-induced increases in blood pressure and plasma aldosterone concentrations, suggesting that the antihypertensive effects of TAK-536 observed in the other hypertensive models were derived form its specific antagonistic activity on angiotensin-mediated effects. The lack of efficacy for TAK-536 in salt-dependent hypertensive rats supports the pharmacologic specificity of this compound on angiotensin II type 1 receptors.

On a mg/kg basis, TAK-491 and TAK-536 had consistently more potent and longer lasting antihypertensive effects than the clinically used angiotensin II receptor blockers, olmesartan and losartan.

Secondary pharmacodynamic studies

Secondary pharmacodynamics *in vitro*

In addition to its effect on hypertension, angiotensin II plays a pivotal role in insulin resistance and this effect too appears to be mediated through stimulation of the angiotensin II type I receptor. Hence, next to evaluating the primary antihypertensive effects and the potential off-target activity of TAK-491 and TAK-536, the applicant examined the anti-diabetic activity of TAK-491 and TAK-536.

Results of the various binding studies revealed that it is unlikely that TAK-491 will induce potential off-target activity in human patients orally treated with clinical doses up to 80 mg.

The effects of TAK-536 on IRS-1 phosphorylation in the presence of insulin and angiotensin II were evaluated in rat primary skeletal muscle cells. Treatment of cells with TAK-536 significantly blocked the effects of angiotensin II and restored IRS-1 phosphorylation.

Secondary pharmacodynamics *in vivo*

TAK-491 significantly inhibited the progression of albuminuria and proteinuria in a rat model of type 2 diabetes with overt nephropathy.

TAK-491 did not have any effect on plasma insulin obtained before glucose infusion and during steady state in spontaneous hypertensive rats.

TAK-536 dose-dependently suppressed the increase in plasma glucose levels occurring during an Oral Glucose Tolerance Test (OGTT) in obese type 2 diabetes mice, suggesting an improvement in insulin sensitivity. TAK-536 also increased glucose uptake into tissues, especially skeletal muscles and adipose tissue.

Safety pharmacology programme

A general non-clinical pharmacology screen (non-GLP) was conducted to evaluate the potential effect of 3-300 mg/kg TAK-536 on the cardiovascular, renal, gastrointestinal, immune, reproductive, central and autonomic nervous systems in various animal species including mice, rats, guinea pigs, rabbits, cats and dogs. GPL-compliant safety pharmacology studies were performed to examine the potential effects of TAK-491 and TAK-536 on cardiovascular, respiratory and central nervous systems.

Next to the expected decreasing effect on blood pressure, no significant TAK-491-related effects were seen on cardiovascular, respiratory or central nervous systems at clinically relevant or even supra-therapeutic dosages.

Pharmacodynamic drug interactions

Angiotensin II receptor blockers and anti-diabetic PPAR$_\gamma$ agonists are often used together in patients suffering from hypertension and type-2 diabetes. Hence, the effect of the combination TAK-536 and pioglitazone on diabetic parameters and myocardial infarct size in diabetic rats was evaluated. Co-administration of TAK-491 and the anti-diabetic agonist pioglitazone tended to attenuate left ventricular remodelling and improved left ventricular function after infarction in rats. The clinical significance of this finding is unknown.

2.3.3 Pharmacokinetics

Non-clinical pharmacokinetic studies were conducted in mice, rats, rabbits, dogs, and monkeys. The formulation used in the non-clinical pharmacokinetic and metabolism studies was similar to those used in the toxicology studies. The *in vitro* biotransformation of azilsartan medoxomil was investigated in mice, rats, dogs, monkeys, and humans. The overall results of these investigations are reported below.

Methods of analysis

TLC was used to identify and quantify azilsartan medoxomil, azilsartan, M-I and M-II in urine and faeces of the pre-clinical species (mice, rats, rabbits, dogs and monkeys). In urine and faeces samples from humans, LC-MS/MS was used to identify and quantify the pro-drug, drug and its 2 major metabolites. LC-MS/MS was used to determine the plasma concentrations of the salt free form of azilsartan medoxomil, azilsartan, M-I, and M-II from mice, rats, rabbits, dogs and monkeys. The analysis method used was sufficiently validated and was stable under the different investigated storage conditions.

Absorption

Azilsartan medoxomil was mostly absorbed from the jejunum, duodenum, and ileum and was poorly absorbed from the stomach and colon. Non-clinical data suggest that lymphatic absorption is not important for this compound. Oral absorption and bioavailability of azilsartan medoxomil were assessed in rats, dogs and monkeys. After oral administration, conversion from azilsartan medoxomil to azilsartan was rapid and the radioactivity in the plasma was mainly attributed to azilsartan. Systemic exposure to azilsartan medoxomil was negligible after oral dose administration of [14C]azilsartan medoxomil. Cmax was reached in 1 to 2.5 h and faster under fasted conditions as compared to fed conditions. The half-life of azilsartan in plasma was between 4 and 6 h in rats and dogs and ~12 h in humans. Systemic exposure to azilsartan medoxomil was negligible after oral dose administration of [14C]azilsartan medoxomil, except in juvenile animals. In the plasma, the concentration of azilsartan was highest, followed by M-I and M II (<10% in plasma). In rats and dogs, the increases in Cmax and AUC for azilsartan were dose proportional after oral azilsartan medoxomil administration up to 200 mg/kg in rat and 300 mg/kg in dog. At higher dosages the increases in AUC and Cmax were less than dose proportional in rats. No higher dose than 300 mg/kg was investigated in dogs. Following repeated daily oral doses of azilsartan medoxomil, slight increases were noted in Cmax and AUC values and steady state was reached in 4 to 7 days.

Distribution

The volume of distribution of azilsartan was similar in dogs and humans. In rats and monkeys, the volume of distribution was around a factor 2 smaller. The clearance was larger in dogs than in rats and monkeys (a factor 10 to 4 smaller, respectively). In humans, the clearance was lower than in the pre-clinical species. The slower clearance in humans was in agreement with the longer observed half-life in the plasma. Data for monkeys were provided for azilsartan. However, the major pre-clinical species were rats and dogs. In addition, monkeys were not dosed with the pro-drug only but with the drug. In general, increases in exposure to M-I and M-II (as measured by Cmax and/or AUC values) were dose proportional at low dosage levels, but were less than dose proportional at higher dosage levels. The bioavailability of azilsartan after oral administration of azilsartan medoxomil was 12% in rats, 54% in dogs and 58% in humans. In contrast, after oral administration of azilsartan the bioavailability of azilsartan was 41% in fasted rats, 39% in fasted dogs, 14% in monkeys and 75% in humans. The bioavailability was lower under fed as compared to fasted conditions. However, in clinical studies no influence of food on the bioavailability of azilsartan medoxomil was observed. The bioavailability of M-II after oral administration was low and dosages of up to 2 g/kg/day were needed to reach adequate AUC levels for toxicological evaluation.

Azilsartan medoxomil and its metabolites are highly bound to plasma proteins and the major binding protein of azilsartan was albumin in human plasma. The distribution of azilsartan into blood cells of animals and in humans is very limited (<5%). Azilsartan medoxomil derived material does not have any affinity for melanin. Distribution of radioactivity in tissues was similar in animals dosed with [14C]azilsartan compared to animals dosed with [14C]azilsartan medoxomil.

After a single oral dose of [14C]azilsartan medoxomil, only the liver had a ratio compared to plasma of >1 and radioactivity was eliminated rapidly in all tissues (including the liver) and in the plasma. After repeated dosing with azilsartan medoxomil for 14 days in rats, steady state tissue levels were achieved in 4 to 7 days. However, in the kidney concentrations of radioactivity increased across the 14 days of treatment indicating that after daily oral dosing in humans accumulation in the kidney could occur. However, toxicology results did not show liver or kidney toxicity, indicating that accumulation was limited. Azilsartan medoxomil related radioactivity gradually transferred into the foetuses and the major radioactive component in maternal and foetal plasma was azilsartan. Metabolite M-I was transferred over the placenta to the foetus with a ratio of 17 and metabolite M-II with a ratio of ~1.

Metabolism

Azilsartan medoxomil is rapidly hydrolysed to the active moiety azilsartan by esterases in the gastrointestinal tract and/or during drug absorption. Based on vitro studies, the enzymes involved in the hydrolysis of azilsartan medoxomil to azilsartan in human plasma, and in human liver and small intestinal cytosol seem to be similar to those involved in the hydrolysis of olmesartan medoxomil. Currently, no drug interactions are listed for the hydrolysis of azilsartan medoxomil. The enzyme carboxymethylenebutenolidase is a recently discovered hydrolysis mechanism for azilsartan medoxomi in the intestine and liver, but no interactions with other drugs have been reported for this enzyme in the DIDB database. Also no interactions have been reported for human serum albumin or arylesterases. Since there are multiple esterase pathways involved in the conversion of azilsartan medoxomil to azilsartan, the potential for interactions via this pathway is considered to be minimal.

The metabolites M-I and M-II were formed by decarboxylation and dealkylation of azilsartan, respectively, and are pharmacologically inactive. CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 are all capable of metabolising azilsartan. However, CYP2C9 showed the highest activity in metabolising azilsartan to M-II and CYP2C8 in metabolising azilsartan to M-I.

Excretion

In animal species, the faecal excretion route is dominating (87-95% of the dose) and only a small fraction is excreted via urine (<10% of the dose) and entero-hepatic circulation occurs to a small degree. In humans, a major fraction of the radioactivity (42%) is excreted via urine. Metabolite M-II is mainly excreted via urine. Azilsartan related radioactivity was excreted in milk of lactating rats. Most of the radioactivity in rat milk consists of azilsartan (95% of the radioactivity in milk), but after 24 hours 41% of the radioactivity are non-identified metabolites. In addition, metabolite M-II is transferred from plasma to milk with a ratio of >1 after 4 h (based on concentration in milk versus plasma).

Pharmacokinetic drug interactions

Azilsartan medoxomil is not a substrate for P-glycoprotein and is a low permeability drug. The involvement of P-glycoprotein in the transport of azilsartan was difficult to evaluate due to extremely low transport in Caco-2 cells, but based on the *in vitro* results it can be concluded that azilsartan is a low permeability drug. Azilsartan medoxomil is an inhibitor for P-glycoprotein-mediated efflux activity, while azilsartan is not an inhibitor for P-glycoprotein. Because azilsartan medoxomil is converted rapidly to azilsartan and because azilsartan is not a P-glycoprotein inhibitor, clinically significant drug-drug interactions based on azilsartan medoxomil inhibitory effect on P-glycoprotein are unlikely. In addition, these conclusions are supported by clinical trials results.

Azilsartan medoxomil inhibited CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A4, but did not inhibit CYP2D6 and 2E1. Azilsartan medoxomil showed the highest inhibition potential for CYP2C. Azilsartan decreased the activities of recombinant CYP2C9 and CYP2C8, but had no inhibitory effect on other CYP isoforms. Intestinal CYP2C activity is limited and azilsartan medoxomil is hydrolyzed extensively to azilsartan during intestinal absorption. The mean Cmax of azilsartan in humans is 12 µmol/L after repeated oral dosing with 80 mg azilsartan medoxomil (highest proposed dose). Therefore, clinical drug-drug interactions based on CYP inhibition by azilsartan medoxomil and azilsartan are unlikely. In addition, a clinical relevant drug-drug interaction between azilsartan medoxomil and pioglitazone or chlorthalidone is unlikely.

A clinical DDI study of azilsartan with caffeine did not lead to a drug-drug interaction via CYP1A2. The results from the *in vitro* CYP1A2 and 2B6 induction studies indicated that neither azilsartan medoxomil nor azilsartan are inducers of CYP1A2 or CYP2B6.

2.3.4 Toxicology

The toxicity of TAK-491, TAK-536 and TAK-536 M-II has been evaluated in an extensive non-clinical programme. The toxicology programme included single-dose and repeat dose toxicity studies in rats and dogs, in vivo and in vitro genotoxicity studies, reproduction and developmental toxicity studies and carcinogenicity studies. Most toxicity findings were related to known direct and indirect effects of inhibition of the RAAS by AT1 receptor blockade.

Single dose toxicity

The acute toxicity of the prodrug (TAK-491) and/or the active compound (TAK-536) has been evaluated in single-dose studies in mice (oral gavage) and rats (oral gavage and IV bolus), single escalating-dose studies in beagle dogs (oral gavage) and cynomolgus monkeys (oral gavage). For rodent studies (except toxicokinetic studies), clinical signs and body weight were recorded for up to 2 weeks post-dose, and necropsy was performed at the end of the observation period. In non-rodent escalating-dose studies, clinical signs, body weight, and food consumption were recorded for up to 2 weeks post-dose but necropsy was not performed. The effects in dogs included short-term effects on food consumption, and exaggerated pharmacodynamic effects of inhibition of the RAAS, including effects on the hematopoietic system (decreased erythroid parameters), renal function (increased BUN, creatinine), and electrolyte disturbances (increased inorganic phosphorus, potassium, gastrointestinal effects). Similar effects were also observed in an escalating-dose oral gavage study of TAK-536 in monkeys.

Repeat dose toxicity

Repeat-dose toxicity studies with TAK-491 and/or TAK-536 have been performed by oral administration (gavage or dietary admixture) for time intervals up to 13 weeks in mice, 26 weeks in rats, and 52 weeks in dogs.

Mice

CByB6F1 mice and the repeat-dose dietary toxicity of TAK-536 was evaluated in a 13-week study in B6C3F1 mice. Evaluation for TAK-491 and TAK-536-related effects included clinical observations, body weight, food consumption, haematology, clinical chemistry, organ weights, gross pathology, and histopathology. The NOAEL for TAK-491 was in the 4-week study and < 20 mg/kg.day in the 13-week study for males and females. For TAK-536 in the 13-week study, 300 mg/kg/day was considered the maximum tolerated dietary dose based on the changes in body weight gain. The target organs were the kidneys (juxtaglomerular hypertrophy, hyperplasia of the afferent glomerular arterioles, tubular damage, papillary mineralisation, and decreased renal function), the heart (decreased weight), the hematopoietic system (decreased erythrocytes, haemoglobin concentration), the gastrointestinal tract (mucosal irritation, inflammation/erosions) and the adrenals (cortical hyperplasia). The effects on the kidney were associated with elevated circulating levels of BUN and the slight calcifications of the renal papilla. The effect on the hematopoietic system seems to be caused by the suppression of erythropoietin production, whereas effects on the heart seem to reflect the decreased heart pre- as well as after load mediated by the hypotensive action of TAK-536 by lowering peripheral vascular resistance. These effects on the heart and kidneys were consistent with the induced hypotension by inhibition of the RAAS reducing renal perfusion. These pharmacologically-mediated undesirable effects are known from non-clinical studies with both angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists. In patients, TAK-491 is intended to restore normal blood pressure; under these circumstances, the hypotensive states necessary for reductions in renal blood pressure and consequent pathology would not arise.

Rats

F344 rats were administered TAK-491 at oral gavage doses of 0, 2, 20, 200, or 2000 mg/kg/day for 4 consecutive weeks, doses of 0, 200, 600, or 2000 mg/kg/day for 13 consecutive weeks. F344 rats were administered TAK-491 at oral gavage doses of 0, 2, 20, 200, or 2000 mg/kg/day for 26 consecutive weeks. F344 rats were administered TAK-536 at oral gavage doses of 0, 3, 30, 300, or 3000 mg/kg/day for 4 consecutive weeks, doses of 0, 3, 30, 300, or 3000 mg/kg/day for 13 consecutive weeks and doses of 0, 1, 10, 100, or 1000 mg/kg/day for 26 consecutive weeks. The target organs were the same as those in mice, and the observed effects were related to exaggerated pharmacodynamics of TAK-491 and/or TAK-536. The histopathological effects on the kidney were associated with elevated circulating levels of BUN and slightly increased urine production and/or water consumption. The persistence of the cell atrophy within the zona glomerulosa of the adrenals was not unexpected given the known direct effects of AT1 receptor blockade on aldosterone synthesis and release. Changes in serum enzymes were observed, but there were no changes in weight or histopathology of the liver in the tested dose range. The CHMP considered these changes not relevant for human.

Dogs

The repeat-dose oral toxicity of TAK-491 was evaluated in pivotal 4- and 26-week studies in beagle dogs. Prior to these studies, a 2-week preliminary study has been performed. The repeat-dose oral toxicity of TAK-536 was evaluated in 4-, 13-, 26- and 52-week studies in beagle dogs. Beagle dogs were administered TAK-491 at oral gavage doses of 0, 3, 12, 60, or 300 mg/kg/day for 4 consecutive weeks. Beagle dogs were administered TAK-491 at oral gavage doses of 0, 3, 12, or 60 mg/kg/day for 26 consecutive weeks. Beagle dogs were administered TAK-536 at oral gavage doses of 0, 30, 100, 300, or 1000 mg/kg/day for 4 consecutive weeks, at doses of 0, 10, 30, 100, or 500 mg/kg/day for 13 consecutive weeks. A 52-week repeat-dose oral toxicity study with TAK-536 in dogs was bridged to TAK-491 development and substituted for a 39-week study of TAK-491 in dogs. A 52-week study with a 26-week interim sacrifice was performed to assess the chronic toxicity of TAK-536 in dogs. Beagle dogs were administered TAK-536 at oral gavage doses of 0, 10, 30, 100, or 300 mg/kg/day for 26 or 52 consecutive weeks.

The target organs were the same as those in mice and rats, but dogs were more sensitive. The observed effects were related to exaggerated pharmacodynamics of TAK-491 and/or TAK-536. Changes in serum enzymes were observed, but there were no changes in weight or histopathology of the liver in the tested dose range. These changes are not relevant for human. The provided NOAEL values are based on findings in the kidney (basophilic tubules with dilatation) and stomach (erosions).

Genotoxicity

In vitro

In the *in vitro* reverse mutation assays with TAK-491, azilsartan medoxomil salt free (TAK-491F) and the active moiety (TAK-536), the salt-free substance, showed a weak positive response in the in *E.Coli* strain WP2*uvr*A in the presence of S9 activation. The positive response with TAK-491F in this assay is likely to be due to the medoxomil side chain on the molecule. Hydrolysis of the medoxomil side chain includes diacetyl, which has been demonstrated to be associated with genotoxicity *in vitro*. These findings were considered not to be relevant to human safety. The diacetyl compound is classified as generally-recognized-as-safe (GRAS) by the US FDA and is found in various foods and beverages. Additionally, exposure to diacetyl would be expected to be very limited since it would be metabolized rapidly *in vivo* to the non-genotoxic compounds acetoin or 2,3-butanediol. In the chromosomal aberration tests in Chinese hamster lung (CHL) cells TAK-491 showed positive results in the absence of

S9 activation and TAK-536 showed positive results both in the presence and the absence of S9 activation. The induced structural chromosomal aberrations were seen at concentrations that were associated with cytotoxicity. Additionally, threshold effects in genotoxicity assays have been recognized for certain classes of drugs, including angiotensin II receptor blockers (ARBs). In the forward mutation assay at the HGPRT locus in Chinese hamster ovary (CHO) cells and the mutagenicity assay in L5178Y TK+/- mouse lymphoma cells TAK-536 showed negative results.

In vivo

Unscheduled DNA Synthesis (UDS) assays in rat hepatocytes with TAK-491 and TAK-536 showed negative results. The micronucleus and chromosomal aberrations assays in the bone marrow of mice and rats with TAK-491 and TAK-536 were negative. To conclude TAK-536, TAK-491 and TAK-491F did not show a genotoxic risk.

Carcinogenicity

Long-term studies

Two-year carcinogenicity studies were performed with TAK-491 in rats and with TAK-536 in mice and rats. There were no statistically significant increases in tumour incidence associated with any treatment in either species.

Short or medium-term studies

A 26-week carcinogenicity study was performed with TAK-491 in transgenic mice. There were no statistically significant increases in tumour incidence associated with any treatment.

To conclude carcinogenicity studies in mice and rats showed no concerns.

Reproduction Toxicity

Fertility and early embryonic development

In rats TAK-491 and TAK-536 showed no effects on male and female fertility. The F1 litters showed dilated renal pelvis. This is a pharmacodynamic effect of TAK-536 following placental transfer.

Embryo-foetal development

The Segment II studies in rats and rabbits showed adverse effects of TAK-491/TAK-536 on foetal development and growth at maternally toxic doses. These effects consisted of post-implantation loss, resorptions and skeletal abnormalities and reduced viability of the foetus. These effects are presumably due to reduced food consumption and body weights of the dams and decreased perfusion of the placenta secondary to induced hypotension. As pharmacological effect, dilation of the renal pelvis was occasionally observed. There were no teratogenic effects in either species. In addition, TAK-491 is not recommended during the first trimester of pregnancy and contraindicated during the second and third trimester of pregnancy in the SmPC as it is based on observations in humans in compounds of the same pharmacological class. This advice is agreed in view of the above findings.

Prenatal and postnatal development, including maternal function

In the Segment III studies in rats, there was dystocia and a slight delay in physical development (delayed incisor eruption, pinna detachment, eye opening), probably a consequence of reduced body weight gain in the pups, secondary to maternal toxicity. TAK-536 is excreted into milk of lactating rats. Newborn and neonatal rats were sensitive to in utero or milk exposure to TAK-536, resulting in reduced viability, dilation of the renal pelvis and/or ureter, hydronephrosis, polycystic kidneys, and a

rough kidney surface (most likely a reflection of renal calcification). The effects on the kidney are considered to be related to the pharmacodynamics of TAK 536, leading to altered excretion of electrolytes and to an increased water permeability of the renal tubules as the result of decreased vasopressin release from the hypothalamus/neurohypophysis.

Studies in which the offspring (juvenile animals) were dosed and/or further evaluated

With the intention to start a paediatric clinical trial, studies were conducted in juvenile rats with a TAK-491/TAK-536-M-II combination. The studied time intervals enabled evaluation of the target organs of toxicity in 1-year-old children up to adolescence. The pilot studies in 0- and 7-day old rats showed that TAK-491 led to increased mortality, lower body weights and reductions in food consumption, and a dilatation of the renal tubules, which is considered to be a pharmacodynamic effect. The heart weights were reduced, but there were no effects on heart development. The 5-week and 13-week pivotal studies in 7-day-old rats confirmed these findings.

Local Tolerance

Local tolerance studies were conducted to evaluate the haemolytic potential and plasma compatibility of a parenteral formulation of TAK-536 in human blood and to evaluate the intravenous and paravenous tolerance of this formulation in rabbits.

In vitro, haemolytic activity and plasma compatibility were assessed by incubating a 0.5 mg/mL solution of TAK-536 in human blood at a 1:10 ratio or in human plasma at a 1:100 ratio. Incubation of TAK-536 with human blood did not cause haemolysis, and incubation of TAK-536 with human plasma did not cause any macroscopic flocculation, precipitation, or coagulation.

Paravenous tolerance of TAK-536 at 0.5 mg/mL was evaluated in male rabbits. The appropriate dosing solution was injected subcutaneously into the vicinity of the posterior auricular vein at a dose volume of 0.3 mL/site. The results showed slight, but reversible changes at the injection site. At day 1 after injection, slight erythema and slight or mild swelling was noted. These changes lessened gradually thereafter, and had disappeared by 10 and 7 days, respectively. No vascular dilatation or thrombus formation was noted. Slight haemorrhage was noted in a few animals at necropsy 2 days after injection, but no abnormalities were noted in any TAK-536-treated rabbits at necropsy 14 days after injection. In the histopathological examination 2 days after injection, the subcutis was found to have slight cellular infiltration in all 3 TAK-536-treated rabbits, slight oedema in 2 of 3 TAK-536-treated rabbits, and mild haemorrhage in 1 of 3 TAK-536-treated rabbits. In the histopathological examination 14 days after injection, no abnormalities were noted at any injection site. Based on these findings, the TAK-536 solution at 0.5 mg/mL is tolerable for IV clinical use.

The IV tolerance of TAK-536 at 0.5 mg/mL was evaluated in male rabbits. The appropriate dosing solution was injected into the posterior auricular vein using an infusion pump set to a dose volume of 3 mL per site and a rate of 1 mL/minute for 3 minutes. The injection sites were observed for signs of local irritation. No macroscopic changes were observed at the injection sites. Slight endothelial desquamation was observed in all 3 TAK-536 rabbits at 2 days after injection but slight endothelial proliferation was only observed in 1 of 3 TAK-536 rabbits 14 days after injection. Therefore, this endothelial desquamation is considered reversible in TAK-536-treated rabbits. A TAK-536 solution at 0.5 mg/mL was tolerable for IV clinical use.

Other toxicity studies

Metabolites

TAK-536 M-II is a major metabolite of TAK-491 in humans, but is a relatively minor one in in mice, rats, rabbits, and dogs, species used to conduct the safety assessment of TAK-491 and TAK-536. Therefore, a toxicology programme was conducted with direct dosing of TAK-536 M-II.

Initial toxicokinetic studies with TAK-536 M-II indicated superior absorption with SC dosing compared with oral gavage dosing. However, the metabolite produced local irritation with repeated SC dosing and, as a consequence this route of administration was deemed unsuitable for studies longer than 4 weeks in duration. Therefore, TAK-536 M-II was dosed by oral gavage in the 13-week rat and dog studies and in the 2-year rat carcinogenicity study. TAK-536 M-II was dosed as a dietary admixture in 6-month mouse carcinogenicity studies. The results of these studies indicate some weak pharmacologic activity of TAK-536 M-II on AT1 receptors. No toxicologically significant findings were seen in the 13-week repeat-dose oral toxicity studies with TAK-536 M-II. Average exposure margins at the end of 13-week studies were approximately 6.1-fold higher in rats and 6.9-fold higher in dogs (sexes combined) relative to humans given 80 mg TAK-491. Considering 99% *in vivo* protein binding for TAK-536 M-II in humans, any additional contributions of this metabolite to activity at AT1 receptors would be insignificant.

There were no adverse effects of TAK-536 M-II on reproductive or developmental parameters at oral doses up to 3000 mg/kg/day in rats or rabbits.

No new toxicities were seen in the TAK-536-MII toxicity programme. Therefore the CHMP considered that TAK-536 M-II is not a concern for human.

Impurities

Although the level of 2-EH in the rat and mouse studies was below the specification limit of 1%, the limit is considered qualified by means of the toxicological data from the provided reference, from which a large safety margin (366 mg/m2/day versus 0.49 mg/m2/day) can be deduced.

For the positive genotoxicity findings on impurity TAK-491 U-3, the applicant provided the same discussion as for results on TAK-491 and TAK-491F. The formation of diacetyl from the medoxomil group does indeed seem a plausible explanation for the positive results. Although there are no *in vivo* chromosomal aberration data and no carcinogenicity data for TAK-491 U-3 to substantiate the hypothesis, unlike for the parent compound, the mechanism underlying the effect appears to be the same, and no further studies are considered necessary. *In vitro* genotoxic effects of TAK-491 U-3 are not relevant for humans. With regard to general toxicity, a 4-week study was conducted in dogs, in which no additional toxicity was found for TAK-491 U-3 when administered at 0.542 mg/kg/day. This is 17-fold above the maximum human intake at 1% in the drug product, taking a conversion factor of 2 in account for dogs versus human. It can be concluded that TAK-491 U-3 is qualified at a level of 1%.

2.3.5 Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) for azilsartan medoxomil was provided in accordance with the CHMP guideline EMEA/CHMP/SWP/4447/00. TAK-491 is administered as a pro-drug by oral route. Under *in vivo* conditions the pro-drug is rapidly and quantitatively converted to the active pharmaceutical ingredient TAK-536 by hydrolysis. A Phase I environmental risk assessment was performed to evaluate potential environmental risks of TAK-491. Referenced studies were performed with the active pharmaceutical ingredient TAK-536. Based on the log K_{ow} values (from the studies by Oudhoff and by Nishi), TAK-536 is not expected to be a bio-accumulative substance. The $PEC_{surfacewater}$

of 0.32 µg/L exceeded the action limit of 0.01 µg/L. Thus a phase II - Tier A assessment was triggered. Based on the PEC/PNEC ratios calculated above, TAK-536 is not expected to pose unacceptable effects for the surface water, ground water and STP compartment. Since the log K_{oc} is < 10000 L/kg, there is no need to assess the risks of TAK-536 for the soil compartment. Based on the results of the water/sediment study (OECD study 308), a phase II - Tier B assessment was triggered for the metabolites TAK-536 M-I and TAK-536 M-III. $PEC_{sediment}$ for TAK-536-M-I was calculated using Equilibrium partitioning and REACH (EUSES) equations using characteristics for suspended matter (sediment) and soil. EUSES standard suspended matter contains 10% organic carbon and soil contains 2% organic carbon. A K_{oc} of 12900 L/kg was used. However, no sediment toxicity study for the parent or main metabolite was performed. According to CHMP guideline EMEA/CHMP/SWP/4447/00, effects on sediment organisms should be investigated.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following point to be addressed:

- An OECD 219 "Sediment-Water Chironomid Toxicity Using Spiked water" study should be conducted to complete the Environmental Risk Assessment. Once the results are available, the Environmental Risk Assessment should be updated accordingly.

The results from this additional study were not considered required by the Committee before the adoption of the positive CHMP opinion and it is confirmed that these applications comply with Article 6 of Regulation 726/2004 having regard to the requirements of Article 8(3) of Directive 2001/83.

Table 1. Summary of main study results

Substance (INN/Invented Name): Azilzartan			
CAS-number (if available): 147403-03-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential - log K_{ow}	OECD 107		not PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.7 (pH1.5) 1.0 (pH 6.4) 0.44 (pH 7.0)	not B
	BCF [l.kgwwt-1]	6.85 [earthworms] 39.4 [fish]	not B
Persistence	DT_{50} or ready biodegradability		not P
Toxicity	NOEC or CMR		not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (prevalence)	10	µg/L	> 0.01 threshold
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 70 & 284 Llkg (two sludges)	List all values
Ready Biodegradability Test	OECD 301	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	<u>GV system</u> $DT_{50,\ water}$ = 3.4 days $DT_{50,\ sediment}$ =7.2 days $DT_{50,\ whole\ system}$ =6.4 days % shifting to sediment = >10% AR in sediment at or	Not required if readily biodegradable

		after day 14 SW system $DT_{50,\ water/whole\ system}$ =2.3 days			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	77	mg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	10	mg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	8.8	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50}	>100	mg/L	
PEC/PNEC ratios for TAK-536					
Ratio (Based on a worst-case Fpen of 0.32)	PEC (µg/L)	PNEC (µg/L)	PEC/NEC		Trigger
$PEC_{SURFACEWATER}/PNEC_{WATER}$	10	880	0.01		1
$PEC_{SURFACEWATER}/PNEC_{MICROORGANISM}$	10	10,000	0.001		0.1
$PEC_{GROUNDWATER}/PNEC_{GROUNDWATER}$	2.5	1000	0.003		1

2.3.6 Discussion on non-clinical aspects

Studies performed by the applicant clearly demonstrate that TAK-491 and TAK-536 significantly reduce blood pressure in various hypertensive models by potently, selectively and competitively blocking the angiotensin II type 1 receptor. The results of the pharmacodynamic *in vitro* and *in vivo* studies performed clearly demonstrated the antihypertensive effects of TAK-491 and TAK-536. In comparison with clinically used angiotensin II blockers, the antihypertensive effects of TAK-491 and TAK-536 are consistently more potent and longer lasting. In addition to their anti-hypertensive effect, the applicant demonstrated that TAK-491 and TAK-536 may have potential anti-diabetic effects, suggesting that TAK-491 might have beneficial effects in patients suffering from metabolic syndrome. Next to these effects, no potential off-target activity would be expected in human patients orally treated with clinical doses up to 80 mg.

Azilsartan medoxomil was mostly absorbed from the jejunum, duodenum and ileum. After oral administration conversion from azilsartan medoxomil to azilsartan was rapid. Cmax was reached in 1 to 2.5 h. The half life in plasma (rats and dogs) was between 4 and 6h. Following repeated daily oral doses steady state was reached in 4 to 7 days. In animals, the faecal excretion route is dominant. There is currently insufficient knowledge about possible interactions of azilsartan medoxomil with other drugs. At present, drug-drug interactions seem unlikely.

In the toxicology studies, the kidneys heart, hematopoietic system and adrenals were the primary target organs of TAK-536; the stomach was an additional target particularly in rats. TAK-491 and M-II crossed the placenta and were found in the foetuses of pregnant rats and were excreted into the milk of lactating rats. No effect on male and female fertility was reported in the reproduction toxicity studies. TAK-491, TAK-536 and M-II did now show a genotoxic risk *in vivo* and a carcinogenotoxic risk in rats and mice. TAK-536 has no haemolytic potential. The changes observed after subcutaneous or intravenous administration were all reversible. As the current application concerns a tablet formulation, the results of the local tolerance studies are of no further concern.

An Environmental Risk Assessment (ERA) for azilsartan medoxomil was provided in accordance with the CHMP guideline EMEA/CHMP/SWP/4447/00 including a phase I, phase II- Tier A and phase II-Tier B assessment.

2.3.7 Conclusion on the non-clinical aspects

The overall non-clinical development programme was considered adequate to support the marketing authorisation application for azilsartan medoxomil and the concerns identified by the CHMP during its evaluation are considered resolved.

2.4 Clinical aspects

2.4.1 Introduction

This Marketing Authorisation application is a full, stand alone application in accordance with Directive 2001/83/EC Article 8 (3). The Applicant is seeking a Marketing Authorisation for TAK-491 tablets (20, 40, and 80 mg) for the once-daily treatment of essential hypertension in adults, either as monotherapy or taken concomitantly with other antihypertensive agents. The recommended starting dose is 40 mg taken once daily and this dose may be increased to a maximum of 80 mg once daily for patients whose blood pressure is not adequately controlled at the lower dose. A 20 mg dose once daily can be considered as a starting dose for patients at risk of hypotension. Five phase II and eleven phase III studies (including an open-label extension of one of the double-blind, controlled, randomized, versus placebo monotherapy study) were conducted in patients with essential hypertension to establish the therapeutic dose and to assess the efficacy and safety of azilsartan medoxomil. A Paediatric Investigation Plan (P/106/2010) and a waiver for children aged below 6 months of age have been agreed for azilsartan medoxomil with the PDCO. A deferral to complete the PIP has been granted until April 2021. During the evaluation, a modification of the Paediatric Investigation Plan (P/39/2011) and of the waiver now for children below 1 year of age was agreed for azilsartan medoxomil with the PDCO. Scientific advice on the clinical development programme was not thought from the CHMP.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. The table below lists only the main phase II dose-finding and the main phase III studies submitted as part of this Marketing Authorisation Application.

Table 2. Tabular overview of main clinical studies

Study Design and Study Number (Regions)	Population Planned Sample Size	Duration of Double-blind Treatment Dose/Regimen	Endpoints
TAK-536 (Tablets) vs Placebo and Olmesartan Medoxomil 536-002 (US, Lat Am) • 7-arm • Placebo-controlled • Active-controlled	Clinic DBP 95-114 mm Hg N=525 (75/group)	8 weeks • TAK-536 2.5 mg • TAK-536 5 mg • TAK-536 10 mg • TAK-536 20 mg • TAK-536 40 mg • OLM-M 20 mg • Placebo	Clinic DBP
TAK-491 (Capsules) vs Placebo and Olmesartan Medoxomil 491-005 (US, Lat Am) • 7-arm • Placebo-controlled • Active-controlled	Clinic DBP 95-114 mm Hg N=420 (60/group)	8 weeks • TAK-491 5 mg • TAK-491 10 mg • TAK-491 20 mg • TAK-491 40 mg • TAK-491 80 mg • OLM-M 20 mg • Placebo	Clinic DBP
Monotherapy **TAK-491 vs Placebo, Olmesartan Medoxomil, and Valsartan** 491-019 (c) (US, Lat Am) • 5-arm • Placebo-controlled • Active-controlled • Forced-titration (b)	Clinic SBP 150-180 and 24-hr SBP 130-170 mm Hg N=1305 (active=290/group; placebo=145)	6 weeks (2 wks→4 wks) • TAK-491 20→40 mg • TAK-491 40→80 mg • OLM-M 20→40 mg • Valsartan 160→320 mg • Placebo	24-hr mean SBP by ABPM (Clinic SBP)
TAK-491 vs Placebo and Olmesartan Medoxomil 491-008 (c) (US, Lat Am) • 5-arm • Placebo-controlled • Active-controlled	Clinic SBP 150-180 and 24-hr SBP 130-170 mm Hg N=1260 (active=280/group; placebo=140)	6 weeks • TAK-491 20 mg • TAK-491 40 mg • TAK-491 80 mg • OLM-M 40 mg • Placebo	24-hr mean SBP by ABPM (Clinic SBP)
TAK-491 vs Valsartan 491-301 (c) (US, Lat Am) • 3-arm • Active-controlled • Forced-titration (b)	Clinic SBP 150-180 and 24-hr SBP 130-170 mm Hg N=972 (324/group)	24 weeks (2 wks→22 wks) • TAK-491 20→40 mg • TAK-491 20→80 mg • Valsartan 80→320 mg	24-hr mean SBP by ABPM (Clinic SBP)
TAK-491 vs Ramipril 491-020 (c) (Europe, Russia) • 3-arm • Active-controlled • Forced-titration (b)	Clinic SBP 150-180 mm Hg N=890 (270/group)	24 weeks (2 wks→22 wks) • TAK-491 20→40 mg • TAK-491 20→80 mg • Ramipril 2.5→10 mg	Clinic SBP (N/A)
Black Population (TAK-491 vs Placebo) 491-011 (d) (US, Puerto Rico) • 3-arm • Placebo-controlled	Clinic SBP 150-180 and 24-hr SBP 130-170 mm Hg N=411 (137/group)	6 weeks • TAK-491 40 mg • TAK-491 80 mg • Placebo	24-hr mean SBP by ABPM (Clinic SBP)
Coadministration **TAK-491 + Diuretic** 491-009 (c) (US, Lat Am) • 3-arm • Placebo-controlled	Clinic SBP 160-190 and 24-hr SBP 140-180 mm Hg N=540 (180/group)	6 weeks • TAK-491 40 mg + CLD 25 mg • TAK-491 80 mg + CLD 25 mg • Placebo + CLD 25 mg	24-hr mean SBP by ABPM (Clinic SBP)
TAK-491 + CCB 491-010 (c) (US, Lat Am) • 3-arm • Placebo-controlled	Clinic SBP 160-190 and 24-hr SBP 140-180 mm Hg N=540 (180/group)	6 weeks • TAK-491 40 mg + AML 5 mg • TAK-491 80 mg + AML 5 mg • Placebo + AML 5 mg	24-hr mean SBP by ABPM (Clinic SBP)

BP=blood pressure, CCB=calcium channel blocker, CLD=chlorthalidone, AML=amlodipine, Lat Am=Latin America, OLM-M=olmesartan medoxomil, US=United States.
(a) All study drugs were administered once daily.
(b) Forced-titration at Week 2.
(c) Pivotal study (provides data for labeling).
(d) Supportive study (provides data reinforcing pivotal data).

2.4.2 Pharmacokinetics

The clinical pharmacology programme for TAK-491 consisted of 17 phase 1 studies in which TAK-491 was administered, and 18 phase 1 studies and 2 phase 2 studies in which TAK-536 was administered.

The formulation development of TAK-491 progressed from a capsule to a tablet. Consequently, the capsule formulation was used in early phase 1 studies, and the proposed commercial tablet formulation was used in later phase 1 studies and also in all phase 3 studies.

Azilsartan medoxomil (TAK-491) is a prodrug that is hydrolyzed rapidly to the active moiety, azilsartan (TAK-536), in the gastrointestinal tract and/or during absorption.

Several analytical methods were used to determine azilsartan medoxomil, azilsartan and its metabolites in the different studies and were considered adequate. The PK parameters analysed and the statistical methods used were too considered acceptable.

Absorption

The prodrug TAK-491 was undetectable in plasma at the earliest time points measured (5 minutes following administration). TAK-536 was detected early in plasma, with a median t_{max} of 3 hours after single- and multiple-dose administration. Following multiple-dose administration of TAK-491 80 mg (the highest proposed dose) the mean C_{max} and $AUC_{0\text{-}tau}$ of TAK-536 were 5.7 µg/mL and 34 µg·hr/mL, respectively, and mean C_{max} and mean $AUC_{0\text{-}tau}$ of TAK-536 M-II were 1.8 µg/mL and 25 µg·hr/mL, respectively.

The permeability of TAK-491 and TAK-536 across Caco-2 cells was examined in vitro. In the tests TAK-491 am TAK-356 both had a low permeability; however, the permeability for TAK-461 may be underestimated due to rapid conversion to TAK-536.

The absolute bioavailability of TAK-536 derived from the TAK-491 tablet is estimated to be 60%, bridging data from an absolute bioavailability study (study 536-016) and study 491-CHP-017. Study 491-CHP-017 is a relative bioavailability study in which the TAK-536 tablet was compared with the TAK-491 tablet and study 536-016 investigated the absolute bioavailability of the TAK-536 tablet**.**

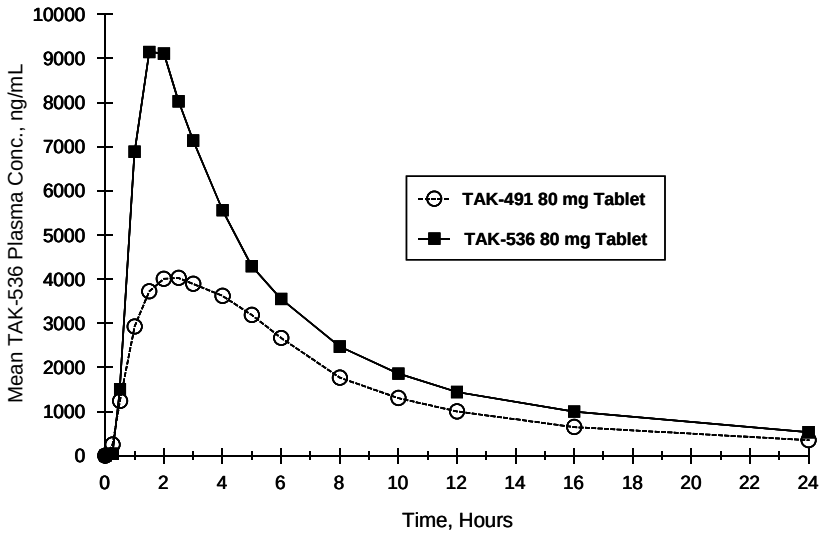
Table 3. Arithmetic Mean Values ± SD of Plasma Pharmacokinetic Parameters (for t_{max} (median and range) of TAK-536, TAK-536 M-I and TAK-536 M-II, N= 22 (study 536-016)

Treatment	AUC_{0-tlqc} ng*hr/ml	$AUC_{0-\infty}$ ng*hr/ml	C_{max} ng/ml	t_{max} hr	$t_{1/2}$ hr
Treatment A: TAK-491, 80mg oral (4x20mg capsule)					
TAK-536	24900 ± 39	25614 ± 39	3438 ± 38	2.5 (1.5-12)	10. 8 ± 8.7
TAK-536 M-I	368 ± 62	(b) 411 ± 59	104 ±133	1.5 (1.0-12)	(e) 9.7 ± 29
TAK-536 M-II	11763 ± 43	13183 ± 44	597 ± 43	5.0 (4.0-12)	14 ± 15
Treatment B: TAK-536, 40 mg oral (4x10mg tablet)					
TAK-536	30677 ± 21	(a) 31255 ± 22	4808 ±23	2.5 (1.0-4.0)	(a) 11.1 ± 14
TAK-536 M-I	393 ± 89	(c)439 ± 54	160 ±150	1.5 (1.0-4.0)	(c) 8.5 ± 37
TAK-536 M-II	15257 ± 27	(a)16993 ± 28	833 ± 27	5.0 (4.0-10)	(a) 14 ± 17
Treatment C: TAK-536, 10 mg IV (infusion over 10 minutes)					
TAK-536	10277 ± 18	10541 ± 18	2664 ± 23	0.33 (0.17-0.58)	11.5 ± 13
TAK-536 M-I	181 ± 53	(d)175 ± 47	192 ±105	0.43 (0.33-0.83)	(d)6.1 ± 44
TAK-536 M-II	4184 ± 22	4678 ± 22	230 ± 25	2.5 (2.5-6.0)	15 ± 17

Three relative bioavailability studies 491-015, 491-001, and 491-CHP-017 were conducted involving the TAK -536 tablets and TAK -491 tablets and capsules. The pharmacokinetic profile of TAK-536 was different between the TAK -536 tablets and the TAK-491 tablets and capsules.

The AUC and the C_{max} after administration of the TAK-491 tablets compared to the TAK-491 capsules was 68% and 77% higher, respectively. The AUC and C_{max} after administration of the TAK-536 tablets compared to the TAK-491 capsules were approximately 100% and 200% times higher, respectively (study 491-001). The AUC and C_{max} after administration of TAK-491 tablets compared to TAK-536 tablets decreased to 62% and 46%, respectively.

Figure 1. Mean Plasma Concentrations of TAK-536 After Administration of Proposed Commercial TAK-491 80 mg Tablet and TAK-536 80 mg Tablet (study 491-CHP-017)



The applicant selected TAK-491 for development rather than TAK-536 as TAK-491 has a better pharmacokinetic profile, with a lower C_{max} and a t_{max} which is found after approximately 3 hours.

The influence of food was evaluated in 4 studies. No food effect was observed following administration of the TAK-491 tablet in study 491-015. The TAK-491 tablet can therefore be administered with or without food. After administration of the TAK-491 capsule, however a food effect was observed (studies 491-001, 491-CPH-001 and 491-CPH-005).

Several studies were conducted with the TAK-491 capsule. These studies can be extrapolated to the TAK-491 tablet. The results of study 491-003 which was designed to evaluate the effects of age, gender, and race on the PK of single and multiple doses of TAK-491 were confirmed by the population PK/PD analysis. The design of studies 491-004 and 491-013 was appropriate to ensure that study results would not be affected by the observed food effect.

Distribution

The volume of distribution of TAK-536, determined after an IV infusion of TAK-536, is approximately 16L. *In vitro* and *ex vivo*, protein binding of TAK-536 is 90% and is similar in subjects with hepatic or renal impairment and in healthy matched controls. No selective uptake of TAK-536 into red blood cells occurs following administration of TAK-491.

Non-clinical studies have been conducted to investigate the reproduction toxicity of azilsartan medoxomil, from these studies it can be concluded that TAK-491 is rapidly hydrolyzed to TAK-536, which crosses the placenta and is found in the milk of lactating rats.

Elimination

After oral administration of TAK-491 approximately 42% of the radioactivity dosed was recovered in the urine with 15% of the dose identified as TAK-536, which indicates TAK-536 was available systemically. The remaining radioactivity (55%) that appeared in faeces after oral administration of

TAK-491 could be attributed either to biliary excretion of TAK-536 and its metabolites or microbial metabolism of unabsorbed TAK-536 (converted from TAK-491) in the gastrointestinal tract.

After administration TAK-491 is rapidly hydrolysed to TAK-536. In study 491-00047 *in vitro* hydrolysis of [^{14}C]TAK-491 (10 µmol/l) in rats, dogs, and human hepatic and intestinal S9 fractions was assessed. TAK-491 was hydrolyzed rapidly to TAK-536 by human hepatic and intestinal S9 fractions. Less than 3% of TAK-491 remained at 5 minutes in human hepatic S9 fractions, and approximately 20% and <1% of TAK-491 remained at 5 minutes and 20 minutes, respectively, in human intestinal S9 fractions. At this moment it is not clear which enzymes are involved, but *in vitro* studies indicated that arylesterase and HAS may contribute to the hydrolysis of TAK-491 to TAK-536.

The metabolism of TAK-536 after TAK-491 administration is extensive, and 2 metabolites are formed in humans: TAK-536 M-I, a minor decarboxylated metabolite which is formed primarily via cytochrome P-450CYP2C8, and TAK-536 M-II, a major *O*-dealkylated metabolite, which is formed primarily via CYP 2C9. *In vitro* tests showed that M-I and M-II are also formed via multiple minor CYP pathways. Exposures (AUC) to these 2 metabolites in human plasma, relative to TAK-536 are <1% and approximately 50% respectively. The affinities of TAK-536 M-I andTAK-536 M-II for AT1 receptors are 1770- and 850-fold less than that of TAK-536 respectively *in vitro*. Therefore, neither metabolite would be expected to contribute to the pharmacological activity at exposures associated with the proposed commercial doses of TAK-491.

Genetic polymorphism is not expected to have consequences with regard to the bioavailability of TAK-536 as there are multiple pathways of metabolism and excretion. This is supported by population PK data which could not identify subgroups that would be indicative of polymorphism.

Dose proportionality and time dependencies

Dose proportionality of exposure to TAK-536 and TAK-536 M-II, the major human metabolite, was established at doses from 20 to 320 mg using data from several single and multiple dose studies. No accumulation of TAK-536 and TAK-536 M-II was observed.

Special populations

Pharmacokinetics in target population

A population PK data study (study 491CLD_302) was submitted. In this study hypertensive patients received TAK-491 and chlorthalidone, either alone or in combination. The PK data of the combination tablets with TAK-491 and chlorthalidone were used in this population PK model. Co-administration of chlorthalidone with TAK-491 resulted in small clinically non significant increases in systemic exposure parameters (AUC and C_{max}) in the DDI study 491-004.

The final population PK model for TAK-536/M-II is a simultaneous parent-metabolite model with first order absorption and elimination with the disposition of TAK-536 and M-II being described by 2 and 1 compartments respectively. Age and body weight were identified as significant covariates. The magnitude of the effects resulting in variability of exposure to TAK-536 of ±20% are considered not clinically relevant.

The population PK model-based simulating exposure estimates for TAK-536 in subjects with hypertension were compared with observed non-compartmental-derived estimates for healthy subjects receiving similar doses of TAK-491. The mean simulated AUC values in subjects with hypertension were up to 27% higher across dose levels, compared with the observed values in healthy subjects. In contrast, mean simulated steady state Cmax was approximately 34% lower across dose levels in subjects with hypertension when compared with the observed values in healthy subjects following administration of TAK-491. The CHMP considered neither of these differences to be clinically relevant.

Additionally a population PK study (536-CCT-001) was conducted with the TAK-536 tablet. The final population PK model of this study was a simplified steady-state model, with age, aspartate aminotransferase (AST) and creatinine levels identified as factors influencing the CL/F of TAK-536. The value of the study is limited as only 1.94 samples/ patient were collected and there was no attempt to characterise the PK profile over a 24 hour period and at C_{max}.

The extrapolation of PK data from healthy volunteers to patients is properly justified.

Variability

The intra-individual variability of the pharmacokinetic parameters of TAK-536 derived from proposed commercial TAK-491 tablet was approximately 25% for AUC and 30% for C_{max} in the different studies.

Renal impairment

Total exposure (AUC) to TAK-536 after a single dose of TAK-491 tended to be higher in subjects with renal impairment than in healthy subjects, with increases of 30%, 25%, 96% in subjects with mild, moderate, and severe renal impairment (study TAK491_103). However, only a 5% increase was observed in patients with End Stage Renal Disease (ESRD). Subjects with ESRD are dialysed and cannot be compared to the other groups. In subjects with renal impairment a 2-5 fold increase of the TAK-536-M-II exposure was observed. This observed increase of TAK-536-M-II is not clinically relevant. Based on the results of study TAK491_103, caution is needed in patients with severe renal impairment and ESRD as reflected in the SmPC.

The PK of unbound TAK-536 and its metabolites (M-I and M-II) were similar to the PK of total drug concentrations in subjects with renal impairment.

Hepatic impairment

Clinical experience treating patients with any type of hepatic impairment is extremely limited. One hepatic impairment study was conducted including 8 patients with mild and 8 patients with moderate hepatic impairment (study 491-102). Steady-state total exposures to TAK-536 were approximately 28% and 64% greater in subjects with mild and moderate hepatic impairment, respectively. Steady-state total exposures to TAK-536 M-II were 27% and 36% greater respectively. Since the individual values for the Child-Pugh scores were not recorded in the CRF, it was not possible to assess properly whether the study population was appropriate. This deficiency does not call for a new study, however caution is needed and a starting dose of 20 mg could be considered in subjects with mild and moderate hepatic impairment. The PK of unbound TAK-536 and its metabolites (M-I and M-II) were similar to the PK of total drug concentrations in subjects with hepatic impairment.

Azilsartan medoxomil has not been studied in patients with severe hepatic impairment and therefore its use is not recommended in this patient group as reflected in the SmPC.

Gender and race

No clinically meaningful differences in exposure to TAK-536 related to gender, race (white versus black) were observed (study 491-003).

In the population PK study (study 491CLD_302) age was identified as a significant covariate. The magnitude of the effects resulting in variability of exposure to TAK-536 of ±20% is considered not clinically relevant.

There are insufficient data to provide a specific analysis for the comparison between the White and Asian population after administration of the TAK-491 tablet. Instead data from study 536-EC101 were compared with data from study 536-CPH-00. In both studies TAK-536 tablets were administered. No differences between the White and Asian subjects observed. The use of the studies with the TAK-536 tablet is properly justified.

Weight

In the population PK study (study 491CLD_302) weight was identified as a significant covariate. The magnitude of the effects resulting in variability of exposure to TAK-536 of ± 20% is considered not clinically relevant.

Elderly population

The mean age of the elderly subjects was 68.7 ± 4.77 years. No clinically meaningful differences in exposure to TAK-536 related to age (<45 years of age vs ≥ 65 years of age) were observed. In the SmPC is mentioned that a starting dose of 20 mg can be considered in the very elderly (≥ 75 years). Although sparse pharmacokinetic data are available for this age group this advice is acceptable based on clinical experience.

Paediatric population

The use of TAK-491 was not evaluated in children. The absence of data in children is acceptable as the application concerns use in the adult population only.

Pharmacokinetic interaction studies

In vitro studies

The potential of TAK-491 and TAK-536 to induce CYP3A is low. The potential of TAK-491 to inhibit cytochrome P450 was investigated for the most relevant CYP enzymes (CYP1A2, CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1) and TAK-536 has been evaluated (CYP2C8, CYP2C9) in vitro using human liver microsomes and B-lymphoblastoid-derived microsomes. From these *in vitro* studies it can be concluded that CYP2C9 and CYP2C8 might be relevant for drug-drug interactions.

The permeability and involvement of Pgp has been investigated sufficiently. The permeability of TAK-491 and TAK-536 is low and TAK-491 had an inhibitory effect on Pgp-mediated efflux activity *in vitro*.

In vivo studies with TAK-491

Following co-administration of TAK491 with an aluminium-magnesium hydroxide antacid (study TAK-491_107) a decreased exposure to TAK-536 of 18% was observed. This decrease is not clinically meaningful. In population PK data study 491CLD-302 the co-administration of TAK491 with Proton Pump Inhibitors (PPIs) was evaluated. The study shows that the median exposure to TAK-536 in subjects who received concomitant PPIs is comparable with the median exposure in subjects who did not receive concomitant PPIs.

Concomitant administration of TAK-491 with either chlorthalidone, amlodipine or digoxine had no clinically significant effect on the pharmacokinetics of TAK-491 or the respective medicinal product.

The interaction between TAK 491 and multiple cytochrome P450CYP probes was investigated. A cocktail of midazolam (3A4), caffeine (1A2), tolbutamide (2C9), dextromethorphan (2D6), and

fexofenadine (PgP-probe) was administered, following multiple dose administration of TAK 491. Co-administration of TAK491 and the drug combination did not have a clinically relevant effect on any of the tested cytochrome P450 probes, the exposure to the P-glycoprotein (PgP) probe was slightly decreased (by 16%). Probably this interaction is not clinically relevant, as no interaction with digoxin was observed in study TAK-491_104.

Two additional *in vitro* studies were submitted during the evaluation which addressed TAK-536's effect on pravastatin and atorvastatin uptake by OATP1B1. No inhibition of the uptake by TAK-536 was seen in these studies. Cyclosporine A was used as a positive control in a concentration of 1 µmol/L and 10 µmol/L, and inhibited the uptake of both substrates significantly (27% and 19% respectively). Other sartans have been shown to be substrates for the OATP transporters, therefore a potential interaction with statins could be of clinical interest. No inhibition of pravastatin or atorvastatin uptake occurred in cryopreserved human hepatocytes. Cyclosporine A is a non-specific inhibitor of several SLC transporters. No specific blocking of other transporters was used in this study. Statins are also substrates of OATP1B3. Hence, results from these studies can be extrapolated to other transporters and it can be concluded that no interaction between azilsartan and statins is expected via uptake transporters.

Thus, *in vitro* study did not suggest that azilsartan inhibits an uptake of statins and no further *in vivo* study is needed. The CHMP considered that the interaction potential has been studied sufficiently.

No drug interaction studies were conducted between TAK-491 or TAK-536 and lithium, non-steroidal anti-inflammatory drugs (NSAIDs), or potassium-sparing diuretics because clinical evidence already informs the potential risks associated with concomitant administration of these drugs and other drugs in the same class as TAK-491. Literature references were provided and this was considered acceptable. The extrapolation of literature data on the interaction of other ARBs with lithium, non-steroidal anti-inflammatory drugs (NSAIDs) and potassium-sparing diuretics can be accepted.

In vivo studies with TAK-536

Additionally, several studies were conducted with TAK-536 the active metabolite. Most of the drug-drug interaction studies conducted with TAK-536 can be extrapolated to TAK-491.

In study 536-006, no interaction between TAK-536 and the CYP2C8 substrate pioglitazone was observed. Negligible inhibition of CYP2C8 activity was observed in *in vitro* studies with TAK-536. However, *in vitro* tests suggest that TAK-491 has a potential for drug-drug interactions with CYP2C8 substrates. As TAK-491 appears to be hydrolysed pre-systematically to TAK-536 entirely and CYP2C8's expression in the GI tract is very small, no first pass interaction is expected. No new drug interaction study with TAK-491 and pioglitazone is therefore required.

In study TAK-536_004 the same drug combination as in study TAK-491_013 was administered. Co-administration of TAK-536 and the drug combination did not have a clinically relevant effect on any of the tested cytochrome P450 probes, but also the exposure to the P-glycoprotein (PgP) probe was also not affected. The results of this support the findings of study TAK-491_013.

Co-administration of the CYP2C9 inhibitor fluconazole and TAK-536 (study TL-536-005) resulted in a 42% increase in TAK-536 $AUC_{(0\text{-inf})}$, a 14% increase in TAK-536 C_{max}, and a 48% increase in $XU_{(0\text{-}24)}$ (total estimated amount of analyte in the urine collected over a 24 h postdose period divided by the ytotal volume of urine collected) relative to administration of TAK-536 alone. Plasma clearance of TAK-536 was reduced with co-administration (0.87 L/hr versus 1.25 L/hr), but renal clearance was not (0.17 L/hr versus 0.16 L/hr) affected, furthermore, $T_{1/2}$ and T_{max} were not affected.

Co-administration of the CYP 3A4 inhibitor ketoconazole and TAK-536 (study TL-536-005) did not result in an increase of exposure of TAK-536 as expected, but resulted in a decrease in TAK-536 $AUC_{0\text{-}}$

$_{inf}$ (by 21%), C_{max} (by 32%) and urinary excretion (by 17%) and delayed Tmax values (3.21 vs 2.06 hr). Neither plasma clearance nor renal clearance nor $T_{1/2}$ of TAK-536 was affected. This is possibly due to reduced absorption of TAK-536 by ketoconazole.

Co-administration of TAK-536 and metformin (study TL-536-011) did not significantly alter the steady-state concentrations of plasma TAK-536 and M-I or the respective medicinal product.

In study 536-009 the drug-drug interaction of TAK-536 and warfarin was evaluated. Warfarin is used as a probe for CYP2C9 (*(S)*-warfarin) and CYP1A2 (*(R)*-warfarin) Multiple doses of TAK-536 did not affect the steady-state pharmacokinetics and pharmacodynamics of warfarin.

The pharmacokinetic profile of glyburide (CYP2C9 probe) was not affected by multiple-dose administration of TAK-536 (study TL-536-010).

2.4.3 Pharmacodynamics

The following studies were performed to assess the antagonistic properties of azilsartan on the AT1 receptor influencing the RAAS system.

Table 4. Phase I PD studies

CSR	Study Objective
Pharmacodynamics	
491-001	Effects on aldosterone, renin, AI and AII (single dose)
491-002	Effects on aldosterone, renin, AI and AII (single and multiple dose)
536-GHBA-328	Pressor effects of the active moiety, TAK-536

Mechanism of action

TAK-536, the active metabolite of TAK-491, is an AT1 receptor blocker that influences the RAAS system. Compensatory hormonal profile is consistent with blockade of AT1 receptors which means increase of plasma renin activity and angiotensin I (AI) and angiotensin II (AII) concentrations and reduction of aldosterone concentrations. The RAAS blockade is known to be associated with reduction in blood pressure with a relative shallow dose-response curve.

Primary and Secondary pharmacology

Primary pharmacology

The effects of the TAK-491 capsule in both fed and fasted conditions, and the effects of the TAK-536 tablet on the pharmacodynamic markers (renin activity and concentrations of aldosterone, angiotensin I and II in the plasma) in study 491-001 were consistent with antagonism of the AT1 receptor. The single-dose pharmacodynamics of TAK-491 capsules under fasted and fed conditions were also examined in 2 double-blind, randomized, placebo-controlled, ascending-dose studies in Japan in which subjects received single doses of TAK-491 that ranged from 0.5 to 160 mg and in 3 double-blind, randomized, placebo-controlled ascending-dose studies in which subjects received single doses of TAK-536 that ranged from 0.3 to 80 mg.

The multiple-dose pharmacodynamics of TAK-491 were examined in subjects who received TAK-491 60, 80, or 160 mg capsules in a randomized, double-blind, placebo-controlled, sequential-panel, ascending-dose study. A dose-response was observed for the pharmacodynamic markers on Day 10 (compared with Day 1), which indicates a cumulative effect of multiple dosing with TAK-491.

In general, the blocking of the AT1 receptor by azilsartan demonstrates the hormonal compensatory mechanism to be expected.

Secondary pharmacology

A clear inhibition of blood pressure increases following angiotensin II injection (vasoconstrictor) was demonstrated in study 536-GHBA-328 in which subjects received IV infusions of angiotensin II before oral doses of placebo or TAK-536 (0.3 to 20 mg). These doses correspond approximately to a TAK-491 tablet dose of 0.5 to 32 mg. The data presented suggest that the vasoconstrictive effect of angiotensin II is dose-dependently blocked at the site of the AT1 receptor. But higher dosages than the 20 mg dose and comparison with other ARBs have not been made. During the evaluation, some additional data were provided indicating a sustained receptor antagonist binding of the TAK-536 in comparison to other AT1 antagonists. One argument put forward was that this tight receptor binding translated into long-lasting antihypertensive effects. A long-lasting antihypertensive effect would also be expected to translate into sustained 24 h antihypertensive effect, in addition to a more potent BP lowering compared to other AT1 antagonists. However, the 24 h antihypertensive effect was not better than for olmesartan (expressed as trough to peak ratio). Also pharmacokinetics properties of azilsartan are not very different from that of olmesartan ($T_{1/2}$ of approximately 10 hours). Thus the more potent effect of azilsartan may primarily be explained by the sustained receptor binding. As also discussed in the non-clinical part, results of indirect kinetic experiments clearly show that azilsartan slowly dissociates from the AT1 receptor and that this dissociation is significantly slower compared to the other ARBs tested. In addition the inverse agonism may contribute as well.

No specific studies have been performed to evaluate pharmacodynamic interactions and for genetically differences in PD response.

Thorough QT/TQc study

In study 491-007 the effect of TAK-491 320 mg on the QTc interval was investigated. This thorough QT/QTc study was a 3 period crossover study. A single dose of TAK-491 320 mg was administered as test therapy and placebo and moxifloxacin 400mg were administered as reference therapy. The pharmacokinetic parameters of TAK-536 and its metabolites were characterized and electrocardiograms (ECGs) were used for QTc assessment. The mean differences between TAK-491 320 mg and placebo for all QTc intervals (QTcF, QTcB, and QTcI) did not exceed 10 ms at any time point. TAK-491 320 mg did not prolong QTc intervals and was well-tolerated in healthy subjects.

2.4.4 Discussion on clinical pharmacology

The clinical pharmacology programme for TAK-491 consisted of a limited number of studies with TAK-491 tablet. Several supportive studies were conducted with TAK-536 formulations. In general the pharmacokinetics of TAK-536 and its metabolites after administration of TAK-491 was sufficiently characterised. The pharmacokinetics in subjects with renal impairment has been sufficiently investigated. Caution is needed in patients with severe renal impairment and ESRD. In subjects with mild and moderate hepatic impairment a starting dose of 20 mg could be considered. The pharmacokinetics of TAK-491 tablets has not been evaluated in subjects with severe hepatic impairment. The effects of age, gender and weight have been sufficiently investigated. The effect of race has been investigated. For the white versus the black population the data showed sufficiently that the differences in pharmacokinetics are not clinically relevant.

A dose dependent modulation of the components of the RAAS was demonstrated with an increase in renin, angiotensin I and angiotensin II and a decrease in aldosterone, as can be expected from an ARB. In multiple dosing these effects were less pronounced. A dose dependent inhibition of blood

pressure was demonstrated by blocking the vasoconstrictory effect of angiotensin II at the site of the AT1 receptor. Higher dosages than the 20 mg dose have not been tested. Although this proposed mechanism could translate into a stronger longer lasting antihypertensive effect, clinical data in terms of 24 hour antihypertensive effect (expressed as through to peak ratio) show similar efficacy between azilsartan and olmesartan.

2.4.5 Conclusions on clinical pharmacology

The non-clinical and clinical data submitted together with the experience with TAK-491 and TAK-536 are considered adequate to support the marketing authorisation and use of azilsartan medoxomil.

2.5 Clinical efficacy

2.5.1 Dose response studies

Dose selection for the phase 3 clinical programme was based primarily on the results of two pivotal dose response trials. In addition, 3 supportive trials were conducted. The primary endpoint was clinical diastolic blood pressure.

Table 5. Pivotal phase II dose ranging trials

Study Design and Study Number (Regions)	Population Planned Sample Size	Duration of Double-blind Treatment Dose/Regimen	Endpoints
TAK-536 (Tablets) vs Placebo and Olmesartan Medoxomil 536-002 (US, Lat Am) 7-arm Placebo-controlled Active-controlled	Clinical DBP 95-114 mm Hg N=525 (75/group)	**8 weeks** TAK-536 2.5 mg TAK-536 5 mg TAK-536 10 mg TAK-536 20 mg TAK-536 40 mg OLM-M 20 mg Placebo	Clinical DBP
TAK-491 (Capsules) vs Placebo and Olmesartan Medoxomil 491-005 (US, Lat Am) 7-arm Placebo-controlled Active-controlled	Clinical DBP 95-114 mm Hg N=420 (60/group)	**8 weeks** 1. TAK-491 5 mg 2. TAK-491 10 mg 3. TAK-491 20 mg 4. TAK-491 40 mg 5. TAK-491 80 mg 6. OLM-M 20 mg 7. Placebo	Clinical DBP

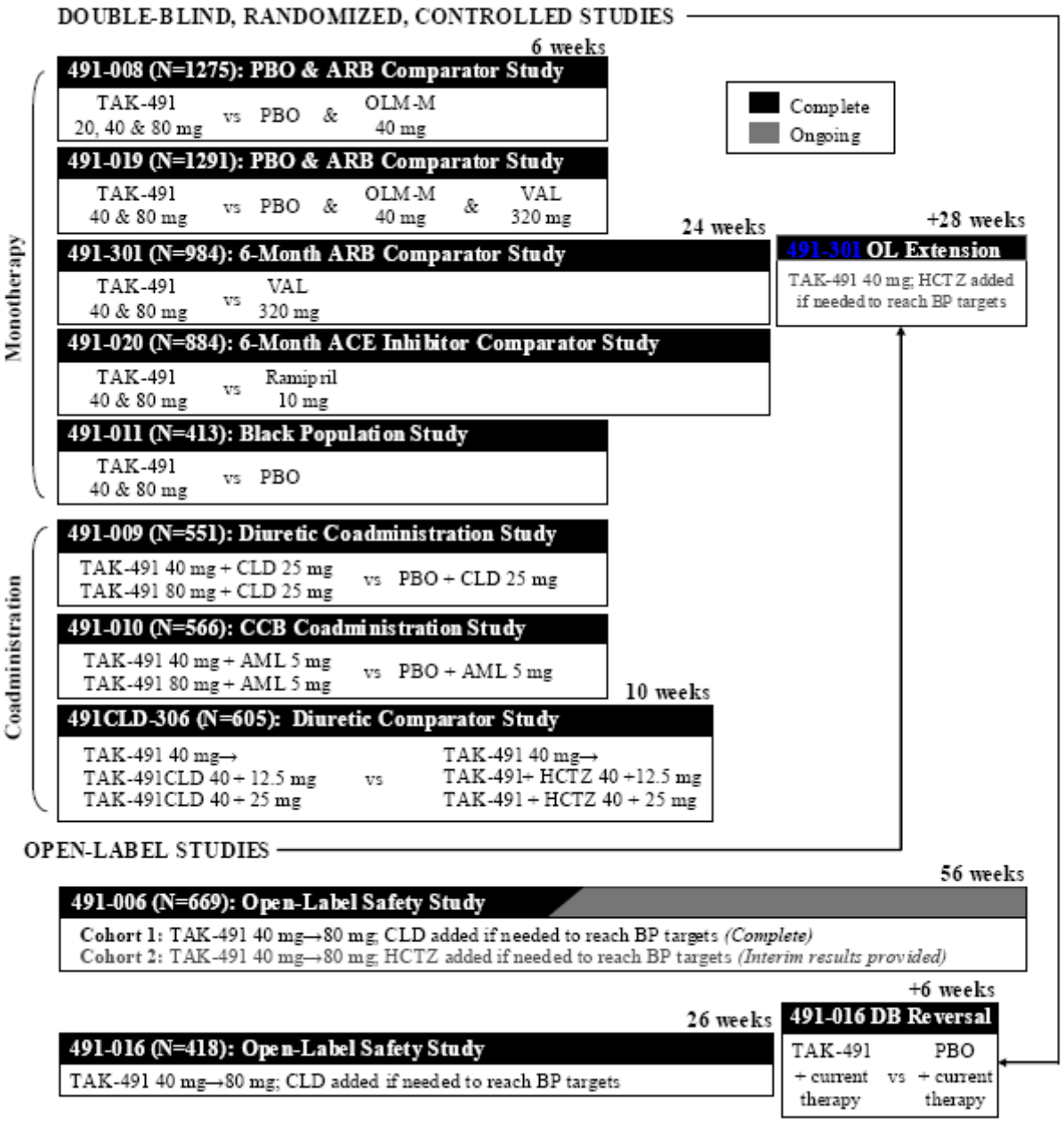
Study 536-002 was a placebo and active-controlled dose-ranging study conducted with TAK-536 tablets 2.5 mg, 5 mg, 10 mg, 20 mg, or 40 mg once daily (approximately corresponds to TAK-491 5 to 80 mg). The active comparator was olmesartan medoxomil 20 mg once daily. Eligible subjects were randomized to 8 weeks of daily treatment after the washout/run-in period. The primary endpoint was clinical DBP. A total of 574 subjects were randomized. The 5 to 40 mg doses of TAK-536 were each associated with statistical significant reductions in both endpoints relative to placebo, and greater reductions were observed with increasing dose: PLB (-6.7, -5.9), TAK-539 2.5 mg (-9.5, -12.5), 5 mg (-10.2, -12.3), 10 mg (-12.0, -14.2), 20 mg (-12.4, -17.5), 40 mg (-14.4, -17.5) and olmesartan 20 mg (-10.1, -12.4).

Study 491-005 was a placebo and active-controlled dose-ranging study conducted with a capsule formulation of TAK-491 at doses of 5 to 80 mg. The active comparator was olmesartan medoxomil 20 mg once daily. The primary endpoint was clinical DBP. Clinical SBP and ABPM parameters of DBP and SBP were secondary endpoints. A total of 449 subjects were randomized (63 to 65 per group). Reduction in DBP and SBP (mmHg) demonstrated the following results: PLB (-7.9, -4.9), TAK-491 5 mg (-10.8, -11.0), 10 mg (-13.1, -15.7), 20 mg (-11.5, -14.7), 40 mg (-13.6, -17.1), 80 mg (-11.6, -13.3) and olmesartan 20 mg (-11.0, -13.5). It was later observed that the tablet formulation of TAK-491 has a more favourable pharmacokinetic profile compared with the capsule (i.e. the tablet has

greater bioavailability and no food effect). As a result, the TAK-491 tablet was administered in subsequent phase 3 studies and is the formulation proposed for commercialisation.

2.5.2 Main studies

Figure 2. Overview of clinical phase III studies



General issues applying to all studies

Methods

Study participants

For inclusion in the studies patients had to fulfil all of the following criteria:

- All double-blind, randomized, controlled monotherapy studies included adult subjects 18 years of age or older with uncomplicated, mild to moderate essential hypertension. Subjects could have been naïve to treatment or previously treated with antihypertensive agents.
- All subjects in the monotherapy placebo and active-controlled studies were required to have a baseline clinical SBP ≥ 150 and ≤ 180 mm Hg and a 24-hour mean SBP ≥130 and ≤170 mm Hg (the latter criterion was not required in study 491-020 as clinical SBP was the primary endpoint of this study).
- In the controlled co-administration studies, subjects were required to have moderate-to-severe essential hypertension, as defined by a baseline clinical SBP ≥ 160 and ≤ 190 mm Hg and a 24-hour mean SBP ≥ 140 and ≤ 180 mm Hg, except FDC study 491CLD-306, where inclusion criteria were based on clinic measures only. Subjects with baseline DBP > 119 mm Hg were excluded.
- Subjects with baseline DBP > 114 mm Hg were excluded.
- In the co-administration studies and active-controlled monotherapy studies without a placebo control, subjects with a history of a cardiovascular event may have been enrolled at the investigator's discretion if the event was distant (> 24 weeks), thereby allowing a reasonable number of higher risk subjects to be enrolled for evaluation across the TAK-491 monotherapy phase 3 programme.

The most important criteria for exclusion from the studies were the following:

- Subjects with a history of a major cardiovascular event or condition (myocardial infarction, unstable angina, heart failure, coronary intervention, hypertensive encephalopathy, cardiovascular accident, or transient ischemic attack) were excluded from all placebo-controlled studies to avoid extended exposure to placebo in these subjects.
- Subjects with history of severe renal disease (calculated glomerular filtration rate [GFR] <30 mL/min/1.73 m2) were excluded from all studies.
- Subjects with known or suspected unilateral or bilateral renal artery stenosis were also excluded.
- Subjects with hyperkalemia.
- Subjects with hypokalemia, were excluded from the chlorthalidone coadministration study 491-009 and FDC study 491CLD-306.
- In controlled studies, subjects receiving other medication classes known to have blood pressure-altering effects were excluded. These medications included other antihypertensive agents, including those prescribed for indications other than hypertension (secondary cardiovascular prevention, related coronary heart disease, benign prostatic hypertrophy, etc).
- Subjects with controlled type 2 diabetes were allowed to enroll in all studies, although use of insulin or thiazolidinediones was prohibited.

- Due to their potential to possibly alter blood pressure, other prohibited medications included tricyclic antidepressants, monoamine oxidase inhibitors, atypical antipsychotics, diet medications, amphetamines, and systemic corticosteroids. Chronic use of common cold medications or nonsteroidal antiinflammatory drugs (NSAIDS) (including high-dose aspirin [>325 mg/day] or cyclooxygenase 2 inhibitors) was also prohibited.

Inclusion and exclusion criteria were considered appropriate although these inclusion criteria lead to recruitment of a rather homogenous population of primarily mild-to-moderate essential hypertension with little comorbidity. This does not seem however to be too different to other recently approved antihypertensives i.e. aliskiren.

Treatments

The randomized, double-blind, controlled, phase 3 studies and the FDC study incorporated a 3 to 4 week washout period for subjects who were previously receiving antihypertensive therapy. These subjects discontinued their previous treatments at screening and remained untreated during the washout, thereby allowing for establishment of a treatment-free baseline blood pressure. All subjects, including subjects who were naïve to treatment, also participated in a 2-week single-blind placebo run-in period. For subjects who were receiving previous antihypertensive treatments, the run-in period coincided with the last 2 weeks of the washout. The purpose of the placebo run-in period was to reduce the influence of placebo effect on the baseline blood pressure measurement. Baseline blood pressures were recorded after completion of the washout/run-in period and before initiation of double-blind study drug. Incorporation of the placebo run-in period also allowed for evaluation of each subject's compliance with the dosing regimen. Subjects who were noncompliant with single-blind placebo (<70% or >130%) were not randomized.

Specific study design are described for each study separately or pooled studies of similar design

The washout period used is considered sufficiently long to exclude a carry-over effect. In addition, suitable measures are taken to exclude patients who may be already initially non compliant.

Outcomes/endpoints

The primary efficacy endpoint was:

- 24-hour mean SBP was chosen as the primary endpoint in the majority of studies, except for studies 491-020 and 491CLD-306.

According to the applicant this was done due to azilsartan medoxomil's improved sensitivity relative to clinic blood pressure in terms of predicting cardiovascular outcomes in observational trials and in accordance with the CHMP Guideline on clinical investigation of medicinal products in the treatment of hypertension.

The following secondary efficacy endpoints were analysed in the order presented using a hierarchical procedure:

- Clinical SBP was identified as the key secondary endpoint in the TAK-491 monotherapy programme in recognition of its importance and widespread use in the traditional evaluation of antihypertensive therapies.
- 24-hour mean DBP by ABPM.
- Clinical DBP (sitting, trough).

- Other ABPM parameters of SBP and DBP: Daytime (6 AM-10 PM), nighttime (12 AM-6 AM), the 0 to 12 hour interval after dosing, and trough (the 22-24 hour interval after dosing).
- Proportion of responders based on the 3 following categories:
    - SBP responders: Subjects with a reduction in clinical SBP to <140 mm Hg and/or a ≥20 mm Hg decrease from Baseline.
    - SBP responders: Subjects with a reduction in clinical DBP to <90 mm Hg and/or a ≥10 mm Hg decrease from Baseline.
    - Joint SBP and DBP responders: Subjects with blood pressure reductions meeting both criterion for SBP and DBP.
    - Trough-to-peak ratios and placebo-corrected trough-to-peak ratios were also calculated based on ABPM data. As described above, the trough interval was defined as the last 2 hours of the 24-hour dosing interval; the peak effect interval was the 2-hour interval in which the maximum decrease from Baseline was observed.

The decision for a 24 hour ABPM systolic blood pressure as primary endpoint is considered appropriate based on the CHMP Guideline on clinical investigation of medicinal products in the treatment of hypertension as it provides a better insight into blood pressure changes during everyday activities and is strongly recommended for the evaluation of new antihypertensive agents. However, the guideline also states that there is still insufficient evidence to accept ABPM as the sole basis of efficacy. Therefore, the CHMP agreed with the choice of clinical SBP at trough as the major secondary endpoint to comply with the current view of the guideline. The proportion of responders is also considered an important endpoint. Furthermore, trough-to-peak ratio is considered important in relation to 24 hour maintenance of blood pressure lowering capacity.

Randomisation

All controlled, phase 3 monotherapy efficacy studies and FDC study TAK-491CLD-306 incorporated a randomized, double-blind study design. In each study (except for 491-020 and 491-011), randomization was stratified by race (Black and non-Black) to ensure equal representation of Black subjects across treatment groups. Enrollment in study 491-020 was stratified by region (Europe and Russia). Study 491-011 enrolled a Black population only.

Randomization personnel of the applicant or designee generated the randomization schedule. All randomization information was stored in a secure area, accessible only by authorized personnel.

General randomisation and stratification for Black or non Black race is considered appropriate. General randomisation procedures are considered appropriate.

Blinding (masking)

The following procedures applied to all randomization studies. The study medication blind was maintained using the IVRS, which was accessed by the study sites for randomization number and study medication assignments. The study medication blind was not to be broken by the investigator unless information concerning the study medication was necessary for the medical treatment of the subject. If possible, the applicant was to be notified before the study medication blind was broken. If a medical emergency requiring unblinding occurred, the investigator or designee at the site was to contact the applicant to assess the necessity to break the study medication blind. The study medication blind could have been obtained by authorized personnel accessing the IVRS.

If the investigator was unblinded, study medication was to be stopped immediately and the subject was to be withdrawn from the study.

The standard procedure used for assuring blinding of study medication and patients was sufficiently secured.

Statistical methods

The primary analyses of 24-hour mean and clinical SBP were based on the FAS. For endpoints evaluated at multiple post-baseline time points, missing data were imputed using the last observation carried forward (LOCF) principle. Only post-baseline data were carried forward.

The primary analysis model was an analysis of covariance (ANCOVA) with treatment as fixed effect and Baseline as covariate. The following statistics were provided: the least squares (LS) mean change from Baseline, LS mean treatment difference for the change from Baseline (i.e. TAK-491 – comparator), and the 95% confidence interval and P-value for the LS mean treatment difference. All tests were conducted as 2-sided and assessed at the 0.05 significance level.

All analyses of other secondary endpoints that were continuous variables used an ANCOVA model similar to that used for the primary and key secondary endpoints. A logistic model with treatment as fixed effect and baseline clinical SBP as a covariate was used to analyze the response criteria for clinical SBP. The odds ratio and its 95% confidence interval (CI) were estimated. A similar logistic model was used to analyze the response criteria for clinical DBP and the joint response criteria for both clinical SBP and DBP.

Studies 491-008, 491-019, 491-020, and 491-301 incorporated step-wise testing procedures to control for type 1 error in the setting of multiple comparisons for the analyses of the primary and key secondary endpoints. Within the framework of the stepwise analysis each dose of TAK-491 (highest to lowest) was compared with placebo first (when applicable). Then, if all TAK-491 doses were found to be superior to placebo, TAK-491 was assessed for non-inferiority and superiority with active comparator(s). The testing sequence proceeded until the condition of a given step was not met. Type 1 error was controlled separately for the analyses of 24-hour SBP and clinical SBP. A stepwise testing procedure was also used to control for type 1 error for the analysis of the primary efficacy endpoint (change from Baseline to Weeks 6 and 10 in clinical SBP) in FDC study 491CLD-306.

In studies 491-009, 491-010, and 491-011, type 1 error was controlled via closed testing. Under this principle, if the hypothesis that "all treatment groups are equal" was rejected at the 0.05 level (ie, the overall P-value <0.05), then the pairwise comparisons proceeded with no P-value adjustments.

No adjustments for multiple comparisons were made in the analyses of the other secondary endpoints or in the subgroup analyses of any endpoint; therefore, nominal P-values are presented for these analyses.

The statistical methods used are considered acceptable. They allow step-wise comparison of efficacy of azilsartan medoxomil versus placebo and active-comparator without the need for inflating the sample size unacceptably because of repetitive testing. The statistical programme does not foresee an evaluation of the dose response – or differential effect between azilsartan medoxomil doses used.

Specific issues applying to studies 491-008 and 491-019: short-term efficacy studies versus placebo

Study 491-008 is a multicenter, double-blind, randomized, placebo and active-controlled, parallel-group study with the primary objective to evaluate the antihypertensive effect of TAK-491 compared to placebo and olmesartan medoxomil (olmesartan) in adults after 6 weeks of treatment. This was the only Phase 3 study to address the 20mg dose.

Study 491-019 is a multicenter, randomized, parallel-group, double-blind, placebo and active-controlled titration study with the primary objective to evaluate the antihypertensive effect of TAK-491 compared with placebo, olmesartan, and valsartan after 6 weeks of treatment.

Methods

Study participants

140 sites for study 491-008 and 131 sites for study 491-019 enrolled subjects in the United States and in Latin America.

Treatments

The total duration of study 491-008 was approximately 11 weeks, including up to 14 days of screening, followed by a 14-day (minimum 10-day) single-blind placebo Run-in Period, a 6-week double-blind treatment Period, and a safety follow-up telephone call at 1 week after last dose of study drug.

After a 2-week run-in period of single-blind placebo, subjects who met the entry criteria for study 491-019 were randomized to receive TAK-491 20 mg, TAK-491 40 mg, valsartan 160 mg, olmesartan 20 mg, or placebo for 2 weeks. At the end of 2 weeks, subjects were force-titrated to the higher dose: TAK-491 40 mg or 80 mg, valsartan 320 mg, olmesartan 40 mg, or remained on placebo, respectively. Subjects remained at the higher dosage for the remainder of the study. ABPM occurred on Day -1 for 24 hours prior to the first dose of double-blind study medication and at Week 6 or Early Termination for 24 hours following the last administration of study medication. Clinical DBP and SBP were measured at screening, randomization, Week 2, Week 4, and Week 6.

Objectives

The primary objective of study 491-008 was to evaluate the antihypertensive effect of TAK-491 compared with placebo and olmesartan after 6 weeks of treatment.

The primary objective of study 491-019 was to evaluate the antihypertensive effect of TAK-491 compared with placebo, olmesartan, and valsartan after 6 weeks of treatment.

Sample size

For study 491-008, assuming an SD of 13 mm Hg for mean change from Baseline in 24-hour mean SBP by ABPM and a 15% dropout rate, a total of approximately 1260 enrolled subjects (280 per TAK-491 and olmesartan treatment groups and 140 for placebo treatment group) was calculated to be sufficient for achieving at least 90% power to detect a difference of 5.5 mm Hg between the active treatment groups and placebo with a 2-sided significance level of 5%.

For study 491-019, a total of 1305 enrolled subjects (290 per TAK-491, valsartan, and olmesartan treatment groups, and 145 for placebo treatment group) were needed. This sample size also provided approximately 90% power to detect a difference of 4 mm Hg between TAK-491 and olmesartan by a 2-sample t-test of the mean change from Baseline in 24-hour mean SBP by ABPM with a 2-sided significance level of 5%.

Randomisation

Randomization was stratified by race (Black and non-Black) to ensure equal representation of Black subjects across treatment groups. Randomization personnel of the applicant or designee generated the randomization schedule. All randomization information was stored in a secure area, accessible only by authorized personnel.

Blinding (masking)

For study 491-008, the study medication consisted of 3 tablets (TAK-491 and matching placebo for the 3 treatment arms of TAK-491) and 1 capsule (olmesartan and matching placebo) and was identical in appearance because of the encapsulation of the olmesartan tablets with matching placebo capsules.

Statistical methods

Similar statistics were used for both trials. All statistical tests were 2-sided and results were presented with 95% confidence intervals (CIs) and P-values at the 5% significance level. To control the type 1 error in these multiple treatment group comparisons, a pre-specified sequential testing procedure of pair wise comparisons was applied to compare the 3 active treatment groups with placebo and with olmesartan in study 491-008. For the active comparisons pooled analyses, non-inferiority analyses were followed by superiority analyses. For both the placebo and active comparisons, TAK-491 80 mg was tested first followed by TAK-491 40 mg. Tests for superiority were conducted at the 0.05 significance level; the non-inferiority margin was the same as that applied to the individual studies (ie, 1.5 mm Hg). Type I error was controlled separately for 24-hour mean SBP and clinical SBP.

Results

Participant flow

Table 6. Disposition by individual Phase 3 pivotal studies

	Monotherapy Placebo-Controlled Studies									
	491-008					491-019				
	PBO	TAK-491			OLM	PBO	TAK-491		VAL	OLM
Discontinuation Reason	N=142	20 mg N=283	40 mg N=283	80 mg N=285	40 mg N=282	N=154	20→ 40 mg N=280	40→ 80 mg N=285	160→ 320 mg N=282	20→ 40 mg N=290
Overall	12 (8.5)	24 (8.5)	22 (7.8)	24 (8.4)	14 (5.0)	13 (8.4)	23 (8.2)	30 (10.5)	28 (9.9)	22 (7.6)
TEAE	5 (3.5)	11 (3.9)	3 (1.1)	6 (2.1)	4 (1.4)	4 (2.6)	7 (2.5)	9 (3.2)	8 (2.8)	6 (2.1)
Protocol deviation	3 (2.1)	1 (0.4)	1 (0.4)	2 (0.7)	0	1 (0.6)	3 (1.1)	2 (0.7)	2 (0.7)	0
Lost to follow-up	0	1 (0.4)	4 (1.4)	1 (0.4)	2 (0.7)	3 (1.9)	1 (0.4)	6 (2.1)	2 (0.7)	4 (1.4)
Voluntary withdrawal	0	4 (1.4)	8 (2.8)	6 (2.1)	1 (0.4)	1 (0.6)	4 (1.4)	11 (3.9)	5 (1.8)	7 (2.4)
Pregnancy	0	0	0	0	0	--	--	--	--	--
Lack of efficacy	3 (2.1)	1 (0.4)	5 (1.8)	4 (1.4)	5 (1.8)	4 (2.6)	3 (1.1)	1 (0.4)	5 (1.8)	2 (0.7)
Other (g)	1 (0.7)	6 (2.1)	1 (0.4)	5 (1.8)	2 (0.7)	0	5 (1.8)	1 (0.4)	6 (2.1)	3 (1.0)

Recruitment

Study 491-008 was conducted from 25 June 2007 until 08 October 2008. Study 491-019 was conducted from 02 April 2008 until 19 August 2009.

Conduct of the study

There were 2 amendments to the original protocol for study 491-008 and 3 for study 491-019 which were considered acceptable.

Baseline data

Table 7. Demographic and baseline characteristics by individual monotherapy placebo-controlled studies

	491-008					491-019				
	PBO	TAK-491			OLM	PBO	TAK-491		VAL	OLM
	N=142	20 mg N=283	40 mg N=283	80 mg N=285	40 mg N=282	N=154	20 mg→ 40 mg N=280	40 mg→ 80 mg N=285	160 mg→ 320 mg N=282	20 mg→ 40 mg N=290
Age (years)										
Mean	59.4	57.1	57.4	58.1	58.9	56.3	56.5	55.9	54.6	56.4
(SD)	(10.53)	(11.02)	(9.62)	(11.56)	(11.57)	(10.98)	(11.64)	(11.12)	(10.87)	(10.91)
Categories [n (%)]										
<45 years	11 (7.7)	32 (11.3)	29 (10.2)	37 (13.0)	32 (11.3)	20 (13.0)	41 (14.6)	38 (13.3)	56 (19.9)	39 (13.4)
45 to 64 years	84 (59.2)	173 (61.1)	187 (66.1)	161 (56.5)	153 (54.3)	98 (63.6)	170 (60.7)	184 (64.6)	178 (63.1)	185 (63.8)
≥65 years	47 (33.1)	78 (27.6)	67 (23.7)	87 (30.5)	97 (34.4)	36 (23.4)	69 (24.6)	63 (22.1)	48 (17.0)	66 (22.8)
Gender [n (%)]										
Male	76 (53.5)	133 (47.0)	142 (50.2)	149 (52.3)	140 (49.6)	90 (58.4)	147 (52.5)	151 (53.0)	152 (53.9)	159 (54.8)
Female	66 (46.5)	150 (53.0)	141 (49.8)	136 (47.7)	142 (50.4)	64 (41.6)	133 (47.5)	134 (47.0)	130 (46.1)	131 (45.2)
Race [n (%)]										
American Indian or Alaska Native	29 (20.4)	51 (18.0)	49 (17.3)	52 (18.2)	50 (17.7)	32 (20.8)	49 (17.5)	46 (16.1)	41 (14.5)	44 (15.2)
Asian	3 (2.1)	7 (2.5)	7 (2.5)	4 (1.4)	4 (1.4)	2 (1.3)	6 (2.1)	4 (1.4)	3 (1.1)	2 (0.7)
Black/African American	16 (11.3)	32 (11.3)	31 (11.0)	31 (10.9)	31 (11.0)	27 (17.5)	51 (18.2)	49 (17.2)	51 (18.1)	54 (18.6)

Native Hawaiian or Other Pacific Islander	0	0	0	0	0	1 (0.6)	1 (0.4)	0	0	3 (1.0)
White	103 (72.5)	202 (71.4)	205 (72.4)	209 (73.3)	209 (74.1)	96 (62.3)	177 (63.2)	190 (66.7)	189 (67.0)	191 (65.9)
Multiracial	9 (6.3)	10 (3.5)	9 (3.2)	10 (3.5)	11 (3.9)	4 (2.6)	4 (1.4)	4 (1.4)	2 (0.7)	4 (1.4)
Missing	0	1 (0.4)	0	0	0	0	0	0	0	0
BMI (kg/m^2)										
Median	29.1	29.6	29.6	29.0	28.7	29.62	30.75	29.80	30.54	30.37
Min, max	20, 46	19, 57	19, 53	20, 52	21, 51	20.1, 46.8	18.6, 51.8	14.4, 52.1	16.5, 50.0	20.4, 48.8

Numbers analysed

Table 8. Study 491-008

	Placebo (N=142)	TAK-491 20mg (N=283)	TAK-491 40mg (N=283)	TAK-491 80 mg (N=285)	Olmesartan 40 mg (N=282)	Total (N=1275)
Randomized But Not Treated	0	0	2 (0.7)	1 (0.4)	0	3 (0.2)
Safety Analysis Set	142 (100.0)	283 (100.0)	281 (99.3)	284 (99.6)	282 (100.0)	1272 (99.8)
Full Analysis Set	142 (100.0)	283 (100.0)	281 (99.3)	284 (99.6)	282 (100.0)	1272 (99.8)
Per-Protocol Set	121 (85.2)	257 (90.8)	249 (88.0)	258 (90.5)	251 (89.0)	1136 (89.1)

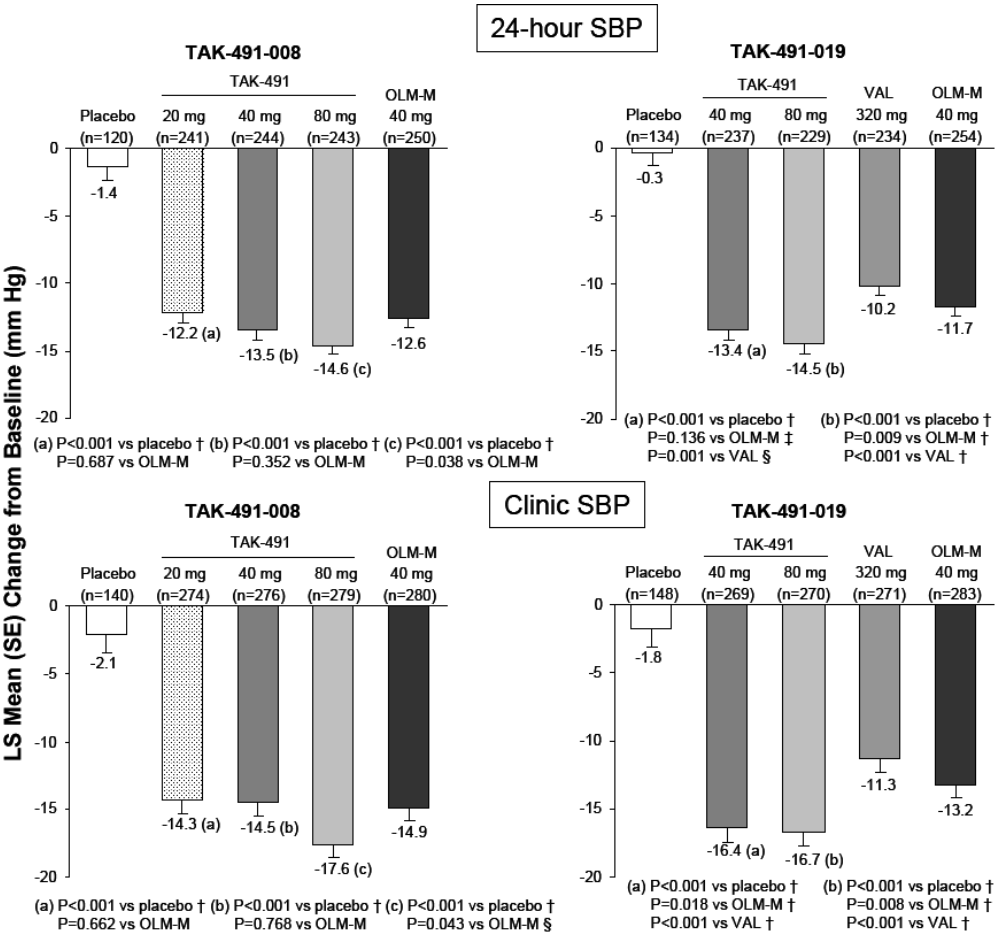
Table 9. Study 491-019

	Placebo	TAK-491 20 mg Titrated to 40 mg	TAK-491 40 mg Titrated to 80 mg	Valsartan 160 mg Titrated to 320 mg	Olmesartan 20 mg Titrate d to 40 mg	Total
Randomized	154	280	285	282	290	1291
Randomized But Not Treated	0	0	2 (0.7)	4 (1.4)	0	6 (0.5)
Full Analysis Set	154 (100.0)	280 (100.0)	283 (99.3)	278 (98.6)	290 (100.0)	1285 (99.5)
Per-Protocol Set	143 (92.9)	255 (91.1)	259 (90.9)	253 (89.7)	268 (92.4)	1178 (91.2)
Treated	155	280	284	277	290	1286
Treated But Not Randomized	0	0	1 (0.4)	0	0	1 (0.1)
Safety Analysis Set	155 (100.0)	280 (100.0)	284 (100.0)	277 (100.0)	290 (100.0)	1286 (100.0)

An ITT procedure was followed for both studies.

Outcomes and estimation

Figure 3. 24h mean reduction in SBP and clinical SBP at week 6 in studies 491-008 and 491-019



Responder rates

In the pooled analyses the responder rates for clinical SBP for placebo, TAK-491 40 mg, TAK-491 80 mg and olmesartan 40 mg were 57 of 288 (19.3%), 291 of 545 (51.9%), 314 of 549 (55.4%) and 287 of 572 (50.2%) respectively. Responder rates were significantly higher against placebo ($p<0.001$) for all treatment arms. Only the 80 mg dose azilsartan medoxomil responder rate was significantly higher ($p=0.035$) versus olmesartan responder rate.

Significant blood pressure reduction versus placebo was demonstrated. Only the highest dose was superior in BP reduction compared to olmesartan. Superiority could also be demonstrated versus valsartan for the 40 mg dose and the highest dose. A larger proportion of responders were observed for the highest dose based on the clinical SBP versus the comparator olmesartan. Maximum blood pressure was observed after 4 weeks of treatment, similar to olmesartan. A slightly better trough-to-peak ratio could be observed in study 491-008, however, in study 491-019 a slightly better ratio was observed for olmesartan. This indicates that 24 h blood pressure lowering efficacy maintenance was not better for azilsartan medoxomil than for olmesartan and was not based on azilsartan medoxomil's pharmacokinetic profile. An alternative explanation could be a better pharmacodynamic profile.

Ancillary analyses

Overall, subgroups demonstrated consistent efficacy across subgroups versus olmesartan. Olmesartan and azilsartan medoxomil are both ARBs which can be expected to have similar effects. In addition, the subgroup analyses versus placebo also showed consistent results except for the age group of >75 years of age and for the black population. It is expected that the black population would respond less due to less RAAS activation compared to a white population of patients. It would be informative to know how patients with additional CV risk factors responded to antihypertensive therapy.

Specific issues applying to studies 491-301 and 491-020: long-term efficacy studies versus comparators

Methods

Study 491-020 was a phase 3, multicenter, double-blind, randomized, parallel-group study in subjects with essential hypertension (sitting SBP between 150 and 180 mm Hg, inclusive). TAK-491 (40 or 80 mg) was compared versus ramipril 10 mg once daily during a 24-week treatment period; each treatment was force titrated from a low to high dose at week 2. After a 2-week run-in period of single blind placebo, eligible subjects were randomized to receive TAK-491 20 mg or ramipril 2.5 mg for 2 weeks. Forced titration to a higher dose occurred at Week 2: TAK-491 20mg was titrated to 40 or 80 mg and ramipril 2.5 mg was titrated to 10 mg. Subjects remained at the higher active treatment dose for the remaining 22 weeks of the study. Clinic blood pressure was measured at each visit. ABPM was performed on Day -1, before initiation of treatment, and at Week 24, although a qualifying baseline ABPM was not required.

Study 491-301 was a phase 3, multicenter, double-blind, randomized, parallel-group, active-controlled study to evaluate the efficacy and safety of TAK-491 compared to valsartan over a 6-month treatment period in subjects with essential hypertension (trough clinical sitting SBP ≥150 mm Hg and ≤180 mm Hg on Day -1 and 24-hour mean SBP ≥130 mm Hg and ≤170 mm Hg on Day 1). Subsequent to the 6-month double-blind treatment period, subjects could have continued in an optional 28-week open-label extension phase with TAK-491 to contribute to the long-term safety evaluation.

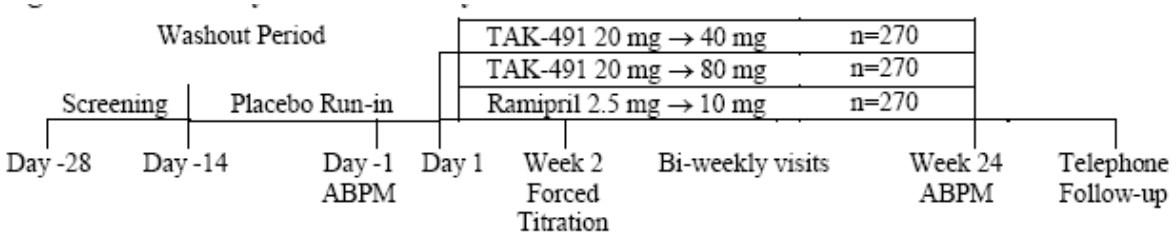
Study participants

For study 491-020, 101 sites enrolled subjects in Europe and in Russia. For study 491-301, 103 sites enrolled subjects into the placebo run-in period in the United States and in Latin America.

Treatments

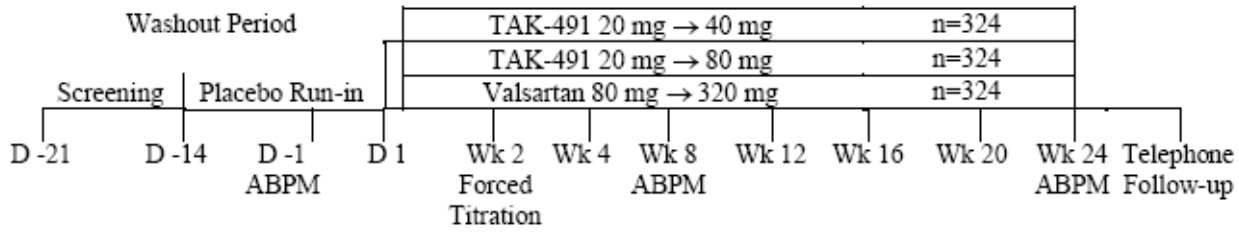
The total duration of study 491-020 was up to 32 weeks, including up to 28 days of screening (with washout for any antihypertensive medication, followed by a 14-day single-blind placebo run-in period, a 24-week double-blind treatment period, and a safety follow-up telephone call at 1 week after last dose of study drug.

Figure 4. Study 491-020



For study 491-301, after a 2-week run-in period of single-blind placebo, subjects who met the entry criteria were randomized to receive TAK-491 20 mg once daily (QD) force titrated to 40 mg QD after 2 weeks, TAK-491 20 mg QD force titrated to 80 mg QD after 2 weeks, or valsartan 80 mg QD force titrated to 320 mg QD after 2 weeks, with treatment for 6 months. ABPM occurred on Day -1 for 24 hours prior to the first dose of double-blind study medication, at Week 8, and at Week 24 or Early Termination for 24 hours following the last administration of double-blind study medication. Clinical DBP and SBP were measured at Screening (Day -21/-28, Day -14, Day -7, Day -1).

Figure 5. Study 491-301



Objectives

The primary objective for study 491-020 was to evaluate the change in clinical systolic blood pressure (SBP) in response to TAK-491 compared with ramipril for 6 months in subjects with essential hypertension.

The primary objective for study 491-301 was to evaluate the antihypertensive effect of TAK-491 compared with valsartan 320 mg after 6 months of treatment, as measured by the primary endpoint of change in 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM).

Sample size

For study 491-020 a minimum of 810 subjects were to be randomized (270 per treatment group) to achieve at least 90% power to detect a difference of 4.75 mm Hg between TAK-491 treatment groups and ramipril (with a 2-sided significance level of 5%) with the assumed standard deviation of 14.5 mmHg and 20% dropout rate. There was at least 90% power for demonstrating non-inferiority with a margin of 1.5 mm Hg between TAK-491 and ramipril on the mean change from baseline in SBP.

For study 491-30 a total of approximately 972 subjects were to be randomized (324 per treatment group) to achieve at least 90% power to detect a difference of 4.25 mm Hg between TAK-491 treatment groups and valsartan (with a 2-sided significance level of 5%) with the assumed standard deviation of 13 mmHg for mean change from baseline in 24-h mean SBP by ABPM and 30% dropout rate. There was at least 90% power for demonstrating non-inferiority with a margin of 1.5 mm Hg between TAK-491 and valsartan on both primary and key secondary efficacy endpoints.

Randomisation

Randomization was stratified by race (Black and non-Black) to ensure equal representation of Black subjects across treatment groups. Randomization personnel of the applicant or designee generated the randomization schedule. All randomization information was stored in a secure area, accessible only by authorized personnel.

Blinding (masking)

For study 491-020, the study medication consisted of 3 tablets (TAK-491 and matching placebo) and 1 capsule (ramipril and matching placebo) and was identical in appearance because of the encapsulation of the ramipril tablets with matching placebo capsules.

Statistical methods

Results

Participant flow

Table 8. Summary of disposition in pooled 491-301 and 491-020 studies.

	TAK-491 40 mg	TAK-491 80 mg	Active Comparator
Randomized Subjects	622	623	623
Discontinued Study	107 (17.2)	109 (17.5)	122 (19.6)
Adverse Event	28 (4.5)	35 (5.6)	31 (5.0)
Major Protocol Deviation	6 (1.0)	2 (0.3)	6 (1.0)
Lost to Follow-up	12 (1.9)	12 (1.9)	12 (1.9)
Voluntary Withdrawal	34 (5.5)	36 (5.8)	35 (5.6)
Pregnancy	1 (0.2)	0	1 (0.2)
Lack of Efficacy	19 (3.1)	11 (1.8)	29 (4.7)
Investigator's Discretion	1 (0.2)	1 (0.2)	1 (0.2)
Other	6 (1.0)	12 (1.9)	7 (1.1)

Recruitment

Study 491-020 was conducted from 24 January 2008 until 21 April 2009. Study 491-301 was conducted from 09 November 2007 until 03 September 2009 (double-blind phase) and from 04 March 2009 to 13 March 2010 (open-label extension phase).

Conduct of the study

Protocols were amended extensively for both studies and similar calculation errors as in previous studies of cGFR were observed and corrected. In study 491-020 there were 63 subjects with at least 1 major protocol deviation (excluding them from PPS analyses). In study 491-301 there were 108 (11.0%) subjects with at least 1 major protocol deviation (excluding them from PPS analyses). The most common major protocol deviations were receipt of prohibited medication (72 subjects), subjects that had a baseline 24-hour mean SBP <130 mm Hg (17 subjects), and study drug compliance <80% (10 subjects).

Baseline data

Table 9. Demographic and baseline characteristics by individual long-term active-controlled studies

	491-301(DB)			491-020		
	TAK-491		VAL	TAK-491		RAM
	20 mg→ 40 mg N=327	20 mg→ 80 mg N=329	80 mg→ 320 mg N=328	20 mg→ 40 mg N=295	20 mg→ 80 mg N=294	2.5 mg→ 10 mg N=295
Age (years)						
Mean	57.8	56.8	58.1	56.9	56.8	56.8
(SD)	(12.08)	(10.72)	(10.88)	(11.49)	(11.30)	(10.49)
Median	59.0	57.0	58.5	57.0	58.0	57.0
Min, max	18, 83	24, 79	24, 87	24, 83	22, 85	20, 86
Categories [n (%)]						
<45	43 (13.1)	39 (11.9)	31 (9.5)	40 (13.6)	45 (15.3)	30 (10.2)
45 to 64	181 (55.4)	208 (63.2)	199 (60.7)	166 (56.3)	168 (57.1)	195 (66.1)
≥65	103 (31.5)	82 (24.9)	98 (29.9)	89 (30.2)	81 (27.6)	70 (23.7)
Gender [n (%)]						
Male	164 (50.2)	169 (51.4)	176 (53.7)	159 (53.9)	158 (53.7)	146 (49.5)
Female	163 (49.8)	160 (48.6)	152 (46.3)	136 (46.1)	136 (46.3)	149 (50.5)
Race [n (%)]						
American Indian or Alaska Native	27 (8.3)	16 (4.9)	22 (6.7)	0	0	0
Asian	7 (2.1)	7 (2.1)	7 (2.1)	1 (0.3)	0	0
Black/African American	49 (15.0)	50 (15.2)	49 (14.9)	1 (0.3)	1 (0.3)	1 (0.3)
Native Hawaiian or Other Pacific Islander	0	1 (0.3)	1 (0.3)	0	0	0
White	247 (75.5)	256 (77.8)	251 (76.5)	293 (99.3)	293 (99.7)	294 (99.7)
Multiracial	3 (0.9)	1 (0.3)	1 (0.3)	0	0	0
BMI (kg/m^2)						
Median	30.12	30.14	30.01	29.1	29.1	29.0
Min, max	21.1, 57.8	19.7, 47.5	20.3, 52.9	20, 46	19, 42	20, 44

Although some slight differences between treatment groups is noted, in general, randomisation seems successful. Sufficient subjects older than 65 years are included. However, only limited numbers of patients of 75 years and older are included. Also the numbers of patients with diabetes included in the studies is limited.

Numbers analysed

Table 10. Study 491-020

	Treatment		
	TAK-491 40 mg N=295	TAK-491 80 mg N=294	Ramipril 10 mg N=296
	n (%)		
Randomized but not treated	1 (0.3)	1 (0.3)	3 (1.0)
FAS	294 (99.7)	293 (99.7)	292 (98.6)
Safety analysis set	294 (99.7)	293 (99.7)	293 (99.0)
PPS	269 (91.2)	273 (92.9)	274 (92.6)

Table 11. Study 491-301

	TAK-491 20 mg titrated to 40 mg QD (N=327)	TAK-491 20 mg titrated to 80 mg QD (N=329)	Valsartan 80 mg titrated to 320 mg QD (N=328)	Total (N=984)
Randomized But Not Treated	0 (0.0)	0 (0.0)	2 (0.6)	2 (0.2)
Safety Analysis Set	327 (100.0)	329 (100.0)	326 (99.4)	982 (99.8)
Full Analysis Set	327 (100.0)	329 (100.0)	326 (99.4)	982 (99.8)
Per-Protocol Set	290 (88.7)	295 (89.7)	289 (88.1)	874 (88.8)
Open Label (Subjects Who Received Study Drug)	55 (16.8)	60 (18.2)	55 (16.8)	170 (17.3)

Sufficient numbers of patients were analysed to comply with the power calculation.

Outcomes and estimation

Table 12. Pooled Analyses of Studies 491-301 and 491-020: Change in 24-Hour Mean and Clinical SBP and DBP at Week 24—TAK-491 vs Active Comparator

	TAK-491 40 mg N=621	TAK-491 80 mg N=622	Active Comparator N=619
24-Hour Mean SBP: LS Mean Change from Baseline at Week 24			
n	415	406	404
BL (SE)	143.48 (0.530)	142.71 (0.533)	143.21 (0.536)
Change from BL (SE)	-13.93 (0.605)	-14.07 (0.609)	-9.95 (0.613)
Difference vs AC (a)	-3.98	-4.12	--
(95% CI)	(-5.59, -2.38)	(-5.74, -2.51)	--
P-value vs AC	<0.001†	<0.001†	--
Clinical SBP (LOCF) : LS Mean Change from Baseline at Week 24			
n	606	593	606
BL (SE)	159.59 (0.467)	158.90 (0.471)	159.30 (0.467)
n	614	600	612
Change from BL at Week 24 (SE)	-17.17 (0.694)	-18.49 (0.700)	-11.42 (0.694)
Difference vs AC (a)	-5.76	-7.07	--
(95% CI)	(-7.62, -3.89)	(-8.94, -5.20)	--
P-value vs AC	<0.001†	<0.001†	--
24-Hour Mean DBP: LS Mean Change from Baseline at Week 24			
n	415	406	404
BL (SE)	87.24 (0.461)	87.40 (0.464)	87.21 (0.467)
Change from BL (SE)	-8.67 (0.397)	-9.10 (0.399)	-6.33 (0.402)
Difference vs AC (a)	-2.33	-2.76	--
(95% CI)	(-3.39, -1.28)	(-3.82, -1.70)	--
P-value vs AC	<0.001*	<0.001*	--
Clinical DBP (LOCF) : LS Mean Change from Baseline at Week 24			
n	606	593	606
BL (SE)	93.97 (0.409)	94.44 (0.412)	93.65 (0.409)
n	614	600	612
Change from BL at Week 24 (SE)	-8.14 (0.406)	-8.49 (0.410)	-4.31 (0.406)
Difference vs AC (a)	-3.82	-4.17	--
(95% CI)	(-4.91, -2.73)	(-5.27, -3.08)	--
P-value vs AC	<0.001*	<0.001*	--

Significant more systolic blood pressure reduction was demonstrated for both doses of azilsartan medoxomil 40 and 80 mg compared to valsartan and ramipril. These results were consistent with the reduction in diastolic blood pressure. Also responder rates demonstrated consistent results in this respect. However, only minor increments in BP lowering were observed with the 80mg compared to the 40 mg dose. The responder rate in clinical SBP for the 80 mg group was slightly higher.

Ancillary analyses

Consistent findings were observed for the blood pressure lowering according to subgroups. The only exception is less efficacy in the >75 years of age subgroup, although the confidence interval was wide due to limited number of patients. It would be informative to know how patients with additional CV risk factors responded to antihypertensive therapy.

Specific issues applying to studies 491-009, 491-010 and 491-306: Efficacy studies during co-administration

Methods

Study 491-009 was a phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy and safety of TAK-491 when co-administered with chlorthalidone 25 mg once daily (QD) in subjects with essential hypertension. After a 2-week Run-In Period of single-blind placebo, subjects who met the entry criteria were randomized to receive placebo plus chlorthalidone 25 mg QD (chlorthalidone monotherapy), TAK-491 40 mg QD plus chlorthalidone 25 mg QD, or TAK-491 80 mg QD plus chlorthalidone 25 mg QD for 6 weeks. ABPM occurred on Day -1 for 24 hours prior to the first dose of double-blind study medication and at Week 6 or Early Termination for 24 hours following the last administration of study medication. Clinical SBP and DBP were measured at Screening, randomization, Week 2, Week 4, and Week 6.

Study 491-010 was a phase 3, multicenter, randomized, parallel-group, double-blind, placebo-controlled study to evaluate the efficacy and safety of TAK-491 when combined with amlodipine 5 mg once daily (QD) in subjects with essential hypertension (trough clinical sitting SBP ≥160 mm Hg and ≤190 mm Hg and 24-hour mean SBP ≥140 mm Hg and≤180 mm Hg). After a 2-week run-in period of single-blind placebo, subjects who met the entry criteria were randomized to receive placebo plus amlodipine 5 mg QD, TAK-491 40 mg QD plus amlodipine 5 mg QD, or TAK-491 80 mg QD plus amlodipine 5 mg QD for 6 weeks. ABPM occurred on Day -1 for 24 hours prior to the first dose of double-blind study medication and at Week 6 or Early Termination for 24 hours following the last administration of study medication. Clinical DBP and SBP were measured at Screening, randomization (Day 1), Week 2, Week 4, and Week 6.

Study 491-306 was a phase 3, multicenter, double-blind, randomized, parallel-group efficacy and safety study evaluating TAK-491 in FDC with chlorthalidone compared with TAK-491 co-administered with HCTZ over 10 weeks of treatment, which included a 2-week single-blind monotherapy treatment period and an 8-week double-blind treatment period, in subjects with moderate to severe essential hypertension, defined as systolic blood pressure (SBP) between 160 and 190 mm Hg, inclusive. After a 2-week Single-Blind Placebo Run-In Period, subjects who met the entry criteria were randomized to receive single-blind treatment starting on Day 1 consisting of TAK-491 40 mg and double-blind treatment starting at the end of Week 2, consisting of FDC of TAK-491 40 mg and chlorthalidone 12.5 mg (TAK-491CLD 40 mg/12.5 mg) or TAK-491 40 mg plus HCTZ 12.5 mg (TAK-491 40 mg + HCTZ 12.5 mg). For subjects who did not achieve target blood pressure by Week 6, the dose of TAK-491CLD 40 mg/12.5 mg was titrated to TAK-491CLD 40 mg/25 mg and the dose of TAK-491 40 mg + HCTZ 12.5 mg was titrated to TAK-491 40 mg + HCTZ 25 mg. Subjects who achieved both SBP and DBP targets by Week 6 continued to receive TAK-491CLD 40 mg/12.5 mg or TAK-491 40 mg + HCTZ 12.5 mg for the duration of the study.

Study Participants

74 sites for study 491-009 and 65 sites for study 491-010 enrolled subjects into the placebo run-in period in the Unites States and in Latin America. For study 491-306 66 sites enrolled subjects in the United States and in Russia

Treatments

Figure 6. Study 491-009

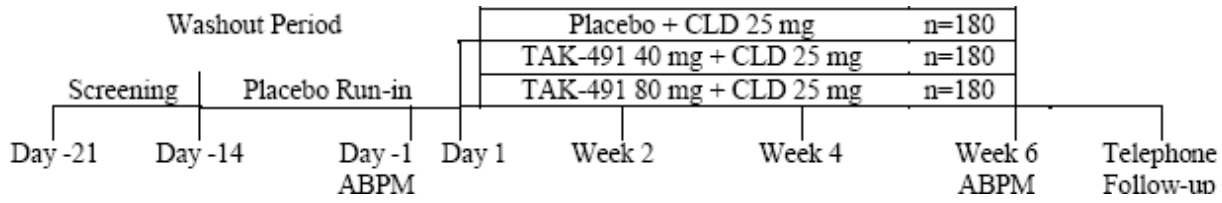


Figure 7. Study 491-010

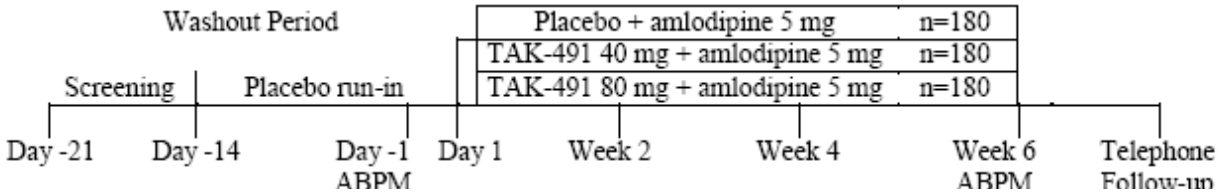
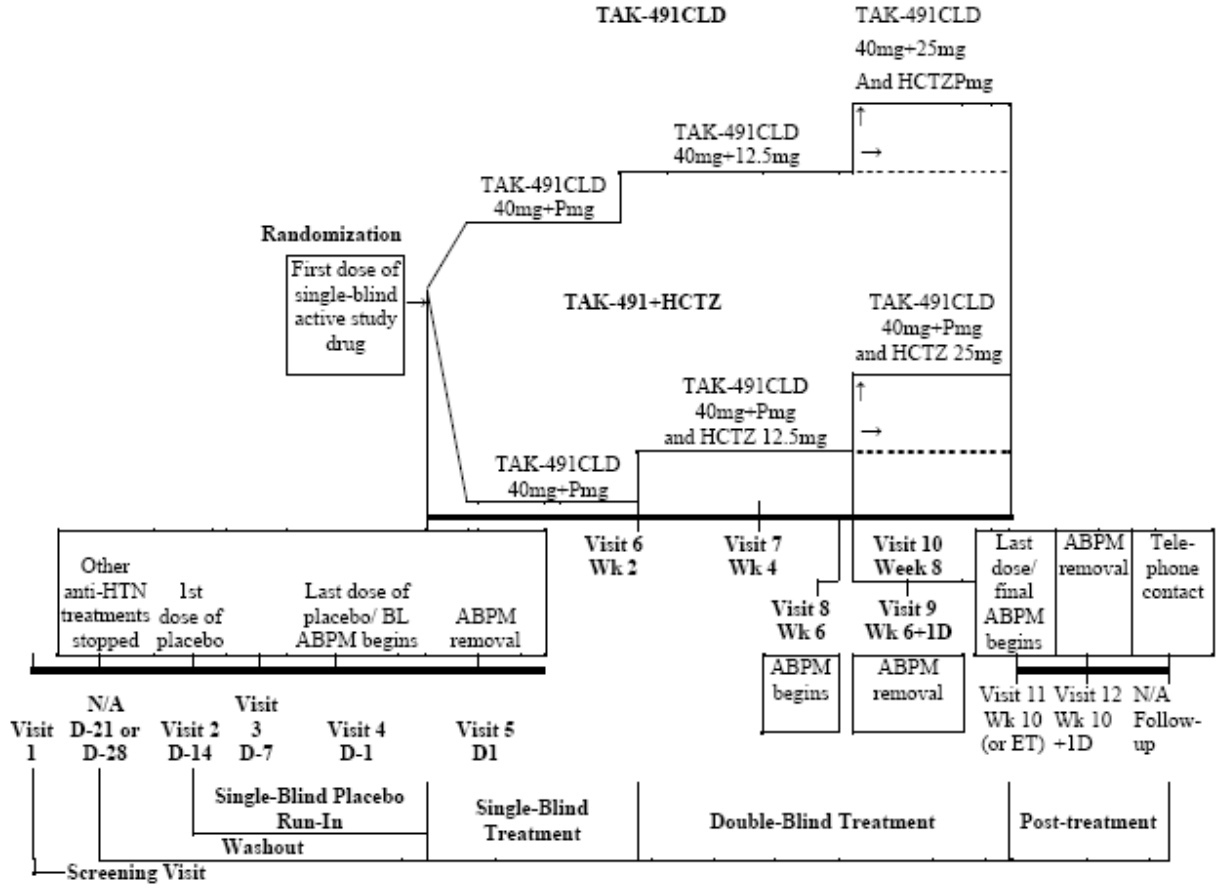


Figure 8. Study 491-306



Objectives

The primary objective of study 491-009 was to evaluate the antihypertensive effect of TAK-491 when co-administered with chlorthalidone compared with chlorthalidone monotherapy, as measured by the primary endpoint of 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM).

The primary objective of study 491-010 was to evaluate the antihypertensive effect of TAK-491 when co-administered with amlodipine compared with amlodipine monotherapy, as measured by the primary endpoint of 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM).

For study 491-306, the primary objective was to compare the antihypertensive effect of chlorthalidone versus hydrochlorothiazide (HCTZ) when each was used in combination with TAK-491 in subjects with moderate to severe essential hypertension.

Sample size

For studies 491-009 and 491-010, 540 subjects were to be randomized (180 per group) to achieve at least 90% power to detect a difference of 5 mm Hg between the active treatment groups and placebo (with a 2-sided significance level of 5%).

For study 491CLD-306, assuming a SD of 14 mmHg and a 15% drop-out rate, a total of 600 subjects was considered sufficient to achieve 90% power to detect a difference of 4 mmHg in the mean change from baseline in trough, sitting clinical SBP with 2 sided significance level of 5%.

Randomisation

Randomization was stratified by race (Black and non-Black) to ensure equal representation of Black subjects across treatment groups. Randomization personnel of the applicant or designee generated the randomization schedule. All randomization information was stored in a secure area, accessible only by authorized personnel.

Blinding (masking)

For study 491-009, medication dispensed during the double-blind treatment period was dispensed as 2 kits and 1 bottle at randomization and 1 kit and re-dispensed bottle at Visit 7. The daily dose during run-in was 2 placebo tablets. The daily dose during the double-blinded treatment period was 3 tablets: 2 TAK-491 (active and placebo) and 1 chlorthalidone tablet.

For study 491-010, the daily dose during run-in was 2 placebo tablets. The daily dose during the double-blinded treatment period was 3 tablets: 2 TAK-491 (active and placebo) and 1 amlodipine tablet.

Throughout study 491-306, chlorthalidone (or matching placebo) was administered in an FDC with TAK-491 (i.e. the TAK-491CLD FDC), whereas HCTZ (or matching placebo) was administered as an individual capsule.

Results

Participant flow

Table 11. Participating flow according to trial

Discontinuation Reason	Coadministration Studies							
	491-009			491-010			491CLD-306	
	PBO + CLD 25 mg N=184	TAK-491 40 mg + CLD 25 mg N=185	TAK-491 80 mg + CLD 25 mg N=182	PBO + AML 5 mg N=189	TAK-491 40 mg + AML 5 mg N=190	TAK-491 80 mg + AML 5 mg N=188	TAK-491CLD N=303	TAK-491 + HCTZ N=306
Overall (any discontinuation)	16 (8.7)	16 (8.6)	24 (13.2)	14 (7.4)	9 (4.7)	11 (5.9)	51 (16.8)	46 (15.0)
TEAE	6 (3.3)	9 (4.9)	9 (4.9)	3 (1.6)	2 (1.1)	2 (1.1)	28 (9.2)	19 (6.2)
Protocol deviation	0	2 (1.1)	3 (1.6)	1 (0.5)	0	0	2 (0.7)	2 (0.7)
Lost to follow-up	1 (0.5)	1 (0.5)	4 (2.2)	0	0	1 (0.5)	3 (1.0)	2 (0.7)
Voluntary withdrawal	3 (1.6)	2 (1.1)	5 (2.7)	5 (2.6)	6 (3.2)	2 (1.1)	16 (5.3)	14 (4.6)
Pregnancy (d)	0	0	0	0	0	0	0	0
Lack of efficacy	2 (1.1)	1 (0.5)	2 (1.1)	0	0	2 (1.1)	0	2 (0.7)
Other (g)	4 (2.2)	1 (0.5)	1 (0.5)	5 (2.6)	1 (0.5)	4 (2.1)	2 (0.7)	7 (2.3)

Overall no large differences appear in the dispositition within a study. A higher discontinuation due to co-administration with CLD is noticed. This seems to be lower with HCTZ and amlodipine.

Recruitment

Study 491-009 was conducted from 07 September 2007 until 05 March 2009. Study 491-010 was conducted from 03 October 2007 until 03 April 2009. Study 491-306 was conducted from 20 January 2009 until 30 November 2009.

Conduct of the study

For study 491-009, there were 68 subjects with at least 1 major protocol violation, which included the following categories: study drug compliance outside the acceptable range of 80% to 120%, baseline 24-hour mean SBP <140 mm Hg, prohibited medication use, and wrong treatment received, excluding them from PPS analyses. The number of subjects with major protocol deviations across treatment groups ranged between 20 (10.9%) and 25 (13.5%) subjects. Five subjects withdrew from the study due to major protocol deviations; each of these subjects failed to meet the SBP entrance criteria and were discontinued after randomization.

For study 491-010, there were 56 subjects (9.9%) with at least 1 major protocol deviation, with a similar percentage in each group excluding them from PPS analyses. The most common major protocol deviations were receipt of prohibited medication (21 subjects) and subjects that had a Baseline 24-hour mean SBP <140 mm Hg (16 subjects).

For study 491CLD-306, there were 29 subjects with at least 1 major protocol violation, which included the following categories: treatment/dosing violation, study drug compliance outside the acceptable range of 80% to 120%, and prohibited medication use. As such, data from these subjects were not eligible for inclusion in the PPS analyses. A listing by subject and summary of reasons that individual subjects were excluded from the PPS analyses are presented in Appendix 16.2.3 and Table 15.1.5, respectively. Four subjects withdrew from the study due to major protocol deviations; each of these subjects had unsuccessful ABPM measurements and were discontinued after randomization.

Baseline data

Table 12. Demographic and baseline characteristics by individual co-administration studies

	491-009			491-010			491CLD-306	
	PBO + CLD 25 mg N=184	TAK-491 40 mg + CLD 25 mg N=184	80 mg + CLD 25 mg N=182	PBO + AML 5 mg N=189	TAK-491 40 mg + AML 5 mg N-189	80 mg + AML 5 mg N-188	TAK-491CLD N=303	TAK-491 + HCTZ N=306
Age (years)								
Mean	59.0	58.2	59.0	58.9	57.8	58.2	56.8	55.9
(SD)	(11.60)	(11.08)	(10.89)	(11.04)	(11.44)	(11.84)	(10.79)	(10.97)
Categories [n (%)]								
<45	16 (8.7)	21 (11.4)	15 (8.2)	15 (7.9)	28 (14.8)	23 (12.2)	43 (14.2)	50 (16.3)
45 to 64	113 (61.4)	114 (61.6)	110 (60.4)	115 (60.8)	97 (51.3)	111 (59.0)	189 (62.4)	195 (63.7)
≥65	55 (29.9)	50 (27.0)	57 (31.3)	59 (31.2)	64 (33.9)	54 (28.7)	71 (23.4)	61 (19.9)
Gender [n (%)]								
Male	102 (55.4)	89 (48.1)	94 (51.6)	94 (49.7)	90 (47.6)	103 (54.8)	145 (47.9)	151 (49.3)
Race [n (%)]								
American Indian or Alaska Native	44 (23.9)	37 (20.0)	51 (28.0)	42 (22.2)	35 (18.5)	38 (20.2)	6 (2.0)	1 (0.3)
Asian	2 (1.1)	4 (2.2)	0	6 (3.2)	12 (6.3)	10 (5.3)	3 (1.0)	2 (0.7)
Black/African American	29 (15.8)	30 (16.2)	29 (15.9)	30 (15.9)	29 (15.3)	30 (16.0)	46 (15.2)	38 (12.4)
Native Hawaiian or Other Pacific Islander	1 (0.5)	1 (0.5)	1 (0.5)	0	1 (0.5)	1 (0.5)	1 (0.3)	0
White	109 (59.2)	114 (61.6)	103 (56.6)	111 (58.7)	114 (60.3)	109 (58.0)	252 (83.2)	265 (86.6)
Multiracial	1 (0.5)	1 (0.5)	2 (1.1)	0	2 (1.1)	0	5 (1.7)	0
Missing	1 (0.5)	0	0	0	0	0	0	0
BMI (kg/m^2)								
Median	29.73	29.91	29.28	29.33	29.57	29.53	30.1	30.8
Min, max	21.1, 47.8	17.9, 54.7	19.7, 50.0	16.9, 51.8	18.2, 55.4	20.2, 50.6	19, 57	19, 54

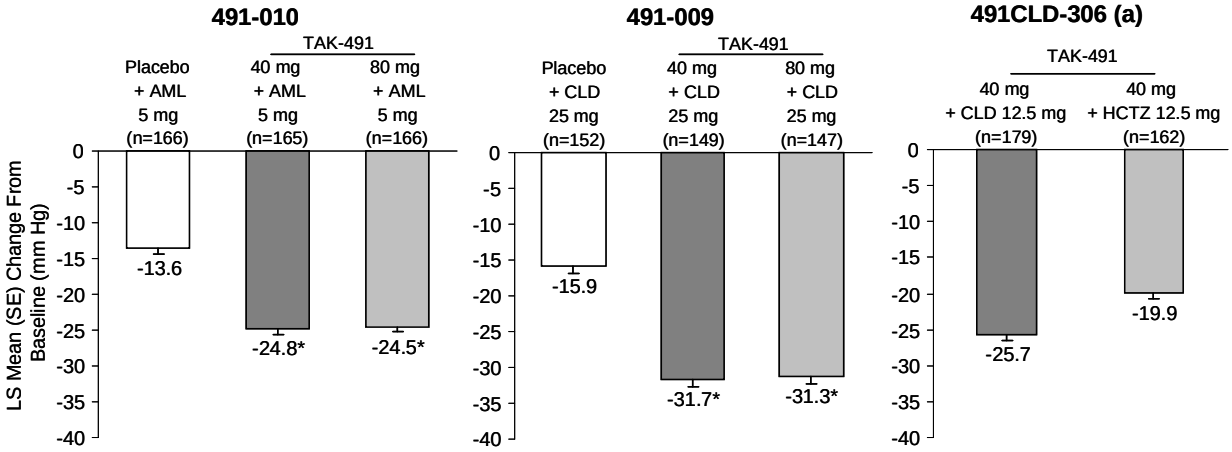
Some differences appear within study 491-009 and 491-010. There are some differences between treatment groups for gender. Whether this could have influenced results remains questionable. Within the other placebo controlled trials no difference for race subgroup was observed.

Numbers analysed

An ITT procedure was followed.

Outcomes and estimation

Figure 9. Co-administration studies (491-009, 491-010, and 491CLD-306): Absolute Reductions in 24-Hour Mean SBP at Week 6



Both the 40 mg and 80 mg azilsartan medoxomil demonstrated additional efficacy when combined with amlodipine or chlorthalidone. However the 80 mg azilsartan medoxomil could not demonstrate more blood pressure lowering in combination than the 40 mg azilsartan medoxomil in combination with either additional antihypertensives. The fixed dose combination of 40 mg azilsartan medoxomil with CLD 12.5 mg had significantly larger SBP reduction when measured clinically (primary endpoint) but comparable BP lowering efficacy as 40 mg azilsartan medoxomil combined with 12.5 mg HCTZ when measured as 24h SBP reduction.

Ancillary analyses

Consistent with the results of the primary endpoint the proportion of responders in the highest 80 mg group was less than with the 40 mg group in study 491-009. In study 491-010, slightly more patients on the highest azilsartan medoxomil dose responded while blood pressure lowering was comparable with the 40 mg dose This questions the additional efficacy with the highest dose in combination with other antihypertensives.

Also for the patients on the FDC the proportion requiring addition of high dose HCTZ is consistent with the blood pressure achieved.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13. Summary of Efficacy for trial 491-008

Title: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-491 in Subjects With Essential Hypertension						
Study identifier	01-05-TL-491-008					
Design	Double-blind, randomized, placebo-controlled, active-controlled, parallel-group study to examine the antihypertensive effect of TAK-491compared with placebo and olmesartan medoxomil (OLM-M)					
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 weeks 2 weeks (single-blind placebo run-in) not applicable				
Hypothesis	To evaluate the antihypertensive effect of TAK-491 compared with placebo and olmesartan after 6 weeks of treatment, as measured by the primary endpoint of change in 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM).					
Treatments groups	Placebo	Number randomized = 141 (Duration 6 Wks)				
	TAK-491 20 mg	Number randomized = 283 (Duration 6 Wks)				
	TAK-491 40 mg	Number randomized = 283 (Duration 6 Wks)				
	TAK-491 80 mg	Number randomized = 285 (Duration 6 Wks)				
	OLM-M 40 mg	Number randomized = 282 (Duration 6 Wks)				
Endpoints and definitions	Primary Efficacy Endpoint	Change from Baseline to Week 6 in 24-hour mean SBP by ABPM				
	Key Secondary Endpoint	Change from Baseline to Week 6 in trough clinical sitting SBP				
Database lock	18 February 2009					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	Intent to Treat population assessment of 24-hour mean SBP change from baseline to Week 6 by ABPM					
Descriptive statistics and estimate variability	Treatment group	Placebo	TAK-491 20 mg	TAK-491 40 mg	TAK-491 80 mg	OLM-M 40 mg
	Number of subjects	120	241	244	243	250
	LS mean change (mm Hg)	-1.40	-12.15	-13.48	-14.62	-12.56
	Standard Error	1.004	0.709	0.704	0.706	0.696
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value					

Effect estimate per comparison: Placebo Comparison	Primary endpoint	Comparison groups			TAK-491 80 mg, 40 mg and 20 mg difference vs placebo	
		LS Mean Difference			-13.21; -12.08; -10.75	
		95% CI			-15.62, -10.81; -14.48, -9.67; -14.48, -9.67	
		P-value vs placebo			<0.001	
Effect estimate per comparison: Olmesartan Comparison	Primary endpoint	Comparison groups			TAK-491 80 mg, 40 mg and 20 mg difference vs OLM-M	
		LS Mean Difference			-2.06; -0.92; 0.352	
		95% CI			-4.00, -0.12; -2.87, 1.02; -1.55, 2.35	
		P-value vs OLM-M			0.038; 0.352; 0.687	
Analysis description	**Key Secondary analysis**					
Analysis population and time point description	Intent to Treat population assessment of trough clinical sitting SBP change from baseline to Week 6					
Descriptive statistics and estimate variability	Treatment group	Placebo	TAK-491 20 mg	TAK-491 40 mg	TAK-491 80 mg	OLM-M 40 mg
	Number of subject	140	274	276	279	280
	LS mean change (mm Hg)	-2.06	-14.28	-14.47	-17.58	-14.87
	Standard Error	1.337	0.956	0.952	0.947	0.945
Effect estimate per comparison: Placebo Comparison	Key Secondary endpoint	Comparison groups			TAK-491 80 mg, 40 mg and 20 mg difference vs placebo	
		LS Mean Difference			-15.53; -12.42; -12.23	
		95% CI			-18.74, -12.31; -15.64, -9.20; -15.45, -9.00	
		P-value vs placebo			<0.001	
Effect estimate per comparison: Olmesartan Comparison	Key Secondary endpoint	Comparison groups			TAK-491 80 mg, 40 mg and 20 mg difference vs OLM-M	
		LS Mean Difference			-2.71; 0.40; 0.59	
		95% CI			-5.34, -0.09; -2.24, 3.03; -2.05, 3.22	
		P-value vs placebo			0.043‡; 0.768; 0.662	

Table 14. Summary of Efficacy for trial 491-019

Title: A Double-Blind, Randomized, Placebo-Controlled, 5-Arm Titration Study to Evaluate the Efficacy and Safety of TAK-491 When Compared With Valsartan and Olmesartan in Subjects With Essential Hypertension						
Study identifier	01-06-TL-491-019					
Design	Double-blind, randomized, placebo-controlled, 5-arm force titration, parallel-group study to examine the antihypertensive effect of TAK-491 compared with placebo, olmesartan medoxomil (OLM-M), and valsartan					
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 weeks 2 weeks (single-blind placebo run-in) not applicable				
Hypothesis	To evaluate the antihypertensive effect of TAK 491 compared with placebo, olmesartan, and valsartan after 6 weeks of treatment, as measured by the primary endpoint of change in 24 hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM)					
Treatments groups	Placebo	Number randomized = 154 (Duration 6 Wks)				
	TAK-491 20 mg titrated to 40 mg	Number randomized = 280 (Duration 6 Wks)				
	TAK-491 40 mg titrated to 80 mg	Number randomized = 285 (Duration 6 Wks)				
	Valsartan 160 mg titrated to 320 mg	Number randomized = 282 (Duration 6 Wks)				
	OLM-M 20 mg titrated to 40 mg	Number randomized = 290 (Duration 6 Wks)				
	Note: Subjects were randomized to receive TAK-491 20 mg, TAK-491 40 mg, valsartan 160 mg, olmesartan 20 mg, or placebo for 2 weeks. At the end of 2 weeks, subjects were force-titrated to the higher dose: TAK-491 40 mg or 80 mg, valsartan 320 mg, olmesartan 40 mg, or remained on placebo, respectively.					
Endpoints and definitions	Primary Efficacy Endpoint	Change from Baseline to Week 6 in the 24-hour mean SBP assessed by ABPM				
	Key Secondary Endpoint	Change from Baseline to Week 6 in trough clinical sitting SBP				
Database lock	30 September 2009					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	Intent to Treat population assessment of 24-hour mean SBP change from Baseline to Week 6 by ABPM					
Descriptive statistics and estimate variability	Treatment group	Placebo	TAK-491 40 mg	TAK-491 80 mg	Valsartan 320 mg	OLM-M 40 mg
	Number of subjects	134	237	229	234	254
	LS mean change (mm Hg)	-0.25	-13.42	-14.53	-10.22	-11.99
	Standard Error	0.917	0.690	0.702	0.696	0.666
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value					

Effect estimate per comparison: Placebo Comparison	Primary endpoint	Comparison groups			TAK-491 80 mg and 40 mg difference vs placebo	
		LS Mean Difference			-14.27; -13.16	
		95% CI			-16.54, -12.01; -15.41, -10.91	
		P-value vs placebo			<0.001	
Effect estimate per comparison: Olmesartan Comparison	Primary endpoint	Comparison groups			TAK-491 80 mg and 40 mg difference vs OLM-M	
		LS Mean Difference			-2.54; -1.43	
		95% CI			-4.44, -0.64; -3.31, 0.45	
		P-value vs OLM-M			0.009; 0.136	
Effect estimate per comparison: Valsartan Comparison	Primary endpoint	Comparison groups			TAK-491 80 mg and 40 mg difference vs valsartan	
		LS Mean Difference			-4.31; -3.20	
		95% CI			-6.25, -2.37; -5.12, -1.27	
		P-value vs valsartan			<0.001; 0.001	
Analysis description	**Key Secondary analysis**					
Analysis population and time point description	Intent to Treat population assessment of trough clinical sitting SBP change from Baseline to Week 6					
Descriptive statistics and estimate variability	Treatment group	Placebo	TAK-491 40 mg	TAK-491 80 mg	Valsartan 320 mg	OLM-M 40 mg
	Number of subjects	148	269	270	271	283
	LS mean change (mm Hg)	-1.83	-16.38	-16.74	-11.31	-13.20
	Standard Error	1.293	0.959	0.957	0.955	0.935
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value					
Effect estimate per comparison: Placebo Comparison	Key Secondary endpoint	Comparison groups			TAK-491 80 mg and 40 mg difference vs placebo	
		LS Mean Difference			-14.92; 14.55	
		95% CI			-18.07, -11.76; -17.71, -11.40	
		P-value vs placebo			<0.001	
Effect estimate per comparison: Olmesartan Comparison	Key Secondary endpoint	Comparison groups			TAK-491 80 mg and 40 mg difference vs OLM-M	
		LS Mean Difference			-3.54; -3.18	
		95% CI			-6.17, -0.92; -5.81, -0.55	
		P-value vs OLM-M			0.008; 0.018	
Effect estimate per comparison: Valsartan Comparison	Key Secondary endpoint	Comparison groups			TAK-491 80 mg and 40 mg difference vs valsartan	
		LS Mean Difference			-5.43; -5.07	
		95% CI			-8.09, -2.78; -7.73, -2.42	
		P-value vs valsartan			<0.001	

Table 15. Summary of Efficacy for trial 01-06-TL-491-020

Title: A Double-Blind, Randomized, Parallel-Group Study to Compare the Efficacy and Safety of TAK-491 With Ramipril in Subjects With Essential Hypertension				
Study identifier	01-06-TL-491-020			
Design	Double-blind, randomized, parallel-group, 3-arm study to assess the antihypertensive effect of TAK-491 compared with ramipril for 6 months			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 2 weeks (single-blind placebo run-in) not applicable		
Hypothesis	To evaluate the change in clinical systolic blood pressure (SBP) in response to TAK-491 compared with ramipril for 6 months in subjects with essential hypertension			
Treatments groups	TAK-491 20 mg titrated to 40 mg	Number randomized = 295 (Duration 24 Wks)		
	TAK-491 20 mg titrated to 80 mg	Number randomized = 294 (Duration 24 Wks)		
	Ramipril 2.5 mg titrated to 10 mg	Number randomized = 296 (Duration 24 Wks)		
	Note: Subjects randomized to receive TAK-491 20 mg were up-titrated to 40 mg QD after 2 weeks, TAK-491 20 mg up-titrated to 80 mg after 2 weeks, or ramipril 2.5 mg up titrated to 10 mg after 2 weeks, continuing on double-blind treatment for a total of 6 months.			
Endpoints and definitions	Primary Efficacy Endpoint	Change from Baseline to Week 24 in trough clinical sitting SBP		
Database lock	25 August 2009			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to Treat population assessment of change from Baseline to Week 24 of sitting trough clinical SBP			
Descriptive statistics and estimate variability	Treatment group	TAK-491 40 mg	TAK-491 80 mg	Ramipril 10 mg
	Number of subjects	291	289	290
	LS mean change (mm Hg)	-20.63	-21.24	-12.22
	Standard Error	0.946	0.949	0.948
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value			
Effect estimate per comparison: Ramipril Comparison	Primary endpoint	Comparison groups	TAK-491 80 mg and 40 mg difference vs ramipril	
		LS Mean Difference	-9.03; -8.41	
		95% CI	-11.66, -6.39; -11.04, -5.78	
		P-value vs ramipril	<0.001	

Table 16. Summary of Efficacy for trial TAK 491-301

Title: A Double-Blind, Randomized, Parallel-Group Study to Compare the Efficacy and Safety of TAK-491 With Valsartan in Subjects With Essential Hypertension				
Study identifier	TAK 491_301			
Design	Double-blind, randomized, parallel-group, active-controlled, force-titration study to assess the antihypertensive effect of TAK-491 compared with valsartan for 24 weeks followed by an optional 28-week open-label extension			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 2 weeks (single-blind placebo run-in) 28 weeks (open-label)		
Hypothesis	To evaluate the antihypertensive effect of TAK-491 compared with valsartan 320 mg after 6 months of treatment, as measured by the primary endpoint of change in 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM)			
Treatments groups	TAK-491 20 mg titrated to 40 mg	Number randomized = 327 (Duration 24 Wks)		
	TAK-491 20 mg titrated to 80 mg	Number randomized = 329 (Duration 24 Wks)		
	Valsartan 80 mg titrated to 320 mg	Number randomized = 328 (Duration 24 Wks)		
	Note: At Week 2, all subjects were force titrated based on their assigned randomization. Subjects that were started on TAK 491 20 mg were up-titrated to TAK 491 40 mg or 80 mg. Subjects that were started on valsartan 80 mg were up-titrated to valsartan 320 mg. Subjects continued at the higher dose for the remainder of the 6-month treatment period.			
Endpoints and definitions	Primary Efficacy Endpoint	Change from Baseline to Week 24 in the 24-hour mean SBP assessed by ambulatory blood pressure monitoring ABPM		
	Key Secondary Endpoint	Change from Baseline to Week 24 in trough clinical sitting SBP		
Database lock	9 November 2009			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to Treat population assessment of 24-hour mean SBP change from Baseline to Week 24 by ABPM			
Descriptive statistics and estimate variability	Treatment group	TAK-491 40 mg	TAK-491 80 mg	Valsartan 320 mg
	Number of subjects	284	271	277
	LS mean change (mm Hg)	-14.93	-15.32	-11.29
	Standard Error	0.698	0.715	0.707
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value			
Effect estimate per comparison: Valsartan Comparison	Primary endpoint	Comparison groups	TAK-491 80 mg and 40 mg difference vs valsartan	
		LS Mean Difference	-4.03; -3.64	
		95% CI	-6.01, -2.06; -5.59, -1.69	
		P-value vs valsartan	<0.001	
Analysis description	**Key Secondary analysis**			
Analysis population and time point	Intent to Treat population assessment of trough clinical sitting SBP change			

description	from Baseline to Week 24			
Descriptive statistics and estimate variability	Treatment group	TAK-491 40 mg	TAK-491 80 mg	Valsartan 320 mg
	Number of subjects	323	311	322
	LS mean change (mm Hg)	-14.86	-16.92	-11.59
	Standard Error	0.948	0.966	0.949
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value			
Effect estimate per comparison: Valsartan Comparison	Key Secondary endpoint	Comparison groups	TAK-491 80 mg and 40 mg difference vs valsartan	
		LS Mean Difference	-5.34; -3.27	
		95% CI	-8.00, -2.68; -5.90, -0.63	
		P-value vs valsartan	<0.001; 0.015	

Table 17. Summary of Efficacy for trial TAK-491-009

Title: A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-491 When Co-Administered With Chlorthalidone in Subjects With Essential Hypertension				
Study identifier	01-05-TL-491-009			
Design	Multicenter, 6-week randomized, parallel group, double-blind, placebo-controlled study			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 weeks 2 weeks (single-blind placebo run-in) not applicable		
Hypothesis	To evaluate the antihypertensive effect of TAK-491 when coadministered with chlorthalidone (CLD) compared with chlorthalidone monotherapy, as measured by the primary endpoint of 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM)			
Treatments groups	TAK-491 40 mg with CLD 25 mg	Number randomized = 185 (Duration 6 Wks)		
	TAK-491 80 mg with CLD 25 mg	Number randomized = 182 (Duration 6 Wks)		
	Placebo with CLD 25 mg	Number randomized = 184 (Duration 6 Wks)		
Endpoints and definitions	Primary Efficacy Endpoint	Change from Baseline to Week 6 in 24-hour mean SBP assessed by ABPM.		
	Key Secondary Endpoint	Change from Baseline to Week 6 in trough clinical sitting SBP		
Database lock	06 May 2009			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to Treat population ABPM assessment of 24-hour mean SBP change from baseline to Week 6			
Descriptive statistics and estimate variability	Treatment group	Placebo + CLD 25 mg	TAK-491 40 mg + CLD 25 mg	TAK-491 80 mg + CLD 25 mg
	Number of subjects	152	149	147
	Week 6 LS mean change (mm Hg)	-15.85	-31.72	-31.30

	Week 6 Standard Error	0.957	0.966	0.973
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value			
Effect estimate per comparison:	Primary endpoint	Comparison groups	TAK-491 40 mg and 80 mg +CLD 25 mg difference vs CLD 25 mg monotherapy	
		LS Mean Difference	-15.86; -15.45	
		95% CI	-18.54, -13.19; -18.13, -12.76	
		P-value vs placebo	<0.001	
Analysis description	**Key Secondary Endpoint**			
Analysis population and time point description	Intent to Treat population assessment of change from Baseline in trough clinical sitting SBP at Week 6			
Descriptive statistics and estimate variability	Treatment group	Placebo + CLD 25 mg	TAK-491 40 mg + CLD 25 mg	TAK-491 80 mg + CLD 25 mg
	Number of subjects	178	179	176
	Week 6 LS mean change (mm Hg)	-21.76	-36.16	-34.44
	Week 6 Standard Error	1.229	1.226	1.236
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value			
Effect estimate per comparison:	Key Secondary endpoint	Comparison groups	TAK-491 40 mg and 80 mg +CLD 25 mg difference vs CLD 25 mg monotherapy	
		LS Mean Difference	-14.40; -12.68	
		95% CI	-17.81, -10.99; -16.10, -9.25	
		P-value vs placebo	<0.001	

Table 18. Summary of Efficacy for trial TAK-491-010

Title: A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of TAK-491 When Coadministered With Amlodipine 5 mg in Subjects With Essential Hypertension		
Study identifier	01-05-TL-491-010	
Design	Multicenter, 6-week randomized, parallel group, double-blind, placebo-controlled study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 weeks 2 weeks (single-blind placebo run-in) not applicable
Hypothesis	To evaluate the antihypertensive effect of TAK-491 when coadministered with amlodipine (AML) compared with amlodipine monotherapy, as measured by the primary endpoint of 24-hour mean systolic blood pressure (SBP) by ambulatory blood pressure monitoring (ABPM)	
Treatments groups	TAK-491 40 mg with AML 5 mg	Number randomized = 190 (Duration 6 Wks)
	TAK-491 80 mg with AML 5 mg	Number randomized = 188 (Duration 6 Wks)

	Placebo with AML 5 mg	Number randomized = 189 (Duration 6 Wks)		
Endpoints and definitions	Primary Efficacy Endpoint	Change from Baseline to Week 6 in 24-hour mean SBP assessed by ABPM.		
	Key Secondary Endpoint	Change from Baseline to Week 6 in trough clinical sitting SBP		
Database lock	16 July 2009			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to Treat population ABPM assessment of 24-hour mean SBP change from baseline to Week 6			
Descriptive statistics and estimate variability	Treatment group	Placebo + AML 5 mg	TAK-491 40 mg + AML 5 mg	TAK-491 80 mg + AML 5 mg
	Number of subjects	166	165	166
	Week 6 LS mean change (mm Hg)	-13.60	-24.79	-24.51
	Week 6 Standard Error	0.754	0.757	0.754
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value			
Effect estimate per comparison:	Primary endpoint	Comparison groups	TAK-491 40 mg and 80 mg + AML 5 mg difference vs AML 5 mg monotherapy	
		LS Mean Difference	-11.19; -10.91	
		95% CI	-13.29, -9.09; -13.00, -8.81	
		P-value vs placebo	<0.001*	
Analysis description	**Key Secondary Endpoint**			
Analysis population and time point description	Intent to Treat population assessment of change from Baseline in trough clinical sitting SBP at Week 6			
Descriptive statistics and estimate variability	Treatment group	Placebo + AML 5 mg	TAK-491 40 mg + AML 5 mg	TAK-491 80 mg + AML 5 mg
	Number of subjects	179	187	183
	Week 6 LS mean change (mm Hg)	-15.94	-26.96	-25.50
	Week 6 Standard Error	1.060	1.037	1.048
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value			
Effect estimate per comparison:	Key Secondary endpoint	Comparison groups	TAK-491 40 mg and 80 mg + AML 5 mg difference vs AML 5 mg monotherapy	
		LS Mean Difference	-11.02; -9.56	
		95% CI	-13.93, -8.10; -12.48, -6.63	
		P-value vs placebo	<0.001	

Table 19. Summary of Efficacy for trial TAK-491CLD-306

Title: A Phase 3, Double-Blind, Randomized, Efficacy and Safety Study of the TAK-491 Plus Chlorthalidone Fixed-Dose Combination Compared With TAK-491 and Hydrochlorothiazide Coadministration Therapy in Subjects With Moderate to Severe Essential Hypertension			
Study identifier	TAK-491CLD-306		
Design	Multicenter, double-blind, randomized parallel-group study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	10 weeks (included a 2-week single-blind monotherapy treatment period and an 8-week double-blind treatment period) 2 weeks (single-blind placebo run-in) not applicable	
Hypothesis	To compare the antihypertensive effect of chlorthalidone (CLD) versus Hydrochlorothiazide (HCTZ) when each was used in combination with TAK-491 in subjects with moderate to severe essential hypertension.		
Treatments groups	TAK-491CLD Fixed Dose Combination (FDC) (40 mg TAK-491+ 12.5/25 mg CLD)	Number randomized = 303 (Duration 10 Wks)	
	B: TAK-491+HCTZ (coadministered) (40 mg TAK-491+ 12/25 mg HCTZ)	Number randomized = 306 (Duration 10 Wks)	
	Note: Subjects took TAK-491 40 mg throughout the study, with titration to 12.5 mg CLD or HCTZ at Week 2 and then to 25 mg CLD or HCTZ, if needed, at Week 6.		
Endpoints and definitions	Primary Efficacy Endpoint	Change from Baseline in trough clinical sitting SBP at Week 6 and Week 10	
Database lock	05 February 2010		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to Treat population assessment of trough clinical sitting SBP change from baseline to Week 6 and Week 10		
Descriptive statistics and estimate variability	Treatment group	TAK-491CLD	TAK-491+HCTZ
	Number of subjects	295	292
	Week 6 LS mean change (mm Hg)	-35.1	-29.5
	Week 6 Standard Error	0.97	0.98
	Week 10 LS mean change (mm Hg)	-37.8	-32.8
	Week 10 Standard Error	0.91	0.91
	Note: Analyses included subjects with both a baseline and at least 1 post-baseline value		

Effect estimate per comparison:	Primary endpoint Week 6 Comparison	Comparison groups	TAK-491CLD difference vs TAK-491+HCTZ
		LS Mean Difference	-5.6
		95% CI	-8.3, -2.9
		P-value vs placebo	<0.001*
	Primary endpoint Week 10 Comparison	Comparison groups	TAK-491CLD difference vs TAK-491+HCTZ
		LS Mean Difference	-5.0
		95% CI	-7.5, -2.5
		P-value vs placebo	<0.001*

Analysis performed across trials (pooled analyses and meta-analysis)

Pooled analyses were used to explore the sub-group differences and have been described above together with the individual studies.

Clinical studies in special populations

A separate placebo-controlled, phase 3 study (study 491-011) was completed to characterize the efficacy of TAK-491 monotherapy in a study of Black subjects with mild to moderate essential hypertension. The study was similar in design as the placebo-controlled short term trials 491-008 and 491-019. This trial demonstrated less efficacy compared to the other two trials. This is not unexpected as only a black population was included. However, a clinically and statistically significant BP lowering efficacy compared to placebo was demonstrated.

Supportive studies

The 24-week, controlled study 491-301 was extended with a 28 week extension part to evaluate open-label long-term maintenance of antihypertensive effect during chronic administration of TAK-491 during 52 weeks, and the 2 uncontrolled, open-label studies (491-006 for 56 weeks, 491-016 for 26 weeks) provided additional long-term experience. The study designs and objectives are appropriate to allow both scheduled treatment intensification and regular assessment of tolerability of proper antihypertensive therapy. Sufficient number of patients were analysed to comply with the power calculation. A larger proportion of diabetic patients was included in the open-label studies. However, as with the randomised studies, a limited proportion of patients older than 75 years of age was included. A more severe hypertensive patient group was included in the open-label phase in conformity with the inclusion criteria.

Studies 491-016 and 491-006 demonstrated that TAK-491 efficacy was maintained during the study period followed. However, for study 491-301, blood pressure lowering capacity slightly diminished from week 28 until the end of the study period. Addition of CLD or HCT resulted in additional blood pressure lowering. Maintenance of efficacy was further demonstrated with the reversal phase in study 491-016 where treatment continuation was associated with significant larger blood pressure reduction compared to patients assigned to placebo, who demonstrated loss of blood pressure lowering effect.

2.5.3 Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant conducted an elaborate clinical programme to support both monotherapy and co-administration of azilsartan medoxomil with other antihypertensives. For the studies performed in patients with uncomplicated essential hypertension, inclusion and exclusion criteria are considered appropriate. However, a relatively homogenous patient population has been selected with limited co-morbidity.
Sufficient duration has been applied to reach maximum blood pressure lowering and the washout period used is considered sufficiently long to exclude a carry-over effect. In addition, suitable measures are taken to exclude patients who initially do not comply with study medication intake. The comparators, one ACE-inhibitor (ramipril) and 2 ARB's (olmesartan and valsartan) can be considered as representative drugs of their class and are given at their maximum accepted dose.
The decision to use 24 hour ABPM systolic blood pressure as primary endpoint is considered appropriate. In the revised guideline on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95 Rev. 3)*:* ABPM is required for the evaluation of new antihypertensive agents. ABPM provides good insight into blood pressure changes during everyday activities. However, it is also mentioned that measurements with a calibrated mercury sphygmomanometer are still the standard. For this reason, the applicant has chosen to use clinical SBP at through as the major secondary endpoint to comply with the current view of the guideline. Also, the applicant has used clinical SPB as primary endpoint in some of the trials (studies 491-020 and 491CLD-306). Other important secondary endpoints (the proportion of responders and trough-to-peak ratio) to measure antihypertensive efficacy have also been taken into account.
The statistical methods used are considered appropriate. The hierarchical test procedure is considered appropriate to allow multiple testing without requiring tightening of the p-value.

Efficacy data and additional analyses

The applicant demonstrated significant blood pressure reduction versus placebo in the short-term 6 weeks monotherapy trials for dose range of 20 – 80 mg. Superiority of azilsartan medoxomil could be demonstrated versus valsartan for both the 40 mg and the 80 mg azilsartan medoxomil dose, whereas only the highest dose of azilsartan medoxomil (80 mg) was superior in reducing BP compared to olmesartan 40 mg. A larger proportion of responders was observed for the highest 80 mg dose based on the clinical SBP versus the comparator olmesartan. A significant effect was present after two weeks and maximal blood pressure lowering efficacy was observed after 4 weeks of treatment, similar to olmesartan. In addition, the subgroup analyses versus placebo also showed consistent results except for the age group of >75 years of age and for the black population. However, it was expected that the Black population would respond less due to less RAAS activation compared to White. This was observed in study 491-011 where only black patients were included.

In the long-term (24 weeks) comparative studies, azilsartan medoxomil 40 and 80 mg (both doses) reduced systolic blood pressure significantly more than valsartan and ramipril. Reduction in diastolic blood pressure and responder rates were consistent with these results. However, the 80 mg appears not to have greater response than the 40 mg dose azilsartan medoxomil as BP and responder rates are only marginally higher. This is probably due to the shallow dose response curve often seen with ARBs. Again, consistent findings were observed for the blood pressure lowering across subgroups.

In the co-administration studies, both the 40 mg and 80 mg azilsartan medoxomil demonstrated additional efficacy when combined with amlodipine, chlorthalidone and HCTZ (the latter only for SBP). However, 80 mg azilsartan medoxomil did not reduce blood pressure more than 40 mg azilsartan medoxomil when co-administered with either AML or CLD. A higher discontinuation rate was observed when azilsartan medoxomil was combined with CLD versus CLD alone compared to combination of azilsartan medoxomil with HCTZ or amlodipine versus monotherapy.
The long-term open-label studies, studies 491-016 and 491-006 demonstrated that TAK-491 efficacy was maintained during the entire study period. However, in study 301 (open-label extension of azilsartan medoxomil monotherapy), blood pressure lowering capacity slightly diminished from week 28 to end of study period. Nevertheless, when CLD, amlodipine or HCT were added this resulted in additional blood pressure lowering in all of these long-term studies. To obtain more insight in the numbers of responders after each treatment step, the applicant has provided results of patients not initially responding to a 40 mg dose and who were then titrated up to the 80 mg dose. Additional efficacy of approximately 5 mmHg was shown for these patients, best reflecting the benefit of the highest dose in clinical practice. The benefit in this non-responder subgroup of all patients who were up titrated to 80 mg was clearly more pronounced. The analysis supports a step-wise up-titration.
Maintenance of efficacy was further demonstrated with the reversal phase in study 491-016 where treatment continuation was associated with significant larger blood pressure reduction compared to patients assigned to placebo, who demonstrated loss of blood pressure lowering effect.

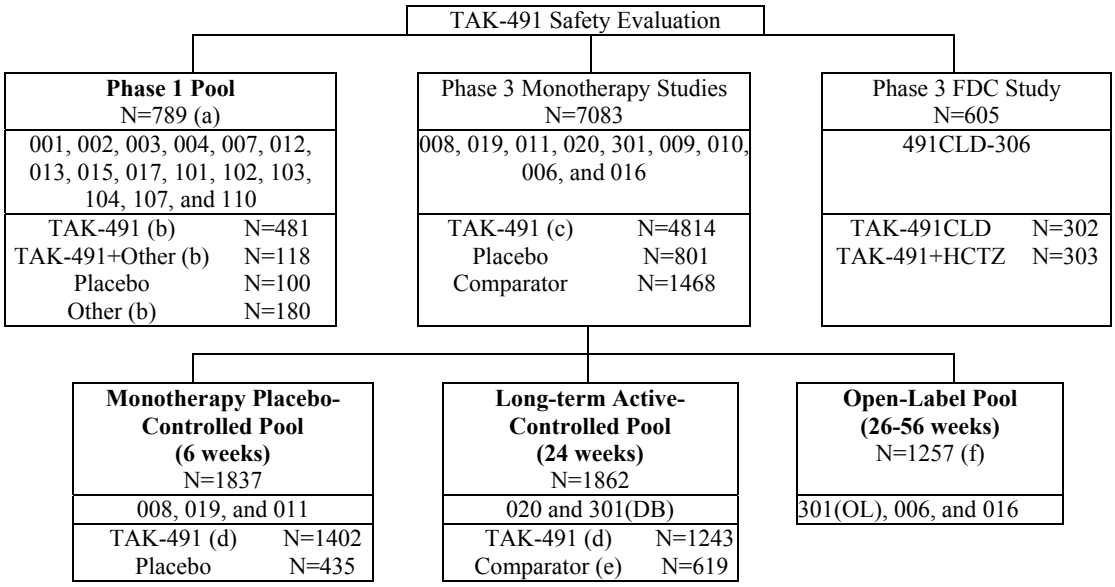
The clinical trial programme is considered appropriate to evaluate the antihypertensive efficacy with and without other antihypertensives in patients with uncomplicated mild to moderate hypertension up to 75 years of age, both in men and women. A more severe hypertensive patients group was included in the open-label phase conform with the inclusion criteria and a sufficient number of severe patients were analyzed to assess antihypertensive efficacy. Only limited data were obtained in complicated patients, i.e. patients with co-morbidity such as patients with DM and heart failure, patients at high risk for cardiovascular disease, and the very elderly (>75 years). In particular, in the very elderly patient azilsartan medoxomil showed to be slightly less efficacious. Other important subgroups, e.g. patients with diabetes mellitus, heart failure or who had activated RAAS were too small to be able to draw conclusions. This limits external validity of the clinical programme. The uncertainty of the information in these populations has been addressed in the SmPC through the inclusion of cautionary statements, in particular the recommendation to consider a starting dose of 20 mg instead of 40 mg in these populations. This is reasonable as azilsartan medoxomil is a drug in a class of antihypertensive agents with a well-known mechanism of action (AT1 antagonism). Patients with pre-existent cardiovascular events/co-morbidities were allowed in the studies. The applicant analysed the efficacy in high risk population according to the classes of CV risk stratification as proposed in the ESC and ESH guidelines showing similar efficacy with the overall population.

2.5.4 Conclusions on the clinical efficacy

Azilsartan medoxomil is a new drug in the well known class of AT1 antagonists. Antihypertensive efficacy with and without other antihypertensives (diuretics and amlodipine) in patients with uncomplicated mild to severe hypertension up to 75 years of age has been demonstrated for the dose range of 20 – 80 mg of azilsartan medoxomil, both in short term and long term studies. The 40 mg dose is considered an acceptable starting dose in these patients. The benefit/risk of azilsartan medoxomil 80mg dose showed additional benefit over the 40 mg dose with respect to BP lowering efficacy. A limitation of the dossier is the paucity of data in complicated patients,patients with co-morbidities such as DM and heart failure, and the very elderly both in terms of efficacy and safety. In the SmPC it is recommended to lower the starting dose to 20 mg in such populations.

2.6 Clinical safety

Figure 10. Overview of safety population



In total, sufficient numbers of patients have been evaluated. In addition, sufficient numbers of patients compared to placebo were evaluated. Also extensive numbers of patients were evaluated against comparators. Furthermore sufficient numbers of patients have been included to evaluate long-term safety.

Patient exposure

Table 13. Exposure Overview: TAK-491 Phase 3 Studies in the Monotherapy Programme

Exposure	Placebo (a) (N=801)	TAK-491 20 mg (b) (N=283)	TAK-491 40 mg (c) (N=1808)	TAK-491 80 mg (c) (N=2783)	TAK-491 All Doses (d,e) (N=4814)	Comparator (f) (N=1468)
Days of exposure						
Mean (SD)	41.3 (7.43)	41.2 (7.45)	94.0 (77.27)	149.5 (128.99)	124.2 (116.55)	86.4 (61.21)
Median (min-max)	42 (1-63)	43 (1-57)	44 (1-379)	132 (1-427)	46 (1-427)	44 (1-190)
Cumulative exposure (n)						
≥1 day	801	283	1808	2783	4814	1468
≥2 weeks	782	276	1777	2690	4683	1438
≥4 weeks	758	269	1734	2609	4552	1394
≥8 weeks	3	2	692	1539	2173	556
≥12 weeks	0	0	660	1472	2074	532
≥24 weeks	0	0	499	1249	1704	386
≥48 weeks	0	0	51	482	588	0

Table 14. Exposure by Individual Phase 3 Pivotal Studies

	Monotherapy Placebo-Controlled Studies												
	491-008					491-019					491-011		
	PBO	TAK-491			OLM	PBO	TAK-491		VAL	OLM	PBO	TAK-491	
Days of Exposure	N=142	20 mg N=283	40 mg N=281	80 mg N=284	40 mg N=282	N=155	20→40 mg N=280	40→80 mg N=284	160→320 mg N=277	20→40 mg N=290	N=138	40 mg N=137	80 mg N=137
n	141	283	281	283	281	155	280	284	277	290	138	137	137
Mean	41.8	41.2	41.5	41.5	41.9	40.8	41.2	40.5	41.0	41.5	41.6	41.4	39.4
(SD)	(6.28)	(7.45)	(6.44)	(7.03)	(5.38)	(8.09)	(7.32)	(8.96)	(7.80)	(7.22)	(8.14)	(8.07)	(11.07)
Median	43.0	43.0	43.0	43.0	43.0	42.0	42.0	42.0	43.0	42.5	43.0	43.0	42.0
min, max	2, 50	1, 57	1, 56	1, 52	8, 55	1, 59	1, 57	1, 54	1, 51	1, 55	2, 63	1, 56	1, 56

	Active-Controlled Studies						Open-Label Studies						
	491-301(DB) (a)			491-020			491-016(OL) (b)		491-006 Interim-2 (b,c)			491-301(OL) (b)	
Days of Exposure	TAK-491 20→40 mg N=327	TAK-491 20→80 mg N=329	VAL 80→320 mg N=326	TAK-491 20→40 mg N=294	TAK-491 20→80 mg N=293	RAM 2.5→10 mg N=293	TAK-491 N=179	TAK-491 + CLD N=239	TAK-491 N=269	TAK-491 + CLD N=216	TAK-491+ HCTZ N=184	TAK-491 N=55	TAK-491 + HCTZ N=115
n	327	329	326	294	293	293	179	239	268	216	184	55	115
Mean	145.3	142.1	142.2	158.7	157.7	154.7	124.6	171.8	260.2	353.2	321.0	180.1	186.8
(SD)	(49.07)	(53.99)	(51.88)	(33.87)	(37.08)	(40.82)	(72.23)	(32.62)	(161.24)	(87.30)	(96.84)	(44.39)	(30.55)
Median	168.0	168.0	168.0	168.0	168.0	168.0	181.0	183.0	347.5	392.0	332.0	195.0	195.0
min, max	1, 187	1, 183	1, 189	1, 187	3, 200	4, 190	1, 196	29, 214	1, 427	34, 425	57, 407	3, 203	29, 214

	Coadministration Studies							
	491-009			491-010			491CLD-306	
Days of Exposure	PBO + CLD 25 mg N=181	TAK-491 40 mg + CLD 25 mg N=184	TAK-491 80 mg + CLD 25 mg N=182	PBO + AML 5 mg N=185	TAK-491 40 mg + AML 5 mg N=190	TAK-491 80 mg + AML 5 mg N=188	TAK-491CLD N=302	TAK-491 + HCTZ N=303
n	181	184	182	185	190	187	302	303
Mean	41.4	41.0	40.2	41.5	42.4	41.8	65.8	65.3
(SD)	(6.77)	(8.80)	(10.11)	(7.16)	(5.56)	(7.22)	(15.40)	(16.35)
Median	42.0	42.0	43.0	43.0	43.0	43.0	71.0	71.0
min, max	2, 56	1, 56	1, 66	1, 50	2, 56	1, 56	1, 81	1, 84

Sufficient numbers of patients have been included to evaluate long-term safety: 1704 patients for more than 26 weeks and 588 patients for more than 48 weeks. Although the ICH E1 guideline "Population Exposure: The extent of Population Exposure to assess Clinical Safety (CPMP/ICH/375/95)" stipulates 100 patients should be treated for at least one year, this slightly shorter period seems acceptable as the total number of patients exposed long-term is much larger.

Adverse events

Placebo controlled short term studies

There was no major difference in the incidence of AEs with respect to treatment group (placebo, azilsartan medoxomil, and active comparator), although the overall incidence of AEs seems to be slightly higher in the 80 mg dose group. Headache was the most common AE and was generally reported less frequently in azilsaran (20, 40, and 80 mg) groups (4.6%, 3.2%, and 5.6% in study 491-008) than in the placebo group (7.0% in study 491-008). Dyslipidaemia was the only other AE reported in ≥ 5% of subjects in any of the treatment groups and was most found in the highest dose of azilsartan medoxomil (2.5-5.6%). AEs occurring in ≥ 2% of subjects in any group that were reported more frequently in the azilsartan medoxomil groups than in the placebo group included dizziness, oedema peripheral, nasopharyngitis, back pain, fatigue, and diarrhoea. Diarrhoea, dizziness and fatigue were found to be related to study drug and seem to be dose-related: 0, 0.7 and 1.3%; 0.9, 1.9 and 2.3%; and 0.2, 0.4 and 1.1% for placebo, azilsartan medoxomil 40 and 80 mg, respectively.

Active controlled studies

The proportion of subjects who experienced AEs in the azilsartan medoxomil group (40 and 80 mg) (53.7%) was slightly higher than in the comparator group (49.4%), and was not dose related. Headache was the most common AE with similar incidence across all treatment groups (range 3.4-10.1%).

The incidence of treatment related AEs (TRAE) was generally similar between azilsartan medoxomil and comparator. In case of a TRAE the investigators considered the AE as possibly, probably, or definitely related to study drug. Dizziness was the most commonly reported TRAE, which occurred at a higher rate in the azilsartan medoxomil group (4.1%) than in the active comparator group (1.9%). Overall, there was no difference in TRAE incidence between azilsartan medoxomil at 40 and 80 mg. However, the incidence of TRAEs hypotension, dizziness and blood CK increased were higher in the azilsartan medoxomil arms and seemed dose-related (1.3%, 1.8%, and 0.8%; 3.9%, 4.3% and 1.9%; 0.3%, 1.6% and 0.8% for azilsartan medoxomil 40 and 80 mg and comparator, respectively). Cough and proteinuria occurred at a higher rate (3.6% and 1.1%) in the comparator than in the azilsartan medoxomil group (0.7% and 0.2%, respectively).

Comparison with other ARBs

Events reported more often with azilsartan medoxomil compared with olmesartan were dyslipidaemia, diarrhoea, and UTI in the short-term studies. Events reported more often with azilsartan medoxomil compared with valsartan were diarrhoea, dizziness, UTI, and fatigue in the 6-week study (study 491-019); and headache, dizziness, UTI, fatigue, blood CK increased, back pain, pain in extremity, and bronchitis in the 24-week study (study 491-301).

Events reported more often in patients treated with olmesartan compared with azilsartan medoxomil were dizziness (only in study 491-008), fatigue, and peripheral oedema. Events reported more often with valsartan compared with azilsartan medoxomil were headache, nausea, and peripheral oedema in the 6-week study; and nasopharyngitis, dyslipidaemia, arthralgia, upper respiratory tract infection, haematuria, and proteinuria in the 24-week study.

Co-administration studies

There were no major differences across treatment groups in the overall frequency of AEs: chlorthalidone (CLD) monotherapy (51.9%), CLD + azilsartan medoxomil 40 mg co-administration (52.2%), and CLD+azilsartan medoxomil 80 mg co-administration (51.6%) in study 491-009. In study 491-010 amlodipine (AML) monotherapy (46.5%), AML+azilsartan medoxomil 40 mg co-administration (48.4%) and AML+azilsartan medoxomil 80 mg co-administration (39.9%). In study 491-306 comparing the fixed dose combination azilsartanmedoxomil-chloorthalidone (52.3%) and azilsartan medoxomil co-administered with HCTZ (47.5%).

The most common AEs across these studies were dizziness and headache. The incidence of dizziness was dose related for azilsartan medoxomil when co-administered with chlorthalidone but not with amlodipine.

Overall treatment related AE incidences were 24.7% in study 491-009, 14.6% in study 010, and 32.6% in study 491-306. The most frequent TRAEs included dizziness (azilsartan medoxomil 4.1% and comparator 1.9%), headache (3.0% and 2.9%), increased blood CK (1.0% and 0.8%), fatigue (1.7% and 1.5%), and hypotension (1.5% and 0.8%).

Open-label studies

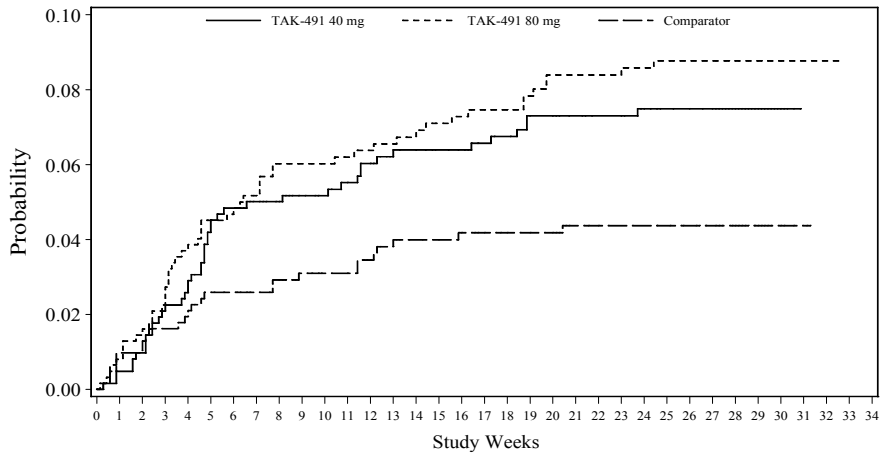
The adverse event profile from the pooled analyses was consistent with that presented for the individual studies, with a slightly higher incidence of AEs than in controlled studies due to longer treatment duration. Overall, 66.7% of subjects experienced at least one AE, with most being mild or moderate in severity. Approximately half of subjects had AEs that occurred within the first 3 months of treatment. TRAEs occurring in at least 2% of subjects were dizziness (8.5%), fatigue (4.2%), headache (3.5%), blood creatinine increased (2.4%), and hypotension (2.5%). Other frequently reported TRAEs (1.1% to 1.5%) were dizziness postural, blood CK increased, hypokalaemia, muscle spasms, orthostatic hypotension, diarrhoea, nausea, and hyperuricaemia.

Hypotension and dizziness

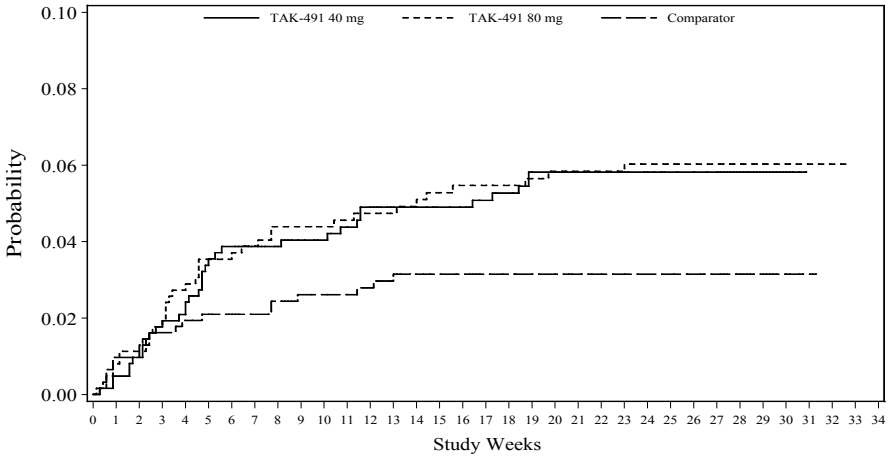
Incidence of hypotension and dizziness were also assessed over time. Patients treated with azilsartan medoxomil had roughly a two-fold increased probability of having a first hypotensive or dizziness adverse event (see figures below).

Figure 13. Time-to-First-Event Analysis: Hypotension Cluster in Long-term Active-Controlled Studies

Hypotension



Dizziness



Renal events

Renal adverse events were observed in 0.5%, 0.7% and 0.6% in placebo, azilsartan medoxomil 40 mg and azilsartan medoxomil 80 mg treated patients in the short-term studies. In the long-term controlled studies this was 1.5%, 1.1% and 2.1% in the comparator, 40 and 80 mg azilsartan medoxomil groups. The detailed named adverse events were generally 0.1-0.2% (1 patient) for a specific treatment arm, except for blood creatinine increase (0.2%, 0.6% and 0.4% in short-term studies and 0, 0.6% and 1.1% in long-term studies), blood urea increased (0, 0.6% and 0.1% in short-term studies and 0, 0.3% and 0.6% in long-term studies).

Serious adverse event/deaths/other significant events

Short-term monotherapy placebo and active-controlled studies

In monotherapy placebo-controlled studies, no SAE was reported by more than 1 subject in any single treatment group in any individual study. SAEs resolved for all but 1 subject, who died due to gastrointestinal haemorrhage and shock. Total numbers were 14, 14 and 4 for studies 491-008, 491-491-019, and 491-011 respectively. The percentage of subjects with SAEs, by treatment group, for studies 491-008, 491-019, and 491-011, respectively, was 2.1%, 1.3%, and 0 in the placebo group; 2.8% in the azilsartan medoxomil 20 mg group (study 491-008 only); 0, 0.7%, and 2.2% in the azilsartan medoxomil 40 mg group; and 0.4%, 1.1%, and 0.7% in the azilsartan medoxomil 80 mg group. The percentage of subjects with SAEs was 0.7% (study 491-008) and 1.4% (study 491-019) in the olmesartan group, and 1.1% in the valsartan group (study 491-019). SAE incidences did not increase with dose in the azilsartan medoxomil treatment groups and were not disproportionately represented by a particular system organ class (SOC) or preferred term.

Long-term active-controlled studies

In long-term active-controlled studies, the most frequently reported SAE was fall, reported for 2 active comparator–treated subjects. Both events were accidental falls (e.g. slipping on wet surface) and not associated with hypotensive episodes, dizziness, or syncope.

Open-label studies

In open-label studies, there were 64 (5.1%) of total subjects with at least 1 serious adverse event. The most frequently reported SAEs were noncardiac chest pain, syncope, and hypotension (3 subjects, 0.2%, each). Treatment related SAEs were 6 (0.5%) in total.

Co-administration studies

The incidence of SAEs in co-administration studies was 7 (1.3%) in study 491-009, 4 (0.7%) in study 491-010, and 11 (1.8%) in study 7491-306. The most frequently reported SAEs were syncope and renal failure. Syncope was reported for 3 subjects (2 received azilsartan medoxomil with chlorthalidone and 1 received azilsartan medoxomil with amlodipine), 1 of which was associated with orthostatic hypotension. Renal failure was reported for 2 subjects (both received azilsartan medoxomil-CLD), 1 of whom had concurrent chronic kidney disease.

Deaths

A total of 10 deaths occurred during the whole study programme, seven were considered cardiovascular deaths. Five deaths occurred in patients treated with azilsartan medoxomil; one in a patient receiving TAK-536 (metabolite) (assessed as non-related to study drug); two in placebo and two in active control treated patients (olmesartan and valsartan).

Three of the 5 deaths associated with azilsartan medoxomil treatment occurred during the phase 3 monotherapy studies in which 4814 subjects received at least 1 dose of azilsartan medoxomil; the 2 other deaths occurred in the FDC programme (study 491CLD-306) in which all 605 subjects received at least 1 dose of azilsartan medoxomil. Four deaths occurred in subjects who received azilsartan medoxomil alone, 1 in a subject who received azilsartan medoxomil 40 mg+chlorthalidone 12.5 mg. Of the 4 fatal SAEs in subjects treated with azilsartan medoxomil alone, 3 were considered not related to study drug and 1 (sudden death; 491CLD-306/1023/024) to be possibly related (see description below). One subject died (sudden death) after having received treatment with azilsartan medoxomil for 14 days and with azilsartan medoxomil 40 mg+chlorthalidone 12.5 mg for 1 day. The event was determined to be unrelated to study drug.

Description of the single death possibly related to study drug:

Subject 491CLD-306/1023/024 (azilsartan medoxomil 40 mg), a 61-year-old, 124 kg, black woman experienced a fatal SAE of sudden death on Day 6 of the active (single-blind) Treatment Period. An autopsy was not performed and details regarding the event are unknown. Due to the lack of a definitive diagnosis, the event was recorded as possibly related to study medication by default. The death certificate was provided and reports the immediate cause of death as sudden death with unknown cause. The subject's relevant medical history included hypertension, sleep apnea, obesity, and lower extremity pitting oedema. Concurrent medications were furosemide, potassium chloride, and ibuprofen (as required).

Neoplasm and cancer risk

Across controlled short-term (up to 6 weeks) studies, AEs that coded to the neoplasms SOC were reported for 2 azilsartan medoxomil–treated subjects (<0.1%), neither of which was considered malignant. Across controlled long-term (up to 24 weeks) studies in 1243 subjects, including co-administration studies, AEs that coded to the neoplasms SOC were reported for 11 azilsartan medoxomil–treated subjects (0.9%), of which, events were identified as malignant for 4 subjects (0.3%). 1 subjects out of 619 subjects treated with a comparator coded to the neoplasm SOC which was not considered malignant. In the Open-Label Pool (up to 56 weeks), 9 subjects (0.7%) had AEs that coded to the neoplasms SOC, of which for 4 subjects (0.3%) were identified as malignant. The interpretation of these neoplasm data is limited by relatively short exposure duration and the overall small number of events.

Laboratory findings

General findings

In the short-term placebo controlled studies abnormal lab values which were higher than 0.1% in every treatment group were creatinine > 1.5×BL and > ULN (0.2%, 0.4% and 0.3% for placebo, azilsartan medoxomil 40 mg and 80 mg respectively), AST > 3×ULN (0.7%, 0.7% and 0.9%), ALT >3×ULN (0.2%, 0.6% and 0.7%), GGT > 3×ULN (2.3%, 1.7% and 3.2%), triglycerides > 2.5×ULN (1.4%, 3.3% and 4.5%), uric acid increase (0.9%, 0.9% and 1.0%), and CK > 10×ULN (0.5%, 0.4% and 0.3%).

The most frequently observed abnormal lab values in the long-term active controlled studies were potassium levels > 6.0 mEq/L (1.1%, 2.3% and 2.0% for comparator, azilsartan medoxomil 40 mg and 80 mg respectively), GGT > 3×ULN (5.2%, 5.5% and 5.4%), triglycerides > 2.5×ULN (2.7%, 2.8% and 2.6%), and uric acid increase (1.1%, 3.4% and 3.1%).

Open-label pool

Percentages of subjects with abnormal values of creatinine, GGT, triglycerides and uric acid at any visit were 7.7%, 6.3%, 7.6%, and 11.9% respectively. In these studies, subjects were allowed to add diuretics and other non-ARB antihypertensive agents, which likely contributed to the higher incidences of abnormal values of creatinine, triglycerides, and uric acid. For the majority of subjects, most of the abnormal values returned to baseline or had stabilized by the final visit or at subsequent follow-up visits. Concurrent elevations of ALT and AST > 3×ULN occurred in 0.7% of subjects, and elevations of either ALT or AST > 5×ULN occurred in 0.2% and 0.4% of subjects, respectively. No subject had a value > 10×ULN or had a concurrent elevation of ALT or AST with total bilirubin > 2×ULN or ALP > 3×ULN. An in depth evaluation for these cases was provided. Two cases were related to study drug, of whom one patient was withdrawn from the study due to an hepatic adverse event.

Twenty-four (of 1257) subjects had ALT and/or AST > 3×ULN. Eight subjects had ALT and AST > 3×ULN, and for 3 of these 8 subjects, the elevations were reported as AEs (1 subject prematurely discontinued). AEs associated with abnormal chemistry values that were considered to be SAEs or resulted in premature discontinuation in the Open-Label Pool occurred in 19 subjects out of 1257.

Serum creatinine elevation

Serum creatinine elevations were observed in some subjects, especially in subjects who received azilsartan medoxomil co-administered with chlorthalidone 25 mg, consistent with the transient and reversible profile of creatinine elevations known to occur with other RAAS blockers. In the short-term placebo-controlled studies >3 0% creatinine level elevation was observed in 4 (0.9%), 8 (1.2%), and 9

(1.3%) patients at any visit treated with placebo, azilsartan medoxomil 40 and 80 mg, respectively. This was 0.5%, 0,6% and 0.7% at the final visit. For long-term comparator studies these findings were 4 (0.7%), 26 (4.2%) and 35 (5.8%) for any visit for comparator, azilsartan medoxomil 40 and 80 mg and 0, 0.6% and 1.8% at the final visit. When azilsartan medoxomil was co-administered with CLD these rates were 16.3% versus 6.9% in the monotherapy arms in the open-label study 491-016 and 26.9% vs 7.4% in the open-label study 491-006. These elevations were associated with greater blood pressure reductions in the long-term active controlled studies, which is also consistent with the pharmacodynamic drug effects.

The most convincing demonstration of the reversibility of creatinine elevations comes from study 016 where study treatment was withdrawn in a randomised manner: twenty-one subjects with a creatinine elevation ≥ 30% entered the 6-week double-blind reversal phase of study 491-016 (7.9% (12/151) on placebo and 6.2% (9/146) on azilsartan medoxomil). During this phase of the study, (9.9%) of the subjects who remained on azilsartan medoxomil treatment still had creatinine elevation ≥ 30%. For the subjects in whom azilsartan medoxomil was withdrawn creatinine elevation ≥30% decreased to 2.7%.

Immunological events

A small increase in the number of patients with a decrease in haemoglobin was found comparable to what is found in the comparators (5 (0.4%) for azilsartan medoxomil, 3 (0.5%) comparator). In addition, a slightly higher incidence of decreased haematocrit was found for the study drug, although incidences were low (7 (1.2%) for azilsartan medoxomil 80 mg, 2 (0.3%) for azilsartan medoxomil 40 mg, and 4 (0.7%) for comparator).

Safety in special populations

Renal impairment

In phase 3 studies, across both (active and placebo) controlled-study pools, the moderate/severe renal impairment subgroup was small (5.6% of all subjects). The overall incidence of AEs was higher with azilsartan medoxomil 80 mg in the moderate to severe subgroup in the placebo-controlled pool. However, there were no consistent patterns in any of the most frequently reported AEs across renal function subgroups with azilsartan medoxomil treatment. In the placebo-controlled pool, headache occurred more frequently with azilsartan medoxomil 80 mg in the moderate/severe impairment subgroup (16.7% [5 of 30 subjects]) compared with the mild impairment (4.0% [13 of 326 subjects]) or normal renal function (5.5% [19 of 347 subjects]) subgroups. In contrast, in the long-term active-controlled pool, headache occurred more frequently with azilsartan medoxomil 40 mg in the normal subgroup (10.2% [21 of 206 subjects]) compared with the mild (6.2% [23 of 370 subjects]) or moderate/severe impairment subgroups (0 of 45 subjects). Also in this long-term active-controlled pool, azilsartan medoxomil treatment in the moderate/severe impairment subgroup was associated with a higher frequency of elevated creatinine, sodium, potassium, and high uric acid compared with the normal and mild subgroups. Azilsartan medoxomil exposure was only modestly elevated in mild (AUC +29%) and moderate (AUC +25%) renal impairment, but exposure was doubled (AUC +98%) in severe renal impairment. Patients with severe renal impairment or end stage renal disease should not be treated with azilsartan medoxomil as they were excluded from the clinical studies. This is reflected in the SmPC.

Hepatic impairment

Treatment of subjects with severe hepatic impairment (Child-Pugh score >9) is not recommended according to the SmPC.

Age

There were no consistent differences between the < 65 and ≥ 65 years subgroups with azilsartan medoxomil treatment in the overall incidence of AEs, SAEs, or AEs that led to study drug interruption or premature discontinuation. Dizziness occurred more frequently in the ≥ 65 years subgroup with placebo treatment. Cough occurred more frequently in the azilsartan medoxomil 80 mg group (3.1%) in subjects ≥65 years compared with azilsartan medoxomil 40 mg group (1.0%) but was lower than for the active comparator group (4.1%) in the long-term active-controlled pool. Blood CK increased adverse events occurred more frequently with comparator and with azilsartan medoxomil treatment in the <65 years subgroup in the long-term active-controlled pool.

Although the proportion of very elderly subjects (≥ 75 years) in both phase 3 controlled pools was relatively small (4.3% in the monotherapy placebo-controlled pool and 5.1% in the long-term active-controlled pool), their overall safety profile was similar to those < 75 years. Nevertheless, in the long-term active-controlled pool, hypotension occurred more frequently in the ≥ 75 years subgroup than the < 75 years subgroup in the active comparator group (12.9% [4 subjects] vs 3.7%) but not in the azilsartan medoxomil 40/80 mg group (6.2% [4 subjects] vs 7.9%); these AEs reported with azilsartan medoxomil were not dose-dependent.

Safety related to drug-drug interactions and other interactions

Drug-drug interactions have only been studied with regard to pharmacokinetics.

Discontinuation due to adverse events

Overall, few subjects permanently discontinued study drug due to adverse events. Overall, dizziness, hypotension and headache were the most frequently reported AEs that led to premature discontinuation. Occurrence of hypotension was more frequent in the longer term studies and appeared to be dose related for azilsartan medoxomil but not when co-administered with other antihypertensive agents as described below.

Monotherapy placebo-controlled studies

In monotherapy placebo-controlled studies, rates for discontinuation due to adverse events were low (2.3% in study 008, 2.6% in study 491-019, and 1.7% in study 491-011) and similar between placebo and azilsartan medoxomil, with no difference between the 40 and 80 mg groups. In study 491-008, more subjects (11/283 (3.9%)) permanently discontinued the study due to adverse events in the azilsartan medoxomil 20 mg group compared with the other treatment groups (5/142 (3.5%) for placebo, 3/283 (1.1%) for azilsartan medoxomil 40 mg, 6/285 (2.1%) for azilsartan medoxomil 80 mg, and 4/282 (1.4%) for olmesartan medoxomil); none of the discontinuation events in the 20 mg group occurred in more than 1 subject except headache (2 subjects).

Long-term active-controlled studies

In long-term active-controlled studies, rates for discontinuation due to adverse events were lower in study 491-020 [ramipril control] (3.3%) than in study 491-301 [valsartan control] (6.6%). Nonetheless, discontinuation rates in both studies were similar between active comparator (34(5.5%)) and azilsartan medoxomil (66 (5.3%)), with no difference between the 40 and 80 mg groups (30 (4.8%) and 36 (5.8%)).

Open-label studies

In open-label long-term studies, rates for discontinuation due to adverse events were generally low but slightly higher in study 491-006 (7.3%), a 56-week study, than in study 491-016 (6.5%) and study 491-301 (4.7%), 26- and 28-week studies, respectively.

Co-administration studies

In co-administration studies, rates for discontinuation due to adverse events were generally low but more frequent with diuretic co-administration (4.4% in study 009 [chlorthalidone] and 7.7% in study 491-306 [chlorthalidone or HCTZ]) than with amlodipine co-administration (1.2% in study 491-010). No differences were observed between the azilsartan medoxomil 40 and 80 mg groups in the 491-009 and 491-010 studies. In study 306, the incidence was higher in subjects who received the FDC (9.2%) than in subjects who received azilsartan medoxomil co-administered with HCTZ (6.2%).

Post marketing experience

There is no post-marketing experience with this product (it is not yet marketed in any country).

2.6.1 Discussion on clinical safety

An adequate number of patients has been evaluated to establish azilsartan medoxomil's safety profile. 1704 patients have been treated for more than 26 weeks and 588 for more than 48 weeks. Although the ICH E1 Guideline "Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CMPM/ICH/375/95)" stipulates 100 patients should be treated for at least one year, this slightly shorter period appears acceptable as the total number of patients exposed long-term is much larger.

The applicant provided data on adverse events of azilsartan medoxomil against placebo and against comparative ARBs. The adverse events of dizziness, fatigue, headache, blood creatinine increased AEs, hypotension, postural dizziness, and blood CK increased AEs were consistently found during study drug (azilsartan medoxomil) treatment across the different controlled and open-label trials. Diarrhoea, dizziness, hypotension and fatigue appear to be dose-related and occur most often in the highest dose group (80 mg azilsartan medoxomil). In particular, the higher incidence of dizziness and hypotension can be explained by the stronger antihypertensive effect observed with the highest azilsartan medoxomil dose. Data on the incidence of hypotension and dizziness over time indicate a dose-related higher incidence with azilsartan medoxomil already occurring within a few weeks for both of these adverse events. These adverse events also demonstrated to lead to more treatment discontinuations, although this was only slightly more compared to placebo.

A detailed description of renal adverse events showed that incidences were low and not much higher than for placebo. However, in the long-term trials there appeared to be a dose-dependent relation for blood creatinine increase (or GFR decrease) and blood urea increase. Increase in the level of serum creatinine is known to be associated with RAAS blockade, and represents most of the time a reversible hemodynamic effect associated with a higher blood pressure reduction. In addition, reversibility has been shown from data of the reversible phase of study 491-016.

In general the incidence of laboratory abnormalities was low. Hyperkalemia did occur. It is known to be associated with RAAS blockade and is also observed with other ARBs and ACE-inhibitors. In contrast to other ARBs an increase in uric acid increase was observed, in particular in the longer term. This could be partly explained by reduced GFR, however, this should be further followed post-approval. Furthermore, some abnormalities in liver enzymes (ALT, AST and triglycerides) were noticed, but this was not consistent across all trials and was also observed for the comparators (valsartan and ramipril). Specific cases have been described in detail. A small increase in the number of patients with a

decrease in haemoglobin was found comparable to what is found in the comparators. In addition, a higher incidence of decreased haematocrit was found for the study drug, although incidences are low.

The incidence of serious adverse events was generally low and not significantly different compared to the comparators (ARB, ACE, placebo). There seems not to be any relation between study drug and the four deaths that occurred, although in one case of sudden death the information was limited.

Several subgroup analyses were performed. Based on the data provided no trend towards a higher incidence of neoplasm or cancer could be observed, but the incidence was very low and no conclusions can be drawn. A recent meta-analysis identified no increased risk with ARBs in contrast to previous publications.

The use of azilsartan medoxomil according to renal impairment showed no clear trend towards more adverse events, discontinuation due to adverse events or severe adverse events with increasing impairment of renal function. No consistent pattern in terms of more adverse events in severe renal impairment on the highest azilsartan medoxomil dose is observed. However, laboratory adverse events related to blockade of the RAAS (creatinine, potassium, sodium, etc.) were increased during long-term treatment in moderate and severe renal impaired patients. Exposure to azilsartan medoxomil may be doubled in these patients (see pharmacokinetic section). This warrants more careful up-titration in patients with moderate to severe impairment as has been reflected in the SmPC.

Severe hepatic impaired patients were not included in the studies. This is covered in the SmPC.

In addition, typical adverse events associated in the elderly are found such as hypotension and dizziness. However, this was not seen to be different for azilsartan medoxomil than for the comparators. However, numbers of very elderly were limited. This also applies to the patients with co morbidities and at high CV risk (see also above under efficacy). Therefore, the safety profile of azilsartan medoxomil in these patients is not clearly established.

2.6.2 Conclusions on the clinical safety

In general, adverse events associated with azilsartan medoxomil were mild to moderate of origin and not different from what is known from other ARBs. The adverse events of dizziness, fatigue, increase in blood creatinine, hypotension, dizziness postural, and blood CK increased were consistently found during study drug treatment across the different controlled and open-label trials. Most appear to be dose-related and occurred most often in the highest dose group (80 mg azilsartan medoxomil). A dose-dependent increase in blood creatinine was observed that is known to be associated with RAAS blockade and represents most of the time a reversible hemodynamic effect associated with more blood pressure reduction. Similarly, hyperkalaemia did occur, as also observed with other ARBs and ACE-inhibitors. An unexpected increase in uric acid was observed, which could partly be related to a reduced GFR, but further follow-up is warranted.

Only limited information was available in high risk groups, such as the very elderly and patients who have an activated RAAS such as patients with heart failure. Renal impaired patients did not demonstrate a higher safety risk profile, although exposure is increased in severe renal impairment which warrants more careful titration. Patients with severe hepatic impairment should not be treated with azilsartan medoxomil as reflected in the SmPC.

2.7 Pharmacovigilance

2.7.1 Detailed description of the pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.7.2 Risk Management Plan

The applicant submitted a risk management plan.

Table 15. Summary of the risk management plan

Safety Concern	Pharmacovigilance Activities (Routine and Additional)	Risk Minimization Activities (Routine and Additional)
Identified Risks		
Elevated serum creatinine	Routine Pharmacovigilance	Section 4.4 Special Warnings and Precautions For Use: Concurrent Renal Impairment, Section 4.8 Undesirable Effects: Laboratory Findings in the Summary of Product Characteristics, and in the Package Leaflet.
Hypotension-related events	Routine Pharmacovigilance	Section 4.4 Special Warnings and Precautions For Use: Hypotension in Volume- and/or Salt-Depleted Patients, Section 4.8 Undesirable Effects: Adverse Reactions and Description of Selected Adverse Reactions of the Summary of Product Characteristics, and in the Package Leaflet.
Diarrhoea	Routine Pharmacovigilance	Section 4.8 Undesirable Effects: Adverse Reactions of the Summary of Product Characteristics and in the Package Leaflet.
Foetotoxicity	Routine Pharmacovigilance	Section 4.3 Contraindications, Section 4.4 Special Warnings and Precautions for Use: Pregnancy, Section 4.6 Fertility, Pregnancy and Lactation of the Summary of Product Characteristics, and in the Package Leaflet
Potential Risks		
Blood uric acid increased	Routine Pharmacovigilance	Section 4.8 Undesirable Effects: Adverse Reactions of the Summary of Product Characteristics and in the Package Leaflet.
Dyslipidemia	Routine Pharmacovigilance	Section 4.8 Undesirable Effects: Adverse Reactions of the Summary of Product Characteristics and in the Package Leaflet.
Oedema peripheral	Routine Pharmacovigilance	Section 4.8 Undesirable Effects: Adverse Reactions of the Summary of Product Characteristics and in

		the Package Leaflet.
Important Missing Information		
Limited experience in:		
Patients with moderate and severe renal impairment and ESRD	Routine Pharmacovigilance	Information in the Summary of Product Characteristics Section 4.2 Posology and Method of Administration: Special Populations, Section 4.4 Special Warnings and Precautions for Use: Concurrent Renal Impairment, Section 5.2 Pharmacokinetic Properties: Characteristics in Specific Groups of Persons: Renal Impairment, and in the Package Leaflet.
Elderly patients ≥75 years old	Routine Pharmacovigilance	Information in the Summary of Product Characteristics in Section 4.2 Posology and Method of Administration: Special Populations, Section 5.2 Pharmacokinetic Properties: Characteristics in Specific Groups of Patients: Geriatric Use, and in the Package Leaflet.
Pregnant females	Routine Pharmacovigilance	Summary of Product Characteristics language, consistent with the class labeling of other AIIRAs, in Section 4.3 Contraindications, Section 4.4 Special Warnings and Precautions for Use: Pregnancy, Section 4.6 Fertility, Pregnancy and Lactation, and in the Package Leaflet.
No experience in:		
Pediatric patients <18 years old	Routine Pharmacovigilance Pediatric development programme with planned phase 1 and phase 3 studies. Drug utilization study 1 year and 5 years post-launch in the EU, including special attention to any pediatric prescribing.	Information in the Summary of Product Characteristics in Section 4.2 Posology and Method of Administration: Special Populations, and Section 5.2 Pharmacokinetic Properties: Characteristics in Specific Groups of Patients, and in the Package Leaflet. A detailed Pediatric Investigation Plan is included in Module 1.10 of this MAA filing.
Nursing mothers	Routine Pharmacovigilance	Information in the Summary of Product Characteristics in Section 4.6 Fertility, Pregnancy and Lactation and in the Package Leaflet.
Patients with hepatic impairment (ALT >2.5×ULN, active liver disease, or jaundice)	Routine Pharmacovigilance	Information in the Summary of Product Characteristics in Section 4.2 Posology and Method of Administration: Special Populations, Section 5.2 Pharmacokinetic Properties: Characteristics in Specific Groups of Patients, and in the Package Leaflet.
Congestive heart failure	Routine Pharmacovigilance	Information in the Summary of Product Characteristics Section 4.2

		Posology and Method of Administration and Section 4.4 Special warnings and precautions for use:
Renal artery stenosis	Routine Pharmacovigilance	Information in the Summary of Product Characteristics in Section 4.4 Special warnings and precautions for use:
Off Label use	Routine Pharmacovigilance Drug utilization study 1 year and 5 years post-launch in the EU	The Summary of Product Characteristics specifies the therapeutic indication in section 4.1

No additional risk minimisation activities were required beyond those included in the product information.

The CHMP, having considered the data submitted, was of the opinion that the below Pharmacovigilance activity in addition to the use of routine Pharmacovigilance is needed to investigate further some of the safety concerns:

Description	Due date
Drug utilization study 1 year and 5 years post-launch in the EU	Protocol for the drug utilization study will be submitted within 3 months of approval.

2.8 User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Azilsartan medoxomil is a selective AT1 receptor blocker (ARB) indicated for the treatment of essential hypertension. Significant blood pressure reduction versus placebo in the *short-term* trials of 6 weeks was demonstrated for the whole range of azilsartan medoxomil formulations of 20mg, 40mg and 80 mg in patients with mild to moderate uncomplicated essential hypertension (-12.2 mmHg to -14.6 mmHg 24h SBP). The 40 mg and the 80 mg azilsartan medoxomil doses were superior to (maximal dose) valsartan 320mg (-10.2 mmHg, $p<0.001$) and the 80 mg dose was superior compared to a maximal dose of olmesartan (-11.7 mmHg versus -12.6 mmHg 24h SBP, $p=0.038$) on ABPM, clinical SBP and responder rates (56.6-57.8% AZI 80 vs 48.7-53.2% OLM, $p=0.035$). A more severe

hypertensive patients group was included in the open-label phase conform with the inclusion criteria and sufficient numbers of patients were analyzed to assess antihypertensive efficacy.

Consistent efficacy was found across subgroups, including patients with renal insufficiency, except for the age group of > 75 years of age and in the black population versus placebo. A lower, but still significant response for the black subjects was also demonstrated in the clinical study including only a black population. This is known from other ARBs and ACE-inhibitors and possibly due to the higher prevalence of low-renin states in black hypertensive patients.

For the *long-term* (24 weeks) comparative studies, significant more systolic blood pressure reduction was demonstrated for both doses of azilsartan medoxomil 40 and 80 mg compared to valsartan (24h SBP –14.9, -15.3 and -11.3 mmHg, resp. ($p<0.001$ vs. valsartan) and ramipril (clinical SBP for 40 mg, 80 mg dose and ramipril is -20.6, -21.4 and -12.2 mmHg, resp. ($p<0.001$ vs. ramipril)). Reduction in diastolic blood pressure and responder rates were consistent with these results. Consistent findings were observed for the blood pressure lowering across subgroups.

In the *co-administration* studies, both the 40 mg and 80 mg azilsartan medoxomil demonstrated additional efficacy when combined with amlodipine and chlorthalidone (-24.8, -24.5 vs -13.6 (AML) and -31.7, -31.3 vs -15.9 (CLD) mmHg 24h SBP, respectively).

The long-term *open-label* studies demonstrated that azilsartan medoxomil efficacy was maintained during the entire study period. Addition of CLD, amlodipine or HCT resulted in additional blood pressure lowering in these studies. Maintenance of efficacy was further demonstrated with the reversal phase in study 491-016 where treatment continuation was associated with significant larger blood pressure reduction compared to patients assigned to placebo. In addition, a post-hoc analysis demonstrated additional efficacy of the 80 mg dose in non-responders to 40 mg of approximately 5 mmHg SBP.

Patients with pre-existent cardiovascular events/co-morbidities (n=378) were allowed in the studies, and showed similar antihypertensive efficacy to the overall population.

Uncertainty in the knowledge about the beneficial effects.

Twenty-four hour blood pressure lowering efficacy maintenance (trough-to-peak ratio) was not different for azilsartan medoxomil compared to olmesartan (0.952 and 0.771 for 80 mg azilsartan medoxomil and 0.915 and 0.892 for olmesartan 20 mg during 24h in 2 studies) and this stronger effect of azilsartan medoxomil does not appear related to its PK properties, but possibly to a slower dissociation of the AT1 receptor (see also non-clinical section).

Only limited data were obtained in more complex patients, i.e. patients with co-morbidity such as heart failure and diabetes mellitus, and the very elderly. Less efficacy in the > 75 years of age subgroup was demonstrated for azilsartan medoxomil versus comparator and placebo in the short and long-term studies with wide confidence interval due to limited number of patients. High risk patients (according to ESC (clinical SBP ≥ 180 mm Hg or DBP ≥ 110 mm Hg, clinical SBP > 160 mm Hg and DBP < 70 mm Hg, metabolic syndrome, ≥ 3 CV high risk factors, subclinical organ damage, CV/renal disease, or diabetes) and SCORE classification (≥ 5% risk of CV death within a 10-year period)) showed similar efficacy as to the overall population.

Beneficial effects of azilsartan medoxomil on mortality and cardiovascular morbidity and target organ damage are currently unknown.

Risks

Unfavourable effects

An adequate number of patients treated with azilsartan medoxomil have been evaluated compared to placebo and active comparators. Furthermore sufficient numbers of patients have been included to evaluate long-term safety: 1704 for more than 26 weeks and 588 for more than 48 weeks.

The adverse events of dizziness, fatigue, headache, blood creatinine increased, hypotension, dizziness postural, and blood CK increased were consistently found during study drug treatment across the different controlled and open-label trials.

Adverse events of diarrhoea, dizziness, hypotension and fatigue are well known from other ARBs and appear to be dose-related as they occur most often in the highest dose group. In the placebo controlled studies incidences of these side effects were 0, 0.7 and 1.3% for placebo; 0.9, 1.9 and 2.3% for azilsartan medoxomil 40 mg; and 0.2, 0.4 and 1.1% for azilsartan medoxomil 80 mg, respectively. They may occur within a few weeks and are generally mild in nature. Only slightly more patients discontinued on azilsartan medoxomil than on placebo and generally, treatment was tolerated well. The incidence of serious adverse events was generally low.

A detailed description of renal adverse events showed that incidences were low and not much higher than for placebo. A dose-dependent relation for blood creatinine increase (or GFR decrease) may occur that was most pronounced in the long term studies: 1.1%, 3.4% and 3.1% for comparator, azilsartan medoxomil 40 and azilsartan medoxomil 80 mg. Increase in the level of serum creatinine is known to be associated with RAAS blockade and has been observed with other ARBs. The use of azilsartan medoxomil according to renal impairment showed no clear trend towards more adverse events, discontinuation due to adverse events or severe adverse events with increasing impairment of renal function.

Uncertainty in the knowledge about the unfavourable effects

The number of patients treated for more than 52 weeks is unknown, although approximately 588 patients were treated for 48 weeks or more.

In contrast to other ARBs an increase in uric acid increase was observed, in particular in the longer term. This could partly be explained by a reduction in GFR that fits with the potent AT1 antagonist effect. The increase in uric acid levels was not combined with an increased number of related adverse events such as gout and nephrolithiasis.

Some abnormalities in liver enzymes (ALT, AST and triglycerides) were noticed, but were not consistent for all trials and were of a similar level as for the comparators (valsartan, ramipril). Some detailed description has been provided.

There seems not to be a relation between study drug and the death cases that occurred, however, for one case this was uncertain, in particular because of lack of information.

Based on the data provided here, no trend towards a higher incidence of neoplasm or cancer could be observed, but incidences were very low and no conclusions can be drawn. A recent meta-analysis identified no increased risk with ARBs in contrast to previous publications.

Laboratory adverse events related to blockade of the RAAS (creatinine, potassium, sodium, etc.) were increased during long-term treatment in these moderate and severe renal impaired patients. Conclusions regarding dose recommendation for the renally impaired patients cannot be made based on these results. Exposure to azilsartan medoxomil may be doubled in these patients (see pharmacokinetic section). More careful up-titration in patients with severe impairment has been recommended in the SmPC.

Clinical experience treating patients with any type of hepatic impairment is extremely limited. The applicant conducted one hepatic impairment study, which included 8 patients with mild and 8 patients with moderate hepatic impairment. In these patients a slight increase (1.3 to 1.5 fold) in azilsartan medoxomil exposure was observed but still adverse event patterns could be different due to an increased pharmacodynamic response. Severe hepatic impaired patients were not included in the studies. Therefore caution is needed and a starting dose of 20 mg azilsartan medoxomil could be considered in subjects with mild and moderate hepatic impairment. The use of azilsartan medoxomil cannot be recommended in patients with severe hepatic impairment as reflected in the SmPC.

Although numbers of elderly were limited, typical adverse events associated with the more elderly are found such as hypotension and dizziness. However, these were similar between azilsartan medoxomil and comparator. Numbers of very elderly, diabetes mellitus, and heart failure or activated RAAS were more limited. Therefore, the safety profile of azilsartan medoxomil in these patients is not clearly established. The external validity for such patients is limited.

Benefit-risk balance

Importance of favourable and unfavourable effects

Antihypertensive treatment is indicated to reduce the risk for cardiovascular events. Reduction of blood pressure is directly associated with reduction of CV events. The choice of 24 hour ABPM systolic blood pressure as primary endpoint is considered appropriate. It provides an appropriate insight into blood pressure changes during everyday activities and is strongly recommended for the evaluation of new antihypertensive agents. In addition, the choice of clinical SBP at trough as the major secondary endpoint is important as the best evidence for association between blood pressure reduction and reduction of CV risk still comes from SBP.

Azilsartan medoxomil is a new ARB, belonging to a group of antihypertensives that has an established place in the treatment of hypertension. Its antihypertensive effects as demonstrated in the development programme are considered clinically relevant and at least comparable to other antihypertensive agents.

Beneficial effects of azilsartan medoxomil on mortality and cardiovascular morbidity and target organ damage are currently unknown.

The observed AE include mainly diarrhoea, hypotension, dizziness and fatigue and these are generally well tolerated. Laboratory abnormalities may occur, in particular increases in creatinine and serum potassium. This is similar to other ARBs and manageable in the tested population. Unexpected uric acid increase was observed which could be partly related to a reduced GFR.

Clinical experience in very elderly patients (> 75 years), patients with renal and hepatic impairment and high CV risk (heart failure, DM) is limited. Uncertainties still remain on the safety profile of azilsartan medoxomil and the dosing recommendations for these patients.

Benefit-risk balance

The balance between favourable and unfavourable effects of azilsartan medoxomil is considered positive. Its antihypertensive efficacy has been established in patients with uncomplicated mild to severe essential hypertension in dosages ranging from 20-80 mg. The 40 mg dose is considered an acceptable starting dose in these patients. The AE observed with azilsartan medoxomil are similar to those observed with other ARBs and appear to be dose-related. AEs may occur within a few weeks and are generally mild in nature.

Discussion on the benefit-risk balance

The overall benefit/risk of azilsartan medoxomil is considered positive for the indication: *"Treatment of essential hypertension in adults"*.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Edarbi in the treatment of essential hypertension in adults is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.