



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## CHMP assessment report

**TWYNSTA**

**International Nonproprietary Name: telmisartan / amlodipine**

**Procedure No. EMEA/H/C/001224**

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



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# 1. Background information on the procedure

## 1.1. *Submission of the dossier*

The applicant Boehringer Ingelheim International GmbH submitted on 3 September 2009 an application for Marketing Authorisation to the European Medicines Agency for TWYNSTA, through the centralised procedure falling within the Article 3(2)(a) and point of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 November 2008.

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

### Replacement therapy

Patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of TWYNSTA containing the same component doses.

### Add on therapy

TWYNSTA is indicated in patients whose blood pressure is not adequately controlled on amlodipine.

### Initial therapy

TWYNSTA may also be used as initial therapy in patients who are likely to need multiple drugs to achieve their blood pressure goals. The choice of TWYNSTA as initial therapy for hypertension should be based on an assessment of potential benefits and risks.

The legal basis for this application refers to Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for new fixed combination products.

The application submitted is a new fixed combination medicinal product.

### **1.1.1. Information on paediatric requirements**

Pursuant to Article 7 of Regulation (EC) No 1901/2006 the application included an Agency Decision P/13/09 for the following condition:

Arterial hypertension

on the granting of a product-specific waiver

### **1.1.2. Scientific advice:**

The applicant received Scientific Advice from the CHMP on 26 January 2006. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

### **1.1.3. Licensing status:**

A new application was filed in the following countries: USA.

The product was not licensed in any country at the time of submission of the application.

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

## ***1.2. Steps taken for the assessment of the product***

- The application was received by the Agency on 3 September 2009.
- The procedure started on 23 September 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2009. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 December 2009.
- During the meeting on 18 – 21 January 2010, 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 26 January 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 March 2010.
- The summary report of the GMP inspection carried out at the site Cipla Ltd, Manufacturing Division, Plot No L-139 to L-146, Goa, India between 16 and 20 November 2009 was issued on 03 February 2010.
- The summary report of the GCP inspection carried out at two sites in Manila, Philippines between 13 – 18 January 2010 and in Alkmaar, The Netherlands between 1 – 5 February 2010 was issued on 6 April 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 April 2010.
- During the CHMP meeting on 17-20 May 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 28 June 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 06 July 2010.
- During the CHMP meeting on 19-22 July 2010, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 19 – 22 July 2010, 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 TWYNSTA on 22 July 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 21 July 2010.

## 2. Scientific discussion

### 2.1. Introduction

Twynsta is a fixed combination product consisting of two well known active substances: amlodipine besilate and telmisartan.

Telmisartan is an orally active angiotensin II antagonist acting on the AT<sub>1</sub> receptor subtype thus blocking the effect of angiotensin II in the renin angiotensin system (RAS) cascade. Telmisartan induces both an increase in plasma renin activity and in plasma angiotensin II concentrations.

The therapeutic indication for telmisartan is for the treatment of hypertension. and the prevention of CV events

Adverse experiences have generally been mild and transient in nature and only infrequently require discontinuation of therapy. The most common reasons for discontinuation of therapy with telmisartan are headache and dizziness. The proposed therapeutic dose is 20-80 mg total daily.

Amlodipine is an orally active long lasting dihydropyridine calcium channel blocker (CCB) approved for the treatment of hypertension, angina, and in some countries angiographically documented coronary artery disease and is available in doses of 5 and 10 mg and in some countries in a 2.5 mg dose for once daily administration.

Amlodipine administered as mono-therapy is generally well tolerated at doses up to 10 mg daily. Some of the more common side effects of dihydropyridine CCBs, including amlodipine, based on their pharmacologic site of action, include headache, and other dose dependent effects such as oedema, dizziness, flushing, and palpitations.

It has been recognized in the European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension that one of the rational combinations is the combination of a renin-angiotensin aldosterone system antagonist, such as an angiotensinII antagonist, with a CCB.

Both AT II- antagonists and CCBs lower blood pressure by reducing peripheral resistance, but calcium influx blockade and reduction of angiotensin II vasoconstriction are complimentary mechanisms. The edema induced by dihydropyridine CCBs results from the increased capillary hydrostatic pressure from pre-capillary vasodilatation. AT II antagonists produce postcapillary vasodilatation thereby normalizing transcapillary pressure and reducing oedema.

The objectives of formulation development were to generate an immediate release tablet containing this two widely used active ingredients amlodipine and telmisartan. As the drug substances could not be combined in a common blend to obtain a stable product, therefore a bilayer approach was selected. The tablets were formulated in four strengths for oral administration with a combination of amlodipine besylate equivalent to 5 mg or 10 mg of amlodipine free base with 40 mg or 80 mg of telmisartan.

### 2.2. Quality aspects

#### 2.2.1. Introduction

Twynsta is a fixed combination containing telmisartan and amlodipine (as besilate) as active substances. four strengths are proposed containing 40 mg/ 5 mg, 40 mg /10 mg, 80 mg/ 5 mg and 80 mg / 10 mg. They are presented as tablets.

Apart from this difference in strength, the formulations are identical, the excipients are colloidal anhydrous silica, brilliant blue FCF (E 133), ferric oxide black (E172), ferric oxide yellow (E172), magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide and sorbitol (E420).

The tablets are supplied in aluminium/aluminium blisters (PA/Al/PVC/Al) and aluminium/aluminium perforated unit dose blisters (PA/Al/PVC/Al)

### 2.2.2. Active substance

#### Telmisartan

This active substance has been authorised as a result of an earlier centralised procedure for the same applicant for telmisartan tablets.

Telmisartan is a white or yellowish solid substance. The solubility of Telmisartan is strongly pH dependent. It is very slightly soluble in 0.1 M HCl, practically insoluble in water, and freely soluble in 1 M NaOH. The telmisartan molecule possesses no asymmetric center and thus does not rotate plane polarised light.

Telmisartan is manufactured by chemical synthesis, in four steps. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents, have been presented. The batch synthesis data for each manufacturing site presented show a reproducible manufacturing process leading to homogeneous batches.

Telmisartan specifications includes tests for appearance, identification (IR, UV, HPLC), solubility, colour of solution, purity (HPLC), residual solvents (GC), heavy metals, water content, loss on drying, sulphated ash, assay (HClO<sub>4</sub> titration).

Batch analysis data of 9 batches of active substance are provided. The tests and limits in the specifications are considered appropriate for controlling the quality of this active substance.

Stability data are presented for three production-scale batches of telmisartan, stored for 60 months under long-term conditions and for 6 months under accelerated ICH conditions.

The following tests were conducted at each time point: appearance, chromatographic purity, water content and assay (titration). All acceptance criteria and analytical procedures were identical to those used for release testing of the drug substance

The active substance remained unchanged at all time points and under all conditions tested. No trends have been observed for any test parameter under any conditions.

The results justify a retest period proposed. In accordance with EU GMP guidelines<sup>1</sup>, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

#### Amlodipine besilate

Amlodipine besilate is a white or almost white powder slightly soluble in water, freely soluble in methanol, sparingly soluble in ethanol, slightly soluble in 2-propanol.

Amlodipine besilate is known to exist in three polymorphic forms. The amlodipine in the drug product exists exclusively as the anhydrate. It could be shown that no conversion of the different hydrates occurs under long term storage conditions. The active substance is used as a racemic mixture (R and S isomers).

Amlodipine besilate complies with the monograph of the Ph Eur. and the certificate of suitability has been provided.

Amlodipine besilate is tested according to specifications, limits and methods set in the respective Ph Eur monograph. The following parameters are additionally tested: heavy metals (Ph Eur), benzene sulphonic acid (potentiometric titration), isopropanol, methanol, and particle size (laser diffraction

Stability data for production 5 batches stored at long term conditions for 60 months (3 batches) and 36 months (2 batches) and for 3 production batches stored at accelerated conditions for 6 months are presented. No significant change has been observed. Based on the presented stability data the proposed re-test period is considered acceptable.

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<sup>1</sup> 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

### **2.2.3. Finished Medicinal Product**

- ***Pharmaceutical Development***

Twynsta is a combination of two existing oral antihypertensives. The product was developed to be bioequivalent to the commercial products containing the individual active substances and showing the same dissolution characteristics.

A compatibility study was conducted in order to investigate whether the active substances could be combined in one blend. The results demonstrated that a bilayer tablet would be necessary.

The development of the final formulation of the amlodipine layer, i.e. the telmisartan/amlodipine tablets has been described and justified. The proposed final formulation was used from lab scale batches on and has not been changed during scale up.

Bioequivalence was performed in using the lowest strength and highest strength 80/10 mg of the finished product. Bioequivalence studies were performed between the fixed combination and the corresponding dosage forms of the monocomponents. Equivalency of the remaining strengths was demonstrated by comparative dissolution. Development of the dissolution methods and comparison of dissolution profiles are described sufficiently, the discriminatory power of the dissolution method has been proven.

Excipients are used at unexceptional concentrations and have been shown compatible with the active substances.

The excipients used are colloidal anhydrous silica, brilliant blue FCF (E 133), ferric oxide black (E172), ferric oxide yellow (E172), magnesium stearate, maize starch, meglumine, microcrystalline cellulose, povidone K25, pregelatinized starch, sodium hydroxide and sorbitol. The selection and function of the excipients has been described. Except for the pigment blend, all excipients are compendial excipients, which are tested and released according to Ph Eur.

The container closure system consists of aluminium/aluminium blisters (PA/Al/PVC/Al). Specifications and certificates of analysis for the two aluminium foils are provided. IR spectrum of the primary packaging material is provided. The suitability of this container is justified by stability data. Compatibility of telmisartan / amlodipine layered tablets and the blisters have been established by stability testing of the drug product under long term and accelerated testing conditions. The suppliers have confirmed that all materials of construction that are in contact with the drug product comply with applicable food additive regulations.

- ***Adventitious agents***

Twynsta does not contain any substance of animal origin.

- ***Manufacture of the product***

The manufacture of the final product involves standard manufacturing processes such as blending and compression.

The manufacturing process has been validated by a number of studies for the major steps of the manufacturing process and is satisfactory. The in process controls are adequate for this tablet preparation.

The batch analysis data on three consecutive batches shows 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 specifications include tests by validated methods for appearance, identification of the active substances (HPLC, TLC), hardness, water content, uniformity of dosage units (HPLC), dissolution, assay of the active substance (HPLC), active ingredient degradation (HPLC), and microbiological quality.

Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.

The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Batch analysis data confirm satisfactory uniformity of the product at release.

- **Stability of the product**

Three primary pilot scale batches of each strength packed in the proposed commercial primary packaging were stored for up to 24 months at 25°C/60%RH and up to 6 months at 40°C/75%RH. The parameters tested during stability study are appearance, resistance of crushing, water content, dissolution, active substance degradation, assay and microbiological quality.

One commercial size batch of each strength packed in the proposed primary packaging under ICH stress conditions to assess the influence of heat, humidity, and light. The parameters tested were appearance, water content, average weight, resistance to crushing, dissolution of the active substances, active substance degradation and assay.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

In accordance with EU GMP guidelines<sup>2</sup>, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

## **2.2.4. Discussion on chemical, pharmaceutical and biological aspects**

Information on development, manufacture and control of the active substances and finished product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory 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.

## **2.3. Non-clinical aspects**

### **2.3.1. Introduction**

Twynsta is a Fixed Dose Combination (FDC) of telmisartan and amlodipine besilate in the strengths of 40mg/5 mg, 40 mg/10mg, 80mg/5 mg, 80mg/10mg respectively.

The nonclinical part of the dossier consists of bibliographic data on amlodipine and data for telmisartan which were already part of the original Marketing Authorisation Application.

Additional non clinical studies have been provided to supplement data for the FDC in this application as follows :

- a single oral dose pharmacokinetic study in hypertensive rats,
- a protein binding study,
- and a 13 week toxicity study in normotensive rats comparing the effects of both compounds individually and in combination.

### **2.3.2. Pharmacology**

The pharmacodynamics of Telmisartan and Amlodipine are both well characterised and no specific study is provided in this application, which is acceptable.

#### ***Primary pharmacodynamic studies***

##### **Telmisartan**

The pharmacodynamics of telmisartan have been investigated in vitro and in vivo in rodents, guinea pigs, rabbits and dogs. Data from in vitro studies support that Telmisartan is a potent specific antagonist of the angiotensinII subtype 1 (AT1) receptor. Telmisartan has no affinity to the AT2 receptor.

Ang II is a potent regulator of renal function which includes control of the transglomerular pressure gradient and proximal fluid and Na<sup>+</sup> reabsorption.

Telmisartan induces an increase of both plasma renin activity and plasma angiotensin II concentrations. Telmisartan is an antihypertensive agent in various models of hypertension. The effects of telmisartan on blood pressure in the species studied last for about 24 hours, no major effects on heart rate are observed and no evidence of tachyphylaxis is observed.

##### **Amlodipine**

The pharmacodynamic actions of amlodipine - reduction of total peripheral resistance and improvement of myocardial ischemia, in animals, which are of importance in explaining its usual clinical uses in treating cardiovascular diseases - hypertension and angina - have been extensively reviewed by several different authors.

The pharmacological profile of amlodipine has been extensively evaluated both in laboratory species and in humans. The compound is a potent, long-acting calcium channel blocker which interacts with both dihydropyridine and benzothiazepine receptor sites.

Amlodipine is an effective antihypertensive agent in laboratory models of hypertension accompanied by diuretic and natriuretic effects and the compound does not appear to produce tolerance when administered over prolonged periods.

Amlodipine inhibits cardiac slow action potentials with no effect on the fast sodium channel and induces marked dilatation of coronary and peripheral blood vessels at dosage levels which cause only minimal depression of either cardiac contraction or electrical conduction.

Amlodipine has also been demonstrated to possess significant anti-ischaemic activity when tested in several animal test species. Newer results extended the knowledge regarding the mode of action of amlodipine. Nitric Oxide production, inhibition of Angiotensin Converting Enzyme (ACE), reduction of ventricular hypertrophy as well as of vascular remodelling, reduction of O<sub>2</sub>-consumption in the myocardium, reduction of vascular inflammation and anti-atherosclerotic properties support the well known beneficial vasodilator and anti-ischemic efficacy.

##### **FDC**

Due to their distinct mechanism of action of the two classes of drugs, the FDC of telmisartan and amlodipine is anticipated to be more effective than telmisartan monotherapy for treating hypertensive patients to achieve the target goal of blood pressure.

Using equivalent, submaximal blood pressure lowering doses in combination (1mg/kg Telmisartan + 5mg/kg Amlodipine), the combination dosing resulted in a profile exhibiting a more rapid onset of blood pressure lowering than observed with the monotherapy treatments, and a significantly greater decrease in blood pressure compared to either single treatment alone.

#### ***Secondary pharmacodynamic studies***

##### **Telmisartan**

Telmisartan is a very lipophilic compound. Together with its high volume of distribution it penetrates into tissue and cells better than other compounds in its class (ARBs).

Telmisartan has demonstrated multiple beneficial properties on cardiovascular parameters beyond blood pressure lowering. It has shown benefits in vascular dysfunction and reducing oxidative stress by the prevention of Ang II stimulation of smooth muscle and endothelial cells as well as reversing eNOS uncoupling. In addition, telmisartan inhibits ROS generation and decreases mitochondrial and xanthine oxidase derived ROS.

Telmisartan also has strong anti-atherosclerotic effects. In various animal models it has been shown to significantly decrease lesion size and plaque burden as well as influence plaque composition towards a more stable plaque phenotype with less necrotic lipid core and thicker fibrous cap.

Based on these mechanistic considerations preclinical studies have been initiated to analyze the potential synergistic and/or additive effects of the combination of telmisartan and amlodipine in preclinical models. Particularly, effects in vascular dysfunction (ROS, eNOS) models of atherosclerosis and models of diabetes and diabetes-related diseases (diabetic nephropathy) have been implemented for these studies.

#### Amlodipine

Amlodipine has strong lipophilic properties. It not only easily penetrates the plasma membrane to interact with the L-type calcium channel, but also has additional biologic activity, independent of the L-type calcium channel.

Amlodipine has effects on cell types other than vascular smooth muscle cells (VSMC), specifically also on cells in which L-type calcium channels are non-existent or play only minor roles. For example amlodipine has been shown to beneficially affect both nitrite release and the nitric oxide (NO)-dependent regulation of cardiac oxygen consumption.

Amlodipine had no effect on oxygen consumption in the heart from B2-kinin receptor-knockout mice, which links amlodipine directly to bradykinin-mediated eNOS activation.

In addition, amlodipine has been shown to inhibit NADPH oxidase in neutrophils as well as in endothelial cells.

Amlodipine has also demonstrated potent inhibition of VSMC proliferation and migration. Similarly, experiments with rat aortic VSMCs suggested that in contrast to nifedipine, amlodipine elicited inhibition of serum-, thrombin-, and basic fibroblast growth factor-triggered VSMC proliferation.

Taken together, these data suggest that amlodipine could positively influence vascular dysfunction of various origins by the reduction of reactive oxygen species (ROS). Its additional effect on VSMC proliferation and migration might be of specific value in atherosclerosis.

#### FDC

Two well-known compounds are proposed in combination.

Currently ongoing experimental studies are aimed to investigate the potential additive or synergistic effects due to compound specific properties that have been described for telmisartan and amlodipine in the preclinical/clinical literature on top of their blood pressure lowering effect.

During the assessment, it was agreed that the results of these studies would be submitted in the second half of 2010 or in 2011 as a follow up measure.

### ***Safety pharmacology programme***

Nonclinical studies investigating the effects of Telmisartan or Amlodipine alone on cardiovascular function, respiratory function, CNS testing, gastrointestinal effects and renal function have been reviewed.

The combination of telmisartan and amlodipine is not expected to display concerns in safety pharmacology studies, therefore nonclinical safety pharmacology studies with the combination are not needed.

### 2.3.3. Pharmacokinetics

#### • Pharmacokinetic studies

The pharmacokinetics of Telmisartan and Amlodipine are both well characterised. Additionally, a single oral dose pharmacokinetic study in SHR and SD rats and a protein binding study have been performed comparing the effects of both compounds individually and in combination.

##### **3.3.3.1 Summary of literature data**

All preclinical studies combining telmisartan and amlodipine were performed with free combinations of both drugs, and the plasma concentrations of both drugs were analysed separately. Therefore, an analytical method for the FDC in animal matrix was not developed. Original data on validated analytical methods for amlodipine in animal matrix are not available. However, measurement of amlodipine and telmisartan concentrations in rat plasma have been performed according to validated methods.

The pharmacokinetics of the FDC has not been specifically investigated in animal studies but has been characterised and compared to single drug treatment in a 13-week toxicity study in rats. No further non clinical investigations are requested. A brief summary of the properties of individual components is provided

#### **Absorption**

##### Telmisartan

Telmisartan is rapidly absorbed after oral administration in all species, and the bioavailability is 56-75% in mice, 66% in rats and 14-22% in dogs.

##### Amlodipine

Amlodipine was well and completely absorbed following oral administration to each of mouse, rat, rabbit, dog and man. The oral bioavailability of unchanged amlodipine ranged from about 30% in rabbits to approximately 100% in rats with the value for humans being about 64%.

#### **Distribution**

##### Telmisartan

In vitro binding to plasma proteins is high (about 99.6% in mice, rats and humans and 98.7% in dogs). Tissue distribution studies showed that telmisartan-related radioactivity is mainly located in the liver, and only small amounts were detected in the CNS. In pregnant rats, telmisartan crossed the placenta and was excreted into breast milk of lactating rats.

##### Amlodipine

As for other dihydropyridine-derived calcium channel blockers, amlodipine was highly bound to plasma protein with values of 94%, 97% and 97% for rat, dog and man, respectively. Tissue distribution studies were performed in rats, rabbits and dogs. In each species the volume of distribution for unchanged amlodipine was large and only low levels of the drug were detected in blood, brain and amniotic fluid. Highest concentrations of the drug were found in liver, lung, kidneys and adrenal glands.

#### **Metabolism**

##### Telmisartan

The metabolism of telmisartan is similar in all species (mice, rats, dogs, humans) and consisted mainly in glucuronidation to a 1-O-acylglucuronide without antagonist activity. Telmisartan circulates preferentially as parent compound in the plasma of most species.

##### Amlodipine

Amlodipine is extensively metabolised in all species tested although small amounts of unchanged drug (up to about 5% of the dose) are found in urine.

Amlodipine is extensively metabolized in all animal species investigated. The primary and predominant metabolic step is the oxidation of the dihydropyridine (DHP) moiety to the pyridine catalyzed by

cytochrome P450 (CYP3A4 isoenzyme), which also terminates the pharmacological activity of amlodipine.

In man, following oxidation to its pyridine derivative, subsequent metabolism involves both of the routes observed in the rat and dog. None of the metabolites identified and then synthesized were found to have significant calcium antagonist activity relative to amlodipine.

### **Excretion**

#### Telmisartan

The major route of elimination of telmisartan is via biliary elimination of the 1-O-acylglucuronide.

#### Amlodipine

About half of drug-related radioactivity was recovered in faeces, with the remainder recovered in urine.

### **3.3.3.2 Pharmacokinetic drug interactions**

#### *Single oral dose pharmacokinetic study in rats*

In spontaneously hypertensive rats (SHR) and Sprague Dawley (SD) rats, the pharmacodynamic effects of 1 mg/kg telmisartan, 5 mg/kg amlodipine and both drugs in combination were compared. Additionally, the respective plasma concentration-time profiles were measured and pharmacokinetically evaluated in separate animals of both strains. Telmisartan exposure in SHR and SD rats were unaffected by amlodipine co-medication. Similarly, amlodipine exposure in SD rats was unaffected by telmisartan. In SHR, amlodipine exposure was higher when given in combination with telmisartan, but due to the small sample size, the associated variability, and the absence of similar observations in the control (SD) animals, this observation in SHR was considered incidental and not an unequivocal effect of co-medication.

Due to the high extent of plasma protein binding of telmisartan and amlodipine, the pharmacokinetics of both drugs could potentially be affected by mutual interaction or interaction with other drugs in terms of displacement from plasma protein binding. However, as the volume of distribution was high for both telmisartan and amlodipine, a relevant drug-drug interaction based on plasma protein displacement was considered unlikely, and no mutual displacement from plasma protein binding was observed in an *in vitro* study investigating interaction of telmisartan and amlodipine in human plasma, probably due to their moderate and large volume of distribution, respectively.

#### *Protein binding study*

As multiple UGTs participate in the glucuronidation of telmisartan, it is considered unlikely that amlodipine, which is not known as an inhibitor of UGTs, will cause changes of the metabolic clearance of telmisartan. Similarly, it is considered unlikely that amlodipine, as a cationic compound at physiological pH, would interact with these anion uptake carriers. Similarly, the extensive oxidative metabolism of amlodipine catalysed by the 3A4 isoform of cytochrome P450 would not interact with telmisartan which inhibits the CYP3A4 catalysed nifedipine oxidation even at a telmisartan concentration of 10 µM (more than 7-fold above the average C(max) value) to less than 10%.

Due to the high extent of plasma protein binding of telmisartan and amlodipine, the pharmacokinetics of both drugs could potentially be affected by mutual interaction or interaction with other drugs in terms of displacement from plasma protein binding. However, as the volume of distribution was high for both telmisartan and amlodipine, a relevant drug-drug interaction based on plasma protein displacement was considered unlikely, and no mutual displacement from plasma protein binding was observed in an *in vitro* study investigating interaction of telmisartan and amlodipine in human plasma, probably due to their moderate and large volume of distribution, respectively.

As multiple uridine diphosphate glucuronyl transferase (UGTs) participate in the glucuronidation of telmisartan, it is considered unlikely that amlodipine, which is not known as an inhibitor of UGTs, will cause changes of the metabolic clearance of telmisartan. Similarly, it is considered unlikely that amlodipine, as a cationic compound at physiological pH, would interact with these anion uptake carriers.

In conclusion, telmisartan does not inhibit CYP450 activities to any significant extent and is mainly eliminated by biliary excretion of glucuronide, whereas amlodipine is cleared metabolically. Thus, the pharmacokinetic drug interaction potential between telmisartan and amlodipine is considered low. Relevant pharmacokinetic interactions of T/A may occur only with strong inhibitors of CYP3A enzymes given concomitantly. No specific study was conducted.

### **Overall conclusions on pharmacokinetics**

#### **Telmisartan**

Telmisartan is rapidly absorbed after oral administration in all species, and bioavailability is 6-75% in mice, 66% in rats and 14-22% in dogs. In vitro binding to plasma proteins is high (about 99.6% in mice, rats and humans and 98.7% in dogs).

The volume of distribution of telmisartan is 3-5-fold higher when compared to total body water, indicating a preferential distribution of telmisartan into the tissue. Half-life of elimination of telmisartan from plasma after oral administration is between 4 and 20 hours in all species. Tissue distribution studies showed that telmisartan-related radioactivity is mainly located in the liver, and only small amounts were detected in the CNS. In pregnant rats, telmisartan crossed the placenta and was excreted into breast milk of lactating rats.

The metabolism of telmisartan is similar in all species (mice, rats, dogs and humans) and consisted mainly in glucuronidation to a 1-O-acylglucuronide. (inactive metabolite). The major route of elimination of telmisartan is via biliary elimination of the 1-O-acylglucuronide.

#### **Amlodipine**

The most important pharmacokinetic properties of amlodipine - late occurrence of plasma peak, linear kinetics, prolonged terminal elimination half-life - result in a slowly developing and long lasting efficacy. This may be important not only for providing protection over a full 24-h period, but possibly for reducing end-organ damage which has been linked to variability in blood pressure.

Telmisartan does not inhibit CYP450 activities to any significant extent and is mainly eliminated by biliary excretion of glucuronide, whereas amlodipine is cleared metabolically. Thus, the pharmacokinetic drug interaction potential between telmisartan and amlodipine is considered low. Relevant pharmacokinetic interactions of Telmisartan/Amlodipine may occur only with strong inhibitors of CYP3A enzymes given concomitantly. No specific study was conducted.

## **2.3.4. Toxicology**

The toxicological properties of Telmisartan and Amlodipine are both well characterised. Additionally, one 3-month repeat dose toxicity study in rats has been performed comparing the effects of both compounds individually and in combination. Concomitant toxicokinetic studies were conducted to demonstrate adequate exposure of the toxicity test animals, as well as to characterise the pharmacokinetics of the two drugs in combination treatment.

### ***Single dose toxicity***

In accordance with the guideline CHMP/SWP/302413/08 single dose toxicity studies are not included in this application documentation.

### ***Repeat dose toxicity***

#### **Summary of literature data**

#### **Telmisartan**

The effects of telmisartan in chronic toxicity studies were similar to those reported for other AT<sub>1</sub> antagonists and ACE inhibitors. The toxicologic target organs are the kidney and the gastrointestinal tract. It is assumed that the principal side effects (on the kidney and on the gastrointestinal tract) after oral administration of telmisartan are directly or indirectly linked to specific blockade of AT<sub>1</sub> receptors.

The rat and rabbit seemed to be the most sensitive species towards telmisartan-induced gastrointestinal toxicity, whereas the dog seemed to be less susceptible and no gastrointestinal adverse effects were observed in mice. Gastrointestinal damage was not due to local irritation because they were observed after both oral and i.v. administration of telmisartan. Therefore, ulcerogenicity seems to be a pharmacologically-mediated class effect of drugs blocking the angiotensin converting enzyme or the AT<sub>1</sub> receptor.

Furthermore, telmisartan induced reductions in red cell parameters. These effects are well known effects of ACE inhibitors and AT<sub>1</sub> antagonists in chronic toxicity studies, since the renin angiotensin system seems to be involved in the regulation of erythropoietin production in the kidneys.

### Amlodipine

Amlodipine has been tolerated well in experimental animals. Signs of toxicity are related to the cardiovascular efficacy of this drug. Amlodipine did not show any evidence of genotoxicity and carcinogenicity. All parts of the reproductive cycle have been evaluated. The results indicated that amlodipine at dosage levels up to 10 mg/kg/day did not adversely affect fertility in either male or female rats. However, at 10 mg/kg/day, the compound did cause difficult labour which significantly prolonged the gestation period and reduced the mean litter size. Surviving pups (F<sub>1</sub> generation) showed no evidence for external visceral or skeletal abnormalities and their reproductive ability, at 3 months of age, was unimpaired. Amlodipine was neither foetotoxic nor teratogenic in standard teratology tests in rats and rabbits and the compound had no significant adverse effects on lactation or foetal development when administered to maternal rats throughout the lactation period until weaning. Overall, these results suggest that amlodipine is unlikely to exert significant adverse effects in human females if administered during pregnancy or lactation.

### FDC

#### *13-week toxicity study in normotensive rats*

#### *Study Methods*

An oral 13-week toxicology study has been conducted with the fixed combination of telmisartan and amlodipine in Sprague-Dawley Crl:CD (SD) rats.

Dose levels of the co-medication groups were 3.2/0.8, 10/2.5 and 40/10 mg/kg/day telmisartan/amlodipine, respectively (Table 1). In additional mono-administration groups, 40 mg/kg/day telmisartan or 10 mg/kg/day amlodipine were administered. Additional animals given 0/0 (Control), 40/10 (High dose combination), 40/0 (High dose telmisartan mono) or 0/10 (High dose amlodipine mono) mg/kg/day telmisartan/amlodipine were used for a 4-week recovery period without dosing.

Table 1

<b>Study ID</b>	<b>Species/Sex/ Number/Group</b>	<b>Dose/Route mg/kg T/A p.o.</b>	<b>Duration</b>	<b>NOAEL (mg/kg/ day) T/A</b>	<b>Major findings</b>
U09-1802 GLP	SD-rat 10M+10F	0 40/0 0/10 3.2/0.8 10.0/2.5 40/10	13 weeks with recovery of 5/sex control and 5/sex highest dosed rats after 4 weeks	3.2/0.8	Consistent with pharmacological mechanisms of action, see below

In the study, plasma exposure to telmisartan and amlodipine following mono-administration and co-medication of the highest dose levels (40mg/kg and 10mg/kg, respectively) was compared on Days 1 and 86.

Neither on Day 1 nor on Day 86, significant differences of AUC 0-24h of amlodipine were observed after co-medication in comparison to mono-administration. On Day 1, AUC 0-24h of telmisartan was slightly lower after co-medication with amlodipine (8.84 µg·h/mL) than after mono-administration (12.8 µg·h/mL). On Day 86, it was significantly higher after co-medication (80.3µg·h/mL) than after

mono-administration (17.1 µg-h/mL). Because on Day 1 the plasma levels of telmisartan after co-medication were lower than after mono-administration and because there was no effect on telmisartan plasma concentrations in the pharmacological study, the high plasma levels of telmisartan were considered the result of inter-animal variation and the composite design of the toxicokinetic analyses in the 13-week toxicology study rather than a consistent effect of co-medication.

In 13-week repeated toxicity study (U09-1802), combinations were comparable with the proposed clinical ratio of 4:1, telmisartan/amlodipine, respectively. Data indicating that the kidney and heart are the principal targets for telmisartan/amlodipine repeated treatment. In rats, telmisartan/amlodipine co-treatment also resulted with some clinical chemistry parameters (BUN, APTT, creatinine, phosphorus, magnesium) and RBC parameters (RBC counts, haemoglobin, haematocrit) changes. These changes regressed or were not apparent during the 4-week recovery period.

All changes noted in treated animals were well-known class effects of these kinds of drug and have already been described in the respective preclinical studies with telmisartan and amlodipine alone. Exaggerated pharmacological effects of angiotensin receptor or calcium channel blockade may explain these changes. New toxicities and additive adverse effects were not observed in the 13-week toxicology study in rats.

In conclusion, no new target organ toxicity has been identified with the combination of telmisartan and amlodipine.

Exposure to telmisartan and amlodipine, respectively to NOAEL in rat toxicity studies were up to 2.8 and 5.6 times higher than those at the highest doses in human, indicating a moderate safety margin for humans.

Exposure to telmisartan increased almost proportionally to dose, whereas that to amlodipine increased slightly more than proportionally to dose. Co-administration had no impact on the toxicokinetics of amlodipine while an effect on the toxicokinetics of telmisartan cannot be excluded completely as the exposure to telmisartan seemed to be higher in the combination as compared to telmisartan administered alone.

Gender-differences were apparent for amlodipine as the exposure in females had a tendency to be higher than that in males. No gender-difference was observed for telmisartan.

### ***Genotoxicity***

In accordance with the guideline CHMP/ICH/126642/08 genotoxicity studies are not included in this application documentation. There is no concern from studies with single components.

Telmisartan has been tested according to standard protocols for evaluating the mutagenic and clastogenic potential. In summary, standard genotoxicity testing with telmisartan did not indicate any mutagenic or relevant clastogenic effects.

Amlodipine did not show any evidence of genotoxicity

### ***Carcinogenicity***

In accordance with CHMP/ICH/140/95 (ICH S1A) carcinogenicity studies are not included in this application documentation. There is no concern from studies with telmisartan and amlodipine single components where no evidence of carcinogenicity was shown.

Because no direct interactions of telmisartan and amlodipine with respect to their target sites, their pharmacokinetics and their toxicity were shown, it was considered adequate not to conduct carcinogenicity studies in mice and rats with the combined administration of telmisartan and amlodipine.

### ***Reproduction Toxicity***

#### **Telmisartan**

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The reprotoxicity of telmisartan has been fully evaluated.

Angiotensin receptor antagonists are known to decrease placental perfusion and to cause renal damage to the rat fetus during late gestation and early lactation. In the rat, Telmisartan-concentrations increased in the fetal compartment during late pregnancy from about 27% on day 12 p. c. to about 60% on day 18 p. c. Moreover Telmisartan is excreted in rat's milk at concentrations of 1.5 – 2-fold the maternal plasma concentration 4 -8 hours post dosing and remained detectable for more than 48 hours.

There is a possible association between ACE inhibitor treatment and adverse fetal outcome which may indicate that effects on the renin-angiotensin-aldosterone system during pregnancy may negatively influence the fetal development. Accordingly, there is a possible association between AT<sub>1</sub> receptor antagonists (like telmisartan) and adverse fetal development, and, therefore, telmisartan - like other AT<sub>1</sub> receptor antagonists - should be avoided especially in the second and third trimesters of pregnancy.

Several case reports describe oligohydramnios, fetal growth retardation, pulmonary hypoplasia, limb contractures, calvarial hypoplasia and neonatal death in association with maternal losartan, candesartan, valsartan or telmisartan treatment during the second and third trimesters of pregnancy. Surviving infants may exhibit renal damage. The fetal abnormalities are probably related to extreme sensitivity of the fetus to the hypotensive effect of these drugs, and both ACE inhibition and AT<sub>1</sub> receptor blockade seem to disrupt fetal vascular perfusion and renal function. Oligohydramnios seems to result from decreased foetal renal function (reviews in Alwan et al. 2005, Bois et al. 2005).

Chung et al. (The Lancet 2001, 357: 1620) believe that AT<sub>1</sub> receptor antagonists should never be used during pregnancy or in women who are likely to become pregnant, particularly since AT<sub>1</sub> receptor antagonists may lead to activation of the angiotensin II AT<sub>2</sub> receptor, which is thought to be involved in vascular development and growth. In early embryos, AT<sub>2</sub> receptors are involved in multiple aspects of the morphogenesis of the kidney and urinary tract (Miyazaki and Ichikawa 2001, Comparative Biochemistry and Physiology 128: 89-97).

Cooper et al. (N Engl J Med 2006, 354: 2443-2451) studied a cohort of 29,507 infants enrolled in Tennessee Medicaid and found that infants with only first-trimester exposure to ACE inhibitors had an increased risk of major congenital malformations of the cardiovascular system and of the central nervous system, and the authors concluded that exposure to ACE inhibitors during the first trimester cannot be considered safe and should be avoided (Editorial by Friedman, N Engl J Med 2006, 354: 2498-2500).

Following a review of the data, the PHvWP/CHMP concluded that a contraindication during the first trimester of pregnancy is not justified and that no data exist to support the contraindication for use of ACE inhibitors or AT<sub>1</sub> receptor antagonists in breast-feeding recommending therefore, A wording concerning lactation to be included in Section 4.6 of the SPC for AIIRAs and in PLs.

Therefore, the wording concerning pregnancy and lactation in the SPC (sections 4.3, 4.4 and 4.6) and in the PIL is adopted to the actual wording recommended by the PhVWP/CHMP. The issue of usage of antihypertensive drugs during pregnancy and breastfeeding is still under discussion at PhVWP and final outcome still pending.

## Amlodipine

### *Fertility and peri- and postnatal studies (Segments I and III)*

All parts of the reproductive cycle have been evaluated. The results indicated that amlodipine at dosage levels up to 10 mg/kg/day did not adversely affect fertility in either male or female rats. However, at 10 mg/kg/day, the compound did cause difficult labour which significantly prolonged the gestation period and reduced the mean litter size. Surviving pups (F<sub>1</sub> generation) showed no evidence for external visceral or skeletal abnormalities and their reproductive ability, at 3 months of age, was unimpaired. Amlodipine was neither foetotoxic nor teratogenic in standard teratology tests in rats and rabbits and the compound had no significant adverse effects on lactation or foetal development when administered to maternal rats throughout the lactation period until weaning. Overall, these results suggest that amlodipine is unlikely to exert significant adverse effects in human females if administered during pregnancy or lactation. However, it is not known, whether amlodipine crosses the placenta or is excreted in milk.

## FDC

No studies were conducted with T/A, which is acceptable.

### ***Local Tolerance***

In the local tolerance studies conducted with either telmisartan or amlodipine, both compounds were well tolerated. Because no direct chemical interactions between the two compounds do occur, it was considered adequate not to conduct additional local tolerance studies with the combined administration of telmisartan and amlodipine.

### ***Other toxicity studies***

The applicant has adequately elaborated on the impurity levels of Twynsta. Further qualification is not needed in accordance with the current guidelines ICH Q3A/B and CHMP guideline on limits of genotoxic impurities.

## **2.3.5. Ecotoxicity/environmental risk assessment**

The applicant provided a revised environmental risk assessment for the active ingredients telmisartan and amlodipine. Some minor corrective changes in the Phase II assessment of telmisartan were included. The changes made for telmisartan have no influence on the overall conclusion of the risk assessment of telmisartan.

For the active ingredient amlodipine besilate a detailed environmental risk assessment was provided. Based on the study results no environmental risk for the aquatic environment can be expected. However, a study on sediment dwelling organisms is missing and is requested as a Follow Up Measure.

## **2.3.6. Discussion on non-clinical aspects**

Two well-known compounds are proposed in combination.

Amlodipine has been tolerated well in experimental animals. The signs toxicity observed are related to the cardiovascular efficacy of this drug. Amlodipine did not show any evidence of genotoxicity and carcinogenicity. All parts of the reproductive cycle have been evaluated. Overall, these results suggest that amlodipine is unlikely to exert significant adverse effects in human females if administered during pregnancy or lactation.

Using equivalent, submaximal blood pressure lowering doses in the spontan hypertensive rat model, the combination (1mg/kg Telmisartan + 5mg/kg Amlodipine), dosing resulted in a profile exhibiting a more rapid onset of blood pressure lowering than observed with the monotherapy treatments, and a significantly greater decrease in blood pressure compared to either single treatment alone.

The combination of telmisartan and amlodipine is not expected to display concerns in safety pharmacology studies, therefore nonclinical safety pharmacology studies with the combination are not needed. This was acceptable by the CHMP.

## **2.3.7. Conclusion on the non-clinical aspects**

The Applicant has performed an abridged toxicological evaluation of the fixed combination of telmisartan and amlodipine, comprising 13-week repeat dose toxicity study in the rat. This in line with the guideline on the non-clinical development of fixed combinations of medicinal products (CHMP/SWP/258498/2005).An assessment of the ecotoxicity/environmental risk was also made.

The principal findings of 13-week rat repeated dose toxicity study were changes in some clinical chemistry parameters (BUN, creatinine, phosphorus, magnesium) and RBC parameters (RBC counts, haemoglobin, haematocrit). Data indicated also that the kidney and heart were the principal targets for telmisartan/amlodipine repeated treatment. These changes regressed or were not apparent during the 4-week recovery period.

All changes noted in treated animals were well-known class effects of these kinds of drug and have already been described in the respective preclinical studies with telmisartan and amlodipine alone. Exaggerated pharmacological effects of angiotensin receptor or calcium channel blockade may explain these changes. New toxicities and additive adverse effects were not observed in the 13-week toxicology study in rats.

Exposure to telmisartan and amlodipine, respectively to NOAEL in rat toxicity studies were up to 2.8 and 5.6 times higher than those at the highest doses in human, indicating a moderate safety margin for humans.

Co-administration had no impact on the toxicokinetics of amlodipine while an effect on the toxicokinetics of telmisartan cannot be excluded completely as the exposure to telmisartan seemed to be higher in the combination as compared to telmisartan administered alone. Gender-differences were apparent for amlodipine as the exposure in females had a tendency to be higher than that in males. No gender-difference was observed for telmisartan.

No genotoxicity, carcinogenicity, reproductive toxicity, local tolerance and other toxicity studies have been conducted which is in line with applicable guidelines.

The impurity limits for both substances are well below the ICH qualification limits for DS and DP.

The applicant provided a revised environmental risk assessment for the active ingredients telmisartan and amlodipine. However, a study on sediment dwelling organisms is missing and is requested as a Follow Up Measure.

## **2.4. Clinical aspects**

### **2.4.1. Introduction**

This is an application for Twynsta, a fixed dose combination product containing telmisartan and amlodipine besilate for 4 strengths 40/5 mg, 40/10 mg, 80/5 mg, 80/10 mg tablets, in the frame of the centralised procedure, according to article 3(2) of Regulation (EC) No 726/2004 and article 10 b of directive 2001/83/EC as amended.

Article 7 of the Paediatric Regulation applies to this application since the medicinal product is not authorised in the community on 26 July 2008. The application includes a Product-Specific Waiver Waiver Decision Number: EMEA/26624/2009 P/13/2009 (Procedure EMEA-000337-PIP01-08) granted on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

Scientific advice was given by the CHMP on 2006-01-26 concerning quality, preclinical and clinical development. The advice was followed in most points with the exception of the change of formulation in the long term follow up trial.

### **Overview of clinical studies**

The objective of the clinical program was to demonstrate the efficacy and safety of the combination of telmisartan and amlodipine for 4 strengths in the treatment of hypertension.

The clinical program consisted of :

Five phase I pharmacokinetic (PK) and bioavailability (BA) studies:

- Two studies to demonstrate the bioequivalence of the single components telmisartan 40 mg and amlodipine 5 mg with the respective FDC tablets.
- Two drug-drug interaction studies to determine the effect of concomitant administration of amlodipine on the steady-state pharmacokinetics of telmisartan and vice versa
- A food effect study on the fixed-dose combination,

A Bioequivalence approach was used to bridge the clinical data obtained with a combination of the mono components for the strengths containing 40/5 and 80/10 mg T/A to the final FDC formulation.

Five Phase III trials studies have been performed to establish efficacy and safety:

- An 8-week placebo-controlled, 4x4 factorial design trial to evaluate telmisartan 20, 40 and 80 mg in combination with amlodipine 2.5, 5 and 10 mg in patients with hypertension, (1235.1).
- Two 8-week active-controlled, double-blind, non-responder studies to demonstrate the efficacy and safety of the fixed dose combinations in patients with hypertension who tolerated but failed to respond adequately to treatment with amlodipine 5mg (1235.5) or amlodipine 10mg monotherapy (1235.6)
- Two open-label long-term follow-up trials over 34 weeks to determine the efficacy and safety of chronic administration of the fixed dose combinations alone or in combination with other antihypertensive medications in patients who did not adequately respond to treatment with amlodipine 5mg (1235.7) or amlodipine 10mg monotherapy (1235.8).

## **GCP**

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.

Following the request of the CHMP, an inspection of the conduct of the clinical trial No. 1235.5 was conducted at the investigator sites in Manila, Philippines and at the sponsor site in the Netherlands.

The report revealed several major and critical GCP issues for the evaluation of the primary efficacy endpoint of study 1235.5. These issues were also relevant for studies 1235.1, 1235.6 and the associated extension studies.

The main issue relates to the precision with which the Blood Pressure measurements were made. The impact of these deficiencies was analysed. There was no evidence of a systematic bias. The expected impact might be a reduction of the sensitivity to detect a difference.

On request the applicant provided additional sensitivity analyses to further determine the possible impact of the two quantifiable parameters of concern (terminal digit bias and close time of blood pressure measurements) that were indicators of lack of reliability of the data. All centres where 35% or more of the terminal digits were rounded to "0" were excluded as well as all data from patients where the time interval of measurements was less than 5 minutes of another patient measurements at the same site.

Even after exclusion of up to 34-47% of patients assuming imprecise measurements and/or recording in a worst case scenario for each study, there was still a statistically significant superiority of the combination therapy group versus the monotherapy group, supporting the original efficacy conclusion of the studies. Given that the study was a superiority study which achieved significance, the impact of these deficiencies was not thought to change the conclusions of the study.

## **2.4.2. Pharmacokinetics**

### ***Introduction***

Since the pharmacokinetic properties of telmisartan and amlodipin are well known, no new studies for the individual substances are provided. A summary of the pharmacokinetic of single components is described below :

### ***Absorption***

Absorption of telmisartan is rapid although the amount absorbed varies. The mean absolute bioavailability for telmisartan is about 50 %. When telmisartan is taken with food, the reduction in the area under the plasma concentration-time curve (AUC<sub>0-∞</sub>) of telmisartan varies from approximately 6 % (40 mg dose) to approximately 19 % (160 mg dose). By 3 hours after administration, plasma concentrations are similar whether telmisartan is taken fasting or with food.

After oral administration of therapeutic doses, amlodipine is well absorbed with peak blood levels between 6-12 hours post dose. Absolute bioavailability has been estimated to be between 64 and 80%. Amlodipine bioavailability is not affected by food ingestion.

#### ***Linearity/non-linearity:***

The small reduction in AUC is not expected to cause a reduction in the therapeutic efficacy. There is no linear relationship between doses and plasma levels. C<sub>max</sub> and to a lesser extent AUC increase disproportionately at doses above 40 mg. Amlodipine exhibits linear pharmacokinetics.

#### ***Distribution***

Telmisartan is largely bound to plasma protein (>99.5 %), mainly albumin and alpha-1 acid glycoprotein. The mean steady state apparent volume of distribution (V<sub>ds</sub>) is approximately 500 l. The volume of distribution of amlodipine is approximately 21 l/kg. In vitro studies have shown that approximately 97.5% of circulating amlodipine is bound to plasma proteins in hypertensive patients.

#### ***Metabolism***

Telmisartan is metabolised by conjugation to the glucuronide of the parent compound. No pharmacological activity has been shown for the conjugate. Amlodipine is extensively (90%) metabolised by the liver to inactive metabolites.

#### ***Elimination***

Telmisartan is characterised by biexponential decay pharmacokinetics with a terminal elimination half-life of >20 hours. The C<sub>max</sub> and, to a smaller extent, the AUC, increase disproportionately with dose. There is no evidence of clinically relevant accumulation of telmisartan taken at the recommended dose. Telmisartan is nearly exclusively excreted with the faeces, mainly as unchanged compound.

Amlodipine elimination from plasma is biphasic, with a terminal elimination half-life of approximately 30 to 50 hours consistent with once daily dosing. Steady-state plasma levels are reached after continuous administration for 7-8 days. Ten per cent of original amlodipine and 60% of amlodipine metabolites are excreted in urine.

#### ***Special Populations***

No pharmacokinetic data are available in the paediatric population. (age below 18 years).

##### *Gender effects:*

Differences in plasma concentrations of telmisartan were observed, with C<sub>max</sub> and AUC being approximately 3- and 2-fold higher, respectively, in females compared to males.

##### *Elderly patients:*

The pharmacokinetics of telmisartan do not differ in young and elderly patients. The time to reach peak plasma concentrations of amlodipine is similar in elderly and younger subjects. In elderly patients, amlodipine clearance tends to decline with resulting increases in AUC and elimination half-life.

##### *Patients with renal impairment:*

In patients with mild to moderate and severe renal impairment, doubling of plasma concentrations of telmisartan was observed. However, in patients with renal insufficiency undergoing dialysis lower plasma concentrations were observed. The elimination half-life is not changed in patients with renal impairment. The pharmacokinetics of amlodipine are not significantly influenced by renal impairment.

##### *Patients with hepatic impairment:*

Pharmacokinetic studies in patients with hepatic impairment showed an increase in absolute bioavailability of telmisartan up to nearly 100 %. The elimination half-life of telmisartan is not changed in patients with hepatic impairment. Patients with hepatic insufficiency have decreased clearance of amlodipine with resulting increase of approximately 40-60% in AUC.

## ***Bioequivalence***

The following PK studies were submitted.

- Two open-label, randomised, two-sequence, two-period crossover trials to demonstrate the bioequivalence of the single entity tablets of telmisartan 40 mg and amlodipine 5 mg (1235.3) and telmisartan 80 mg and amlodipine 10 mg (1235.4) with the respective FDC tablets.
- An open-label, randomised, two-sequence, two-period crossover study to investigate the effect of food intake on the bioavailability of the fixed-dose combination of telmisartan 80 mg and amlodipine 10 mg following a high fat breakfast (1235.12)
- Two open-label, randomised, two-way crossover drug-drug interaction studies were performed to determine the effect of concomitant administration of amlodipine on the steady-state pharmacokinetics of telmisartan (1235.2) and vice versa (502.126).

In addition, dissolution testing was conducted to investigate in vitro equivalence of the intermediate FDC dose strengths T40/A10 or T80/A5.

### **Study 1235.3**

#### **Methods/design**

Bioequivalence of 40 mg telmisartan/5 mg amlodipine fixed dose combination compared with its mono components in healthy male and female volunteers. An open-label, randomised, single-dose, two-period crossover study

The time points and sampling periods are appropriate for both compounds. Methods were validated appropriately.

#### *Pharmacokinetic parameters:*

primary endpoints: AUC<sub>0-∞</sub> and C<sub>max</sub>

secondary endpoints : AUC<sub>0-tz</sub>;, t<sub>max</sub>, λ<sub>z</sub>, t<sub>1/2</sub>, MRT<sub>po</sub>, CL/F, V<sub>z</sub>/F

Upon request of the CHMP clarification on the choice of AUC<sub>0-∞</sub> as primary endpoint was provided by the MAH for both studies 1235.3 and 1235.4. In addition, statistical analysis of AUC<sub>0-t</sub> as required in the NfG CPMP/EWP/QWP/1401/98 Rev.1 was provided. The data for both AUC<sub>0-∞</sub> and AUC<sub>0-t</sub> were consistent with the assumption of bioequivalence.

#### **Results**

Altogether 84 subjects (42 male, 42 female) participated in the treatment phase of the study. None of the subjects discontinued the study. No important protocol violations occurred.

One subject after the individual tablet treatment exhibited unexpected plasma concentration-time profiles for both telmisartan and amlodipine, with a large delay in t<sub>max</sub>. This subject had reported nausea throughout the dosing period, which was considered to be a likely cause of the abnormal pharmacokinetics. This data set was therefore not used for descriptive pharmacokinetic statistics or bioequivalence analysis.

For telmisartan, the plasma samples of one subject exhibited interference in the bioanalytical assay and both treatments of this subject were excluded from pharmacokinetic data analysis.

Upon request from the CHMP, the applicant clarified the reasons for excluding the patient. Considering that it was an outlier and that repeat measurements did not reveal consistent results, the exclusion from the analysis can be accepted.

For both telmisartan and amlodipine, geometric mean plasma concentration-time profiles were closely similar between the FDC and individual tablet treatments. The ratios are shown in table 12.

Table 12

Table 11.5.2.2: 1 Summary of pharmacokinetic parameters of telmisartan after administration of telmisartan (40 mg) and amlodipine (5 mg) fixed dose combination and as individual tablets

		Telmisartan / Amlodipine FDC (N=83)		Telmisartan (Micardis®) + Amlodipine (Norvasc®) (N=82)	
		gMean	gCV [%] <sup>a</sup>	gMean	gCV [%] <sup>a</sup>
AUC <sub>0-∞</sub> <sup>b,d</sup>	[ng·h/mL]	629	82.3	656	80.2
%AUC <sub>0-∞</sub> <sup>b,d</sup>	[%]	6.17	86.3	6.38	73.8
AUC <sub>0-t<sub>z</sub></sub>	[ng·h/mL]	578	81.6	599	79.0
t <sub>z</sub> <sup>c</sup>	[h]	72.0 (24.0 – 72.3)		72.0 (48.0 – 72.7)	
C <sub>max</sub>	[ng/mL]	61.9	83.9	58.9	66.4
t <sub>max</sub> <sup>c</sup>	[h]	1.00 (0.250 – 8.05)		1.50 (0.250 – 8.00)	
t <sub>1/2</sub> <sup>e</sup>	[h]	20.4	40.5	21.5	38.4
MRT <sub>po</sub>	[h]	22.6	36.9	23.0	33.6
CL/F	[mL/min]	1060	82.3	1020	80.2
V <sub>z</sub> /F	[L]	1870	81.8	1850	84.5

<sup>a</sup> intersubject variability

<sup>b</sup> AUC extrapolation to infinite time based on predicted value of last data point, see [section 15.6.2](#)

<sup>c</sup> median and range

<sup>d</sup> N=79 for individual tablet treatment

<sup>e</sup> N=81 for individual tablet treatment

BI Trial No.:1235.0003.\Telmisartan\_Amlodipine\1235\_0003\Project\_Data\Data\_Reporting\Section\_15\_6\

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Source data: [Tables 15.6.2.1:1](#) and [3](#)

For both telmisartan and amlodipine, the 90% CIs for both AUC<sub>0-∞</sub> and C<sub>max</sub> were contained in the bioequivalence acceptance range of 80-125%. The intrasubject variability of telmisartan C<sub>max</sub> was high (40.9%), whereas the intrasubject variabilities of telmisartan AUC<sub>0-∞</sub> (23.1%), and of amlodipine AUC<sub>0-∞</sub> and C<sub>max</sub> (8.9 and 10.4% respectively) were much lower.

#### Effect of gender

AUC<sub>0-∞</sub> was 5% lower for women than men with the FDC, and 1.7% higher for women with the individual tablets. The female C<sub>max</sub> was 41% higher than for the males with the FDC and 37% for the individual tablets. Intersubject variability was comparable for both genders.

AUC<sub>0-∞</sub> was 12% higher for the women than the men with the FDC, and 16% higher with the individual tablets. The corresponding female-to-male increases for C<sub>max</sub> were 27 % for the FDC and 28% for the individual tablets.

The study provides information on the gender specificity of PK, however. C<sub>max</sub> of telmisartan was higher in females as compared to males and overall exposure (c<sub>max</sub> and AUC) was higher in females for amlodipin. The clinical relevance is further assessed in the light of the efficacy studies.

## Study 1235.4

### Methods/design

Bioequivalence of 80 mg telmisartan/10 mg amlodipine fixed dose combination compared with its monocomponents in healthy male and female volunteers. An open-label, randomised, single-dose, two-sequence crossover study

#### *Pharmacokinetic parameters:*

- primary endpoints: AUC<sub>0-∞</sub> and C<sub>max</sub>
- secondary endpoints : AUC<sub>0-t<sub>z</sub></sub>, t<sub>max</sub>, λ<sub>z</sub>, t<sub>1/2</sub>, MRT<sub>po</sub>, CL/F, V<sub>z</sub>/F

### Results

Forty-four male 40 and female subjects participated in the treatment phase of the study. Three subjects discontinued the study due to adverse events. No important protocol violations occurred

Eighty-two pharmacokinetic data sets were analyzed for the fixed dose combination (44 male, 38 female) and 83 for the individual tablets (44 male, 39 female). For both telmisartan and amlodipine, geometric mean plasma concentration-time profiles were closely similar between the FDC and individual tablet treatments. Table 13 and 14 summarise the pharmacokinetic parameters of telmisartan and amlodipin after administration of 80 mg and 10 mg respectively as FDC and individual tablets.

For telmisartan, the point estimate of the geometric mean ratio (FDC/individual tablets) of AUC<sub>0-inf</sub> was 103.3% within the confidence limits were 98.6%. For C<sub>max</sub>, the geometric mean ratio was 108.2% and within the 90% confidence limits. The intrasubject coefficient of variation was higher for C<sub>max</sub> (40.3%) than for AUC<sub>0-inf</sub> (18.0%).

For amlodipine, the point estimate of the geometric mean ratio (FDC/individual tablets) of AUC<sub>0-∞</sub> was within the 90% confidence limits were 103.3%. For C<sub>max</sub>, the geometric mean ratio was 102.9% within the confidence limits.

Table 13

Table 11.5.2.2: 1 Summary of pharmacokinetic parameters of telmisartan after administration of telmisartan (80 mg) and amlodipine (10 mg) fixed dose combination and individual tablets

parameter	units	Telmisartan / Amlodipine FDC (N=82)		Telmisartan (Micardis®) + Amlodipine (Norvasc®) (N=83)	
		gMean	gCV % <sup>a</sup>	gMean	gCV% <sup>a</sup>
AUC <sub>0-∞</sub> <sup>b</sup>	[ng·h/mL]	961	73.3	941	76.5
%AUC <sub>0-∞</sub> <sup>b</sup>	[%]	6.71	64.1	5.91	67.0
AUC <sub>0-tz</sub>	[ng·h/mL]	885	72.1	873	76.5
t <sub>z</sub> <sup>c</sup>	[h]	72.0 (24.0 – 72.1)		72.0 (24.0 – 72.1)	
C <sub>max</sub>	[ng/mL]	199	95.3	187	101
t <sub>max</sub> <sup>c</sup>	[h]	0.983 (0.500 – 2.02)		1.00 (0.500 – 4.00)	
t <sub>1/2</sub>	[h]	24.1	39.0	23.2	33.2
MRT <sub>po</sub>	[h]	19.5	38.9	18.5	39.1
CL/F	[mL/min]	1390	73.3	1420	76.5
V <sub>d</sub> /F	[L]	2890	70.5	2840	78.0

<sup>a</sup> intersubject variability

<sup>b</sup> AUC extrapolation to infinite time based on predicted value of last data point, see [section 15.6.2](#)

<sup>c</sup> median and range

BI Trial No.: 1235.0004.\Telmisartan\_Amlodipine\1235\_0004\Project\_Data\Data\_Reporting\Section\_15\_6\

BT\_1235\_0004\_15\_6\_3\_V1\_080115.doc

Source data: [Tables 15.6.2.1.1](#) and [3](#)

Table 14

Table 11.5.2.2: 2 Summary of pharmacokinetic parameters of amlodipine after administration of telmisartan (80 mg) and amlodipine (10 mg) fixed dose combination and individual tablets

		Telmisartan / Amlodipine FDC (N=82)		Telmisartan (Micardis <sup>®</sup> ) + Amlodipine (Norvasc <sup>®</sup> ) (N=83)	
		gMean	gCV % <sup>a</sup>	gMean	gCV % <sup>a</sup>
AUC <sub>0-∞</sub> <sup>b</sup>	[ng·h/mL]	312	28.6	295	25.1
%AUC <sub>0-∞</sub> <sup>b</sup>	[%]	6.15	55.3	5.84	58.0
AUC <sub>0-tz</sub>	[ng·h/mL]	290	28.0	275	24.5
t <sub>z</sub> <sup>c</sup>	[h]	168 (168 – 169)		168 (168 – 169)	
C <sub>max</sub>	[ng/mL]	6.07	25.5	5.90	22.0
t <sub>max</sub> <sup>c</sup>	[h]	6.02 (2.00 – 12.1)		6.02 (2.00 – 12.0)	
t <sub>1/2</sub>	[h]	43.3	19.4	42.3	20.2
MRT <sub>po</sub>	[h]	60.6	19.0	59.8	18.9
CL/F	[mL/min]	534	28.6	565	25.1
V <sub>z</sub> /F	[L]	2000	31.7	2070	28.8

<sup>a</sup>intersubject variability

<sup>b</sup>AUC extrapolation to infinite time based on predicted value of last data point, see [section 15.6.2](#)

<sup>c</sup>median and range

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BT\_1235\_0004\_15\_6\_3\_V1\_080115.doc

Source data: [Tables 15.6.2.1.2](#) and [4](#)

#### Effect of gender

Overall exposure (AUC but not C<sub>max</sub>) of telmisartan was higher in females as compared to males. For amlodipine overall exposure (C<sub>max</sub> and AUC) was higher in females. The gender specific differences were similar in both BE studies with the exception of study 1235.3 and 1235.4. Taken both studies together, the data are consistent with a moderately higher exposure in females.

### **Influence of food**

A food study was submitted in this application.

## **Trial 1235.12**

### **Methods/design**

Influence of food on the bioavailability of 80 mg telmisartan/10 mg amlodipine fixed dose combination in healthy male and female volunteers. An open-label, randomised, single-dose, two period, crossover study

*Criteria for evaluation:* Pharmacokinetics of telmisartan and amlodipine

- primary endpoints: AUC<sub>0-∞</sub>, and C<sub>max</sub>
- secondary endpoints : AUC<sub>0-tz</sub>, t<sub>max</sub>, λ<sub>z</sub>, t<sub>1/2</sub>, MRT<sub>po</sub>, CL/F, V<sub>z</sub>/F

Statistical methods:

Pharmacokinetic parameters of telmisartan and amlodipine were evaluated separately. Two-sided 90% confidence intervals (CIs) for the intrasubject fed-to-fasted ratio (as estimated by the ratio of the geometric means) of each of AUC<sub>0-∞</sub> and C<sub>max</sub> were calculated. Absence of food effect on bioavailability was to be concluded if the 90% CIs of the ratios were contained within the acceptance limits of 80-125%.

### **Results**

Forty subjects participated in the treatment phase of the study. One subject discontinued the study due to private reasons. No important protocol violations occurred.

Thirty-nine pharmacokinetic data sets (20 male, 19 female) were evaluable for each treatment. One female subject was excluded from the statistical analysis of relative bioavailability because this subject did not finish the meal. Therefore 39 data values were available each for the fasted and the fed state.

With food a moderate reduction in AUC was observed in both gender (male 21% and women 29%).

The food effect study suggests a clinically relevant decrease by 25% of exposure to telmisartan as estimated by AUC<sub>0-inf</sub> and a more pronounced decrease of C<sub>max</sub>. This food effect is more pronounced in females and may be of clinical relevance. These data are consistent with previous results observed with telmisartan. Further discussion about the relevance of this finding and whether the intake of the tablet is to be restricted to the fasting state was provided by the applicant upon request from the CHMP.

In summary it can be accepted that the SPC is consistent with the SPC of the originator for Telmisartan in monotherapy. There is no reason to assume that the issue is different in the FDC as compared to the monotherapy.

The posology proposes that TWYNSTA can be taken with or without food.

## **Interactions**

### **TRIAL 1235.2**

#### **Methods**

Title : Pharmacokinetics of repeated oral doses of 80 mg telmisartan (Micardis®) at steady state alone and in combination with repeated oral doses of amlodipine 10 mg (Norvasc®) at steady state. A two-way crossover, open, randomised design study

Treatment sequence A was 80 mg telmisartan, followed after a washout period of at least 15 days by 80 mg telmisartan+10 mg amlodipine. Sequence B was 80 mg telmisartan+10 mg amlodipine, then 80 mg telmisartan (20 entered, 20 treated, 20 analysed for primary endpoint). Medication was taken in the fasted state.

Primary endpoint: Comparison of AUC<sub>ss</sub> and C<sub>max,ss</sub> of telmisartan in combination with amlodipine (T80+A10), with the reference treatment, telmisartan alone (T80).

The secondary endpoints were AUC<sub>τ,ss</sub> and C<sub>max,ss</sub> of amlodipine, and the following pharmacokinetic parameters of both telmisartan and amlodipine: C<sub>max</sub>, t<sub>max</sub>, AUC<sub>τ,1</sub>, C<sub>pre,N</sub>, t<sub>max,ss</sub>, C<sub>min,ss</sub>,  $\square_{z,ss}$ , t<sub>1/2,ss</sub>, MRT<sub>po,ss</sub>, CL/F<sub>ss</sub>, V<sub>z</sub>/F<sub>ss</sub>, RA, AUC, RA, C<sub>max</sub>.

Statistics: Point estimates (geometric means) of the median intrasubject ratios of AUC<sub>τ,ss</sub> and C<sub>max,ss</sub> and their two-sided 90% confidence intervals were calculated.

The design of the trial is acceptable. PK of Telmisartan is nonlinear due to a saturable first-pass metabolism. In this case investigation of interactions at the highest applied dose should represent the most sensitive approach. The chosen dose was appropriate.

#### **Results**

Thirty-eight healthy caucasian volunteers, 20 women and 18 men, were entered in this study and began treatment with 80 mg telmisartan and 10 mg amlodipine.

Treatment was discontinued in two subjects. No deviations from protocol are noted that can be considered relevant for the PK results.

Geometric mean AUC<sub>τ,ss</sub> of telmisartan for the 36 subjects who received the entire dosage regimen (18 men and 18 women) was 1020 ng.h/mL when administered alone and 999 ng.h/mL with amlodipine.

Geometric mean  $C_{max,ss}$  was 272 ng/mL for telmisartan alone and 242 ng/mL for telmisartan with amlodipine. A higher systemic exposure to telmisartan was observed in the female subjects. The gender difference seen on  $C_{max,ss}$  of telmisartan on coadministration is not considered clinically relevant, compared to the males. This is consistent with previously reported results.

The total and peak systemic exposure achieved for amlodipine was comparable with previously published data and was therefore adequate to ensure a valid assessment of its interaction potential towards telmisartan.

In summary, the values for  $C_{max,ss}$  and  $AUC_{0,ss}$  are within the acceptance limits. Therefore, the study does not indicate a clinically relevant influence of amlodipin 10 mg on PK of telmisartan.

## TRIAL 502.126

### Methods

Title : Pharmacokinetics of repeated oral doses of 10 mg amlodipine daily and of 10 mg amlodipine and 120 mg telmisartan daily in a cross-over randomised open study in healthy subjects.

Open, randomised, two way cross-over trial with a wash out period of 13 days between the two treatments, in 12 healthy male volunteers. The two treatments were 9 days of amlodipine 10 mg/day alone and 9 days of amlodipine 10 mg plus telmisartan 120 mg/day concomitantly.

The pharmacokinetic evaluation included plasma levels of telmisartan and amlodipine,  $AUC_{SS}$ ,  $AUC_{day1}$ ,  $C_{max}$ ,  $C_{max,ss}$ ,  $t_{max}$ ,  $t_{max,ss}$ ,  $t_{1/2}$ ,  $MRT_{SS}$ ,  $Cl_{tot}/f$ ,  $V_z/f$ ,  $R_A$ ,  $A_e$ .  $CL_{ren}$  was determined for amlodipine.

### Results

Table 24 (geometric mean values except  $t_{max}$ , for which the median is given)

parameter	units	Amlodipine without telmisartan	amlodipine with telmisartan	telmisartan (with amlodipine)
$C_{max}$	ng/ml	5.4	5.55	311
$C_{max,ss}$	ng/ml	17.7	18.7	494
$t_{max}$	h	7	8	1.25
$AUC_{0,24h}$	ng.h/ml	90.5	95.8	1000
$AUC_{SS}$	ng.h/ml	331	352	1590
$t_{1/2}$	h	56	52	19
$A_e$	%	8	9.4	--

The values for  $C_{max,ss}$  and  $AU_{ss}$  are within the acceptance limits. The data do not indicate a clinically relevant influence of telmisartan on the PK of amlodipin at the fasting state.

Considering the knowledge of the the PK of Telmisartan and Amlodipin and the two interactions studies, there are no indications that there may be a clinically relevant PK interaction in healthy volunteers.

### 2.4.3. Pharmacodynamics

#### *Primary and Secondary pharmacology*

The Pharmacodynamic properties of Telmisartan and Amlodipin are well known. No new studies were submitted. The pivotal clinical studies sufficiently characterise the interaction on the main clinical and pharmacodynamic endpoint, blood pressure.

## 2.4.4. Discussion on clinical pharmacology

A Bioequivalence approach was used to bridge the clinical data obtained with a combination of the mono components for the strengths containing 40/5 and 80/10 mg T/A to the final FDC formulation. Four FDCs strengths containing T40/A5, T40/A10, T80/A5, and T80/A10 are proposed. Only for two of these FDCs (T40/A5 and T80/A10) BE studies were conducted.

In addition, in vitro dissolution is to be used to bridge the bioequivalence studies conducted with T40/A5 and T80/A10 strengths to the other strengths (T80/A5 and T40/A10 mg).

The intermediate strengths contain different relative ratios. According to the NfG CPMP/EWP/QWP/1401/98, a waiver of BE studies is considered when the relative amount of active substances to excipients is the same. However, considering that the amlodipin component makes up for less than 5% and the similarity of the in vitro dissolution, the transferability of the bioequivalence data to the immediate strengths is acknowledged.

The food effect study suggests a clinically relevant decrease by 25% of exposure to telmisartan as estimated by AUC<sub>0-inf</sub> and a more pronounced decrease of c<sub>max</sub>. This food effect is more pronounced in females. These data are consistent with previous results observed with telmisartan. There is no reason to assume that the issue is different in the FDC as compared to the monotherapy, and the SPC proposal is identical to Telmisartan in monotherapy.

The posology proposes that TWYNSTA can be taken with or without food.

## 2.5. Clinical efficacy

Pivotal studies

Five Phase III trials studies have been performed to establish efficacy and safety:

- An 8-week placebo-controlled, 4x4 factorial design trial to evaluate telmisartan 20, 40 and 80 mg tablets in combination with amlodipine 2.5, 5 and 10 mg capsules in patients with hypertension, including an ABPM sub-study (1235.1).
- Two 8-week active-controlled, double-blind, non-responder studies to demonstrate the efficacy and safety of the fixed dose combinations in patients with hypertension who tolerated but failed to respond adequately to treatment with amlodipine 5mg (1235.5) or amlodipine 10mg monotherapy (1235.6)

Supportive studies

- Two open-label long-term follow-up trials over 34 weeks to determine the efficacy and safety of chronic administration of the fixed dose combinations alone or in combination with other antihypertensive medications in patients with hypertension who did not adequately respond to treatment with amlodipine 5mg (1235.7) or amlodipine 10mg monotherapy (1235.8, interim report).

### 2.5.1. Dose response study(ies)

See below (study 1235.1)

### 2.5.2. Main study(ies)

#### Trial 1235.1

This study is the key study for dose finding and is also the pivotal study for the first line indication.

#### Methods

- **Study Participants**

Main inclusion criteria: Male and female patients  $\geq 18$  years of age with Stage I or II hypertension defined as a mean seated cuff DBP (DBP)  $\geq 95$  and  $\leq 119$  mmHg at visit 3.

Inclusion of both stage I and stage II hypertension patients was planned in order to use this study as the pivotal study for the first line indication for patients with severe hypertension.

• **Treatments**

Patients assigned to treatment with amlodipine 10 mg were dosed with amlodipine 5 mg for the first two weeks and up-titrated to target dose for the remaining six weeks of treatment. Patients randomized to combination therapy received one of nine treatment combinations:

- T20+A2.5 or T20+A5 or T20+A10 or
- T40+A2.5 or T40+A5 or T40+A10 or
- T80+A2.5 or T80+A5 or T80+A10

(A10 mg was supplied as two 5 mg capsules)

Duration of treatment: Eight weeks

Figure 9.1.1 below summarises the study design.

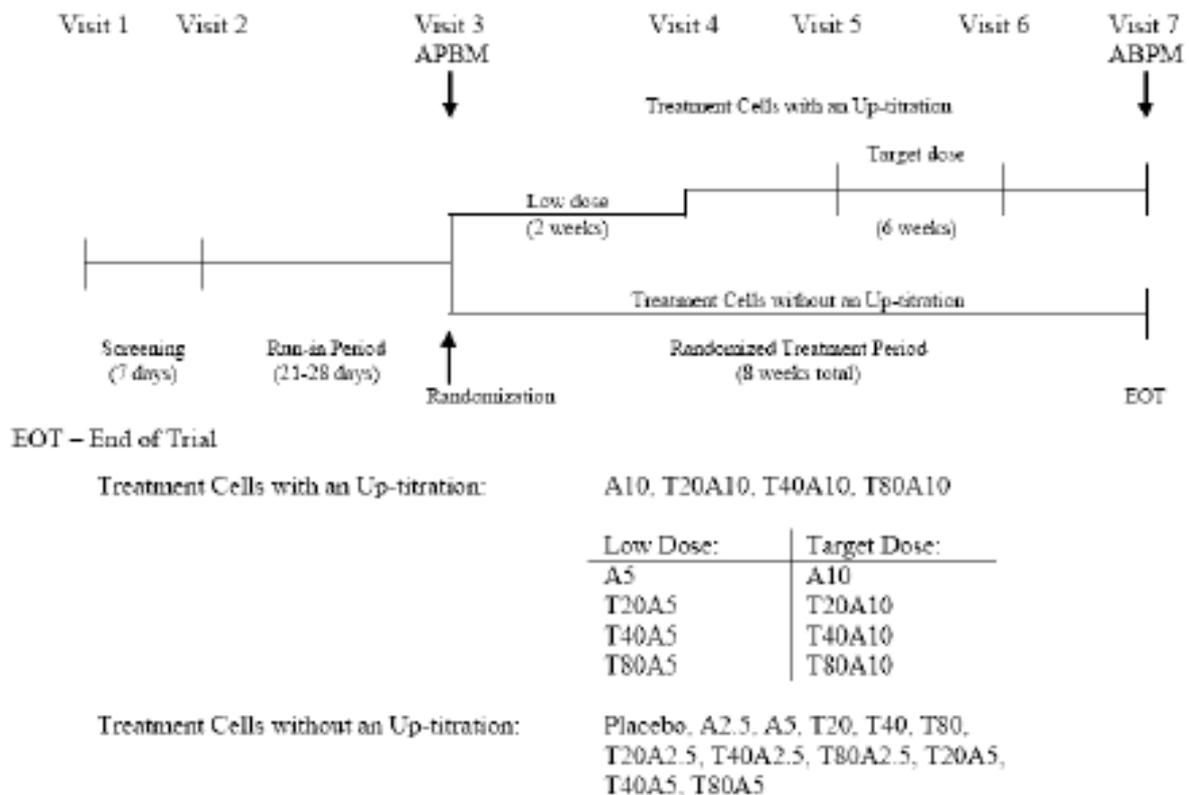


Figure 9.1: 1 Study design

• **Objectives**

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

• **Outcomes/endpoints**

Primary: Change from baseline in the in-clinic seated trough cuff DBP after eight weeks of treatment

Secondary: Change from baseline in the in-clinic seated trough cuff systolic blood pressure (SBP); Percentage of patients responding to treatment based on in-clinic mean seated trough cuff BP measurements; Changes from baseline in the in-clinic standing trough cuff DBP and SBP.

ABPM Sub-study: Changes from baseline in DBP and SBP hourly means over the 24-hour dosing interval as measured by ABPM; Changes from baseline in the 24-hour ABPM mean (relative to dosetime) for DBP and SBP.

The primary focus on DBP acceptable albeit systolic blood pressure may clinically more relevant. However, since usually effects on systolic blood pressure are more pronounced than on DBP it can be expected that in case of significant changes on DBP these will translate to significant changes in SBP.

- **Blinding (masking)**

Telmisartan 20, 40, and 80 mg tablet doses were provided by using respective active or placebo tablets in a double-dummy technique.

- **Statistical methods**

The primary analysis involved an Analysis of Covariance (ANCOVA) including the main effects of treatment with telmisartan and treatment with amlodipine to show that treatment with either active therapy resulted in a significant ( $\alpha=0.05$ ) dose response in the reduction in the in-clinic trough cuff DBP after eight weeks of treatment. Baseline DBP was included as a covariate.

All secondary analyses of the primary and secondary endpoints were evaluated using the FAS and using  $\alpha = 0.05$  (2-sided) to evaluate significance of effects and treatment comparisons. Subgroup analyses were performed on the primary endpoint of change from baseline in in-clinic trough cuff DBP using the same statistical models as described for the primary endpoint were used.

Responder rates were evaluated using Mantel-Haenszel test statistics.

For the ABPM sub-study results, the hourly means over the 24-hour dosing interval for both DBP and SBP were summarised for each treatment. As well, in order to evaluate any possible peak effects, the 24-hour profiles of the changes from baseline were graphically presented.

Analysis of the changes from baseline in the 24-hour ABPM mean DBP and SBP followed that described for the secondary analysis of in-clinic BPs to evaluate treatment effects.

In addition, following database lock a second definition identifying patients with moderate or severe hypertension at baseline based on SBP was defined. This subgroup was defined as patients with a SBP  $\geq 160$  mmHg at baseline.

## **Results**

- **Disposition of patients**

Two thousand six hundred seven (2607) patients were enrolled into this trial of which 1461 were randomised to receive either placebo: 46 patients, Telmisartan mono (20, 40 or 80 mg): 307 patients, Amlodipine mono (2.5, 5 or 10 mg): 319 patients or combination therapy: 789 patients. A total of 1344 (92.0%) patients completed the eight week trial.

Of 1461 patients randomised/treated with study drug, 1078 were identified as having moderate or severe hypertension (defined as: DBP  $\geq 100$ mmHg) at baseline. Of the 1078 patients, 997 (92.5%) patients completed the eight week trial and 81 (7.5%) patients were prematurely discontinued.

- **Conduct of the study**

321 Important Protocol Violations (IPVs) related to efficacy were identified and the most prevalent IPVs were Concomitant Medication, Entrance Criteria Not Met, Incorrect Timing. For the subset of patients with moderate or severe hypertension at baseline, a total of 188 IPVs related to efficacy were identified.

A total of 36 IPVs related to patient safety were identified of which the most prevalent were Incorrect Timing, Missing data.

- **Baseline data**

Baseline characteristics of patients is presented in Table 28.

*Table 28 Patient analysis sets – overall*

Analysis set	Total
Randomised set	1461 (100.0)
Treated set (TS)	1461 (100.0)
Full analysis set - trough cuff (FAS-TC)	1423 (97.4)
Per-protocol analysis set - trough cuff (PPS-TC)	1155 (79.1)
Full analysis set - ABPM (FAS-ABPM)	562 (38.5)
Treated set - moderate/severe (TS-MS)	1078 (73.8)
Full analysis set - trough cuff - moderate/severe (FAS-TC-MS)	1050 (71.9)
Per-protocol set - trough cuff - moderate/severe (PPS-TC-MS)	892 (61.1)
Full analysis set - ABPM - moderate/severe (FAS-ABPM-MS)	403 (27.6)

Source data: [Table 15.1.3: 1](#)

There was an equal representation of both sexes, most patients were caucasians (79.4%), elderly patients were sufficiently represented.

The overall mean age was 53.1 years with 14.0%  $\geq 65$  years old. The majority of patients had a duration of hypertension  $>5$  years [ $<1$  year: 14.1%, 1-5 years: 30.5%,  $>5$  years: 55.2%, missing: 0.2%]

Among them, 21.0% were not being previously prescribed antihypertensive medication, 36.3% previously treated with antihypertensive monotherapy, and 42.6% previously treated with combination therapy of two or more antihypertensive medications.

The overall mean body mass index (BMI) was 31.3 kg/m<sup>2</sup> with 16.3% of patients being diabetic and 0.8% with renal impairment.

Among the individual treatment groups, there were demographic and baseline characteristics differences but none were considered to have an effect the safety or efficacy evaluations.

The overall mean seated trough cuff SBP/DBP at baseline was 153.2/101.7 mmHg for all treated patients (TS) and 154.7/103.5 mmHg for treated patients with moderate or severe hypertension at baseline (TS-MS), with no appreciable differences found among the 16 treatment groups in the mean in-clinic seated trough cuff DBPs at baseline for either of these two analysis sets.

- **Outcomes and estimation**

**Primary measure of efficacy:** *change from baseline in the in-clinic mean seated trough cuff DBP at the end-of-study visit.*

The data for the overall population and the patients with moderate to severe hypertension at baseline are summarized in table 29 and 30 below,

*Table 29 Mean (SD) observed changes from baseline in in-clinic seated trough cuff DBP (mmHg) (FAS-TC)( Stage I or II hypertensives at baseline)*

	A0	A2.5	A5	A10	Overall
T0	n=46 -5.9 (9.4)	n=48 -10.4 (9.9)	n=137 -13.0 (7.9)	n=124 -16.5 (7.1)	n=355 -13.0 (8.8)
T20	n=42 -13.2 (9.0)	n=44 -18.0 (7.8)	n=45 -15.7 (6.5)	n=40 -18.7 (7.0)	n=171 -16.4 (7.8)
T40	n=129 -13.1 (10.1)	n=47 -16.2 (8.2)	n=141 -16.0 (7.6)	n=123 -19.6 (7.9)	n=440 -16.2 (8.9)
T80	n=132 -13.6 (8.7)	n=46 -15.3 (7.5)	n=143 -17.8 (8.5)	n=136 -19.6 (7.9)	n=457 -16.9 (8.6)
Overall	n=349 -12.3 (9.7)	n=185 -14.9 (8.8)	n=466 -15.6 (8.1)	n=423 -18.6 (7.7)	n=1423 -15.6 (8.8)

SD – Standard Deviation

Source data: [Table 15.2.1.1.1-1](#)

Table 30 Mean (SD) observed changes from baseline in in-clinic seated trough cuff DBP (mmHg) (FAS-TC-MS)( Moderate or severe hypertension\_ at baseline)

	A0	A2.5	A5	A10	Overall
T0	n=35 -5.5 (10.1)	n=37 -11.4 (8.3)	n=101 -13.1 (8.1)	n=83 -17.1 (7.6)	n=256 -13.1 (9.0)
T20	N=33 -13.9 (9.4)	N=34 -18.4 (7.9)	n=34 -15.8 (6.4)	n=28 -19.5 (7.2)	n=129 -16.8 (8.0)
T40	n=100 -13.8 (10.2)	n=30 -18.7 (7.9)	n=108 -16.8 (7.5)	n=96 -19.6 (8.3)	n=334 -16.9 (8.9)
T80	n=89 -13.9 (9.2)	n=36 -16.3 (7.7)	n=106 -18.8 (9.0)	n=100 -20.4 (7.3)	n=331 -17.7 (8.8)
Overall	n=257 -12.7 (10.1)	n=137 -16.0 (8.4)	n=349 -16.3 (8.3)	n=307 -19.2 (7.8)	n=1050 -16.2 (9.0)

SD – Standard Deviation

Source data: [Table 15.2.1.1.3-1](#)

There is a flat dose response relation between Telmisartan 40 and 80 mg in all kinds of combination with or without amlodipin. Based on these results the justification of FDCs containing 80 mg of telmisartan could be questionable. The data indicate a possible difference with respect to stage of Hypertension. The issue will be further addressed in the filter study (ABPM). Dose response may be different in non-responders to amlodipin. These studies have to be taken into consideration for the overall assessment of dose response.

In the group of patients with more severe hypertension similarly only a small effect is observed. Especially in combination with amlodipin 10 mg the difference between T20 and T80 is less than 1 mmHg.

When evaluating the changes from baseline for the FAS-TC (Final Analysis Set- Trough Cuff) there was a significant difference among the four dosage levels of telmisartan irrespective of amlodipine dose (see table 31)

Table 31

Table 11.4.1.1.1: 1 Effect of treatment with telmisartan on change from baseline to end of study (LOCF) in in-clinic seated trough cuff DBP (mmHg) (FAS-TC)

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

<sup>†</sup> Adjusted for country/region (POOLCTR) effect and baseline value

SE – Standard Error

Source data: [Table 15.2.1.1.1: 2](#)

Table 11.4.1.1.1: 2 Effect of treatment with amlodipine on change from baseline to end of study (LOCF) in in-clinic seated trough cuff DBP (mmHg) (FAS-TC)

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

<sup>†</sup> Adjusted for country/region (POOLCTR) effect and baseline value

SE – Standard Error

Source data: [Table 15.2.1.1.1: 2](#)

When evaluating the changes from baseline for patients with moderate or severe hypertension at baseline (Final Analysis Set- Moderate Severe) (FAS-TC-MS) there was a significant difference among the four dosage levels of telmisartan (see table 32)

Table 32

Table 11.4.1.1.1: 3 Effect of treatment with telmisartan on change from baseline to end of study (LOCF) in in-clinic seated trough cuff DBP (mmHg) (FAS-TC-MS)

	Overall T0 effect	Overall T20 effect	Overall T40 effect	Overall T80 effect	Level of significance
N	256	129	334	331	
Adj mean <sup>†</sup> (SE)	-12.7 (0.54)	-17.3 (0.73)	-17.3 (0.48)	-18.0 (0.48)	P<0.0001

<sup>†</sup> Adjusted for country/region (POOLCTR) effect and baseline value

SE – Standard Error

Source data: [Table 15.2.1.1.3: 2](#)

Table 11.4.1.1.1: 4 Effect of treatment with amlodipine on change from baseline to end of study (LOCF) in in-clinic seated trough cuff DBP (mmHg) (FAS-TC-MS)

	Overall A0 effect	Overall A2.5 effect	Overall A5 effect	Overall A10 effect	Level of significance
N	257	137	349	307	
Adj mean <sup>†</sup> (SE)	-12.5 (0.54)	-16.4 (0.71)	-16.7 (0.47)	-19.7 (0.50)	P<0.0001

<sup>†</sup> Adjusted for country/region (POOLCTR) effect and baseline value

SE – Standard Error

Source data: [Table 15.2.1.1.3: 2](#)

Similar results were obtained for those patients presenting with moderate or severe hypertension at baseline identified as SBP ≥160 mmHg.

In conclusion, the primary analysis showed significant overall results among the four dose levels for telmisartan and amlodipin. The results demonstrated the individual contribution of each monosubstance in the combination.

The effects of treatment with each of the four key treatment combinations T40+A5, T40+A10, T80+A5 and T80+A10 on the changes from baseline in in-clinic seated trough cuff DBP were compared to the effects of the respective individual monotherapies using the full ANCOVA that included all sixteen treatment groups and involved the FAS-TC. For the four key combination therapies statistical significance as compared to the respective monotherapies was demonstrated in the FAS-TC and in the FAS-TC-MS group.

The subgroup analysis of the data did not indicate a significant influence of gender, race, and age. Albeit numerically the effect was more pronounced with telmisartan in females than in males the difference was not statistically significant. Therefore, the higher drug exposure seen in the PK study does not translate into statistically significant differences in efficacy in this study.

**Secondary endpoints** : *In-clinic seated trough cuff SBP*

A significant difference among the mean changes of the four dosage levels of telmisartan and of the four dosage levels of amlodipine was observed in the FAS-TC population and FAS-TC-MS populations.

Significant response rates was demonstrated for the four key combination therapies compared to the respective individual monotherapies, with the exception of T40+A10 vs A10 for DBP control and DBP response, and T80+A10 vs A10 for DBP response and SBP response.

The analysis of the responder rate shows that in 32.7 – 51.8 % of patients with moderate to severe HTN can be sufficiently treated with a monotherapy. When starting a FDC in a first line approach to this considerably large group of patients will unnecessarily receive a combination therapy albeit monotherapy is appropriate and sufficient.

- **ABPM sub-study**

Approximately 50% of randomised patients had ABPMs performed at their baseline and end-of-study visits.

*Table 35 Peak changes from baseline (mmHg) in DBP ABPM hourly means (FAS-ABPM)*

	A0	A2.5	A5	A10
T0	Hour 3 -3.6	Hour 6 -7.2	Hour 8 -6.8	Hour 4 -8.6
T20	Hour 8 -8.3	Hour 7 -10.1	Hour 6 -15.5	Hour 4 -12.3
T40	Hour 6 -6.8	Hour 5 -12.6	Hour 5 -13.1	Hour 8 -17.4
T80	Hour 3 -9.8	Hour 2 -17.4	Hour 5 -16.3	Hour 8 -17.1

<sup>†</sup> Peak change defined as the maximum reduction in the mean ABPM hourly mean for the hours relative to dosetime of 2 through 8

Source data: [Table 15.2.3.1.2: 1](#)

The magnitude of overall reductions increased with increasing dosage of both telmisartan and amlodipine. This increasing overall reduction was also found for the changes from baseline in the 24-hour mean SBP. Similar results were seen in the group of patients with moderate to severe hypertension.

In summary the study is appropriate to provide information on the dose response of the combination of telimsartan and amlodipine. The dose response appears to be flat when comparing doses of 40 and

80 mg telmisartan in the presence or absence of amlodipin. This seems to be mainly due to the patients with mild (stage I) HTN and may be different in a population of non responders.

A multifactorial design as provided is the preferred type of study to establish dose response relation for a FDC according to the NfG CPMP/EWP/238/95 Rev. 1.

The study is an appropriate basis for an application for a substitution indication but when aiming for further indications (first line, second line), this cannot be considered sufficient on its own to establish an indication. For a second line indication add on studies (as provided) are required.

For a first line indication the studies should be carried out in a population that is unlikely to show BP control with monotherapy. This is not the case for the patients investigated with moderate to severe HTN. The analysis of the responder rate shows that 32.7 – 51.8 % of those patients with moderate to severe HTN can be sufficiently treated with a monotherapy. When starting a FDC in a first line approach 32.7 – 51.8 % of the patients will unnecessarily receive a combination therapy albeit monotherapy is appropriate and sufficient. The study therefore strongly indicates that in this group of patients a second line approach is preferable to a first line treatment in order to avoid overtreatment in 36 – 41% of patients. This was raised as a Major Objection during the procedure. Subsequently the MAH informed the CHMP in their reply to the D120 List of questions of their intention to withdraw this indication.

In addition for a first line indication efficacy and safety in comparison to an add-on is the preferred approach. It could be acceptable if such a study either shows a benefit with respect to efficacy on the grounds of acceptable safety or that with equal efficacy there is a benefit with respect to time when BP goals are achieved without additional safety concerns especially during the initiation of treatment. Such information cannot be derived from this study.

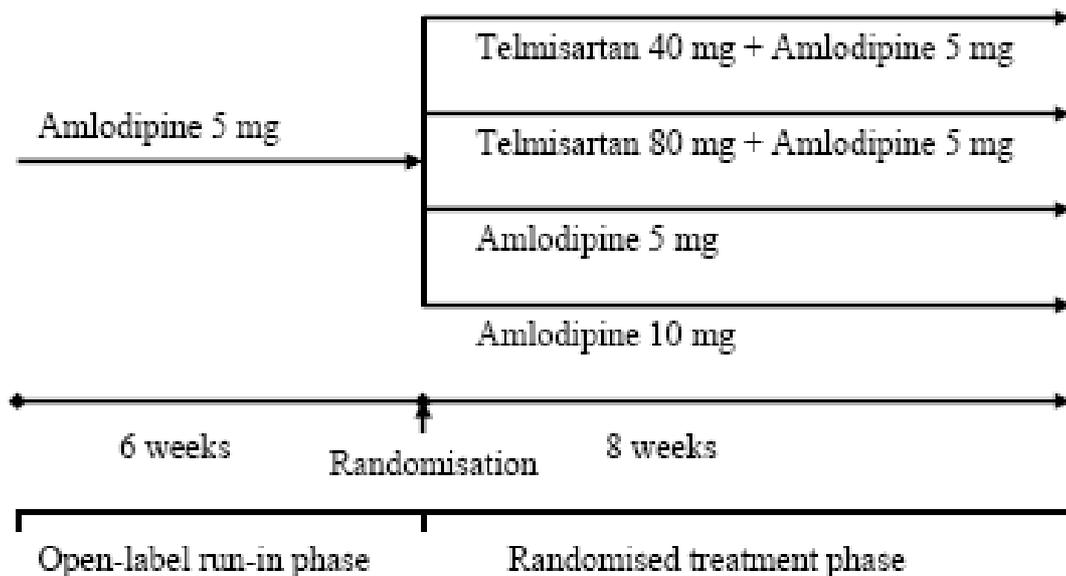
### Study 1235.5 Telmisartan plus Amlodipine Study in Amlodipine 5 mg Non-Responders in Hypertension: TEAMSTA-5

#### Methods

This was a randomised, controlled, double-blind, multi-centre study using a non-responder design in patients with uncontrolled hypertension.

Uncontrolled hypertension was defined as seated DBP  $\geq 95$  mmHg if patients were on antihypertensive treatment or seated DBP  $\geq 100$  mmHg if they were not treatment with antihypertensives.

Fig. 7 Trial design



- **Treatments**

The investigational products were FDCs of 40 mg telmisartan + 5 mg amlodipine (T40/A5) and 80 mg telmisartan + 5 mg amlodipine (T80/A5) and 10 mg amlodipine.

- **Objectives**

The primary objectives of this trial were (a) to demonstrate that the FDC T40/A5 or the FDC T80/A5 was superior over A5 in reducing BP at 8 weeks, (b) to demonstrate that the FDC T40/A5 or the FDC T80/A5 was not inferior vs. A10 in reducing BP at 8 weeks, and (c) to demonstrate that the incidence of oedema was lower for the pooled treatment groups T40/A5 and T80/A5 than for the A10 treatment group. These objectives were assessed in hypertensive patients who failed to respond adequately to A5, i.e. who had a trough seated DBP  $\geq 90$  mmHg after a 6-week treatment with A5.

- **Outcomes/endpoints**

There were 2 co-primary endpoints, the change from baseline to the last visit during the double-blind treatment phase in trough seated DBP and the incidence of oedema during the double-blind treatment phase.

- **Sample size**

Using an estimate of 6.6 mmHg, a sample size of 240 evaluable patients per treatment group would have approximately 90% power to detect a 2.0 mmHg difference between treatments in the reduction from baseline in trough seated DBP (2-sided,  $\alpha=0.05$ ).

The oedema incidence for treatment with A10 was expected to be 10.3% and 2.1% for the combination therapies. Using these estimates and the treatment group size of 240, the power would be approximately 96%.

- **Statistical methods**

Table 41 summarises the sequence of the 7 pre-specified tests and indicates whether the respective null hypothesis could be rejected.

Table 41 Qualitative summary of primary endpoint results according to the hierarchy of testing / FAS, TS

Parameter	Sequence of tests	Test	Treatments	H <sub>0</sub> rejected
Trough seated DBP	1	Superiority	T80/A5 vs. A5	Yes
	2	Superiority	T40/A5 vs. A5	Yes
	3	Non-inferiority	T80/A5 vs. A10	Yes
Oedema incidence	4	Superiority	(T40/A5 pooled with T80/A5) vs. A10	Yes
Trough seated DBP	5	Non-inferiority	T40/A5 vs. A10	Yes
	6	Superiority	T80/A5 vs. A10	Yes
	7	Superiority	T40/A5 vs. A10	Yes

For the analysis of oedema incidence, the TS was used (with a sensitivity analysis using the FAS), for the analyses of DBP, the FAS was employed (with sensitivity analyses using the PPS).

Some changes or extensions of analyses were introduced before DBL. After DBL and unblinding, post-hoc subgroup analyses for mean trough seated DBP and SBP were added based on diabetes status at baseline.

## **Results**

A summary of results for key efficacy endpoints is provided in table 37.

Table 37 Summary of results for efficacy endpoints / FAS, TS

	A5 n=255	A10 n=261	T40/A5 n=270	T80/A5 n=271
<b>Primary endpoint analyses</b>				
Adjusted mean (SE) DBP change [mmHg]	-5.7 (0.5)	-8.0 (0.5)	-9.4 (0.5)	-10.6 (0.5)
Patients with 'general oedema' AEs, n (%)	23 (8.6)	75 (27.2)	14 (5.1)	10 (3.6)
<b>Secondary endpoint analyses</b>				
Adjusted <sup>1</sup> mean (SE) SBP change [mmHg]	-6.2 (0.7)	-11.1 (0.7)	-13.6 (0.7)	-15.0 (0.7)
Patients with DBP control, n (%)	107 (42.0)	148 (56.7)	153 (56.7)	173 (63.8)
Patients with DBP response, n (%)	116 (45.5)	163 (62.5)	177 (65.6)	187 (69.0)
Patients with SBP control, n (%)	100 (39.2)	142 (54.4)	162 (60.0)	178 (65.7)
Patients with SBP response, n (%)	118 (46.3)	166 (63.6)	187 (69.3)	200 (73.8)
<b>Trough seated BP categories, n (%)</b>				
Optimal	2 (0.8)	5 (1.9)	19 (7.0)	21 (7.7)
Normal	23 (9.0)	30 (11.5)	35 (13.0)	51 (18.8)
High normal	42 (16.5)	68 (26.1)	63 (23.3)	67 (24.7)
Stage 1 hypertension	118 (46.3)	126 (48.3)	127 (47.0)	110 (40.6)
Stage 2 hypertension	70 (27.5)	32 (12.3)	26 (9.6)	22 (8.1)

All BP results are for the FAS, whereas results for 'general oedema' are given for the TS. The denominators for the TS are 267 (A5), 276 (A10), 277 (T40/A5), and 277 (T80/A5).

<sup>1</sup> Adjusted for baseline and country.

The disposition of patients is described in table 39.

Table 39 Disposition of patients during the double-blind phase / randomised set

	A5 n (%)	A10 n (%)	T40/A5 n (%)	T80/A5 n (%)	Total n (%)
Patients randomised	267	276	278	277	1098
Treated	267 (100.0)	276 (100.0)	277 (100.0)	277 (100.0)	1097 (100.0)
Completed randomised phase	255 (95.5)	252 (91.3)	273 (98.6)	266 (96.0)	1046 (95.4)
Prematurely discontinued	12 (4.5)	24 (8.7)	4 (1.4)	11 (4.0)	51 (4.6)
Adverse event (AE)	6 (2.2)	22 (8.0)	3 (1.1)	4 (1.4)	35 (3.2)
AE study disease worse	1 (0.4)	0	0	0	1 (0.1)
AE other disease worse	0	2 (0.7)	0	0	2 (0.2)
AE other	5 (1.9)	20 (7.2)	3 (1.1)	4 (1.4)	32 (2.9)
Lack of efficacy	0	0	1 (0.4)	2 (0.7)	3 (0.3)
Non-compliant protocol	1 (0.4)	0	0	3 (1.1)	4 (0.4)
Lost to follow-up	0	1 (0.4)	0	0	1 (0.1)
Consent withdrawn	2 (0.7)	1 (0.4)	0	1 (0.4)	4 (0.4)
Other	3 (1.1)	0	0	1 (0.4)	4 (0.4)

Source data: [Table 15.11.3](#)

### • Conduct of the study

Treatment compliance was above 97% at all time points evaluated.

The proportion of patients with any important protocol violation (PV) was 14.0% which is in the expected range. The influence can be controlled by the comparison of the ITT with the PP analysis.

Further to GCP inspection requested by the CHMP, several major and critical GCP issues were identified for the evaluation of the primary efficacy endpoint of study 1235.5. The GCP deviations are expected to decrease the precision of the measurements of the primary efficacy endpoint (diastolic blood pressure). Although the deviations did not introduce a systematic bias the high number of patients that may have been concerned clearly questioned the overall conduct of study 1235.5 and its ability to

support the application. Additional sensitivity analyses were requested to address this concern (for details see section 3.4 GCP and below).

- **Baseline data**

Demographic and baseline characteristics were reasonably comparable across the 4 treatment groups.

- **Outcomes and estimation**

- *Comparison of T40/A5 and of T80/A5 with A5 for trough seated : see table 42*

Table 42 Analysis of change from baseline to the end of study in trough seated DBP for T40/A5 and T80/A5 vs. A5 / FAS

Trough seated DBP [mmHg]		A5 n=255	T40/A5 n=270	T80/A5 n=271
Baseline:	Mean (SD)	96.4 (5.3)	96.9 (5.1)	96.5 (4.9)
End of study:	Mean (SD)	90.7 (8.6)	87.5 (8.5)	85.9 (8.9)
	Adjusted mean <sup>1</sup> (SE)	90.9 (0.5)	87.2 (0.5)	85.9 (0.5)
Change to end of study:	Mean (SD)	-5.7 (7.6)	-9.4 (8.0)	-10.6 (8.0)
	Adjusted mean <sup>1</sup> (SE)	-5.7 (0.5)	-9.4 (0.5)	-10.6 (0.5)
Difference to A5:	Adjusted mean <sup>1</sup> (SE)	-	-3.6 (0.6)	-4.9 (0.6)
	95% CI	-	(-4.9, -2.4)	(-6.2, -3.7)
	p-value	-	<0.0001	<0.0001

<sup>1</sup> Adjusted for baseline trough seated DBP and country

Source data: [Tables 15.2.1:1](#) and [15.2.1:2](#)

There was a statistically significant and clinically relevant difference on sDBP for both combination therapies as compared to A5.

Table 43 Analysis of change from baseline to the end of study in trough seated DBP for T40/A5 and T80/A5 vs. A10 / FAS

Trough seated DBP [mmHg]		A10 n=261	T40/A5 n=270	T80/A5 n=271
Baseline:	Mean (SD)	96.5 (4.8)	96.9 (5.1)	96.5 (4.9)
End of study:	Mean (SD)	88.6 (8.2)	87.5 (8.5)	85.9 (8.9)
	Adjusted mean <sup>1</sup> (SE)	88.6 (0.5)	87.2 (0.5)	85.9 (0.5)
Change to end of study:	Mean (SD)	-7.9 (7.0)	-9.4 (8.0)	-10.6 (8.0)
	Adjusted mean <sup>1</sup> (SE)	-8.0 (0.5)	-9.4 (0.5)	-10.6 (0.5)
Difference to A10:	Adjusted mean <sup>1</sup> (SE)	-	-1.4 (0.6)	-2.7 (0.6)
	95% CI	-	(-2.7, -0.1)	(-3.9, -1.4)
	p-value	-	0.029	<0.0001

Note that p-values are given for the test of superiority.

<sup>1</sup> Adjusted for baseline trough seated DBP and country

The results of the supportive PP analysis were consistent with those from the FAS analysis. The adjusted mean changes from baseline were -5.8 (A5), -7.7 (A10), -9.2 (T40/A5), and -10.4 mmHg (T80/A5).

Overall, the study indicates a dose dependency of the response in the nonresponder population. There was a 1.2 mmHg difference between T40/A5 and T80/A5. This is sufficient to overcome the questions on dose response raised by the multifactorial trial in a more general group of hypertensive patients.

The maximal treatment effect is not achieved before week 8 in all treatment groups. The data do not indicate, however, that longer treatment periods were required.

*Sensitivity analyses provided upon CHMP request following GCP inspections*

At a number of centers there were deviations from the protocol specified requirements for the measurement of blood pressure that could reduce the precision of the measurement for the primary endpoint. These deviations occurred despite the sponsor's communication of the requirements for blood pressure measurement during investigator meetings, at individual meetings for investigators unable to attend a formal investigators meeting and during routine monitoring visits.

It was considered that up to 34 % of blood pressure data from patients may not have been recorded with the degree of precision that was required in the protocol. However, the sensitivity analyses indicate that the overall results are not changed, when sites with >35% of BP measurements having 0 as final digit and/or patients with any close in time BP measurements were excluded. The data seem to be robust irrespectively of the high number of patients and sites that have to be excluded (34%). The sensitivity analysis provides also reassurance that the possible influence of the terminal digit problem on inclusion of patients may not be relevant for the overall result.

- *Subgroup analyses*

There was no statistical significant difference of the effect in females and males. However numerically the treatment effect was more pronounced in females.

For patients  $\geq 65$  years, the treatment group differences of both T40/A5 and T80/A5 against A5 and A10 were reduced. This was mainly due to larger effects of A5 and A10 in patients  $\geq 65$  years. Similar results were observed for SBP.

In the pooled T/A group, 4.3% of patients experienced new or worsening events included in the pre-defined category 'general oedema', while in the A10 group, the incidence was substantially higher with 27.2%. This resulted in an odds ratio of T/A vs. A10 of 0.12 with an accompanying CI of 0.07 to 0.19 and a p-value of  $<0.0001$ . Similar results were observed for SBP.

Corresponding results were seen on trough seated BP. Significant results were also seen on responder rates for DBP, SBP and control rates for SBP and DBP as well as for the categorial analysis of BP response.

In summary, the responder analyses support the clinical relevance of the additional treatment effect.

*Overall conclusion on the study*

Although the GCP deviations did not introduce a systematic bias the high number of patients that may have been concerned clearly questioned the overall conduct of the study 1235.5.

Following additional sensitivity analyses conducted by the applicant, excluding of up to 34% of patients there was still a statistically significant superiority of the combination therapy group versus the monotherapy group, supporting the original efficacy conclusion of the study.

In conclusion, the design of the trial is considered appropriate for a second line claim in non responders to amlodipin.

The study demonstrated that Telmisartan/amlodipin 40/5 mg and 80/5 mg exerts a statistically significant and clinically relevant dose dependent effect in patients not adequately responding to Amlodipin 5 mg. The treatment effect more pronounced in females seems to be a consistent finding across the studies and correlates to a higher drug exposure to Telmisartan in females.

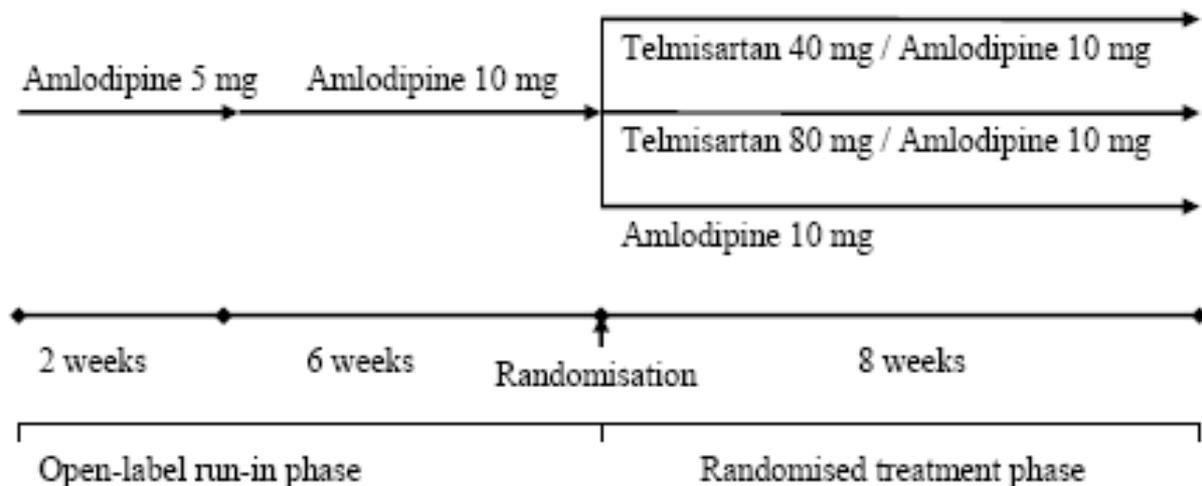
The lower incidence of oedema in T/A group is not unexpected result since oedema is a well known dose related AE of amlodipin. This not sufficient for a safety claim as such a claim is to be based on the totality of AEs and not on a single AE.

## Study 1235.6 Telmisartan plus Amlodipine Study in Amlodipine 10 mg Non-Responders in Hypertension: TEAMSTA-10

### Methods

This was a randomised, controlled, double-blind, double-dummy, multi-centre study using a non-responder design in patients with uncontrolled hypertension. Uncontrolled hypertension was defined as seated DBP  $\geq 95$  mmHg if patients were on antihypertensive treatment or seated DBP  $\geq 100$  mmHg if they were not receiving antihypertensive medication.

The design is appropriate to address a claim for a second line indication.



- **Objectives**

The primary objective of this trial was to demonstrate that the FDC T40/A10 or the FDC T80/A10 was superior in reducing BP at 8 weeks compared with A10 monotherapy. This objective was assessed in hypertensive patients who failed to respond adequately to A10, i.e. who had a trough seated DBP (DBP)  $\geq 90$  mmHg after a 6-week treatment with A10.

- **Outcomes/endpoints**

The primary endpoint was the change in trough seated DBP from baseline to the last visit during the double-blind treatment phase.

Several BP related secondary endpoints were predefined. The preferred method for measuring BP was by traditional manual cuff sphygmomanometry. The results obtained with auscultatory or oscillometric semiautomatic devices may deviate if not appropriately validated. Therefore, upon request from the CHMP, the applicant provided sensitivity analysis to evaluate the impact of the method used on BP measurement. No interaction on the use of different devices was observed.

- **Sample size**

Using an estimate of 6.6 mmHg, a sample size of 240 evaluable patients per treatment group would have approximately 90% power to detect a 2.0 mmHg difference between treatments in the reduction from baseline in trough seated DBP (2-sided,  $\alpha=0.05$ ).

- **Statistical methods**

The primary efficacy endpoint was trough seated DBP. The secondary efficacy endpoints were analysed using ANCOVA or Mantel-Haenszel statistics.

The hypotheses were tested in the following pre-specified sequence, to address issues of multiplicity.

- Firstly, to test if the high strength FDC T80/A10 was superior to the monotherapy A10 at lowering seated trough DBP
- The next stage was to test if the low strength FDC T40/A10 was superior to the monotherapy A10 at lowering seated trough DBP.

Some changes or extensions of analyses were introduced before DBL and unblinding of the study. Among these were:

- SBP control (defined as SBP <140 mmHg) was added as an additional secondary endpoint to further characterise the effect of the treatments on BP.
- DBP control (defined as DBP < 80 mmHg) was added as an additional secondary endpoint A subgroup analysis comparing patients diagnosed with diabetes as a concomitant condition versus those without diabetes was added to the TSAP

The statistical analysis plan and the hierarchical testing procedure are acceptable.

Both doses of combination treatments, T40/A10 and T80/A10 were compared with A10 for superiority.

## **Results**

Table 47 Summary of results for efficacy endpoints FAS/TS

	A10 n=305	T40/A10 n=306	T80/A10 n=310
<b>Primary endpoint analyses</b>			
Adjusted <sup>4</sup> mean (SE) DBP change [mmHg]	-6.5 (0.45)	-9.2 (0.45)	-9.3 (0.45)
Comparison to A10, p-value <sup>1</sup>		<0.0001	<0.0001
<b>Secondary endpoint analyses</b>			
Adjusted <sup>4</sup> mean (SE) SBP change [mmHg]	-7.4 (0.66)	-11.1 (0.66)	-11.3 (0.66)
Comparison to A10, p-value <sup>1</sup>		<0.0001	<0.0001
Patients with DBP control <90 mmHg, n (%)	156 (51.1)	195 (63.7)	206 (66.5)
Comparison to A10, p-value <sup>2</sup>		0.002	<0.001
Patients with DBP control <80 mmHg, n (%)	18 (5.9)	39 (12.7)	39 (12.6)
Comparison to A10, p-value <sup>2</sup>		0.004	0.004
Patients with DBP response, n (%)	163 (53.4)	202 (66.0)	213 (68.7)
Comparison to A10, p-value <sup>2</sup>		0.002	<0.001
Patients with SBP control, n (%)	153 (50.2)	180 (58.8)	187 (60.3)
Comparison to A10, p-value <sup>2</sup>		0.027	0.008
Patients with SBP response, n (%)	165 (54.1)	198 (64.7)	204 (65.8)
Comparison to A10, p-value <sup>2</sup>		0.006	0.002
Trough seated BP categories, n (%)			
Optimal	0 (0.0)	12 (3.9)	6 (1.9)
Normal	36 (11.8)	43 (14.1)	50 (16.1)
High normal	77 (25.2)	91 (29.7)	106 (34.2)
Stage 1 hypertension	157 (51.5)	139 (45.4)	133 (42.9)
Stage 2 hypertension	35 (11.5)	21 (6.9)	15 (4.8)
Comparison to A10, p-value <sup>3</sup>		0.006	<0.001
General oedema, n (%)	22 (7.0)	48 (7.6)	
Comparison to A10, p-value			0.7138

All BP results are for the FAS, whereas results for 'general oedema' are given for the TS. The denominators for the TS are 315 patients for A10 and 632 patients for the pooled oedema data of T40/A10 and T80/A10.

<sup>1</sup> ANCOVA adjusted for baseline and country effect

<sup>2</sup> Mantel-Haenszel statistics adjusted for country effect

<sup>3</sup> Wilcoxon rank sum test stratified for country

<sup>4</sup> Adjusted for baseline and country

Table 49 Disposition of patients for the randomised phase

	A10 n (%)	T40/A10 n (%)	T80/A10 n (%)	Total n (%)
Patients randomised	315	315	319	949
Treated	315 (100.0)	315 (100.0)	317 (100.0)	947 (100.0)
Completed randomised phase	301 (95.6)	297 (94.3)	307 (96.8)	905 (95.6)
Prematurely discontinued	14 (4.4)	18 (5.7)	10 (3.2)	42 (4.4)
Adverse event (AE)	8 (2.5)	10 (3.2)	5 (1.6)	23 (2.4)
AE other disease worse	0 (0.0)	4 (1.3)	1 (0.3)	5 (0.5)
AE other	8 (2.5)	6 (1.9)	4 (1.3)	18 (1.9)
Non-compliant to protocol	3 (1.0)	3 (1.0)	2 (0.6)	8 (0.8)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)
Consent withdrawn	2 (0.6)	3 (1.0)	1 (0.3)	6 (0.6)
Other	1 (0.3)	2 (0.6)	1 (0.3)	4 (0.4)

Source data: [Table 15.1.1: 3](#)

- **Conduct of the study**

The number of protocol violations was 13.1% and within the expected range. The influence can be controlled by the comparison of the ITT with the PP analysis

- **Baseline data**

Demographic baseline characteristics were reasonably comparable across the 3 treatment groups.

- **Outcomes and estimation**

Primary endpoint: change from baseline to the end of the study in trough seated DBP.

Table 51 Analysis of change from baseline to the end of study in trough seated DBP for T40/A10 and T80/A10 vs. A10 / FAS

Trough seated DBP [mmHg]		A10 n=305	T40/A10 n=306	T80/A10 n=310
Baseline:	Mean (SD)	95.6 (4.0)	95.5 (4.0)	95.6 (4.1)
End of study:	Mean (SD)	89.5 (6.7)	86.6 (6.8)	86.7 (6.6)
	Adjusted mean <sup>†</sup> (SE)	89.1 (0.5)	86.3 (0.5)	86.2 (0.5)
Change to end of study:	Mean (SD)	-6.1 (6.5)	-8.8 (7.0)	-8.9 (6.6)
	Adjusted mean <sup>†</sup> (SE)	-6.5 (0.5)	-9.2 (0.5)	-9.3 (0.5)
Difference to A10:	Adjusted mean <sup>†</sup> (SE)		-2.8 (0.5)	-2.8 (0.5)
	95% CI		(-3.8, -1.8)	(-3.8, -1.8)
	p-value		<0.0001	<0.0001

<sup>†</sup> Adjusted for baseline trough seated DBP and country

Source data: [Tables 15.2.1: 1](#) and [15.2.1: 2](#)

The results of the supportive PPS analysis were consistent with those from the FAS analysis. The adjusted mean differences and CIs for both treatment comparisons of interest (T80/A10 and T40/A10 vs. A10) confirmed the superiority results seen for the FAS. Similar results were obtained for SBP.

Table 53 Analysis of change from baseline to the end of study in trough seated SBP / FAS

Trough seated SBP [mmHg]		A10 n=305	T40/A10 n=306	T80/A10 n=310
Baseline:	Mean (SD)	146.8 (10.3)	148.1 (9.4)	147.4 (9.4)
End of study:	Mean (SD)	140.2 (11.3)	137.3 (11.3)	136.7 (10.6)
	Adjusted mean <sup>†</sup> (SE)	140.0 (0.7)	136.3 (0.7)	136.2 (0.7)
Change to end of study:	Mean (SD)	-6.6 (10.0)	-10.8 (10.6)	-10.7 (10.1)
	Adjusted mean <sup>†</sup> (SE)	-7.4 (0.7)	-11.1 (0.7)	-11.3 (0.7)
Difference to A10:	Adjusted mean <sup>†</sup> (SE)		-3.7 (0.8)	-3.9 (0.8)
	95% CI		(-5.2, -2.2)	(-5.4, -2.4)
	p-value		<0.0001	<0.0001

<sup>†</sup> Adjusted for baseline trough seated SBP and country

The effect on systolic blood pressure was similar as the effect on DBP. There was no clinically relevant higher efficacy of T40/A10 as compared to T80/A10

Table 54 Analysis of trough seated DBP and SBP control at the end of study/FAS

	A10 n=305	T40/A10 n=306	T80/A10 n=310
<b>Trough seated DBP control 1, n (%)</b>			
No (DBP $\geq$ 90 mmHg)	149 (48.9)	111 (36.3)	104 (33.5)
Yes (DBP<90 mmHg)	156 (51.1)	195 (63.7)	206 (66.5)
Comparison to A10 <sup>1</sup> : p-value		0.002	<0.001
<b>Trough seated DBP control 2, n (%)</b>			
No (DBP $\geq$ 80 mmHg)	287 (94.1)	267 (87.3)	271 (87.4)
Yes (DBP<80 mmHg)	18 (5.9)	39 (12.7)	39 (12.6)
Comparison to A10 <sup>1</sup> : p-value		0.004	0.004
<b>Trough seated SBP control, n (%)</b>			
No (SBP $\geq$ 140 mmHg)	152 (49.8)	126 (41.2)	123 (39.7)
Yes (SBP<140 mmHg)	153 (50.2)	180 (58.8)	187 (60.3)
Comparison to A10 <sup>1</sup> : p-value		0.027	0.008

Adjusted for pooled country

Similar results were obtained for trough seated DBP and SBP response. The BP response was significantly better for the two combinations as compared to A10 with no difference between T40/A10 and T80/A10.

Incidence of oedema was similar between A10 and T40/A10 and T80/A10 ((A10: 7.0%; T40/A10:6.7%, T80/A10: 8.5%;).

In summary, both combinations T80/A10 and T40/A10 exerted a significant additional effect. There were no clinically relevant differences between the two strengths T40/A10 and T80/A10 with respect to efficacy in the whole group. This is consistent with the results of the multifactorial study in treatment naive patients where T80 was not more effective than T40 when given concomitantly to Amlodipin 10 mg.

### ***Clinical studies in special populations***

No studies were conducted in special patient groups. No data are provided for the very elderly patients (above 70 years).

### ***Supportive study(ies)***

#### **Study 1235.7**

This is an open label follow up trial (following patients from 1235.5) of the efficacy and safety of chronic administration of the combination of telmisartan 40 mg + amlodipine 5 mg or the combination of telmisartan 80 mg + amlodipine 5 mg tablets alone or in combination with other antihypertensive medications in patients with hypertension.

#### ***Methods***

Patients who showed inadequate BP control (defined as DBP  $\geq$ 90 mmHg) at Week 4 or Week 8 were uptitrated to the higher strength FDC of T80/A5. At subsequent visits (Weeks 8, 14 and 22) additional antihypertensive medications were added, if there was inadequate DBP control. Trough seated BP was measured 24 h post-dose at each visit.

#### **• Treatments**

This open-label follow-up trial did not have any randomisation. All patients who completed the preceding trial 1235.5 and provided informed consent for participation in the follow-up trial were eligible to receive the open-label treatment of T40/A5 for 4 weeks.

#### **• Objectives**

The primary objective of this study was to assess the efficacy and safety of the fixed-dose combinations (FDC) of telmisartan 40 mg/amlodipine 5 mg (T40/A5), and telmisartan 80 mg/amlodipine 5 mg (T80/A5) alone or in addition to other antihypertensive therapies during open-label treatment for at least 6 months.

- **Blinding (masking)**

The trial was unblinded

- **Statistical methods**

Only descriptive statistics were used for all analyses; no inferential statistics were used. No hypothesis was tested in this trial.

### Results

- **Disposition of patients**

Out of 976 patients, 930 (95.3%) completed the study, whereas 46 (4.7%) patients discontinued the study prematurely.

- **Conduct of the study**

The proportion of patients with important protocol violations (PV) was 15.1%.

- **Key Outcomes and estimation**

Long-term (at least 6 months), open-label treatment with the FDCs T40/A5 and T80/A5 was effective for the majority of patients (79.5%) in achieving trough DBP <90 mmHg. The proportion of patients who received additional antihypertensive therapy was low (21.3%). Clinically relevant mean reductions in SBP/DBP were achieved in all treatment groups when analysed by dose received prior to EOT visit.

Due to the uncontrolled design it is difficult to draw conclusions on efficacy. However, the data suggest that in a real life setting almost 80% of the patients included can be successfully treated with the combination of telmisartan/amlodipin 40/5 and 80/5. There is no indication of a decrease in efficacy over time.

### **Study 1235.8 (interim analysis)**

It is an open-label follow-up trial (of study 1235.6) of the efficacy and safety of chronic administration of the combination of telmisartan 40 mg + amlodipine 10 mg or the combination of telmisartan 80 mg + amlodipine 10 mg tablets alone or in combination with other antihypertensive medications in patients with hypertension.

The primary objective was to assess the efficacy and safety of the fixed-dose combination (FDC) of telmisartan 40mg + amlodipine 10mg (T40/A10) and the FDC of telmisartan 80mg + amlodipine 10mg (T80/A10) alone or in addition to other antihypertensive therapies during open-label treatment for at least 6 months.

In this an interim analysis, the results are consistent with the assumption that the treatment effect is preserved over at least 6 months. The study meets the requirement for long term data on safety and efficacy. Due to the uncontrolled design the study cannot contribute to the question whether there is an additional effect of T80/10 mg as compared to T40/10mg.

### **2.5.3. Conclusions on the clinical efficacy**

Efficacy of the individual components is well established. Five Phase III trials were conducted to establish efficacy and safety in a substitution indication, an add-on indication and a first line indication.

Studies 1235.5 and 1235.6 demonstrated that in patients not adequately treated by amlodipin 5 mg or 10 mg the addition of telmisartan 40 or 80 mg was associated with an additional statistically significant and clinically relevant effect with respect to systolic and DBP and responder rate.

The GCP deviations on the precision of the measurement and recording of blood pressure values introduced considerable concerns concerning the conduct of study 1235.5 and its ability to support the application. The impact of these deficiencies was analysed. There was no evidence of a systematic bias. The expected impact might be a reduction of the sensitivity to detect a difference.

Given that the study was a superiority study which achieved significance, the impact of these deficiencies was not thought to change the conclusions of the study. In spite of the high number of patients that may have been concerned, additional sensitivity analyses excluding up to 34-47% of

patients in a worst case scenario still confirmed a statistically significant superiority of the combination therapy group versus the monotherapy group.

There were no significant differences in efficacy in the individual studies in most subgroups investigated. There was a consistent and clinically relevant higher efficacy in females in all three pivotal studies in parallel with a higher drug exposure in females for telmisartan shown in the PK studies. This raises a more general question whether there are any differences between male and female. It is however considered that overall these data do not support a different posology for male and females.

These studies were sufficient to demonstrate efficacy of the proposed combinations in a second line add-on indication in non-responders. The data package is also considered sufficient for a substitution indication.

However, the data do not support a first line indication since the claim is based on a subgroup analysis in patients with moderate to severe hypertension. More importantly, for a first line indication an add-on study is the preferred approach and the studies should be carried out in a population that is unlikely to show BP control with monotherapy which is not the case for patients with moderate to severe HTN. Consequently, the applicant further withdrew the first line indication during the assessment.

The number of very elderly patients (above 70 years) is very limited in this age group, consequently the SPC is adapted to mention that very little information is available in this subgroup of patients.

There was no difference in efficacy between the strengths containing amlodipin 10 mg and either 40 or 80 mg of telmisartan in office seated trough cuff measurement. This lack of an additional effect of the highest strength was also demonstrated in the filter study 1235.6, where either telmisartan 40 mg or 80 mg was administered to patients not adequately responding to amlodipin 10 mg. However, considering the additional justification provided by the applicant upon CHMP request, it can be accepted that there may be a subgroup of patients with an additional benefit in clinical practice as indicated in the ABPM substudy in patients with at least moderate hypertension. This is an acceptable justification for the highest strength containing T80/A10 mg.

## **2.6. Clinical safety**

### **Introduction**

Overall 3505 patients with essential hypertension were included in the analysis of safety as they were treated with at least 1 dose of the FDC dose of telmisartan/amlodipine (T/A), the free combination of telmisartan plus amlodipine (T+A), telmisartan monotherapy, amlodipine monotherapy, or placebo in the randomised treatment periods of all phase III trials. In addition, 258 healthy subjects were treated in pooled phase I trials. See below

Trial	Placebo	Amlodipine	Telmisartan	T/A	Total
Phase III					
1235.1	46	319	307	789	1461
1235.5	0	543	0	554	1097
1235.6	0	315	0	632	947
1235.7	0	0	0	976	976
1235.8	0	0	0	437	437
Phase I	0	12	36	258	258

### **Patient exposure**

Mean exposure to randomised treatment ranged in studies 1235.5 and 1235.6 from 55.8-57.6 days, the total exposure to the T/A FDCs ranged from 43.0-50.0 patient years. In trial 1235 the duration of exposure to T+A was 120.3 patient years.

In trials 1235.7 and 1235.8 mean exposure to T/A FDC ranged from 91.8 days in the T40/A10 treatment group to 202.2 days in the T80/A10 treatment group. The total exposure to the T/A FDC ranged from 109.9-403.3 patient years. The majority of patients treated with T40/A5, T80/A5, and T80/A10 were treated for >180 days.

In the 5 pooled phase I trials 258 healthy subjects were exposed to T+A for 849 patient-days; of these 36 were also exposed to telmisartan for 324 patient-days and 12 were also exposed to amlodipine for 108 patient-days.

Long term safety data of at least 6 months are provided for a sufficient number of patients. Upon request of the CHMP, the applicant referred in hits reply to longer term safety data from the ONTARGET trial in more than 3000 patients had an exposure of more than one year with telmisartan and amlodipine.

## Adverse events

### Trials 1235.5 and 1235.6

The most frequently reported AEs according to SOC were general disorders and administration site conditions. This was due to the high incidence of peripheral oedema generally more common in patients treated with amlodipine compared with combination therapies that included A10 or A5.

Table 63 : AEs reported by at least 1% of patients during the randomised treatment period of trials 1235.5 and 1235.6 (treated set)

System organ class Preferred term	Number (%) of patients					
	A5	A10	T40/A5	T40/A10	T80/A5	T80/A10
N	267	591	277	315	277	317
Total with AEs	99 (37.1)	195 (33.0)	98 (35.4)	55 (17.5)	93 (33.6)	68 (21.5)
Cardiac disorders	5 (1.9)	6 (1.0)	5 (1.8)	4 (1.3)	7 (2.5)	0 (0.0)
Palpitations	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	4 (1.4)	0 (0.0)
Tachycardia	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	4 (1.5)	1 (0.2)	5 (1.8)	0 (0.0)	2 (0.7)	0 (0.0)
Vertigo	3 (1.1)	1 (0.2)	4 (1.4)	0 (0.0)	2 (0.7)	0 (0.0)
Gastrointestinal disorders	10 (3.7)	8 (1.4)	11 (4.0)	5 (1.6)	12 (4.3)	4 (1.3)
Nausea	4 (1.5)	1 (0.2)	0 (0.0)	1 (0.3)	1 (0.4)	1 (0.3)
Gen. dis. and administration site conditions	30 (11.2)	102 (17.3)	19 (6.9)	22 (7.0)	21 (7.6)	29 (9.1)
Chest pain	3 (1.1)	2 (0.3)	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)
Fatigue	3 (1.1)	1 (0.2)	1 (0.4)	1 (0.3)	4 (1.4)	0 (0.0)
Oedema peripheral	22 (8.2)	96 (16.2)	14 (5.1)	21 (6.7)	10 (3.6)	27 (8.5)
Infections and infestations	16 (6.0)	22 (3.7)	25 (9.0)	7 (2.2)	22 (7.9)	11(3.5)
Bronchitis	3 (1.1)	4 (0.7)	4 (1.4)	0 (0.0)	0 (0.0)	2 (0.6)
Influenza	2 (0.7)	7 (1.2)	2 (0.7)	1 (0.3)	2 (0.7)	1 (0.3)
Nasopharyngitis	1 (0.4)	2 (0.3)	3 (1.1)	1 (0.3)	3 (1.1)	0 (0.0)
Pharyngitis	3 (1.1)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory tract infection	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	3 (1.1)	0 (0.0)
Upper resp. tract infection	2 (0.7)	3 (0.5)	1 (0.4)	1 (0.3)	4 (1.4)	2 (0.6)
Injury, poisoning and procedural complications	6 (2.2)	5 (0.8)	4 (1.4)	1 (0.3)	4 (1.4)	2 (0.6)
Epicondylitis	3 (1.1)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	9 (3.4)	20 (3.4)	10 (3.6)	10 (3.2)	8 (2.9)	10 (3.2)

Hypercholesterolaemia	4 (1.5)	10 (1.7)	3 (1.1)	7 (2.2)	2 (0.7)	5 (1.6)
Hypertriglyceridaemia	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	16 (6.0)	26 (4.4)	8 (2.9)	4 (1.3)	20 (7.2)	10 (3.2)
Arthralgia	1 (0.4)	5 (0.8)	0 (0.0)	0 (0.0)	1 (0.4)	5 (1.6)
Back pain	4 (1.5)	5 (0.8)	3 (1.1)	2 (0.6)	6 (2.2)	0 (0.0)
Muscle spasms	1 (0.4)	3 (0.5)	1 (0.4)	1 (0.3)	4 (1.4)	1 (0.3)
Neck pain	1 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)
Pain in extremity	3 (1.1)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	15 (5.6)	24 (4.1)	12 (4.3)	5 (1.6)	20 (7.2)	6 (1.9)
Dizziness	4 (1.5)	9 (1.5)	5 (1.8)	0 (0.0)	6 (2.2)	2 (0.6)
Headache	9 (3.4)	9 (1.5)	5 (1.8)	0 (0.0)	6 (2.2)	1 (0.3)
Resp, thoracic and mediastinal disorders	7 (2.6)	5 (0.8)	6 (2.2)	1 (0.3)	9 (3.2)	0 (0.0)
Cough	1 (0.4)	0 (0.0)	3 (1.1)	1 (0.3)	4 (1.4)	0 (0.0)

Table 64 : Incidence of any AE and of peripheral oedema by worst intensity during the randomised treatment period of trials 1235.5 and 1235.6 (treated set)

AE	Number (%) of patients						
	Worst intensity	A5	A10	T40/A5	T40/A10	T80/A5	T80/A10
N		267	591	277	315	277	317
<b>Any AE</b>		<b>99</b>	<b>195</b>	<b>98</b>	<b>55</b>	<b>93</b>	<b>68</b>
		<b>(37.1)</b>	<b>(33.0)</b>	<b>(35.4)</b>	<b>(17.5)</b>	<b>(33.6)</b>	<b>(21.5)</b>
Mild		65 (24.3)	113 (19.1)	69 (24.9)	39 (12.4)	61 (22.0)	48 (15.1)
Moderate		29 (10.9)	69 (11.7)	26 (9.4)	12 (3.8)	31 (11.2)	17 (5.4)
Severe		5 (1.9)	13 (2.2)	3 (1.1)	4 (1.3)	1 (0.4)	3 (0.9)
<b>Oedema peripheral</b>		<b>22 (8.2)</b>	<b>96 (16.2)</b>	<b>14 (5.1)</b>	<b>21 (6.7)</b>	<b>10 (3.6)</b>	<b>27 (8.5)</b>
Mild		18 (6.7)	57 (9.6)	9 (3.2)	18 (5.7)	6 (2.2)	21 (6.6)
Moderate		2 (0.7)	32 (5.4)	5 (1.8)	2 (0.6)	4 (1.4)	6 (1.9)
Severe		2 (0.7)	7 (1.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)

### ***Trials 1235.7 and 1235.8***

In the follow-up trials in which patients were administered the combination therapy of T/A for up to 34 weeks, according to SOC infections and infestations were the most common AEs. The incidence of common Preferred Terms (PTs) other than peripheral oedema was generally comparable across all treatment groups. Back pain, dizziness and hypercholesterolaemia were the only other PTs with an incidence >5/100 PY in at least 1 treatment group.

### ***Trial 1235.1***

In trial 1235.1 in which T+A was administered as initial antihypertensive therapy, the most frequently reported AEs were general disorders and administration site conditions, with the highest incidence for the A mono group (11.9%) and lower incidences for pooled combination therapy (8.5%) and T mono groups (4.2%). Musculoskeletal and connective tissue disorders and nervous system disorders were each reported by ≥5% of patients in both pooled monotherapy groups and the incidences were comparable across all pooled groups.

The most common PTs for the pooled combination therapy group were peripheral oedema (4.8%), headache (4.7%), dizziness (3.0%), and back pain (2.2%). The lower incidence of peripheral oedema observed in the pooled combination therapy group and the A mono group compared with the higher

dose key combination treatment group reflected that the pooled therapies analysis included groups with lowest doses of amlodipine (A2.5) and combination therapies including this low dose.

The incidence of dizziness was higher in the pooled combination therapy group than in either of the pooled monotherapy groups. However, there did not appear to be a dose dependency with regard to incidences across individual combination therapy groups. The incidence of back pain was similar in the pooled combination and amlodipine monotherapy groups.

There were few cases of syncope or hypotension. On combination therapy, syncope was reported by 0.3% of patients compared with none on either telmisartan or amlodipine monotherapy. There were 0.6% patients with hypotension and orthostatic hypotension reported in 0.1% on pooled combination therapy and 0.3% on pooled amlodipine monotherapy (A10). Only one case of hypotension (T20+A5) was reported during the initial treatment period. There were no cases of orthostatic hypotension or syncope during the initial treatment period.

When comparing T40+A10 with T80+10 the rate of AEs was slightly higher with the higher combination.

#### Summary of adverse events in phase III trials

The overall incidences of AEs in the AE profiles of any of the doses of T/A FDC (T40/A5, T40/A10, T80/A5, and T80/A10) were similar. During double-blind treatment, the overall incidences of AEs on the T/A FDCs were comparable with those of amlodipine (A5 and A10), with the exception of peripheral oedema, which was more common on amlodipine monotherapy. There were few severe AEs and SAEs reported in any treatment group.

During the long term open-label follow-up trials, the incidence of AEs or drug-related AEs across the 4 doses of T/A FDC was similar. Overall, the pattern and incidences of AEs were found to be in accordance with the known safety profiles for telmisartan and amlodipine.

### ***Drug-related AEs***

#### ***Trials 1235.5 and 1235.6***

The lowest incidence of drug-related AEs were in the pooled telmisartan monotherapy while the highest incidence was in the pooled combination therapy patients. The most frequently reported drug-related AEs ( $\geq 1\%$ ), for the pooled combination therapy group were peripheral oedema, dizziness and headache; however, the incidences for dizziness and headache were lower than with placebo. With the exception of peripheral oedema, the incidence of drug-related AEs was low and comparable across all monotherapy and combination therapy groups. There were no cases of drug-related syncope or orthostatic hypotension in any treatment group; there was one case of drug-related hypotension (T40/A10).

#### ***Trials 1235.7 and 1235.8***

In the follow-up trials, the incidence of drug-related AEs was similar across all doses of FDC. The most frequently reported drug-related AEs according to SOC were general disorders and administration site conditions. The only drug-related AEs reported by  $\geq 1\%$  of patients in any dose group were peripheral oedema and dizziness.

In conclusion, the pattern and incidences of drug-related AEs were found to be in accordance with the existing SPCs for telmisartan and amlodipine.

#### ***AEs of special interest***

The overall incidences of AEs potentially related to BP lowering were generally low, but slightly higher in the pooled combination therapy group (4.1%) than in the pooled monotherapy groups (1.6% T mono; 1.6% A mono), compared with 2.2% on placebo. The most commonly reported of such AEs was dizziness, corresponding to 3.0% of patients on pooled combination therapy, 1.3% on pooled telmisartan monotherapy, 1.3% on pooled amlodipine monotherapy, and 2.2% on placebo. Dizziness

was reported more frequently in female than male patients. Besides that, no specific pattern for AEs potentially related to BP lowering is evident.

Overall the AEs of special interest (dizziness, hypotension, syncope) were reported more frequently in the group with combination therapy. In this trial it is not possible to differentiate between AEs that are associated with a first line use of the combination and those that are inheritant to a combination therapy itself. The data are not sufficient to exclude a risk for patients at special risk (e.g. the very elderly above 70 or 75 years or patients with diabetes).

### ***Serious adverse event/deaths/other significant events***

#### **Deaths**

There were 4 deaths reported across all clinical trials.

#### **Serious adverse events**

The incidence of SAEs was low and comparable across all treatment groups. Only 2 SAEs were considered related to trial medication (chest pain and hypotonia).

#### ***Laboratory findings***

Changes in laboratory parameters were usually small and consistent with the expected profile of the two active substances across all trials.

### ***Safety in special populations***

The higher incidence of AEs in females in studies 1235.5 and 1235.6 in the T40/A5 and T80/A5 treatment groups is consistent with a higher drug exposure seen in PK studies and a higher efficacy in females. Overall the finding does not change the benefit risk balance for females.

Beyond this there was no consistent pattern of concern for special populations over the studies.

There was no consistent or clinically meaningful pattern of differences in safety profile across subgroups of extrinsic factors for the T/A FDC.

### ***Safety related to drug-drug interactions and other interactions***

There are no specific interactions expected beyond those expected with the interections seen with the monosubstances.

The BP lowering effect of T/A FDC may be increased with concomitant use of other antihypertensive medicinal products. In addition, medicinal products with BP-lowering effects (e.g. barbiturates, narcotics, antidepressants, baclofen, amifostine) and alcohol may potentiate the hypotensive effects of antihypertensive agents including T/A FDC. Corticosteroid containing medicinal products for systemic use may reduce the antihypertensive effect of T/A FDC.

### ***Post marketing experience***

There is no direct experience with the use of the combination of telmisartan and amlodipine. However, telmisartan and amlodipine are frequently co-prescribed with up to 30% in Japan and up to 10% in North America and in EU.

## **2.6.1. Discussion on clinical safety**

The safety database includes 3 controlled studies, 2 long term extension studies and a pool of phase I clinical trials.

The safety exposure data consisted of 3505 patients from the phase III trials, of these 2590 were treated with T/A FDC or T+A combination therapy and 258 healthy subjects from phase I trials. The safety database is largely consistent with the requirements of the NfG for hypertension and ICH E1. There are however very limited data presented for the very elderly patients above 70 years

The rate of SAEs and deaths was in the expected range and none of the deaths were associated with a drug related event.

There is no clear dose related effect of AEs observed. The overall incidences of AEs in the AE profiles of any of the doses of T/A FDC (T40/A5, T40/A10, T80/A5, and T80/A10) were similar. The overall incidences of AEs on the T/A FDCs were comparable with those of amlodipine (A5 and A10), with the exception of peripheral oedema, which was more common on amlodipine monotherapy.

In all 3 phase III trial groupings, incidences of AEs (serious and non-serious) leading to discontinuation were generally low in patients treated with T/A combinations and peripheral oedema was the most frequent observed AE.

In females, there was an indication of a higher rate of AEs in parallel with a higher drug exposure seen in the PK studies and a higher efficacy in the clinical studies in females.

However, there was no consistent or clinically meaningful pattern of differences in the safety profile across subgroups of intrinsic factors as well as for extrinsic factors.

#### *Safety related to drug-drug interactions and other interactions*

There are no specific interactions expected beyond those expected with the interactions seen with the monosubstances.

The BP lowering effect of T/A FDC may be increased with concomitant use of other antihypertensive medicinal products. In addition, medicinal products with BP-lowering effects (e.g. barbiturates, narcotics, antidepressants, baclofen, amifostine) and alcohol may potentiate the hypotensive effects of antihypertensive agents including T/A FDC. Corticosteroid containing medicinal products for systemic use may reduce the antihypertensive effect of T/A FDC.

## **2.6.2. Conclusions on the clinical safety**

Overall the clinical safety is consistent with the known safety profile of the monosubstances and there are no safety concerns that preclude a positive benefit risk balance.

## **2.7. Pharmacovigilance**

### **Detailed description of the pharmacovigilance system**

The applicant has provided documents that set out a detailed description of the Boehringer Ingelheim system of pharmacovigilance (Version 5.4 dated 25 February 2010). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union 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.

### **Risk management plan**

The CHMP did not require the Marketing Authorisation Application to submit a risk management plan for the fixed combination of telmisartan/amlodipine given the wide use of the components.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

## **2.8. Overall conclusions, risk/benefit assessment and recommendation**

### **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 SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### **Non clinical aspects**

The non clinical part of the dossier consists of bibliographic data on amlodipine and on telmisartan as single components and additionally 3 non clinical studies: one single dose oral pharmacokinetic study, a protein binding study and a 13 week toxicity study comparing the effects of both compounds individually and in combination.

The toxicological properties of telmisartan and amlodipine are both well characterised. The additional studies confirmed the known properties of each component and demonstrated a similar profile when used in combination.

Overall, the non clinical safety studies have not identified any important safety concerns which affect the benefit risk assessment.

### **Efficacy**

Twynsta is a fixed combination product consisting of two well known active substances: amlodipine besilate and telmisartan. Four strengths are proposed containing 40 mg/ 5 mg, 40 mg /10 mg, 80 mg/ 5 mg and 80 mg / 10 mg.

A bioequivalence approach was used to bridge the clinical data obtained with a combination of the mono components for the strengths containing 40/5 and 80/10 mg T/A to the final FDC formulation.

Five Phase III trials were conducted to establish efficacy and safety in a substitution indication, an add-on indication and a first line indication.

There were no significant differences in efficacy in the phase III studies in most subgroups investigated for moderate or severe hypertension among the four dose levels for telmisartan and amlodipin. The results demonstrated the individual contribution of each monosubstance in the combination.

The phase III studies demonstrated also that in patients not adequately treated by amlodipin 5 mg or 10 mg the addition of telmisartan 40 or 80 mg was associated with an additional statistically significant and clinically relevant effect with respect to systolic and diastolic blood pressure and responder rate.

The studies were not carried out in a population that is unlikely to show BP control with monotherapy, therefore, the clinical efficacy package was considered insufficient to support a first line indication, which was subsequently withdrawn during the procedure.

These studies were sufficient to demonstrate efficacy of the proposed combinations in a second line add-on indication in non-responders. The data package is also considered sufficient for a substitution indication.

There was no difference in efficacy between the strengths containing amlodipin 10 mg and either 40 or 80 mg of telmisartan in office seated trough cuff measurement. However, based on the ABPM data it was accepted that there may be a subgroup of patients with at least moderate hypertension with an additional benefit in clinical practice.

### **Safety**

The safety database includes 3 controlled studies, 2 long term extension studies and a pool of phase I clinical trials.

The safety exposure data consisted of 3505 patients from the phase III trials, of these 2590 were treated with telmisartan and amlodipine FDC or telmisartan plus amlodipine combination therapy and

258 healthy subjects from phase I trials. The database is largely consistent with the requirements of the NfG for hypertension and ICH E1 guideline. There are however very limited data presented for the very elderly patients above 70 years.

There is no clear dose related effect of AEs observed. The overall incidences of AEs in the AE profiles of any of the doses of T/A FDC (T40/A5, T40/A10, T80/A5, and T80/A10) were similar. The overall incidences of AEs on the T/A FDCs were comparable with those of amlodipine (A5 and A10), with the exception of peripheral oedema, which was more common on amlodipine monotherapy.

However, there was no consistent or clinically meaningful pattern of differences in the safety profile across subgroups of intrinsic factors as well as for extrinsic factors.

The most frequent reported drug-related AEs for the FDC were peripheral oedema, dizziness and headache, in line with what is observed with the single components.

Overall the clinical safety is consistent with the known safety profile of the monosubstances and there are no safety concerns that preclude a positive benefit risk balance.

## **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 product for human use.

### **2.9. Benefit-risk balance**

Phase III studies demonstrated that telmisartan/amlodipine 40/5 mg and 80/5 mg and telmisartan/amlodipine 40/10 mg and 80/10 mg exert a statistically significant and clinically relevant effect on BP parameters in patients not adequately responding to Amlodipine 5 mg or 10 mg respectively.

The package of these studies was appropriate to justify an indication in non-responders to amlodipine as well as a substitution indication but not a first line indication.

The two supportive open label studies 1235.7 and 1235.8 (interim analysis) provided sufficient reassurance that the effect of telmisartan in combination with amlodipine is preserved during long term treatment.

The main benefit of the FDC is to assume better compliance with antihypertensive therapy when the pill burden is reduced in patients who are using double combination therapy with telmisartan and amlodipine free combination.

The main risk relates to the very limited data available in very elderly patients (>70years).

Overall the clinical efficacy and safety of the single components is well known and the data for the FDC are consistent with the known efficacy and safety profile of the individual substances.

In conclusion, there are no efficacy and safety concerns that preclude a positive benefit risk balance.

#### **2.9.1. Risk management plan**

The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.
- no additional risk minimisation activities were required beyond those included in the product information

## **2.10. Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by majority decision that the risk-benefit balance of TWYNSTA in the treatment of essential hypertension in adults:

### Add on therapy

TWYNSTA is indicated in adults whose blood pressure is not adequately controlled on amlodipine.

### Replacement therapy

Adult patients receiving telmisartan and amlodipine from separate tablets can instead receive tablets of TWYNSTA containing the same component doses.

was favourable and therefore recommended the granting of the marketing authorisation.