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ASSESSMENT REPORT FOR KINZALMONO

International non-proprietary name/Common name: telmisartan

Procedure No. EMEA/H/C/000211/II/0072

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

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1.1 Introduction

Telmisartan is an orally effective and specific angiotensin II receptor (type AT1) antagonist (AIIA), which is currently indicated for the treatment of essential hypertension. It can be used alone or in combination with other antihypertensive agents e.g. thiazides-type diuretics such as hydrochlorothiazide. The most commonly used dose in clinical practice is 80 mg although a blood pressure lowering effect can be seen at 40 mg and in some patients even 20 mg.

Telmisartan was approved for the treatment of hypertension in the European Union (EU) and in the United States of America in 1998. Currently telmisartan is approved in more than 70 countries (EU counted as 1 country) and marketed in 20 mg, 40 mg, and 80 mg dose strengths; the most commonly used trade names are Micardis, Pritor and Kinzalmono.

Since the first 5-year renewal in 2003 about fifty studies have been carried out: the focus has been on patients with mild to moderate essential hypertension, except for three trials that enrolled patients at high risk of developing a cardiovascular event, irrespective of their blood pressure status. Overall, results from these studies have confirmed the efficacy profile of telmisartan in long term treatment of essential hypertension.

The second Marketing Authorisation renewal procedure was finalised with a positive CHMP opinion in September 2008 granting unlimited validity on the basis of a favourable re-evaluation of the benefit risk balance.

In this application, the Marketing Authorisation Holder (MAH) originally proposed to extend the indication as follows:

"Prevention of cardiovascular morbidity and mortality in patients 55 years or older at high risk of cardiovascular disease".

Furthermore, the MAH proposed to amend SPC sections 4.2, 4.4, 4.8 and 5.1 as well and to update the Package Leaflet (PL) accordingly. In addition, Annex II has been updated to reflect the latest RMP version as agreed by the CHMP.

Requests for Supplementary Information were adopted during the March 2009 and July 2009 CHMP meetings. The claimed new indication was not considered approvable at that time as major objections with regard to the efficacy in the pivotal trial had been identified.

During its meeting in July 2009, the CHMP agreed to convene a Cardiovascular Scientific Advisory Group (CV-SAG) in order to further elaborate on the major objections of the procedure. The CV-SAG meeting was held on 30 September 2009.

An Oral Explanation took place on 16 October 2009.

1.2 Clinical aspects

Introduction

The new claim for cardiovascular (CV) prevention is beyond CV prevention in patients with essential hypertension that is already covered by the approved indication. The application is based on three controlled clinical studies, the ONTARGET study (n=25620, pivotal study), the TRANSCEND (n=5926) and PRoFESS (n=20332) studies (supportive studies).

The prevention of cardiovascular disease represents one of the most important aspects of preventive medicine today. The terms primary and secondary prevention have been used to encompass patients with or without established clinical evidence of cardiovascular disease. A more comprehensive strategy to prevent CV disease aims at treating patients based on total CV risk. Treatment decisions and definition of high risk for CV disease can be based on CV risk scores (for background see EMEA/CHMP/EWP/311890/2007).

Cardiovascular disease is a continuum; factors such as hypertension, diabetes mellitus, and atherosclerosis lead to end-organ damage and may ultimately result in heart failure, stroke, renal disease, or death. Research has shown that the activation of the renin-angiotensin-aldosterone system (RAAS) plays an important role in all phases of the cardiovascular disease continuum.

Angiotensin II is the main effector peptide of the RAAS. Angiotensin-II induces vasoconstriction, cardiac muscle cell proliferation and migration, inflammatory responses, enhanced coagulation, and collagen synthesis, all of which are important processes in the development of atherosclerosis and acute coronary syndromes. The effects of angiotensin II can be attenuated by inhibiting the angiotensin converting enzyme using an angiotensin converting enzyme inhibitor (ACE-I) or by blocking the angiotensin II subtype 1-receptors using an angiotensin receptor blocker (ARB).

Several studies have investigated the influence of different drugs that negatively regulated the activity of the RAAS in the prevention of CV disease in selected patients with increased CV risk independently of the blood pressure lowering effect. As a key study the HOPE study demonstrated in high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor that ramipril reduced the incidence of the 3-fold composite endpoint of MI, stroke, and death due to cardiovascular causes (CV death) in patients at high risk for such events. The relative risk reduction of 10 mg daily of ramipril compared with placebo over 4.5 years of treatment was 22% for the 3-fold composite endpoint (MI, stroke, and CV death) (N Engl J Med 2000 Jan 20; 342(3):145-53). On the other hand it was less clear, whether an ARB (eprosartan) was effective in the secondary prevention of stroke in hypertensive patients beyond a blood pressure lowering effect (MOSES study, Stroke 2005; 36: 1218-1226).

The recommended dose of telmisartan for the Prevention of cardiovascular morbidity and mortality indication is 80 mg once daily. The MAH states that it is not known whether doses lower than 80 mg of telmisartan are effective in preventing cardiovascular morbidity and mortality.

In accordance with the recommendation provided in the proposed SPC, when initiating telmisartan therapy for the prevention of cardiovascular morbidity, monitoring of blood pressure is recommended, and if appropriate adjustment of medications that lower blood pressure may be necessary.

Summary of Clinical Development Program supporting the new proposed indication

The clinical trial program for telmisartan in reduction of risk for major cardiovascular events such as MI, stroke, CV death, and hospitalisation for CHF, consisted of 3 large, global, prospective, randomised, double-blind outcome trials, namely the ONTARGET (n=25620), TRANSCEND (n=5926), and PRoFESS (n=20332) studies. The planned study durations were up to 5.5 years in ONTARGET, up to 6 years in TRANSCEND, and up to 4.5 years in PRoFESS.

To demonstrate efficacy of telmisartan in the new proposed indication, the ONTARGET trial is considered pivotal, while the TRANSCEND and the PRoFESS trials provide supportive evidence. Data from the TRANSCEND and PRoFESS studies (i.e. from patients who did not receive an ACE-I at any time during these studies) were analysed by the MAH for the purpose of this submission since the use of dual RAAS blockade had been shown to have a negative benefit/risk ratio in the ONTARGET study.

The populations included in these 3 large trials were in general overlapping and constitute a representative cross-section of patients at the moderately-high to very-high risk stages of the cardiovascular disease spectrum. ONTARGET and TRANSCEND included men and women who were 55 years of age or older and at high risk of experiencing a major cardiovascular event.

Being at high risk was defined as having coronary artery disease or peripheral artery disease, previous stroke or transient ischaemic attack (TIA), or high-risk diabetes mellitus with evidence of end-organ damage. Patients who had CHF, uncontrolled hypertension (BP >160/100 mmHg), significant renal artery disease, or hepatic dysfunction at study entry could not participate.

ONTARGET and TRANSCEND trials used the same inclusion and exclusion criteria with only 2 exceptions: patients entered into the TRANSCEND study were to be intolerant to ACE-Is and patients with clinically significant proteinuria were excluded as well due to the ethical consideration.

The blinded study medications were given in addition to medications and other treatments necessary to provide medical care according to practice guidelines and national standards. It is acknowledged that, since the completion of the HOPE trial, there have been improvements in the care of patients at risk of cardiovascular events; in particular the use of statins and other cardioprotective agents such as beta blockers has increased substantially.

The primary endpoint examined in both the ONTARGET and TRANSCEND trials was a 4-fold composite endpoint of time to MI, stroke, CV death, or hospitalisation for CHF. The ONTARGET study investigated the effectiveness of telmisartan (T), ramipril (R), and a combination of both (T/R) while the TRANSCEND study evaluated telmisartan and placebo (PBO). A key secondary endpoint in ONTARGET and TRANSCEND was the 3-fold endpoint of MI, stroke, and CV death, the same endpoint as employed in the HOPE study as the primary endpoint.

Men and women enrolled into the PRoFESS trial were permitted to be slightly younger (50 years of age and older) and were required to have suffered a previous ischaemic stroke within 120 days of enrolment.

The PRoFESS study had a 2x2 factorial design; all patients were randomised to antiplatelet therapy with either a fixed-dose combination of aspirin and extended-release dipyridamole (ASA+ER-DP) or clopidogrel and at the same time to either telmisartan or placebo. The primary endpoint was the incidence of recurrent stroke. The 4-fold composite endpoint of MI, stroke, CV death, new or worsening CHF was analysed as a secondary endpoint, while the 3-fold (HOPE) endpoint (MI, stroke, CV death) was analysed post hoc to relate the PRoFESS results to those of ONTARGET, TRANSCEND, and HOPE, where this endpoint was prespecified. All study medications were given on top of current standard care.

For the confirmatory analysis of efficacy, the intent-to treat principle was followed in all 3 trials. In ONTARGET and TRANSCEND, the full analysis set (FAS) was defined including all patients who were randomised and for whom follow-up information was available. For the primary analyses in PRoFESS, the randomised set (RAN) was employed consisting of those patients who signed informed consent and were randomised.

1.3 Pivotal Study - ONTARGET TRIAL

ONTARGET (**ON**going **T**elmisartan **A**lone and in Combination with **R**amipril **G**lobal **E**ndpoint **T**rial 502.373 / U08-1821-01) was a large scale randomised, double-blind, multicentre, international trial comparing telmisartan 80 mg, ramipril 10 mg, and their combination in the prevention of morbidity and mortality in patients at high risk for cardiovascular events.

Objective

The objective of the ONTARGET trial was to determine if (a) the combination of telmisartan 80 mg and ramipril 10 mg (T/R) is superior to ramipril 10 mg (R) alone and if (b) telmisartan 80 mg (T) is not inferior to ramipril 10 mg alone in reducing the composite endpoint of cardiovascular (CV) death, myocardial infarction (MI), non-fatal stroke, or hospitalisation for congestive heart failure (CHF).

It was also of primary interest (primary renal endpoint) to compare the treatments (T/R vs. R and T vs. R) concerning the composite endpoint of doubling of serum creatinine, progression to end stage renal disease (ESRD) and all-cause mortality in the subgroup of diabetic nephropathy patients (i.e. diabetic patients with macroalbuminuria assessed as a urinary albumin creatinine ratio [UACR] ≥300 mg/g Crea at baseline). Progression to ESRD was defined as initiation of dialysis, estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m2, or need for renal transplantation.

An additional objective, using an exploratory analysis, was to investigate whether T/R is more effective than T concerning these endpoints.

Primary outcome

The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalisation for heart failure.

Secondary outcomes

The main secondary outcome was death from cardiovascular causes, myocardial infarction, or stroke, which was used as the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.

Additional secondary endpoints were the individual components of the primary endpoints, newly diagnosed CHF, CV revascularisation procedures, newly diagnosed diabetes, cognitive impairment and cognitive decline, new onset of atrial fibrillation and nephropathy.

Inclusion criteria

Male or female patients, 55 years of age or older, and at high risk of developing a major CV event were eligible if they had any of the following:

1. Coronary artery disease (CAD) defined as:
   a) Previous MI >2 days post uncomplicated MI prior to informed consent (as revascularisation procedures during the immediate MI period performed to reduce risk may result in a decreased overall risk for the patient, eligibility had to be considered on a case by case basis in these patients), or;
   b) Stable angina or unstable angina (> 30 days prior to informed consent) each with documented multi-vessel coronary disease, > 50% stenosis in at least 2 major coronary arteries on coronary angiography, or positive stress test (ST depression ≥2 mm or a positive nuclear perfusion scintigram), or;
   c) Multi-vessel percutaneous transluminal coronary angioplasty (PTCA) >30 days prior to informed consent, or;
   d) Multi-vessel CABG surgery without angina >4 years prior to informed consent, or with recurrent angina following surgery.
2. Peripheral arterial disease (PAD) defined as:
   a) Previous limb bypass surgery or percutaneous transluminal angioplasty, or;
   b) Previous limb or foot amputation, or;
   c) History of intermittent claudication with an ankle/arm BP ratio δ0.80 on at least one side, or;
   d) Significant peripheral artery stenosis (>50%) documented by angiography or non-invasive testing.
3. Previous stroke (stroke included definite or presumed cerebral infarction, intracerebral haemorrhage, stroke of uncertain subtype, but not subarachnoid haemorrhage).
4. TIA >7 days and <1 year prior to informed consent (TIA was defined as acute loss of focal cerebral or monocular function with symptoms lasting <24 hours and which was thought to be due to inadequate cerebral or ocular blood supply as a result of arterial thrombosis or embolism).
5. High-risk diabetes (insulin-dependent or non-insulin-dependent) with evidence of endorgan damage, i.e. retinopathy, LVH, micro- or macroalbuminuria, or any evidence of previous cardiac or vascular disease.

Duration of Study

The planned duration of the maintenance period was 3.5 to 5.5 years. The figure below shows the up-titration scheme applied in the ONTARGET trial.

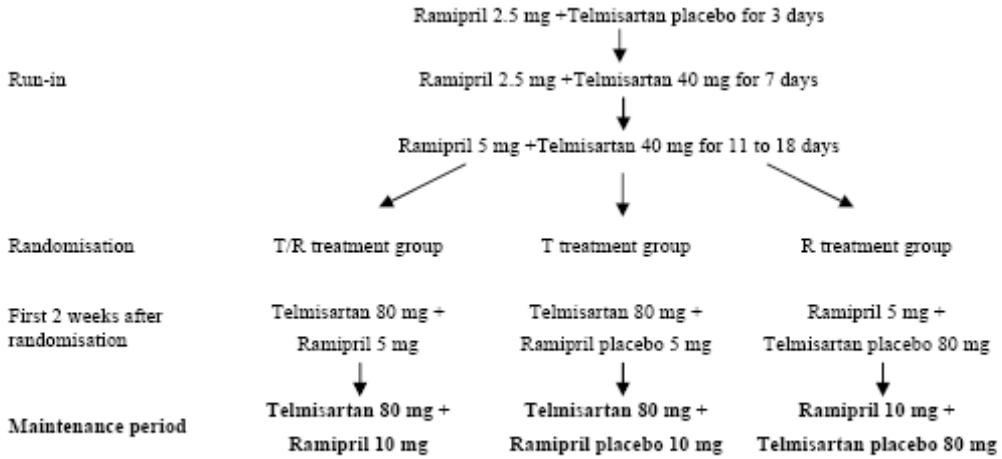


Figure 9.4.1: 1 Up-titration in the ONTARGET trial

Statistical analysis

The primary objective consisted of 2 tests, one for superiority of the T/R combination over ramipril (null hypothesis: HR T/R vs. R ≥1) and one where non-inferiority of telmisartan versus ramipril was

tested (null hypothesis: HR T vs. R ≥1.13); multiple testing was accounted for by the Hochberg procedure [R97-1003].

Both one-sided hypotheses were tested at the full level alpha = 0.025; both null hypotheses could be rejected:

- if both one-sided p-values were less than 0.025;
- or (based on CIs) if the two-sided 95% CI around the hazard ratio of T/R vs. R excluded 1, and the two-sided 95% CI around the hazard ratio of T vs. R excluded the pre-specified margin of 1.13. This margin was chosen to ensure that telmisartan would preserve at least 50% of the effect of ramipril over a putative placebo group, based on the results of the HOPE study.

If this was not the case, but one of the one-sided p-values was <0.025/2, then the respective null hypothesis could be rejected. Based on CIs, if one of the two-sided 97.5% CIs excluded the relevant margin (1 or 1.13), then the respective null hypothesis could be rejected. If both of these null hypotheses could be rejected at the one-sided multiple level 0.025, a third null hypothesis was to be tested. This third null hypothesis was that, in the subgroup of diabetic nephropathy patients, the combination of telmisartan 80 mg / ramipril 10 mg is equally or less effective than monotherapy with ramipril 10 mg in preventing the 3-fold renal endpoint of doubling of serum creatinine, progression to ESRD (as defined by initiation of dialysis, need for renal transplantation, or eGFR <15 mL/min/1.73 m2) and all-cause mortality, i.e. that the respective hazard ratio is greater or equal than 1. It was tested against the one-sided alternative hypothesis that the hazard ratio is smaller than 1.

Patient disposition

A total of 29019 patients were enrolled by 732 centres worldwide. The first patient was enrolled in December 2001; patient recruitment ended in July 2003. The trial was completed (last patient last seen) on 29 February 2008. About half of the patients (47.6%) were enrolled by study centres in Europe and South Africa; North America contributed 21.5% of enrolled patients, Asia and the Middle East 14.7%, Latin America 9.1%, and Australia and New Zealand 7.2%.

All patients who consented to participate in the study and who were eligible after consideration of the inclusion and exclusion criteria entered a run-in period and received single-blind treatment. During this run-in period the doses of the study medications were increased from a daily dose of 2.5 mg ramipril for 3 days to 2.5 mg ramipril + 40 mg telmisartan for 7 days to 5 mg ramipril + 40 mg telmisartan for 11 to 18 days to determine the patient's tolerability to ramipril and telmisartan. Non-compliant patients were not randomized and patients intolerant to ramipril during the run-in period of ONTARGET, were not eligible for ONTARGET but could be enrolled and randomised in the TRANSCEND trial, if they met the entry criteria of TRANSCEND.

A total of 25620 patients were randomised to either the combination of 80 mg telmisartan and 10 mg ramipril daily (n=8502), or 80 mg/day telmisartan (n=8542), or 10 mg/day ramipril (n=8576). 3399 patients (11.7%) were not randomised. The main reasons for nonrandomisation were insufficient compliance (4.6%) and the patient's request to stop treatment (5.5%), persistent symptomatic hypotension (1.7%), hyperkalaemia (0.8%), or azotaemia (0.2%), or other reasons (4.6%). These included 29 patients (0.1%) who died, 943 patients (3.2%) who experienced adverse events (AEs), and 397 patients (1.4%) who were not randomised because of administrative reasons. Of the patients who were not eligible for randomisation due to an AE, 450 patients (47.7%) had developed cough.

Table 10.1: 3 Disposition of patients for the randomised period / FAS

	T/R		T		R		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Randomised	8502	(100.0)	8542	(100.0)	8576	(100.0)	25620	(100.0)
Completed[1]	8485	(99.8)	8524	(99.8)	8561	(99.8)	25570	(99.8)
Deaths	1065	(12.5)	989	(11.6)	1014	(11.8)	3068	(12.0)
Not completed	17	(0.2)	18	(0.2)	15	(0.2)	50	(0.2)

[1] Completed was defined as final visit performed or vital status confirmed (including death) at the end of the trial.

Source data: Table 15.1.1.1: 3

Overall and in all 3 treatment groups, 99.8% of the randomised patients completed the trial. 50 patients (0.2%) did not complete the trial. Of those, 40 patients were lost to follow-up; 10 patients refused to be followed up for their vital status. Demographics and baseline characteristics of the randomised patients were similar in the 3 treatment groups. Overall, the mean age was 66.4 years and 73.3% of patients were male. Most of the patients were of white ethnicity (74.2%); 13.7% of patients were Asian and 2.5% were black. At baseline, hypertension was present in 82.8% of patients and diabetes in 40.9%. During the randomised period, the overall mean observation times were about 4.5 years and comparable between treatment groups.

Table 11.2.1: 1 Demographics by randomised treatment / FAS

	T/R	T	R	Total
Randomised, n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)	25620 (100.0)
Age mean, (SD) [years]	66.4 (7.3)	66.4 (7.1)	66.4 (7.2)	66.4 (7.2)
Age group, %				
<65 years	43.1	42.4	43.2	42.9
≥65 to <75 years	41.8	43.1	42.2	42.4
≥75 years	15.1	14.4	14.6	14.7
Sex, %				
Male	73.5	73.7	72.8	73.3
Female	26.5	26.3	27.2	26.7
Ethnicity[1,2], %				
White	74.4	74.0	74.3	74.2
Black	2.4	2.5	2.4	2.5
Asian	13.7	13.7	13.8	13.7
Other	9.4	9.8	9.5	9.5
Mean BMI (SD) [kg/m^2]	28.11 (4.76)	28.18 (4.75)	28.19 (4.81)	28.16 (4.77)
Mean weight (SD) [kg]	79.5 (15.6)	79.8 (15.7)	79.8 (15.5)	79.7 (15.6)
Mean waist/hip ratio (SD)				
Male	0.96 (0.07)	0.96 (0.07)	0.96 (0.07)	0.96 (0.07)
Female	0.89 (0.09)	0.89 (0.08)	0.89 (0.09)	0.89 (0.09)

[1] As given by the patient; the question to the patient referred to ethnic origin, i.e. the country of ancestral origin, and not to nationality or race.
[2] For 7 patients, ethnicity was not recorded (T/R: 2 patients; T: 3 patients, R: 2 patients).

Source data: Tables 15.1.4.1: 1 and 15.1.4.1: 2

A total of 18.2% of all randomised patients permanently discontinued study medication ((both active treatment and dummy, T/R: 20.3%; T: 17.0%; R: 17.1%, risk ratio T/R vs. R: 1.19; p<0.0001); no difference was seen between the telmisartan and the ramipril groups (risk ratio T vs. R: 0.99, p=0.8678)). Of those who permanently discontinued study medication, 53.8% stopped treatment permanently due to adverse events (T/R: 60.9%; T: 48.1%; R: 51.0%), 3.2% due to SAEs (3.7%, vs. 3.0% vs. 2.7%).

Of the 732 recruiting study centres, 350 centres enrolled patients who were identified as having diabetic nephropathy.

Table 10.1: 6 Disposition of diabetic nephropathy patients / FAS (DN)

	T/R		T		R		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Randomised diabetic nephropathy patients[1]	248	(100.0)	288	(100.0)	238	(100.0)	774	(100.0)
Completed[2]	248	(100.0)	288	(100.0)	238	(100.0)	774	(100.0)
Deaths	75	(30.2)	92	(31.9)	83	(34.9)	250	(32.3)
Not completed	0		0		0		0	

[1] Patients included had to have diabetes (defined as medical history of diabetes or a fasting plasma glucose value of ≥125 mg/dL [7 mmol/L] at run-in) and concomitant macroalbuminuria (defined as UACR ≥300 mg/g Crea at baseline).
[2] Completed was defined as final visit performed or vital status confirmed (including death).

Source data: Table 15.1.1.2: 3

Intrinsic factors

Table 11.2.3: 1 Intrinsic factors / FAS

	T/R		T		R		Total	
Randomised, n (%)	8502	(100.0)	8542	(100.0)	8576	(100.0)	25620	(100.0)
Hypertension[1], %		83.0		82.6		82.8		82.8
With microalbuminuria[2]		11.1		10.8		10.9		10.9
With macroalbuminuria[2]		3.3		3.9		3.3		3.5
Diabetes[3], %		40.8		41.6		40.3		40.9
With hypertension[1]		36.1		37.1		35.6		36.3
With microalbuminuria[2]		7.8		7.8		7.4		7.7
With macroalbuminuria[2]		2.9		3.4		2.8		3.0
Albuminuria								
UACR <30 mg/g Crea		75.8		75.6		76.2		75.9
UACR ≥30 to <300 mg/g Crea		12.2		11.8		11.9		12.0
UACR ≥300 mg/g Crea		3.5		4.1		3.4		3.7
Missing		8.5		8.5		8.5		8.5
Impaired renal function[4], %		24.1		24.6		23.5		24.1
Obesity[5], %		32.1		32.5		32.2		32.3
Metabolic syndrome[6], %		42.0		42.6		42.2		42.3

[1] As given in patient history (68.7%) and/or sitting SBP ≥140 mmHg or DBP ≥90 mmHg at start of run-in (59.8%).
[2] Microalbuminuria was defined as UACR ≥30 mg/g Crea and <300 mg/g Crea, and macroalbuminuria as baseline UACR ≥300 mg/g Crea
[3] Medical history of diabetes (37.5%) and/or fasting plasma glucose level ≥125 mg/dL (7 mmol/L) at run-in (27.6%)
[4] Impaired renal function was defined as eGFR <60 mL/min/1.73 m^2 at baseline
[5] Obesity was defined as BMI ≥30 kg/m^2 in non-Asian patients and BMI ≥27 kg/m^2 in Asian patients.
[6] A patient had to fulfil at least 3 of the following criteria to be diagnosed with the metabolic syndrome: elevated waist circumference (men: ≥102 cm, women: ≥88 cm), elevated triglycerides (≥150 mg/dL), reduced HDL cholesterol (men: <40 mg/dL, women: <50 mg/dL), elevated BP (defined as sitting SBP ≥130 mmHg or DBP ≥85 mmHg at the start of run-in or hypertension recorded as medical history), and elevated fasting plasma glucose (≥100 mg/dL) or use of oral hypoglycaemic agents at run-in.

Source data: Tables 15.1.4.1: 3 and 15.1.4.1: 4

The mean HOPE risk score of patients in this study was 4.076; the 1%-percentile was 3.033 and the 99%-percentile was 5.158. No relevant differences between treatment groups were observed. The score accounts for the risk factors age, sex, smoking, hypertension, LVH, diabetes, prior stroke, history of PAD and/or ankle/arm SBP <0.9, and history of CAD.

Diagnosis for study entry

Table 11.2.5: 1 Diagnosis for study entry as recorded at the run-in visit / FAS

	T/R		T		R		Total	
Randomised, n (%)	8502	(100.0)	8542	(100.0)	8576	(100.0)	25620	(100.0)
Primary reason for study entry, %								
CAD		66.3		66.1		66.0		66.1
PAD		5.8		5.7		5.4		5.6
Previous stroke		11.3		11.0		11.8		11.4
TIA (>7 days and <1 year)		1.9		2.0		2.1		2.0
High-risk diabetes[1]		14.6		15.1		14.6		14.8

[1] Patients with an entry diagnosis of high risk diabetes had to have one of the following: retinopathy, macroalbuminuria, microalbuminuria, LVH, or any other relevant complication at run-in.

Source data: Table 15.1.4.1: 6

The concomitant medication was comparable between the groups. ASA was administered to about 76 % of the patients, statins to 61 – 62%, betablockers to about 57%. Mean baseline blood pressure was also comparable. The overall mean sitting SBP and DBP at baseline were 141.8 mmHg and 82.1 mmHg, respectively.

Protocol Amendments

The trial protocol was amended on 3 occasions, Protocol Amendment 1.1, dated 16 July 2002, Protocol Amendment 2.1, dated 17 April 2003, and Protocol Amendment 3.1, dated 14 February 2006. The changes had generally only minor impact on the conduct of the ONTARGET and TRANSCEND studies.

Results

The primary endpoint in the ONTARGET trial was defined as the time to first occurrence of non-fatal MI, non-fatal stroke, CV death, or hospitalisation for CHF. All outcomes possibly contributing to the primary endpoint were to be centrally adjudicated, including all deaths. A total of 8483 primary events were centrally adjudicated by the Event Adjudication Committee, i.e. 3067 deaths, 1805 MIs, 1487 strokes, and 2124 hospitalisations for CHF. Only 3 events were not centrally adjudicated, in these cases the assessment of the investigator was used for all analyses.

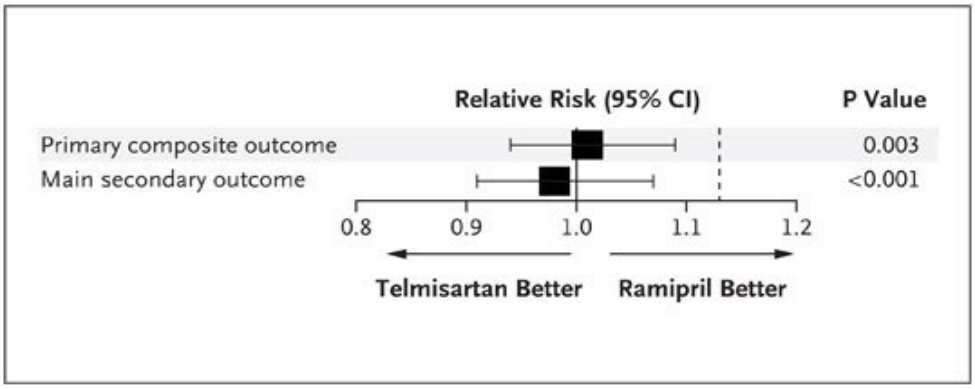
Table 11.4.1.1.1: 1 Incidence and analysis of the primary composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalisation for CHF - first event / FAS

	T/R		T		R	
Randomised, n (%)	8502	(100.0)	8542	(100.0)	8576	(100.0)
Primary endpoint[1], n (%)	1386	(16.3)	1423	(16.7)	1412	(16.5)
CV death	385	(4.5)	367	(4.3)	373	(4.3)
Non-fatal MI	396	(4.7)	399	(4.7)	372	(4.3)
Non-fatal stroke	338	(4.0)	322	(3.8)	377	(4.4)
Hospitalisation for CHF	286	(3.4)	353	(4.1)	312	(3.6)
Total time to event/censoring [years]	36525		36742		36940	
Events per 100 patient years	3.79		3.87		3.82	
Hazard ratio[2] vs. ramipril	0.99		1.01			
95% CI	(0.92, 1.07)		(0.94, 1.09)			
97.5% CI			(0.93, 1.10)			
p-value (conventional, two-sided)	0.8462		0.7248			
p-value (non-inferiority, one-sided)			0.0019			
Hazard ratio[2] vs. telmisartan[3] (95% CI)	0.98 (0.91, 1.05)					
p-value	0.5859					

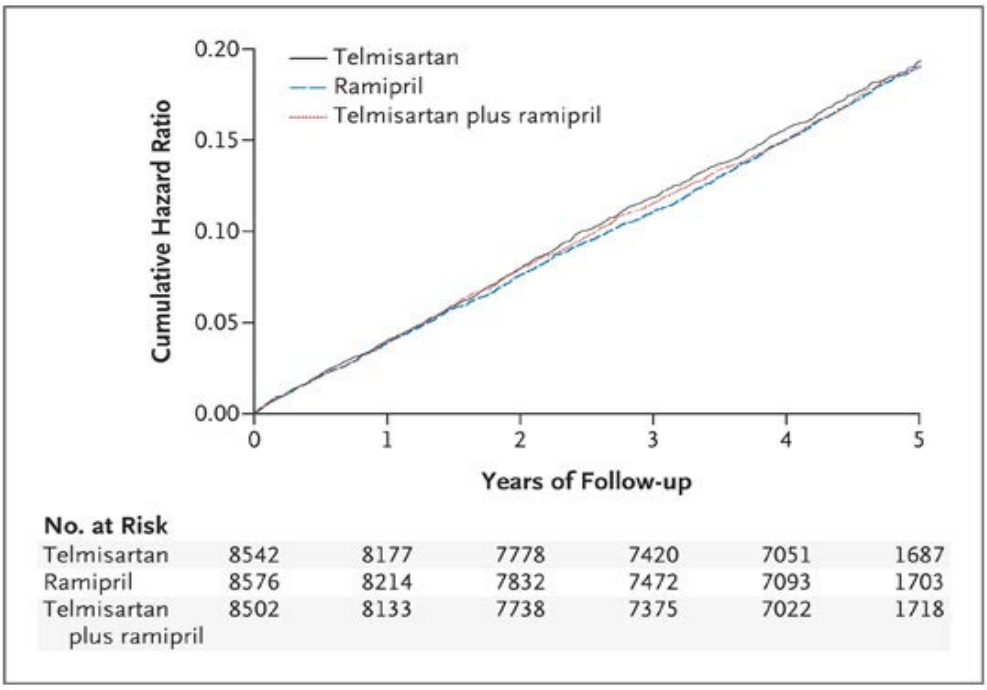
[1] The primary endpoint was defined as the time to first event. In case of multiple simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcomes.
[2] Cox regression
[3] Exploratory analysis

At a median follow-up of 56 months, the primary outcome had occurred in 16.5% of the patients in the ramipril group, as compared with 16.7% of patients in the telmisartan group (Hazard Ratio 1.01; 95% CI, 0.94 to 1.09).

Relative Risk of the Primary Outcome and of the Main Secondary Outcome.



Kaplan-Meier Curves for the Primary Outcome in the Three Study Groups.



No. at Risk						
Telmisartan	8542	8177	7778	7420	7051	1687
Ramipril	8576	8214	7832	7472	7093	1703
Telmisartan plus ramipril	8502	8133	7738	7375	7022	1718

ONTARGET Key results - Incidence of the Primary Outcome, Its Components, and Death from Any Cause

Table 3. Incidence of the Primary Outcome, Its Components, and Death from Any Cause.

Outcome	Ramipril (N=8576)	Telmisartan (N=8542)	Combination Therapy (N=8502)	Telmisartan vs. Ramipril	Combination Therapy vs. Ramipril
	number (percent)			*risk ratio (95% CI)*	
Death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure*	1412 (16.5)	1423 (16.7)	1386 (16.3)	1.01 (0.94–1.09)	0.99 (0.92–1.07)
Death from cardiovascular causes, myocardial infarction, or stroke†	1210 (14.1)	1190 (13.9)	1200 (14.1)	0.99 (0.91–1.07)	1.00 (0.93–1.09)
Myocardial infarction‡	413 (4.8)	440 (5.2)	438 (5.2)	1.07 (0.94–1.22)	1.08 (0.94–1.23)
Stroke‡	405 (4.7)	369 (4.3)	373 (4.4)	0.91 (0.79–1.05)	0.93 (0.81–1.07)
Hospitalization for heart failure‡	354 (4.1)	394 (4.6)	332 (3.9)	1.12 (0.97–1.29)	0.95 (0.82–1.10)
Death from cardiovascular causes	603 (7.0)	598 (7.0)	620 (7.3)	1.00 (0.89–1.12)	1.04 (0.93–1.17)
Death from noncardiovascular causes	411 (4.8)	391 (4.6)	445 (5.2)	0.96 (0.83–1.10)	1.10 (0.96–1.26)
Death from any cause	1014 (11.8)	989 (11.6)	1065 (12.5)	0.98 (0.90–1.07)	1.07 (0.98–1.16)

* Patients could have multiple events in this category. The numbers of events were 2058 (24.0%) in the ramipril group, 2042 (23.9%) in the telmisartan group, and 2000 (23.5%) in the combination-therapy group. The differences were not significant (P=0.83 for telmisartan vs. ramipril, and P=0.38 for combination therapy vs. ramipril).
† This composite was the primary outcome in the Heart Outcomes Prevention Evaluation (HOPE) trial.[5]
‡ Patients could have multiple events in this category. The category includes both fatal and nonfatal events.

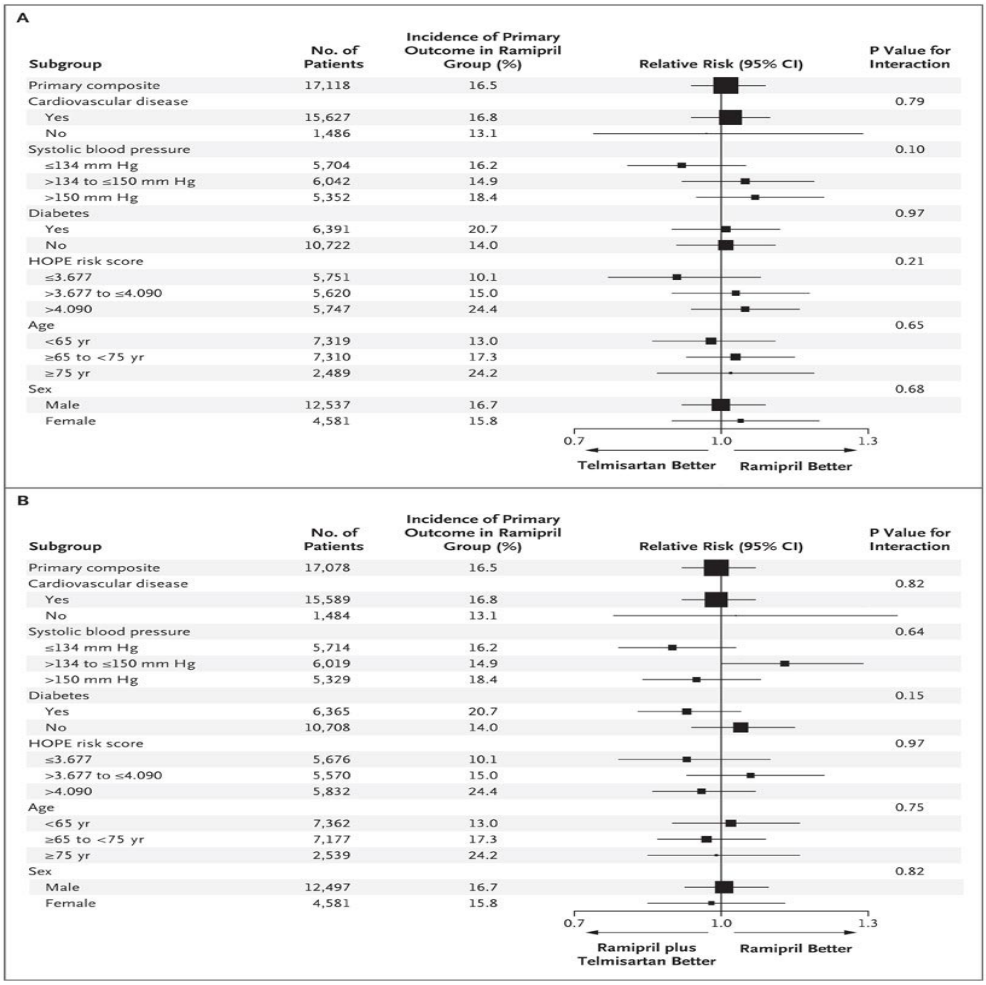
The decrease of blood pressure between the inclusion in the trial and the end of the trial were 6.4/4.3 mmHg in the ramipril group, 7.4/5.0 mmHg in the telmisartan group and 9.8/6.3 mmHg in the combination. Patients in the telmisartan group and in the combination-therapy group continued to have slightly lower blood pressure levels throughout the study period (average reduction 0.9/0.6 mmHg and 2.4/1.4 mmHg, respectively).

Compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs. 4.2%, p<0.001) and angioedema (0.1% vs.0.3%, p=0.01) and a higher rate of hypotensive symptoms, and patients given the combination treatment had higher rates of hypotensive symptoms, syncope, renal dysfunction, and hyperkalaemia, with a trend toward an increased risk of renal function requiring dialysis.

Subgroup analyses

Overall 30 subgroup analyses were performed to investigate the consistency of the treatment effects in various patient groups. For subgroup analyses, the threshold p-value to indicate a subgroup-by-treatment interaction was set to 0.01 to address the issue of multiplicity of testing and to avoid chance findings.

There were no subgroup-by-treatment interactions in any of the subgroups; all p-values but one were above 0.01. The exception was an analysis by the proportion of visits with blood pressure below 140/90 mmHg (subgroup-by-treatment interaction p=0.0018). The results of this analysis were, however, inconclusive. Subgroups analyses for the concomitant use of additional antihypertensive medications such as dihydropyridines, beta-blockers, alpha-blockers, diuretics, and statins did also not show a relevant subgroup-by-treatment interaction (p>0.01). Subgroup analyses were also performed for the individual components of the primary endpoint. No subgroup-by-treatment interaction was observed. The consistency of the treatment effects demonstrates the robustness of the non-inferiority of telmisartan in relation to ramipril.



Comparisons of key subgroups showed similar results between the ramipril group and the telmisartan group (Figure A) as well as between the ramipril group and the combination-therapy group (Figure B). Telmisartan was equivalent to ramipril in patients with vascular disease or high risk diabetes, and was associated with a better tolerability. The risk score from the Heart Outcomes Prevention Evaluation (HOPE) trial ranges from 2.350 to 5.928, with higher scores indicating higher risk. The sizes of the squares are proportioned to the numbers of events.

All-cause mortality

Overall, 3068 of the randomised patients (12.0%) died during the study. The incidence of death from all causes was 12.5% in the T/R combination group, 11.6% in the telmisartan group, and 11.8% in the ramipril group. The hazard ratio for the T/R combination versus ramipril was 1.07 (95% CI 0.98, 1.16; p=0.1453). The hazard ratio of telmisartan versus ramipril was 0.98 (95% CI 0.90, 1.07; p=0.6378). The predominant reasons for death were CV death and malignancies in both the telmisartan and ramipril treatment groups.

Comparison ONTARGET and HOPE trial

As a key secondary endpoint, the composite of CV death, non-fatal MI, and non-fatal stroke, which had been defined as primary endpoint in the HOPE study, was analysed. Although the ONTARGET and HOPE studies had a very similar trial design, some differences are noteworthy. Eligibility and exclusion criteria differed in some minor aspects between the 2 trials. While not allowed at all in the HOPE study, the occurrence of TIA more than 7 days and less than 1 year prior to informed consent was permitted in ONTARGET. However, TIA was recorded for only 3.5% of patients in ONTARGET at run-in and was given as the primary diagnosis for study entry for only 2.0% of patients. Patients with a left ventricular ejection fraction below 40% were to be excluded from the HOPE study, while they could participate in ONTARGET if not diagnosed with symptomatic heart failure. Patients with severe hepatic dysfunction were excluded from the ONTARGET study but were allowed to participate in the HOPE trial.

Table 11.2.13: 1 Comparison of the ONTARGET and HOPE study with respect to the main demographic and baseline characteristics / FAS

	ONTARGET			HOPE	
	T/R	T	R	R	Placebo
Randomised, n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)	4645 (100.0)	4652 (100.0)
Age mean, (SD) [years]	66.4 (7.3)	66.4 (7.1)	66.4 (7.2)	66 (7)	66 (7)
Female sex, %	26.5	26.3	27.2	27.5	25.8
Mean BMI (SD) [kg/m^2]	28.11 (4.76)	28.18 (4.75)	28.19 (4.81)	28 (4)	28 (4)
Mean SBP (SD) [mmHg]	141.9 (17.6)	141.7 (17.2)	141.8 (17.4)	139 (20)	139 (20)
Mean DBP (SD) [mmHg]	82.1 (10.4)	82.1 (10.4)	82.1 (10.4)	79 (11)	79 (11)
Mean PR [bpm]	67.7 (12.2)	68.0 (12.3)	67.9 (12.2)	69 (11)	69 (11)
Current smoking, %	12.9	12.4	12.4	13.9	14.5
Medical history, %					
Hypertension	68.5	68.6	69.0	47.6	46.1
Diabetes	37.9	38.0	36.7	38.9	38.0
MI	49.3	49.3	48.3	51.9	53.4
Stable angina	34.8	34.6	35.4	54.8	56.3
Unstable angina	14.9	15.2	14.7	25.4	25.5
CABG surgery	22.3	22.5	21.7	25.7	25.9
PTCA/atherectomy/PCI	28.6	29.0	29.5	18.4[1]	17.3[1]
Stroke/TIA	20.9	20.6	21.0	10.8	11.0
LVH on ECG, %	12.7	13.1	12.7	8.2	8.7
Baseline medication use, %					
Beta blockers	57.4	56.9	56.5	39.2	39.8
ASA	76.0	75.7	75.5	75.3[2]	76.9[2]
Statins	61.8	62.0	61.0	28.4[3]	28.8[3]
Diuretics	27.7	27.6	28.6	15.3	15.2
CCBs / diltiazem/verapamil[4]	33.8	32.6	33.0	46.3	47.9

[1] PTCA only
[2] Also including other antiplatelet agents
[3] Also included lipid lowering agents other than statins
[4] Concomitant use of CCBs and diltiazem/verapamil at baseline was reported in ONTARGET for 39 patients in the T/R group, 43 patients in the T group, and 34 patients in the R group.

Source data: Section 11.2 and [R00-0562]

Although similar overall, there were some differences in the patient populations included in the 2 trials. In the HOPE study, patients were recruited at centres in North America, South America, and Europe, whereas for ONTARGET, also Asians (13.7%) and patients from Australia/New Zealand (7.1%) were included. The main demographic characteristics such as age, sex, and body mass index [BMI] were similar in the 2 trials. Mean baseline blood pressures were modestly different in the 2 trials (ONTARGET: 142/82 mmHg; HOPE: 139/79 mmHg). The percentage of current smokers was slightly lower in the ONTARGET study (12.6%) than in the HOPE study (14.2%). Other differences were noted in the medical history of the randomised patients. In ONTARGET, 68.7% of patients had a recorded medical history of hypertension compared with only 46.8% in HOPE. The proportion of patients with diabetes recorded as medical history was similar (37.5% vs. 38.5%). Also, the percentage of patients with a previous MI was comparable (49.0% vs. 52.6%). Considerably fewer patients with stable angina (35.0% vs. 55.5%) and unstable angina (14.9% vs. 25.5%) were randomised in ONTARGET than in HOPE. A similar percentage of patients in the 2 trials had previously undergone coronary artery bypass graft [CABG] surgery (22.2% vs. 25.8%). However, PTCA/atherectomy/PCI was reported for 29.0% of patients in ONTARGET but for only 17.8% of patients in HOPE.

The increased use of revascularisation procedures and CV medications would be expected to have resulted in a lower frequency of angina at baseline in ONTARGET than in HOPE, and this was indeed observed. The percentage of patients for whom a stroke/TIA was documented at study entry was twice as high in ONTARGET (20.9%) as in the HOPE study (10.9%). The HOPE study enrolled patients between December 1993 and June 1995, while the first patient was enrolled into ONTARGET in December 2001. Hence, progress in the standard of medical care for patients at high risk for cardiovascular events was observed. This was most pronounced for the use of lipid-lowering agents. In

ONTARGET 62% of patients took statins concomitantly; the percentage increased to over 70% at study end. In contrast, in the HOPE study, only 29% of patients took lipid-lowering agents (statins and other drug classes). Betablocker use was also more common in ONTARGET than in HOPE (56.9% vs. 39.5%). The incidence of the 3-fold endpoint in ONTARGET was similar for all 3 treatments (T/R: 14.1%; T: 13.9%, R: 14.1%) as were the event rates per 100 patient years. Consequently, hazard ratios were close to 1. The incidence of the 3-fold endpoint in patients treated with ramipril was similar in ONTARGET and HOPE (14.1% vs. 14.0%) although the average observation time was longer in ONTARGET. The observation time-adjusted event rate per 100 PY for ramipril was 3.51 in HOPE compared with 3.23 observed in ONTARGET. Sensitivity analyses were performed for the 3-fold endpoint. The analyses based on the per-protocol population (one-sided non-inferiority p=0.0041) and based on the patients who had remained on 10 mg/day ramipril throughout the trial (one-sided non-inferiority p=0.0014) confirmed the findings of the initial analysis. Adjustment for baseline SBP (HR 1.04; 95% CI 1.02, 1.06) as well as for SBP over time (HR 1.02; 95% CI 1.01, 1.04) showed that the results for the 3-fold endpoint were largely independent of differences in SBP between treatments (one-sided non-inferiority p=0.0014).

A summary is provided in Table 2.5.4.1: 3 below.

Table 2.5.4.1: 3 Analysis of the composite of CV death, non-fatal MI, or non-fatal stroke in analogy to the HOPE study / ONTARGET FAS

	ONTARGET			HOPE	
	T/R	T	R	R	Placebo
Randomised, n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)	4645 (100.0)	4652 (100.0)
Three-fold endpoint, n (%)[1]	1200 (14.1)	1190 (13.9)	1210 (14.1)	651 (14.0)	826 (17.8)
CV death	454 (5.3)	438 (5.1)	448 (5.2)	282 (6.1)	377 (8.1)
Non-fatal MI	413 (4.9)	419 (4.9)	389 (4.5)	459 (9.9)	570 (12.3)
Non-fatal stroke	347 (4.1)	347 (4.1)	389 (4.5)	156 (3.4)	226 (4.9)
Total time to event/censoring [years]	37019	37390	37502		
Events per 100 patient years	3.24	3.18	3.23	3.51	4.53
Hazard ratio[2] vs. ramipril	1.00	0.99			
95% Confidence interval	(0.93, 1.09)	(0.91, 1.07)			
97.5% Confidence interval		(0.90, 1.08)			
p-value (conventional, two-sided)	0.9086	0.7384			
p-value (non-inferiority, one-sided)		0.0004			
Hazard ratio[2] vs. placebo				0.78	
95% Confidence interval				(0.70, 0.86)	
p-value				<0.001	

[1] The primary endpoint was defined as the time to first event. In case of multiple simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcomes.
[2] Cox regression

Source data: [Module 5.3.5.1, U08-1821-01, Table 15.2.2.1: 18, Vol. 15] and [R00-0562]

For the 4-fold primary endpoint, the hazard ratio of ramipril versus placebo in the HOPE trial was 0.775 (95% CIs 0.704, 0.854), for telmisartan versus placebo a hazard ratio of 0.785 (95% CI 0.695, 0.887) was calculated. For the 3-fold endpoint (without CHF), the hazard ratio of ramipril versus placebo was 0.780 (95% CI 0.700, 0.860) and for telmisartan versus placebo a hazard ratio of 0.770 (95% CI 0.675, 0.877) was calculated.

Additional analyses were performed for the individual components of the composite primary endpoint including all MIs and strokes irrespective of whether the event was fatal or not. The most frequent event in ONTARGET was CV death (7.1%) followed by MI (5.0%), stroke (4.5%), and hospitalisation for CHF (4.2%). No meaningful differences in risk reduction were observed between treatments for any of the individual components. Further CV endpoints included newly diagnosed CHF, CV revascularisation procedures, new onset of atrial fibrillation, angina (stable, unstable, new, and worsening), and TIA. Again, no relevant differences between treatments for these endpoints were detected.

Discussion ONTARGET

The ONTARGET trial compared monotherapy with ramipril 10 mg, telmisartan 80 mg and a combination of both in a group of patients at high CV risk. Superiority of the combination could not be demonstrated and, on the contrary, a numerically higher rate of all-cause mortality, CV mortality and of AEs and SAEs leading to treatment discontinuations were associated with the use of the combination. However, the combination of telmisartan and ramipril is not relevant for this application.

The predefined criteria for non inferiority were met for the comparison of telmisartan and ramipril for the primary endpoint (4-fold composite). The results for the secondary endpoints are consistent with the primary efficacy analysis. The findings cannot be extrapolated to lower doses and therefore the posology needs to reflect the dosing regimen used in the study.

The design of the study to compare telmisartan and ramipril was based on the results of the HOPE study that was used to estimate an expected treatment effect for ramipril. This is necessary in situations, where a placebo control cannot be included. However, this relies on the estimate from the historical study remaining valid which is frequently questionable because of changes in the patient population and clinical practice. There were relevant differences between the HOPE- and the ONTARGET population e.g. with respect to the presence of hypertension, stable angina, PTCA/PCI, Stroke/TIA and the baseline medication (betablockers, statins). Especially the higher use of statins and betablockers in ONTARGET may have decreased the overall event rate and potentially reduced the magnitude of the ramipril effect.

Further discussion regarding the chosen non-inferiority margin and the assumption of constancy (i.e. that the ramipril effect versus placebo in HOPE remains relevant for the ONTARGET study) also considering the submitted supportive data can be found in the Overall discussion on Clinical Efficacy below.

1.4 Supporting evidence - TRANSCEND trial

The TRANSCEND trial (**T**elmisartan **R**andomised **A**ssessme**N**t **S**tudy in A**CE**-I i**N**tolerant subjects with cardiovascular **D**isease) trial (n=5926) investigated the efficacy of telmisartan 80 mg vs. placebo in addition to standard treatment in the prevention of morbidity and mortality in patients at high risk for vascular events, who are intolerant to ACE-I.

The inclusion and exclusion criteria were the same as in ONTARGET, but only patients intolerant to ACE-Is were included and patients with clinically significant proteinuria were excluded. The primary composite 4-fold endpoint was identical to the primary endpoint in ONTARGET (Composite of CV death, MI, stroke, or hospitalisation for CHF).

The primary endpoint occurred in 15.7% (T) and 17.0% (PBO) of patients; the event rates per 100 patient years [PY] were 3.58 and 3.87, respectively, with a resulting hazard ratio of telmisartan versus placebo of 0.92 (95% CI 0.81, 1.05; p=0.2192). Thus the trial was not able to demonstrate superiority of telmisartan over placebo given on top of standard care.

A post-hoc power calculation showed that to confidently establish a difference between telmisartan and placebo in the 4-fold endpoint based on the event rates observed in the TRANSCEND trial, some 28000 patients would have been needed to achieve a power of 80%. Hence the study was insufficiently powered to demonstrate a relative risk reduction of 8% for telmisartan in the primary 4-fold endpoint.

Results published from the TRANSCEND study, showed that although telmisartan had no significant effect on the primary outcome, which included hospitalisation for HF, it modestly reduces the risk of a composite outcome of CV death, MI, or stroke.

The composite 3-fold endpoint of MI, stroke, and CV death was analysed as a key secondary endpoint in the TRANSCEND trial. For this endpoint the incidence was significantly lower in the telmisartan group (13.0%) than in the placebo group (14.8%); the hazard ratio for this comparison was 0.87 (95% CI 0.76, 1.00; p=0.0483).

The MAH stated that the apparent lack of a difference between telmisartan and placebo with regard to the incidence of hospitalisation for CHF (HR: 1.05; 95% CI 0.82, 1.34; p=0.6940) may be related to

the higher concomitant use of effective medication in the placebo group (at study end: diuretics T: 33.7% vs. PBO 40.0%; calcium channel blockers (dihydropyridines) excluding diltiazem/verapamil T: 30.8% vs. PBO: 39.2%).

A retrospective comparison showed that the event rates in the placebo group of the HOPE trial had been substantially higher than in the placebo group of the TRANSCEND trial. For the 4-fold endpoint, the event rate had been 5.09 (per 100 PY) in the HOPE trial whereas it was only 3.87 in TRANSCEND. Similarly for the 3-fold endpoint, the event rates were 4.53 versus 3.33, respectively. The differences in the composite endpoints between the placebo groups in the trials were largely due to substantially higher event rates for MI (HOPE 3.06 vs. TRANSCEND 1.09).

Telmisartan was well tolerated in patients intolerant to ACE inhibitors (in particular, 377 patients had experienced in the past serious reactions to ACE-I).

TRANSCEND Discussion

The TRANSCEND trial did not formally demonstrate superiority of telmisartan over placebo given on top of standard care in patients intolerant to ACE-Is. TRANSCEND study findings showed that the primary outcome (composite 4-fold endpoint) did not differ significantly between the telmisartan and placebo groups. Since the incidence of the primary endpoint (4-fold composite endpoint) was 15.7% for telmisartan 80 mg and 17% for placebo [HR = 0.92 with 95%CI (0.81; 1.05)] the study is considered not conclusive. When HF hospitalization was omitted from the composite outcome (3-fold composite endpoint), the result was in favour of telmisartan (13% in the telmisartan group compared to 14.8% in the placebo group (14.8%) with a hazard ratio for this comparison of 0.87 (95% CI 0.76, 1.00; p=0.0483)).

During the Cardiovascular Scientific Advisory Group (CV-SAG) meeting the relevance of the 3-fold as compared to the 4-fold combined cardiovascular endpoint was discussed. Experts in methodology of clinical trials raised concerns because the primary endpoint in TRANSCEND formally failed and they considered that in this case the secondary endpoint cannot be analysed. For this reason the statisticians considered the 3-fold secondary endpoint, although indeed identical to the primary endpoint in HOPE study, not adequate for confirmatory conclusions from data of TRANSCEND. They strongly supported the position that the post hoc exclusion of heart failure from the primary analysis in knowledge of the data is not appropriate irrespective of the claimed indication. The SAG chairman, however, underlined that the main secondary end point was a pre-specified end point. Further, the general opinion of clinical experts present at the SAG was that both endpoints were rather similar. Some experts mentioned however that although the 3-fold composite endpoint is clinically relevant, it is not as relevant as the 4-fold endpoint.

TRANSCEND cannot formally be considered a positive study demonstrating superiority of telmisartan versus placebo and the only moderate numerical difference in the TRANSCEND trial has put a further question mark on the assumptions of the treatment effect of ramipril in the ONTARGET trial. The baseline characteristics of the patients are almost identical. Assuming the true treatment effect in this population and in the ONTARGET population is around 8% the appropriateness of the predefined non-inferiority margin in ONTARGET is questionable. Reference is made to the overall discussion on clinical efficacy for further details (see below).

1.5 Supporting evidence - PRoFESS Trial

PRoFESS (**P**revention **R**egimen **F**or **E**ffectively avoiding **S**econd **S**trokes: A double-blind, active and placebo controlled study of Aggrenox→ vs. clopidogrel, with and without Micardis) investigated the role of telmisartan versus placebo, on top of standard antiplatelet therapy in the prevention of secondary stroke.

Objectives:

To compare the efficacy and safety of the fixed-dose combination product Aspirin plus extended-release dipyridamole (Aggrenox, ASA+ER-DP) with that of clopidogrel and to compare the efficacy and safety of telmisartan with that of placebo in the prevention of recurrent stroke.

Primary Endpoint:

Time to first recurrent stroke.

Secondary Endpoints (telmisartan):

(1) Composite outcome defined as time to the first of: recurrent stroke, MI, new or worsening CHF, or death due to vascular causes.
(2) Time to new onset of diabetes mellitus.

Post hoc defined: Time to composite of stroke, MI or death due to vascular causes.

Methodology:

Prospective, randomised, multi-national, double-blind, double-dummy, active and placebo-controlled, parallel-group, 2x2 factorial design. The enrolment period was 2 years and 10 months; total study duration was 4 years and 5 months.

4 groups: ASA+ER-DP/telmisartan treatment group:
Entered:5086 Treated:5013 Analysed (for primary endpoint):5086
ASA+ER-DP/placebo treatment group:
Entered:5095 Treated:5024 Analysed (for primary endpoint):5095
Clopidogrel/telmisartan treatment group:
Entered:5060 Treated:5000 Analysed (for primary endpoint):5060
Clopidogrel/placebo treatment group:
Entered:5091 Treated:5023 Analysed (for primary endpoint):5091

Diagnosis and main criteria for inclusion:

Male or female patients aged at least 50 years who had suffered an ischaemic stroke within 120 days prior to study entry and who were neurologically and clinically stable were enrolled in this study.

20332 patients were included, amongst them 10146 were in the telmisartan arm and were assigned to receive 80 mg telmisartan daily. At baseline 74% had hypertension, 28% diabetes, 46% hyperlipidemia, and 67% received other antihypertensive medications. At baseline the mean BP was 144.1/83.8 mmHg, and the mean difference along the trial between the telmisartan and placebo arms was 3.59/1.65 mmHg.

Results

After 2.5 years of follow-up the primary outcome occurred for 873 patients (8.6%) in the telmisartan arm, and for 924 patients (9.1%) in the placebo arm (HR 0.95, 95% CI: 0.86, 1.04; p=0.2621). Therefore the numerical difference in favour of telmisartan was not statistically significant.

The major haemorrhagic events occurred for 377 patients in the telmisartan arm versus 400 in the placebo arm (HR 0.95, 95% CI: 0.83, 1.10; p=0.49). For the Intracranial bleeds the HR was 0.81, numerically in favour of telmisartan (95% CI: 0.62-1.04; p=0.0972).

The composite 4-fold endpoint of MI, stroke, CV death, and hospitalisation due to CHF, was investigated as secondary endpoint to allow potential comparisons with the results of the other telmisartan outcome trials. The 3-fold composite endpoint of MI, stroke, and CV death was analysed post hoc to provide a link to the results in the ONTARGET, TRANSCEND, and HOPE studies.

The randomisation in the PRoFESS trial was stratified by ACE-I use at baseline; overall, 37.0% of patients had been using ACE-Is at study entry. A post-hoc subgroup analysis of the 4-fold composite endpoint (MI, stroke, CV death, hospitalisation for CHF) based on all patients separated by concomitant ACE-Is use during the study was performed. In patients who did not use ACE-Is, the 4-fold endpoint occurred in 11.6% (T) and 13.1% (PBO) of patients, with a hazard ratio of 0.87 (95% CI 0.79, 0.97); the p-value for the subgroup-by-treatment interaction was 0.0527. Similarly, the 3-fold composite endpoint occurred in 11.2% (T) and 12.6% (PBO) of patients with a hazard ratio of 0.88 (95% CI 0.79, 0.98); the p-value for the subgroup-by-treatment interaction was 0.0624.

This study has provided relevant safety data on telmisartan in patients with a previous stroke. Data show that therapy with telmisartan initiated soon after an ischemic stroke and continued for 2.5 years, do not significantly decrease the rate of recurrent stroke, major cardiovascular events, or diabetes (see safety section below).

PRoFESS Discussion

The results of this study have limited relevance for this application as the primary endpoint was the recurrence of stroke, only one component of the composite endpoint chosen in ONTARGET. Furthermore, the results of the study were influenced by the factorial design used to assess the effect of two different antiplatelet therapies; this design reduced the overall power in the comparison between telmisartan and placebo; there was a time-by-treatment interaction, there were significant differences in the blood pressure between the groups.

The primary endpoint did not reveal a statistically significant result without further statistical calculations. The relevant secondary composite endpoint did not show a significant benefit of telmisartan as compared to placebo. Only after post hoc analyses a difference could be shown. Furthermore, the primary endpoint (stroke) is only one component of the composite endpoint chosen in ONTARGET. Therefore, the data can only be used as supporting evidence.

1.6 Supporting evidence - a pooled analysis of TRANSCEND and PRoFESS for patients not using ACE-Is ('Total/NoACE-I population')

To investigate the effectiveness of telmisartan in comparison with placebo in the prevention of major cardiovascular events in patients who did not use ACE-Is, the respective patient cohorts from the TRANSCEND study (contributing about 1/3) and the PRoFESS trial (contributing about 2/3) were pooled. The resulting "total/NoACE-I" population comprised 16877 patients (T: n=8587, PBO: n=8290).

For the analyses of the pooled data across relevant study populations, essentially the same methodology as pre-specified for ONTARGET and TRANSCEND was used. No new combined endpoints were defined. The 4-fold endpoint was pre-specified in PRoFESS; the 3-fold HOPE endpoint was not pre-specified in PRoFESS, but was used for the post-hoc analyses as pre-specified for ONTARGET and TRANSCEND.

Table 1: Comparison of demographics, relevant medical history, concomitant medication and tobacco use between the HOPE and the ONTARGET studies and the TRANSCEND, PRoFESS studies

	HOPE	**ONTARGET**	**TRANSCEND**	**PROFESS**
HOPE RISK SCORE		4,07	4,02	-
Demographics				
Mean age / > 75 years	66 years	66 years / 15 %	67 years / 16 %	66 years / 19 %
Male sex	73 %	73 %	**57 %**	64 %
Ethnicity: White / Asian	-	74 % / 14 %	62 % / 21 %	57 % / 33 %
Mean BMI (kg/m^2)	28	28	28	27
Relevant medical history				
Hypertension	**48 %**	69 %	76 %	74 %
Previous stroke / TIA	**11 %**	21% / 2.7 %	22 %	**25 % / 8,7 %**
Stable / unstable angina	**55 % / 25 %**	35 % / 15 %	37 % / 15 %	-
History of CAD	80 %	-	-	**16 %**
MI	51 %	49 %	46 %	**7 %**
Intermittent claudiaction	-	6 %	5 %	**PAD = 3 %**
DM	38 %	40 %	36 %	**28 %**
Concomitant medication				
ASA / clopidogrel	75 % (ASA or other)	76% / 9 %	74 % / 8,5 %	**50 % / 16 %**
Statins	**28 % (lipid low agent)**	62 %	55 %	**47 %**
Oral Anti-diabetic treatment	-	25 %	24 %	**6 %**
Insulin	-	10 %	7 %	**19 %**
Beta-blockers	**39 %**	57 %	59 %	**21 %**
CCBs (excl. diltiazem/verapamil)	**48 % (any CCB)**	25 %	31 %	**22 %**
Diuretics	**15 %**	28 %	33 %	**Thiazids = 17 %** **Loop diuretics = 3 %**
Nitrates	-	29 %	34 %	**3 %**
Tobacco use: Former/current	- / 14%	52 % / 13%	43 % / 10 %	**36 % / 21 %**

In both trials, patients were randomly assigned to telmisartan (n=8587) or placebo (n=8290). Of these 13.0% (T) and 14.4% (PBO) reached the composite 4-fold endpoint. The hazard ratio for telmisartan versus placebo was 0.90 (95% CI 0.83, 0.98); the p-value of 0.0107 demonstrated superiority of telmisartan over placebo in this pooled population.

Table 2.5.4.2: 1 Incidence of the 4-fold composite endpoint of MI, stroke, CV death, and hospitalisation for CHF / Total/NoACE-I population

	Telmisartan	Placebo
Randomised, n (%)	8587 (100.0)	8290 (100.0)
Primary endpoint[1], n (%)	1120 (13.0)	1196 (14.4)
CV death	265 (3.1)	291 (3.5)
MI	164 (1.9)	189 (2.3)
Stroke	549 (6.4)	583 (7.0)
Hospitalisation for CHF	166 (1.9)	152 (1.8)
Total time to event/censoring [years]	26238	25314
Events per 100 patient years	4.27	4.72
Hazard ratio[2] vs. placebo	0.90	
95% CI[2]	(0.83, 0.98)	
p-value	0.0107	
Interaction between treatment and study	0.4122	

[1] The primary endpoint was defined as the time to first event. In case of multiple simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcomes.
[2] Cox regression adjusted for study

Likewise, for the 3-fold endpoint, the incidences were 11.8% (T) and 13.3% (PBO), the hazard ratio was 0.88 (95% CI 0.81, 0.96), and the p-value of 0.0029 indicated superiority of telmisartan in this population.

Table 2.5.4.2: 2 Incidence and analysis of the 3-fold composite endpoint of MI, stroke, and CV death / Total/NoACE-I population

	Telmisartan	Placebo
Randomised, n (%)	8587 (100.0)	8290 (100.0)
3-fold composite endpoint[1], n (%)	1015 (11.8)	1106 (13.3)
CV death	265 (3.1)	291 (3.5)
Non-fatal MI	164 (1.9)	189 (2.3)
Non-fatal stroke	549 (6.4)	583 (7.0)
Total time to event/censoring [years]	26519	25557
Events per 100 patient years	3.83	4.33
Hazard ratio[2] vs. placebo	0.88	
95% CI[2]	(0.81, 0.96)	
p-value	0.0029	
Interaction between treatment and study	0.9328	

[1] The endpoint was defined as the time to first event. In case of multiple simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcomes.
[2] Cox regression adjusted for study

Additionally, a sensitivity analysis for the 4-fold composite endpoint using data from all patients who had not taken ACE-Is at baseline in the PRoFESS and TRANSCEND trials (n=18739) was conducted. Such an analysis would not be affected by any post-randomisation decisions to add ACE-Is during the trial which could introduce bias. This analysis yielded a hazard ratio of 0.92 (95% CI 0.86, 1.00) with a p=0.0422 and thus confirmed the results seen in the total/NoACE-I population (i.e., no ACE-I at any time during a study). Furthermore, if data from the complete trial populations of both the TRANSCEND and the PRoFESS trials are combined, irrespective of ACE-I use (n=26258), a positive effect of telmisartan could still be demonstrated (HR 0.93; 95% CI 0.87, 0.99, p=0.0297), albeit of smaller magnitude, as would be expected.

For the total/NoACE-I population, a significant treatment-by-time-period interaction (≤6 months, >6 months) was observed for both the 4-fold (p=0.0151) and the 3-fold (p=0.0178) endpoints. For the period exceeding 6 months, the hazard ratio for the 4-fold endpoint was 0.85 (95% CI 0.78, 0.94); for the 3-fold endpoint, the hazard ratio was 0.83 (95% CI 0.75, 0.92) indicating relative risk reductions in favour of telmisartan of 15% and 17%, respectively. This implies that prolonged treatment with telmisartan increases the protective effect in comparison with placebo. A time-dependent effect was also observed in the individual trials (TRANSCEND, PRoFESS).

In the course of the studies, a substantial reduction in blood pressure was observed in both treatment groups; the individual mean SBP/DBP changes post randomisation were −8.9/−5.1 mmHg in the telmisartan group and −4.3/−2.7 mmHg in the placebo group.

Pooled Analyses discussion

The supportive placebo controlled efficacy data are primarily based on a post-hoc meta-analysis in which, patients from the TRANSCEND and the PRoFESS studies, who did not use ACE-Is, were pooled. The vast majority of the patients in the meta-analysis had participated in the PRoFESS study. However, large differences exists in relevant medical history, concomitant medication and tobacco use (highlighted in table 1 above) between the PRoFESS and the ONTARGET/TRANSCEND study populations. In addition, the objective of the PRoFESS study was different from the objectives of the ONTARGET and TRANSCEND studies. In fact, time to composite of stroke, MI or death due to vascular causes (HOPE) was a post-hoc defined endpoint. Therefore, the pooled analysis is not persuasive as trials with heterogeneous objectives and patient populations are pooled and a subgroup of interest is not prospectively identified. Adjustments for multiple testing are not implemented and the results may anyway not be regarded as providing considerable statistical evidence. Formally, the level of evidence does not meet the standards outlined in the CHMP guidance for accepting data from meta-analyses "points to consider on application with 1. Meta-analyses; 2. One pivotal study" (CPMP/EWP2330/99).

During the review of the application the MAH clarified that the analysis was not considered to provide a formal meta-analysis in the sense of the above mentioned guideline as the ONTARGET study is considered the main body of evidence. However, the MAH considered this information as important supportive evidence because this analysis provides information on about 16000 patients at high cardiovascular risk.

Furthermore, the MAH has performed an additional analysis based on an adapted HOPE risk score to describe the similarity of the study populations. The mean adapted HOPE score was comparable between ONTARGET, TRANSCEND, and PRoFESS (see Table 2:1). The MAH provided justification on the use of the adapted HOPE score and considered the similarity of the adapted HOPE cardiovascular risk score and the similarity of the patient populations as sufficient justification to perform a pooled analysis.

Table 2: 1 Mean adapted HOPE score for ONTARGET, TRANSCEND, and PRoFESS / FAS (ONTARGET, TRANSCEND), RAN (PRoFESS)

Mean	ONTARGET	TRANSCEND	PRoFESS
Factors			
Age	2.787	2.806	2.775
Sex = male	0.255	0.198	0.223
Smoker	0.058	0.045	0.098
Hypertension	0.130	0.135	0.137
LVH	0.027	0.029	0.019
Diabetes	0.144	0.137	0.108
Stroke	0.073	0.078	0.350
CAD	0.398	0.397	0.091
PAD	0.066	0.056	0.011
Adapted HOPE score (SD)	**3.94 (0.47)**	**3.88 (0.46)**	**3.81 (0.50)**

The MAH stated that additional sensitivity analyses were conducted to evaluate the robustness of the main Total/NoACE-I analyses which excluded the concomitant use of ACE-Is and ARBs at any time. One analysis included only the patients as stratified by ACE-I use at baseline, a second sensitivity analysis included all patients in PRoFESS and TRANSCEND, irrespective of ACE-I use, and both demonstrated a statistically significant benefit of telmisartan over placebo. Other sensitivity analyses, e.g. to assess the influence of blood pressure, were also performed in analogy with the pre-specified analyses in ONTARGET and TRANSCEND. Analyses that were not pre-specified had exploratory character. For instance, the additional analysis of the Total/NoACE-I population that showed that the effect of telmisartan became prominent after a lag-phase of about 6 months is considered exploratory.

It is questionable, from the CHMP point of view, whether the information derived from this analysis provides information beyond the information that can be drawn from the single two studies (TRANSCEND and PRoFESS). Taking the data together does not eliminate the problems inherited from the single studies. Furthermore, the analysis mainly reflects the Non-ACE-patients from PRoFESS trial and has mainly the inherited problems such as the two-by-two design.

Independent of the mode of the different kinds of calculation (3-fold and 4-fold endpoint, No-ACE-Inhibitor at all, No ACE-Inhibitor at entry, irrespectively of ACE-Inhibitor use, HR 0.90, 0.88, 0.92, 0.93) all of the results are consistent with the assumption that an expected treatment effect should be much less than the 22% seen in the HOPE study. Furthermore, the analysis of all-cause mortality in a pooled analysis did not reveal any positive effect of telmisartan but even a slight numerical difference in favour of placebo.

In conclusion, the pooled analysis does not significantly contribute additional information beyond the information that can be derived from the single studies. Statistical significance in the pooled analysis should be interpreted with caution.

1.7 All-cause mortality

All-cause mortality was analysed as a tertiary efficacy endpoint in ONTARGET, TRANSCEND, and PRoFESS. In none of the three trials was there any clear indication of an excess risk of death with telmisartan, apart from small numerical differences between the treatment groups, not indicative of clinically meaningful differences.

- In TRANSCEND the incidence of all-cause mortality was 12.3% (telmisartan) vs. 11.7% (placebo) with a hazard ratio of 1.05 (95% CI 0.91 to 1.22).
- In PRoFESS the incidence of all-cause mortality was 7.4% (telmisartan) vs. 7.3% (placebo) with a hazard ratio of 1.03 (95% CI 0.93 to 1.14).
- In ONTARGET the incidence of all-cause mortality was 11.6% (telmisartan) vs. 11.8% (ramipril) with a hazard ratio of 0.98 (95% CI 0.90 to 1.07).

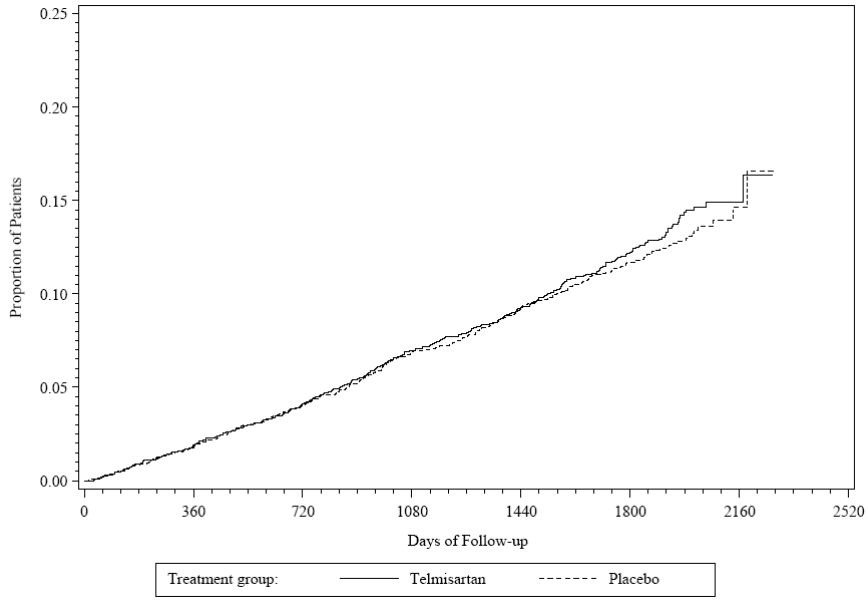
In the placebo-controlled study TRANSCEND, a total of 713 patients died in the course of this study, 364 patients (12.3%) in the telmisartan treatment group and 349 patients (11.7%) in the placebo treatment group. It should be noted that the proportion of TRANSCEND patients taking other cardio-protective medications (i.e., beta blockers and diuretics) at the end of the trial was higher in the placebo group than in the telmisartan group (see Table 2: 1).

Table 2: 1 Concomitant Medications by Visit (%) in TRANSCEND

	Baseline		Final	
	Telmisartan	Placebo	Telmisartan	Placebo
Antiplatelet	79.8	79.0	76.9	77.1
Beta-blockers	59.3	57.2	56.6	59.0
Diuretics	33.2	32.8	33.7	40.0*
CCB	39.9	40.4	38.1	45.9*
Statins	55.7	54.7	63.8	63.1

The MAH argued that this was a very likely consequence of the investigators using guideline recommended strategies to attain goal blood pressure levels in the placebo group, but also likely had the effect of reducing the outcome events in the "placebo group", which in reality was a "placebo plus other guideline driven medications to reduce total CV risk group". The results of the time-to-event analysis of death from any cause (including CV death and non-CV death) in all patients randomised in TRANSCEND is shown in Figure 2:1. The curves of the 2 treatments (telmisartan, placebo) are almost overlapping for most of the trial suggesting there is no difference in all-cause mortality between the two treatment groups.

Figure 2: 1 Kaplan Meier estimates for death of any cause in TRANSCEND



All deaths in the TRANSCEND trial were centrally adjudicated for the occurrence of CV death by blinded experts. Investigators were asked to record the primary cause of death on the Death Report Form (CRF 99), which had pre-specified categories. If the primary cause of death did not fall into one of the pre-specified categories, the investigator was to give the cause of death in a free-text field (under 'other'). The incidence of cardiovascular death was very similar between the treatment groups while there was a small difference in non-cardiovascular deaths. The incidences of deaths due to malignancies were again similar (T: [66 patients] 2.2% vs. PBO [67 patients] 2.3%). The difference between the treatment groups is due to differences in the category of "other causes" of death. In the telmisartan group 71 patients (2.4%) had a reason for death that was categorised as "other" compared with 58 causes of death in the placebo group (2.0%).

Table 2:2 Incidence of all-cause mortality for TRANSCEND

	Telmisartan	Placebo
Randomised n, (%)	2954 (100.0)	2972 (100.0)
Patient who died n, (%)	364 (12.3)	349 (11.7)
CV death	227 (7.7)	223 (7.5)
Non-CV death	137 (4.6)	126 (4.2)
malignancy	66 (2.2)	67 (2.3)
other causes	71 (2.4)	58 (2.0)
HR vs. placebo (95%CI)	1.05 (0.91, 1.22)	

In the placebo-controlled trial PRoFESS, all-cause mortality was analysed as another tertiary endpoint, also employing a Cox proportional hazards regression as for the primary endpoint. Table 2:3 shows no meaningful difference in the number of deaths between the two groups as indicated by the hazard ratio and 95% CI.

Table 2: 3 Analysis of all-cause mortality in PRoFESS

	Telmisartan	Placebo
Randomised n, (%)	10146 (100.0)	10186 (100.0)
Patient who died n, (%)	755 (7.4)	740 (7.3)
HR vs. placebo (95%CI)	1.03 (0.93, 1.14)	

The results above are substantiated by taking the incidence of all-cause mortality in the pooled patient population of TRANSCEND and PRoFESS who did not take ACE-I at any time during the trials and the patients in ONTARGET (comparison telmisartan against ramipril) into account. In the pooled analysis, 788 (9.2%) of patients died in the telmisartan group vs. 745 (9.0%) of patients who died in the placebo group, resulting in a hazard ratio of 1.03 (95% CI 0.93, 1.13).

In the ONTARGET trial, of the 3068 randomised patients, 989 patients died in the telmisartan group and 1014 patients died in the ramipril group (hazard ratio: 0.98; 95% CI 0.90, 1.07).

It is worthwhile to note that in the VALIANT study, a minimally higher mortality rate was shown for the valsartan arm (19.9%) compared with the captopril arm (19.5%); nevertheless the overall study results demonstrated that valsartan is non-inferior to captopril in reducing the risk of death in the patient population studied.

Discussion All-cause mortality

Although in the ONTARGET pivotal trial, mortality was numerically lower in the telmisartan group compared to the ramipril group, the two placebo controlled trials do not indicate that there is any beneficial effect of telmisartan with regard to all-cause mortality. All-cause mortality was numerically increased as compared to placebo. This result was consistent for CV death and non CV death. Also CV death was numerically higher with telmisartan in TRANSCEND (7.7 vs. 7.5%).

Given these results it is not possible to conclude that telmisartan has a beneficial effect neither on all-cause mortality nor on CV mortality. Considering that the treatment effect in the ONTARGET population may have changed as compared to the HOPE study and considering that the result on the heart failure component in ONTARGET was also different to the result in HOPE, the data do not allow to conclude that similar results in ONTARGET for mortality in the two groups indicate a beneficial effect of both medicinal products.

The view of the SAG from a clinical perspective was, taking the totality of the data into account, that there is a treatment effect, although it cannot be reliably estimated in terms of effect size as compared to placebo. In the opinion of the majority of the Group, the undertaken studies do not show that telmisartan improves either all-cause mortality or cardiovascular mortality. It was noted however that mortality was only one of the variables of the combined end-point.

One of the clinical experts was of the opinion that the benefits for patients were not clearly established because the benefit is to be expected considerably smaller than in HOPE and the signals from the supporting studies are more disturbing than assuring. However, on the other hand SAG admitted that the use of telmisartan does not seem to result in any increase of cardiovascular mortality.

The CHMP considered that a claim for improvement in CV mortality cannot be based on the results from the submitted studies.

1.8 Overall Discussion Clinical Efficacy

The pivotal efficacy trial in this submission is the ONTARGET study. The predefined criteria for non inferiority were met for the comparison of telmisartan and ramipril for the primary endpoint (4-fold composite endpoint of MI, stroke, cardiovascular death, and hospitalisation for CHF). The upper limit of the 97.5% confidence interval for the hazard ratio of telmisartan versus ramipril was below the protocol-specified non-inferiority margin. A similar result was also seen for the key secondary 3-fold endpoint of MI, stroke, and cardiovascular death. The results for the 4-fold and for the 3-fold endpoints when analysed to adjust for changes in systolic blood pressure were basically unchanged.

The overall results were also consistent with those observed in most of the 30 analysed subgroups.

The design of the study to compare telmisartan and ramipril in the ONTARGET study was based on the results of the HOPE study that was used to estimate an expected treatment effect for ramipril. This is necessary in situations, where a placebo control cannot be included. However, this relies on the estimate from the historical study remaining valid which is frequently questionable because of changes in the patient population and clinical practice. Referring to historical data requires hypotheses, especially the constancy of the effect over time of the chosen comparator (ramipril here). For ONTARGET the historical effect of ramipril in the HOPE study (treatment benefit of 22% of ramipril over placebo for the primary endpoint) was used. The actual treatment effect of ramipril in ONTARGET is unknown. Furthermore, there are some relevant differences between the HOPE population and the ONTARGET population (e.g. higher use of statins and betablockers in ONTARGET) that could influence the overall result and affect the validity of a straightforward cross trial comparison. Moreover, the TRANSCEND study included in a placebo controlled design a patient population that was almost identical to the population in ONTARGET but did not demonstrate a superior efficacy of telmisartan over placebo for the primary endpoint. These considerations had raised concerns regarding the acceptance of the choice of the noninferiority margin (1.13) in ONTARGET.

The key point of the discussion is that the placebo controlled effect of ramipril seen in the HOPE study might not be transferable to the ONTARGET population and is presumably considerably lower. Therefore, a non-inferiority margin set at 50% of the effect in the HOPE study might not be appropriate to demonstrate that the effect of ramipril is preserved. Taking as an example the assumption of the MAH (13% effect of ramipril) the study was not able demonstrate that at least 50% of the effect of ramipril (required non-inferiority margin in this case: 7.5%) is preserved. In fact it was questionable, whether a 13% difference in comparison to placebo can actually be assumed based on the clinical program. The TRANSCEND study failed to show a statistically significant effect of telmisartan vs. placebo for the primary endpoint. Numerically the difference was only 8%. In the PROFESS study the numerical difference achieved was even smaller (HR 0.94) for both the 3-fold and the 4-fold endpoint. All-cause mortality was numerically increased in both studies, when compared to placebo: (12.3 vs. 11.7 and 7.4 vs. 7.2%), which was by far different from the numerical 16% reduction in mortality seen in HOPE. Taking the data of the two placebo controlled studies together the 3-fold and 4-fold endpoints indicated a numerical risk reduction by only 6 – 13%. All-cause mortality was consistently numerically increased by about 3 – 5% as compared to placebo. Based on these considerations the clinical relevance of an achievable effect nowadays is considerably less clear than at the time of the HOPE study. The improved standard of care might be a plausible explanation for the only borderline significant effect that is observed for telmisartan in the TRANSCEND study as it is nowadays more difficult to show superiority of a medicinal product on top of current best standard of care.

During the assessment the CHMP raised concerns with respect to the verification of assay sensitivity of the ONTARGET trial as the assumptions underpinning the putative placebo comparison remain questionable. In addition, concerns were expressed by the Committee why the evidence for non-inferiority from ONTARGET is adequate to establish (i) indirect superiority to placebo and (ii) absence of a clinically important difference compared to ramipril. This was based on the fact that the result for telmisartan vs. placebo in the TRANSCEND study with an almost identical patient population was formally negative for the primary composite endpoint. The resulting hazard ratio of telmisartan versus placebo was 0.92 and 0.87 depending on the endpoint, indicating a treatment effect of broadly similar magnitude to that selected for the non-inferiority margin for ONTARGET.

In the following the MAH arguments regarding these concerns are outlined as presented during the procedure.

Assay sensitivity

The MAH argued that in general, assay sensitivity in a non-inferiority design trial can be demonstrated by differences with regard to secondary endpoints, differences in the observed safety profiles of the treatments, or by any other established difference. For the ONTARGET trial, the apparent absence of substantial differences between the treatment groups in a number of efficacy endpoints may be related to the fact that the trial tested 2 medications (i.e. telmisartan and ramipril) that affect the same physiological response cascade, namely the renin-angiotension-aldesterone system (RAAS).

Nevertheless, there are a number of observations in the ONTARGET trial that the MAH claimed demonstrate that trial design and conduct were sensitive to the differential effects of the treatments administered:

a) the differences observed in regard to premature discontinuations from the trial because this is an important parameter for long-term tolerability,

b) the differential effect of the treatments on the albumine-creatinine ratio because it had been hypothesized, prior to the ONTARGET trial, that a dual blockade of RAAS would not only provide a more substantial risk reduction for major cardiovascular events but would also have a more pronounced renoprotective effect than treatment with a single RAAS blocking agent,

c) the incidences of adverse events associated with the use of ramipril, and

d) the statistical significant differences in the 3-fold endpoint in favour of telmisartan over placebo in the TRANSCEND study.

With regard to safety the MAH argued that a differential effect of the treatments and hence sensitivity could be demonstrated (see safety section below). In line with the expectations, substantial differences were observed in the incidences of cough and angioedema, adverse events that are associated with the use of ramipril. Treatment discontinuations because of cough and the risks to develop cough were significantly higher in both the T/R combination group and the ramipril group.

Similarly, although angioedema was a rare event, the exposure-adjusted incidences for angioedema and permanent treatment discontinuation were lower in the telmisartan group than in the ramipril group.

Additional sensitivity analyses on the pooled placebo population were performed. However, albeit placebo controlled, neither PRoFESS nor TRANSCEND were able to demonstrate a significant benefit for telmisartan. The conclusions that can be drawn from PRoFESS are largely limited due to the 2x2 design. In addition, there were relevant differences in arterial blood pressure. Only by post hoc analyses a treatment effect could be calculated.

The MAH stated that the overall results were consistent in a number of sensitivity analyses including evaluations of the per-protocol set and the patients who had received the full dose of ramipril (i.e., 10 mg/day) throughout the trial.

Indirect superiority to placebo

The MAH argued that the HOPE trial was a landmark study that has profoundly altered the pattern of medical care for patients at high risk for cardiovascular events. The addition of ramipril to the therapies for patients at high risk became standard thereafter. Consequently the inclusion of a placebo arm in the ONTARGET trial would have been unethical since there already was an effective therapy available.

Hence, the proof of superiority of telmisartan over placebo is based on 2 arguments by the MAH.

The first argument is indirect in that the ONTARGET trial has demonstrated non-inferiority of telmisartan versus ramipril and that the HOPE trial has shown superiority of ramipril over placebo. Both studies were performed in a similar population of patients at high risk for major cardiovascular events. This analysis is supported by the observation that the HOPE risk score was essentially the same for the patients in the HOPE trial and the patients in the ONTARGET and TRANSCEND trials (see below). The HOPE score accounts for the risk factors age, sex, smoking, hypertension, left ventricular hypertrophy, diabetes, prior stroke, history of PAD and/or ankle/arm SBP <0.9, and history of CAD. A summary of the HOPE risk score in the 3 trials is provided in Table 1: 6, below.

Table 1: 6 HOPE Score in the ONTARGET, TRANSCEND, and HOPE trials

	TRANSCEND	ONTARGET	HOPE
Mean (SD)	3.86 (0.47)	3.91 (0.47)	3.91 (0.46)

Note that the HOPE source data are proprietary to PHRI and are not available to the applicant. Therefore, the calculation of the HOPE risk score in this table was performed by PHRI for all 3 studies. The applicant had used slightly different criteria for the calculation of the HOPE risk scores in 2 clinical trial reports of ONTARGET (U08-1821-01) and TRANSCEND (U08-1959-01).

The ONTARGET trial has demonstrated risk ratios for telmisartan versus ramipril that were close to unity for both the 4-fold and the 3-fold endpoints. This observation allows the MAH to conclude that both medications have a comparable clinical efficacy in the prevention of major cardiovascular events. Assuming the clinical equivalence for telmisartan and ramipril, the results of the TRANSCEND trial can be used to estimate the potential benefit of both treatments over placebo given in addition to standard care. The hazard ratio of telmisartan vs. placebo of 0.87 in TRANSCEND, indicates a potential benefit of 13% over placebo in the 3-fold endpoint. This was substantiated with the analysis of the supportive data from the pooled analysis of patients who did not use ACE-Is from the TRANSCEND and the PRoFESS trials. Given the results of ONTARGET, it has to be assumed that the benefit of ramipril in the context of current medical practice would be very similar to that observed for telmisartan, i.e. around 13% over placebo. The HOPE study (patient enrolment 1993 to 1995) however had shown a treatment benefit of 22% of ramipril over placebo. The difference between both estimates (especially given the similarity in the HOPE risk score) is most likely due to improvements in medical care for patients at high risk for major cardiovascular events that have occurred during the about 8 years between the HOPE and the ONTARGET trials.

The second MAH argument for the superiority of telmisartan over placebo is based on a direct comparison of telmisartan with placebo in the TRANSCEND trial. The primary endpoint of the TRANSCEND study was the 4-fold endpoint and superiority of telmisartan over placebo could not be demonstrated. However, for the 3-fold endpoint which was the primary endpoint in the HOPE trial, telmisartan was superior (the hazard ratio for telmisartan vs. placebo was 0.87 (95% CI 0.76, 1.00; p=0.0483). In view of the MAH, the lack of statistical superiority for the 4-fold endpoint appears to be linked to the reduced event rate of the primary endpoint observed in the placebo arm of the TRANSCEND study compared with the HOPE trial, and to the absence of an effect of telmisartan treatment on the frequency of hospitalisations for congestive heart failure (CHF).

The study protocols of both ONTARGET and TRANSCEND had stipulated that patients with "symptomatic CHF" were to be excluded from participation in the trials. This appears to have minimised the participation of patients who were likely to develop symptomatic CHF during the 5 years of study drug treatment. Given the administration of effective co-medication, the incidence of hospitalisation because of CHF in TRANSCEND was too low to detect any difference between telmisartan and placebo treatment and this in turn has 'diluted' the significant effect of telmisartan on the other items of the primary endpoint, i.e. stroke, MI, and cardiovascular death.

The sample size calculation of the TRANSCEND study was based on the results of the HOPE study. Assuming event rates as observed in the HOPE trial, the study would have had the power to demonstrate superiority of telmisartan over placebo provided that at least 6000 patients were entered. A retrospective comparison showed that the event rates in the placebo group of the HOPE trial were substantially higher than in the placebo group of the TRANSCEND trial. For the 4-fold endpoint, the event rate was 5.09 (per 100 PY) in the HOPE trial whereas it was only 3.87 in TRANSCEND. Similarly for the 3-fold endpoint, the event rates were 4.53 versus 3.33, respectively.[1] The differences in the composite endpoints between the placebo groups in the trials were largely due to substantially higher event rates for MI (HOPE 3.06 vs. TRANSCEND 1.09). This result might be a reflection of the improvement of medical care and general use of concomitant medications recommended in guidelines issued by European and US cardiology societies. There was a substantial increase in concomitant treatment with effective medications such as statins, beta-blockers, and diuretics in the TRANSCEND

[1] The calculation of the event rates of the HOPE trial was performed by PHRI on their data base because this information is not available in the publication of the HOPE trial. The communication with PHRI is available in the Clinical Trial Master File of the ONTARGET study.

trial compared with the HOPE trial. Whereas in the HOPE trial, 28.6% of patients were taking lipid-lowering medications (including statins) concomitantly, the percentage was twice as high in the TRANSCEND study (55.2% at baseline, increasing to 63.5% at study end), similar observations were made for beta-blockers (HOPE: 39.8% vs. TRANSCEND 57.2%), and diuretics (HOPE 15.2% vs. TRANSCEND 38.2%).

Thus, since the study populations in ONTARGET, TRANSCEND and HOPE were similar, the difference in cardiovascular event rates is most likely due to the more frequent use of co-medication in ONTARGET and TRANSCEND. The MAH outlined that, despite these changes in medical care, the TRANSCEND study has demonstrated superiority of telmisartan over placebo for the 3-fold endpoint.

Data of the ONTARGET study were investigated for the influence of statins as co-medications: a lower incidence of primary events was observed in patients who took statins. This was seen in all treatment groups and therefore the statin use might have contributed to the improved risk reduction. However, the concomitant use of statins exerted a similar influence in both the telmisartan and the ramipril groups. This was evidenced by the absence of a significant subgroup-by-treatment interaction p-value (p=0.5768).

Absence of a clinically important difference compared to ramipril

The 2 objectives of the ONTARGET trial were to demonstrate superiority of the telmisartan and ramipril combination therapy over ramipril and to establish non-inferiority of telmisartan to ramipril. A total of 25620 patients were randomised (T/R: n=8502; T: n=8542; R: n=8576) in the ONTARGET trial. The primary outcome occurred in 16.3% of patients in the telmisartan/ramipril (T/R) combination group, 16.7% in the telmisartan (T) group, and 16.5% in the ramipril (R) group. The hazard ratio (HR) of T/R versus R was 0.99 (95% confidence interval [CI] 0.92, 1.07; p=0.8462). Thus, the trial failed to demonstrate superiority of the telmisartan/ramipril combination versus ramipril; however, this was considered not relevant for this application. The hazard ratio of telmisartan versus ramipril was 1.01 (97.5% CI 0.93, 1.10; one-sided p-value for non-inferiority: 0.0019). Since the upper limit of the 97.5% CI was below the pre-defined non-inferiority margin of 1.13 and the p-value for non-inferiority was below 0.0125, the trial succeeded in demonstrating the non-inferiority of telmisartan versus ramipril in the prevention of the composite 4-fold endpoint. The treatment effects persisted after correction for differences in SBP at baseline and over time. At the same time, non-inferiority of telmisartan versus ramipril for the 3-fold endpoint of MI, stroke, and CV death could be demonstrated (HR 0.99; 97.5% CI 0.90, 1.08, p-value for non-inferiority 0.0004). Thus, telmisartan was as effective as ramipril in the background of increased use of other medications. The effect of telmisartan was consistent across all subgroups.

The benefit of telmisartan over placebo as shown in the analysis of the 3-fold endpoint in the TRANSCEND study was 13% and was in the range of 8% to 18%, depending upon endpoint (3-fold vs. 4-fold, time period of evaluation, etc.). The benefit of ramipril over placebo in HOPE was about 22%. The difference in effect size is almost certainly due to the substantially increased use of statins, beta blockers, diuretics, and general improvement in the medical care of cardiac patients that have occurred between the time the HOPE and current outcome studies were conducted.

The arguments presented above also formed the basis of the MAH presentation held in the context of the oral explanation.

In conclusion, following the assessment of all efficacy data provided, the CHMP was of the view that telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure. The incidence of the primary endpoint was similar in the telmisartan (16.7 %) and ramipril (16.5 %) groups. The hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13). The all-cause mortality rate was 11.6% and 11.8% among telmisartan and ramipril treated patients respectively

Telmisartan was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 - 1.08, p (non-inferiority) = 0.0004)], the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo.

With reference to TRANSCEND no statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found (15.7% in the telmisartan and 17.0% in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)). There was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95% CI 0.76 - 1.00, p = 0.048)], There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95% CI 0.85 - 1.24).

Combining telmisartan with ramipril did not add further benefit over ramipril or telmisartan alone. CV mortality and all-cause mortality were numerically higher with the combination. In addition, there was a significantly higher incidence of hyperkalaemia, renal failure, hypotension and syncope in the combination arm. Therefore the use of a combination of telmisartan and ramipril is not recommended in this population.

1.9 Clinical Safety

The Tables below summarize the numbers of patients included in the safety sets relevant for the analysis and the time on treatment.

Table 2.5.5: 1 Numbers of patients included in the different safety sets relevant for the analysis of safety

Study	Name of analysis set	Total	T	PBO	R
Run-in periods					
TRANSCEND	TRANSCEND RIS	6665	N.A.	N.A.	N.A.
Randomised periods					
ONTARGET	ONTARGET FAS	17118	8542	N.A.	8576
TRANSCEND	TRANSCEND FAS	5926	2954	2972	N.A.
PRoFESS	Treated set (PRoFESS/NoACE-I)	11011	5661	5350	N.A.

RIS: Run-in set, all patients who were enrolled into the run-in period
FAS: Full analysis set, all patients who were randomised irrespective of treatment
Treated Set: All patients who were randomised and received at least 1 dose of telmisartan or matching placebo and did not use ACE-I concomitantly

Table 2.5.5.2.2: 1 Observation time on treatment in the randomised period of the trials

ONTARGET FAS[1]	Telmisartan		Ramipril	
Number of patients randomised	8542		8576	
Observation time [days]				
Mean (SD)	1507.2	(505.5)	1499.4	(516.2)
Median	1641.0		1640.0	
Overall patient years	35249		35207	
TRANSCEND FAS[1]	**Telmisartan**		**Placebo**	
Number of patients randomised	2954		2972	
Observation time [days]				
Mean (SD)	1526.9	(544.4)	1515.2	(548.7)
Median	1651.5		1644.0	
Overall patient years	12349		12329	
PRoFESS/NoACE-I Treated Set	**Telmisartan**		**Placebo**	
Number of patients randomised	5589		5277	
Observation time [days]				
Mean (SD)	715.9	(398.1)	733.7	(386.5)
Median	764		775	
Overall patient years	10955		10600	

[1]The observation time on treatment was determined as the time difference between the date of the visit at which the permanent stop of the study medications was recorded and the date of randomisation +1 day.

Overall, the established safety profile of telmisartan was confirmed in patients at high risk of CV disease if not used in combination with ramipril. Overall mortality, the frequencies of SAEs on treatment, and the frequencies of adverse events leading to permanent treatment discontinuation were comparable between the monotherapy treatment groups. The analysis of adverse events leading to permanent treatment discontinuation and of SAEs showed that cough and angioedema were less frequently reported in the telmisartan group than in the ramipril group; conversely hypotension was reported more frequently with telmisartan. In TRANSCEND, overall mortality and the frequency of SAEs while on treatment, were comparable between the telmisartan and the placebo groups. Adverse events leading to permanent treatment discontinuation were slightly more frequently reported with telmisartan than with placebo; these were almost all known adverse events associated with the use of telmisartan. In the telmisartan group, hypotensive and gastrointestinal symptoms, renal dysfunction, and increases in creatinine or potassium concentrations led more frequently to permanent treatment discontinuation than in the placebo group. The analysis of the safety data of the PRoFESS/NoACE-I population confirmed the findings in TRANSCEND.

In the TRANSCEND study and the PRoFESS study patients had been started on 80 mg telmisartan without a titration regimen. The observed safety profiles in the run-in period of TRANSCEND and during the first 4 weeks in the PRoFESS study for the PRoFESS/NoACE-I population were similar and consistent. The incidences of SAEs were low and the changes in serum creatinine and potassium levels were small. These data in many thousands of patients clearly support that telmisartan can be started at a dose of 80 mg in patients at high risk for major cardiovascular events.

Total deaths were numerically higher on telmisarten in the TRANSCEND study (364 vs. 349), but not in the ONTARGET study (989 vs. 1014).

Overall the safety profile in the study is consistent with the known profile of telmisartan. However, a prevention strategy with a defined dose of 80 mg of telmisartan, regardless the blood pressure values, is of some concern with respect to a potential risk of hypotension. In fact, in the ONTARGET study a higher rate of hypotensive symptoms has been recorded in telmisartan group versus ramipril group. On the other hand, no specific studies have been performed using telmisartan with lower dosage for this new indication. Thus, a close monitoring of blood pressure with the use of telmisartan in this indication is necessary.

A concomitant use of telmisartan and ramipril was associated with a numerically higher rate of deaths, CV deaths and treatment discontinuations due to AEs. This combination cannot be recommended in

the target patient group. However, findings from combination therapy are not considered to be relevant for this application.

Pharmacovigilance

The CHMP considered that the Pharmacovigilance system as described by the MAH fulfils the legislative requirements.

Risk Management Plan

The MAH submitted an updated risk management plan during the procedure. The RMP has been sufficiently updated; however, a further revision of the RMP reflecting the final agreed indication will be provided as a post-authorisation commitment. In line with the CHMP question on aggregate data, the MAH has agreed to submit annual PSURs and will include analyses by aggregate data for renal dysfunction as a consequence of dual RAAS blockade, sepsis, hypoglycaemia, increase of hepatic related adverse reactions in the Japanese population, and rhabdomyolysis.

Summary of the Risk Management Plan for Telmisartan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Renal dysfunction as a consequence of dual RAAS blockade	Routine pharmacovigilance	Warning in section 4.4 of the SPC that dual RAAS blockade may lead to hypotension and changes in renal function including acute renal failure. Precautionary statement in section 4.4 of the SPC that dual RAAS blockade is not recommended in patients with already controlled blood pressure and that dual RAAS blockade should be limited to individually defined cases with close monitoring of renal function.
Sepsis	Routine pharmacovigilance	Addition of the event under "Undesirable effects" in section 4.8 of the SPC. Insertion of a brief description of the study findings in section 5.1 of the SPC. Addition of a commentary in sections 4.8 and 5.1 of the SPC that at present it is unclear whether the finding represents a chance finding or is related to a mechanism currently unknown.
Rhabdomyolysis	Routine pharmacovigilance	Not applicable
Hypoglycaemia	Routine pharmacovigilance	Not applicable
Increase of hepatic related adverse reactions in the Japanese population	Routine pharmacovigilance	Not applicable

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. Conclusion on Benefit-Risk and SAG outcome

Throughout the assessment of the application there were two different views represented within the CHMP.

View 1
Overall, the clinical benefit of telmisartan, reported in the main trial on the two composite end-points, which define the long-term efficacy in CV prevention, is comparable to ramipril findings and thus, based on a well documented evidence.
The basis of the non-inferiority margin is not questioned because:

1. the comparator ramipril showed well established evidence for efficacy and safety in the HOPE reference trial;
2. the minimal difference in non inferiority does not affect the clinical relevance in both indication, hypertension and CV prevention;
3. Confidence Intervals of ONTARGET are well within the lower boundaries for efficacy.

In the ONTARGET study the degree of reduction of cardiovascular risk was influenced by improvement of standard of care, as the event rates reported by the HOPE trial are not longer seen in patients in primary prevention, at least in Europe.

The MAH's justification that the lower effect observed is based on the increasing use of concomitant medications like statins, beta-blockers in the more recent studies is agreed. Indeed, the results of the ramipril arm of the ONTARGET confirmed that the reduction of the overall cardioprotective effect of ramipril was related to a reduction in the overall risk.

However, the new indication should be reworded to achieve a better identification of the target population.

The safety overall profile of telmisartan in the CV prevention studies is consistent with the known profile of telmisartan in the anti- hypertensive setting and does not raise any new safety concern.

View 2
There are major concerns that preclude a straightforward assessment of a possible effect of telmisartan. Overall the result in the ONTARGET study looks numerically similar to that of the comparator ramipril.

The data do not allow to conclude that the effect of ramipril is preserved (equivalence). Even superiority of telmisartan vs. placebo was not demonstrated neither when compared to a putative placebo in ONTARGET, nor when directly compared to placebo in TRANSCEND and PRoFESS.

Therefore, the decision about an approval will be based on studies indicating a numerical similarity between telmisartan and ramipril in some clinically relevant endpoints without proof of therapeutic equivalence to ramipril or superiority over (putative) placebo.

Nowadays the treatment effect of ramipril is much lower than can be expected from the HOPE study. The data suggest that an obtainable effect may be around 6 – 13% (TRANSCEND and PRoFESS). It may even be lower (ONTARGET), since the overall event rate in ONTARGET was about 10 – 20 % lower than in TRANSCEND and PRoFESS the two studies that were conducted in parallel.

With much smaller effect sizes the clinical relevance of an effect is less clear than in the past for ramipril in the HOPE population. This is especially true in a case like this, where two large scale placebo controlled trials revealed a numerical increase in all-cause mortality by about 3 – 5% with telmisartan. Nowadays there seems to be nothing left of the 16% decrease in mortality seen previously in the HOPE population with ramipril.

Today it is more difficult to demonstrate superiority over placebo, therapeutic equivalence and a clinically relevant effect. Considering that the placebo corrected effect sizes for the 4-fold (primary endpoint) or 3-fold composite endpoint may be around 6 – 13% it is clear that the predefined criteria for conclusion on therapeutic equivalence (Non-inferiority margin: 13%) are not appropriate. When

applying this margin even superiority vs. placebo cannot be demonstrated. Therefore, post hoc pre-specified statistical analysis is not appropriate to support any claim.

Furthermore post hoc, the MAH considered the 3-fold cardiovascular endpoint including CV death, Non-fatal MI and Non-fatal stroke as more relevant than the 4-fold endpoint that also includes hospitalisation for congestive heart failure. This is not convincing for the following reasons:

a) The 4-fold endpoint was the pre-defined primary endpoint in ONTARGET and in TRANSCEND. The choice to base the assessment on the 3-fold endpoint without CHF was a post hoc decision in knowledge of the data.
b) The likely reason for this approach was an unfavourable outcome in the CHF component. In TRANSCEND the HR was 1.05, numerically in favour of placebo, and in the ONTARGET trial 353 patients (4.1%) vs. 312 (3.6%) (telmisartan vs. ramipril) experienced this clinically relevant event. The MAH has not provided convincing arguments that this apparent advantage of ramipril over telmisartan in this clinically relevant aspect was due imbalances in the use of dihydropyridienes or diuretics. Since hospitalization for CHF is clinically relevant and the number of events was high enough there is no reason for a post hoc exclusion from the primary analysis.

Consideration may be given, however, to the undisputed fact that today the effect achievable by this group of agents in general is much lower than at the time of the conduct of the HOPE study. If a treatment effect of about 6 – 13% with respect to cardiovascular endpoints and without a positive effect on mortality is considered clinically relevant and placebo controlled studies cannot be conducted for ethical reasons, a non-inferiority study may not be feasible and the best result available may be a non-inferiority study revealing numerically similar effects.

The CHMP decided during its July meeting to consult the Cardiovascular Scientific Advisory Group (CV-SAG). The below section presents the questions to the CV-SAG followed by the SAG discussion of the issues.

Question 1

Does the SAG consider that based on available data the treatment effect of ramipril in the ONTARGET study can be reliably estimated?

Most experts believed that the effect of the ACE-inhibitors had remained stable over the past decade, other experts believed however that the beneficial effect of ramipril could have reduced over the time period from HOPE patient entry as a result of different usage of statins, antihypertensive etc.

The experts in methodology of clinical trials did not consider that the available data allow for the reliable estimation of the actual treatment effect of ramipril in the ONTARGET. When they were asked whether it is possible to estimate the effect of ACE-inhibitors on the prevention of cardiovascular events they both answered that they were unable to quantify the actual effect.

The Rapporteur team reminded the group that the 3-fold endpoint was identical to the one used in the HOPE study (CV mortality + non fatal MI + non fatal stroke) and therefore more appropriate for comparison. It argued that the endpoints used in ACE-I prevention trials and that, after ramipril, have also led to the MA for prevention of cardiovascular disease also for perindopril do not include HF (HOPE – EUROPA) as a primary composite endpoints (CV mortality + non fatal MI + non fatal stroke).

Additionally it reminded that a similar application of indirect evidence has been adopted by CHMP for the MA of valsartan with submission of the VALIANT trial (HF after MI).

The differences between current application and the HOPE results were presented. In HOPE there was a numerical reduction in all-cause mortality by 16% for ramipril. A non inferiority in all-cause mortality was observed in the ONTARGET pivotal study, while in the supportive studies TRANSCEND and PRoFESS there was a numerical increase in all-cause mortality with telmisartan as compared to placebo by 3 – 5%. However, this point had already been discussed by the Rapporteur who showed that this numerical increase was not related to any increase in cardiovascular or malignancies. In addition in HOPE there was a reduction in heart failure. Non inferiority between telmisartan and ramipril has been found in the pivotal ONTARGET study while in the supportive

TRANSCEND there was a non significant numerical increase in hospitalizations for heart failure compared to placebo. However, it was underlined that this latter study was not powered to detect changes in hospitalization for heart failure.

The Co-rapporteur team noted that in the TRANSCEND study the result for telmisartan vs. placebo with, what it considered, an almost identical patient population (as compared to the patient population in ONTARGET) was negative for the four fold end point. However, most clinical experts agreed that patients intolerant to ACE-inhibitors cannot be compared to patients compliant to ACE-inhibition as shown by several studies assessing the effect of ACE-inhibitors and ARBs in heart failure (i.e. CHARM added, CHARM alternative, VALIANT). Furthermore, it was pointed out that valsartan was granted indication for treatment of heart failure in a non inferiority study similar in terms of design and results to the ramipril/telmisartan arms of ONTARGET.

Following the extensive discussion it was concluded, that ramipril has an effect which is clinically relevant, but the majority of experts were of the opinion that the magnitude of the putative placebo treatment effect in ONTARGET cannot be reliably estimated. The majority of Group felt that it was impossible to quantifying the effect of ramipril and thereby decide where to put the non-inferiority margin. Some experts did not question the validity of 3-fold endpoint, neither the validity of the non-inferiority margin. They believed that the minimal difference in non-inferiority does not affect the clinical relevance in both indications: hypertension and CV disease prevention.

Question 2

Does the SAG consider the assay sensitivity of the ONTARGET study adequate either:

- **to demonstrate indirect superiority vs. putative placebo or**
- **to demonstrate absence of a clinically important difference compared to ramipril**

Whether the non-inferiority of telmisartan to ramipril was demonstrated in the ONTARGET in patients with increased CV risk with respect to the primary 4-fold endpoint and secondary 3-fold endpoint raised a major discussion within the Group.

As a consequence of the response to the first question it was felt that it is not possible to extrapolate from the ONTARGET study the indirect superiority of both ramipril and telmisartan vs. putative placebo.

The Co-rapporteur team emphasized that in view of the results from the TRANSCEND study it was impossible to quantify today the effect of ramipril as compared to placebo.

The bio-statistical experts felt that the confidence limits of non inferiority between ramipril and telmisartan were too wide. In addition experts in methodology stated that not adequate assay sensitivity makes it more likely to receive the results close to zero.

The majority of the experts of the SAG believed that there are no clinically important differences between ramipril and telmisartan however the assay sensitivity of the ONTARGET study was not adequate to demonstrate the absence of clinically important difference compared to ramipril.

It is important to mention that some experts believed that the non-inferiority to ramipril in the ONTARGET trial was demonstrated. They did not question the basis for the non-inferiority margin. They were of the opinion that the comparator ramipril showed a well established evidence for efficacy and safety in the HOPE trial. One of them also underlined that the confidence intervals of ONTARGET were well within the lower boundaries for efficacy.

Question 3

What is the relevance of the threefold as compared to the fourfold combined cardiovascular endpoints in the ONTARGET, TRANSCEND, and PRoFESS study in cardiovascular prevention in this application?

For the Co-rapporteur team and experts in methodology of clinical trials this issue was of particular concern because primary endpoint in TRANSCEND failed and they considered that in this case the secondary endpoint cannot be analysed because it was not pre-specified in the statistical programme. For this reason the biostatisticians considered the 3-fold secondary endpoint, although indeed identical

to the primary endpoint in HOPE study, not adequate for confirmatory conclusions from data of TRANSCEND. They strongly supported the Co-rapporteur's position that the post hoc exclusion of heart failure from the primary analysis in knowledge of the data is not appropriate irrespective of the claimed indication. In addition they mentioned that the results of the secondary endpoint can be valid only if the primary endpoint did not fail which was unfortunately neither the case in TRANSCEND nor in ONTARGET.

The chairman underlined that the main secondary end point was a pre-specified end point and asked to circulate amongst the experts a copy of the main manuscript of the ONTARGET published in the New England Journal of Medicine (NEJM). In this publication it was well stated that the main secondary end point was not a post-hoc analysis and that the ONTARGET showed a non inferiority of telmisartan vs. ramipril on the main 4 fold endpoint and on the main secondary (HOPE) endpoint. Therefore, he believed, that the comment that the results of the secondary end point cannot be evaluated had no scientific and methodological basis. The opinion was split and some experts strongly disagreed with this view.

The SAG wondered why the company used in the first place 4-fold endpoint instead of the endpoint used earlier in HOPE which would make the direct comparison easier. This had been explained earlier during the discussion by the company that stated that the 4-fold endpoint was introduced following the suggestion from an expert and was a basis for the FDA application during the scientific advice they have asked to that agency.

General opinion of clinical experts present in the room was that both endpoints were rather similar. Some experts mentioned however that although the 3-fold composite endpoint is clinically relevant, it is not as relevant as the 4-fold endpoint.

Question 4

Does the SAG consider the clinical studies sufficient to demonstrate that telmisartan improves all-cause mortality or cardiovascular mortality?

From a clinical perspective, taking the totality of the data into account, the view of the SAG was that there is a treatment effect, although it cannot be reliably estimated in terms of effect size as compared to placebo. Therefore, in the opinion of the majority of the Group, the undertaken studies do not show that telmisartan improves either all-cause mortality or cardiovascular mortality. It was noted however that mortality was only one of the variables of the combined end-point.

One of the clinical experts was of the opinion that the benefits for patients were not clearly established because the benefit is to be expected considerably smaller than in HOPE and the signals from the supporting studies are more disturbing than assuring. However, on the other hand SAG admitted that the use of telmisartan does not seem to result in any increase of cardiovascular mortality.

Therefore SAG member were of the opinion, given the above uncertainties, that telmisartan could be used for prevention of cardiovascular morbidity and mortality in patients 55 years or older at high risk of cardiovascular disease in patients who are intolerant to ACE-inhibitors.

Overall Benefit Risk Assessment

Following the assessment of all efficacy and safety data provided, the Committee considered that telmisartan showed a similar effect to ramipril in reducing the primary composite endpoint of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure in ONTARGET [incidence of the primary endpoint for telmisartan (16.7 %) and ramipril (16.5 %); the hazard ratio for telmisartan vs. ramipril was 1.01 (97.5 % CI 0.93 - 1.10, p (non-inferiority) = 0.0019 at a margin of 1.13)]. The all-cause mortality rate was 11.6% and 11.8% among telmisartan and ramipril treated patients respectively. Telmisartan was found to be similarly effective to ramipril in the pre-specified secondary endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.99 (97.5 % CI 0.90 - 1.08, p (non-inferiority) = 0.0004)], the primary endpoint in the reference study HOPE (The Heart Outcomes Prevention Evaluation Study), which had investigated the effect of ramipril vs. placebo.

Furthermore, although in the TRANSCEND study no statistically significant difference in the incidence of the primary composite endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure) was found (15.7% in the telmisartan and 17.0% in the placebo groups with a hazard ratio of 0.92 (95 % CI 0.81 - 1.05, p = 0.22)), there was evidence for a benefit of telmisartan compared to placebo in the pre-specified secondary composite endpoint of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke [0.87 (95% CI 0.76 - 1.00, p = 0.048)]. There was no evidence for benefit on cardiovascular mortality (hazard ratio 1.03, 95% CI 0.85 - 1.24).

The degree of reduction of cardiovascular risk has been influenced by concomitant medications, as the event rate reported by the HOPE trial are not longer seen in patients in primary prevention, at least in Europe. In this respect, the Committee took also into account the conclusions of the CV-SAG in particular regarding the constancy of the effect over time of the chosen comparator ramipril, i.e. that ramipril has an effect which is clinically relevant, but that the magnitude of the putative placebo treatment effect in ONTARGET cannot be reliably estimated. The majority of the CV SAG members felt that it was impossible to quantify the effect of ramipril and thereby decide where to put the non-inferiority margin for ONTARGET. Consideration was given to the fact that the constancy of the effect can not be proven by the submitted data. It was discussed that the effect achievable by this group of agents in general might be lower than at the time of the conduct of the HOPE study. The results of the ramipril arm of the ONTARGET confirmed that the reduction of the overall cardioprotective effect of ramipril was related to a reduction in the overall risk. In this respect, the Committee also took the overall available experience with ACE inhibitors and ARBs into account.

The safety profile for the new patient population is consistent with the known profile of telmisartan. Cough and angioedema were less frequently reported in patients treated with telmisartan than in patients treated with ramipril, whereas hypotension was more frequently reported with telmisartan. There was significantly less discontinuation of telmisartan than both ramipril and placebo in ONTARGET and TRANSCEND, respectively.

Thus, following the overall assessment of the submitted efficacy and safety data and based on the outcome of the SAG meeting, the CHMP concluded that the benefit-risk ratio of telmisartan is positive with regard to the following indication in SPC section 4.1:

Cardiovascular Prevention

Reduction of cardiovascular morbidity in patients with:
i) manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or
ii) type 2 diabetes mellitus with documented target organ damage approvable.

All the proposed consequential changes to SPC sections 4.2, 4.4, 4.8 and 5.1 as well as the package leafet have been agreed. In addition, Annex II has been updated to reflect the latest RMP version as agreed by the CHMP. The full product information can be found in attachment 1.

2. Conclusion

On 22 October 2009 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

Follow-up measures undertaken by the Marketing Authorisation Holder
As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Area	Description	Due date
Pharmaco-vigilance	The MAH commits to submit a revised RMP reflecting the final agreed indication	5 November 2009