Micardis® (Telmisartan)

Cardiovascular and Renal Drugs
Advisory Committee Briefing Document

Meeting date: 29 July 2009

1.0 EXECUTIVE SUMMARY

1.1 INTRODUCTION

Telmisartan, an angiotensin receptor blocker (ARB), was approved by the US Food and Drug Administration (FDA) in 1998 for the treatment of hypertension. It is marketed as MICARDIS tablets in over 80 countries.

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) has submitted a supplemental New Drug Application (sNDA) providing information to support the use of MICARDIS tablets for reducing the risk of cardiovascular (CV) events in patients 55 years or older at high risk of developing major CV events.

1.2 EXPERIENCE FROM OUTCOME CLINICAL TRIALS

Multiple trials in the 1980s and 1990s examined the CV protective effects of angiotensin converting enzyme inhibitors (ACE-Is) in patients with left ventricular (LV) dysfunction and/or overt heart failure. The ACE-I Myocardial Infarction Collaboration Group analyzed individual data from the 12,763 patients in the SAVE, AIRE, TRACE and SOLVD trials. Significant CV benefits for ACE-I on mortality, myocardial infarction (MI) and hospitalization for congestive heart failure (CHF) were demonstrated in patients with left ventricular (LV) dysfunction and/or heart failure, with or without prior MI (Flather et al., 2000). The Heart Outcomes Prevention Evaluation (HOPE) was a landmark study from the 1990s that showed major CV events could be prevented in a broader group of patients. In HOPE, the ACE-I ramipril reduced the incidence of the 3-fold composite endpoint of MI, stroke, and CV death by 22% compared to placebo in patients who were at least 55 years of age with a history of either coronary artery disease, stroke, peripheral vascular disease or diabetes plus at least one other CV risk factor. These results changed guidelines and led to a new indication for ramipril for reduction in the risks of MI, stroke, or death from CV causes.

Despite the well-established cardioprotective benefits of ACE-Is, their use is limited by the frequent occurrence of adverse reactions. Dry cough (up to 39%) and potentially life-threatening angioedema (0.1-1.0%) occur in patients on ACE-Is (Israili et al., 1992). CV outcome studies comparing ACE-Is and ARBs (ELITE II, OPTIMAAL and VALIANT) have consistently demonstrated significantly fewer patients on ARBs discontinue treatment due to AEs. In clinical practice, adherence to antihypertensives is worse than in trials, and also in the practice setting adherence to ARBs is better than ACE-I (Wogen et al., 2003; Siiskonen et al., 2007). Additionally, in an HMO setting (Ho et al., 2007), non-adherence to ACE-I and other medications was evaluated over a median 4.1 year observation time in patients with coronary artery disease. Non-adherence to ACE-I and other medications was present in about 25% of such patients and was associated with significantly increased risks for all-cause mortality, CV mortality, hospitalization for MI or CHF (hazard rations of 1.32 to 1.74). Although ACE-I have proven CV benefits, issues with their tolerability in the clinical practice setting prompted BI to plan a clinical research program with telmisartan, an ARB with placebo-like tolerability.

The Investigators at the Population Health Research Institute (PHRI) designed and executed the HOPE trial. Consequently, BI collaborated with PHRI and over 700 Investigators worldwide to test 2 hypotheses in the ONTARGET trial: (1) telmisartan, an ARB, is as

effective (i.e., non-inferior) in reducing the risk of CV events in patients at CV risk compared to an ACE-I, and (2) dual renin-angiotensin-aldosterone system (RAAS) blockade by the combination of telmisartan and ramipril is more effective in reducing the risk of CV events than an ACE-I. The key secondary endpoint was the 3-fold composite of CV death, non-fatal MI, and non-fatal stroke, since it had been the primary endpoint in HOPE. ONTARGET was a large, randomized, parallel group, double-blind outcome trial that started in 2001. Ramipril was selected as the reference therapy based upon the HOPE results. Telmisartan was selected because of its pharmacologic properties (high receptor binding), long duration of effect, and especially placebo-like tolerability that could result in better medication adherence than an ACE-I. Both ONTARGET and TRANSCEND (placebo controlled comparison with placebo in ACE-I intolerant patients) evaluated CV outcomes on top of current guideline recommended background therapies. Patients were enrolled at least 30 days after percutaneous coronary intervention (PCI) or stable or unstable angina and at least 4 years following CABG surgery. A non-inferiority margin for ONTARGET was selected that was identical to the margin selected for VALIANT (1.13), which resulted in an FDA approval for valsartan to reduce CV mortality in post-MI patients with left ventricular dysfunction. Similar to VALIANT, this margin assured that at least 51% for the 4-fold and 68% for the 3-fold endpoints of the effect of ramipril on CV outcomes would be preserved.

In addition, BI initiated PRoFESS 2 years after the start of ONTARGET. PRoFESS was a 2x2 factorial study testing whether telmisartan was superior to placebo in reducing recurrent strokes in patients on anti-platelet therapy (combination of ASA and dipyridamole or clopidogrel). PRoFESS enrolled a different population than ONTARGET. Patients were enrolled soon after a stroke (40% within 10 days and 69% within 30 days), which had not been done in other stroke prevention studies and had almost one third Asians.

ONTARGET, TRANSCEND and PRoFESS were well designed trials, utilizing proven approaches to ensure the validity of the results and to protect patient safety. There was complete follow-up in >99% of patients in the 3 studies. There was central adjudication of all components of the primary endpoint by independent committees blinded to individual patient treatment allocations. There were Data Safety Monitoring Boards (DSMBs) that met regularly to ensure patient safety. All publications were generated by the members of the Academic Steering Committees of each study.

1.3 EFFICACY RESULTS

The primary endpoint of ONTARGET and TRANSCEND was a 4-fold endpoint of CV death, non-fatal MI, non-fatal stroke, or hospitalization for CHF. This endpoint was utilized since pooled analyses of studies of ACE-I had suggested they produced a benefit in reducing heart failure hospitalizations, although the available studies mainly enrolled patients with LV dysfunction, a group that was underrepresented in ONTARGET and TRANSCEND due to exclusion of patients with symptomatic heart failure.

1.3.1 ONTARGET

A total of 25,620 patients 55 years of age or older at high risk of developing a major CV event were randomized to ramipril, telmisartan or telmisartan and ramipril. The entry criteria used were similar to those in HOPE and included a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes and at least one other CV risk factor (hypertension,

elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria). Patients were enrolled at least 30 days after PCI or stable or unstable angina and at least 4 years after CABG surgery. The median follow-up was 4.6 years The two most important results of ONTARGET are: (1) telmisartan was non-inferior to ramipril (Table 1.3.2:1 below) and better tolerated, (2) dual RAAS blockade provided no better CV risk reduction but had a worse safety profile.

The data demonstrate a consistent and comparable effect of telmisartan compared to ramipril for virtually all subgroups (for example: age, gender, race, geographical region, concomitant medication use, presence of hypertension, and presence of diabetes). There was little impact of both baseline BP and BP changes from baseline on the results using a Cox regression analysis. Additional analyses showed the use of statins significantly reduced rates of MI, however, there was no interaction between statin use and treatment (telmisartan and ramipril) so that telmisartan was equally effective as ramipril whether or not a statin was co-administered. This analysis also was performed for use of beta blockers. Similarly, hospitalization for heart failure was reduced by beta blockers; again there was no beta blocker-by-treatment interaction. Therefore telmisartan was similar to ramipril whether or not a beta blocker was administered.

1.3.2 TRANSCEND

TRANSCEND was designed to test if telmisartan is superior to placebo in reducing CV events in ACE-I intolerant patients. This patient population had never been studied in a controlled outcome study. Patients in TRANSCEND differed from those in ONTARGET in numerous ways including having more females (43% vs. 27%), fewer diabetics with micro- or macroalbuminuria (6% vs. 11%) and less insulin use (7% vs. 10%), more regular diuretic (54% vs. 45%) and dihydropyridine (51% vs 31%) use. TRANSCEND randomized patients 55 years of age or older at high risk of developing a CV event to telmisartan (n=2954) or placebo (n=2972). The median follow-up was 4.8 years. The primary (4-fold) and key secondary endpoints (3-fold) were identical with ONTARGET. The main results are presented in Table 1.3.2:1. The primary endpoint was not met.

Table 1.3.2:1 ONTARGET and TRANSCEND ITT analyses

ONTARGET ITT analysis	Telmisartan		Ramipril	
Randomized, n (%)	8542	(100.0)	8576	(100.0)
4-fold endpoint[1], n (%)	1423	(16.7)	1412	(16.5)
CV death	367	(4.3)	373	(4.3)
Non-fatal MI	399	(4.7)	372	(4.3)
Non-fatal stroke	322	(3.8)	377	(4.4)
Hospitalization for CHF	353	(4.1)	312	(3.6)
Events per 100 patient years	3.87		3.82	
Hazard ratio[2] vs. ramipril; 97.5% CI[3]	1.01 (0.93, 1.10)			
p-value (non-inferiority, one-sided)	0.0019			
3-fold endpoint, n (%)[1]	1190	13.9	1210	14.1
CV death	438	(5.1)	448	(5.2)
Non-fatal MI	419	(4.9)	389	(4.5)
Non-fatal stroke	347	(4.1)	389	(4.5)
Events per 100 patient years	3.18			
Hazard ratio[2] vs. ramipril; 97.5% CI[3]	0.99(0.90, 1.08)			
p-value (non-inferiority, one-sided)	0.004			
TRANSCEND ITT Analysis	Telmisartan		Placebo	
Randomized, n	2954	(100.0)	2972	(100.0)
4-fold endpoint[1], n (%)	465	(15.7)	504	(17.0)
CV death	140	(4.7)	137	(4.6)
Non-fatal MI	106	(3.6)	136	(4.6)
Non-fatal stroke	106	(3.6)	127	(4.3)
Hospitalization for CHF	123	(4.2)	112	(3.8)
Events per 100 patient years	3.58		3.87	
Hazard ratio[2] vs. placebo; (95% CI)	0.92 (0.81, 1.05)			
p-value[4]	0.22			
3-fold endpoint[1], n (%)	384	(13.0)	440	(14.8)
CV death	169	(5.7)	170	(5.7)
Non-fatal MI	111	(3.8)	138	(4.6)
Non-fatal stroke	111	(3.8)	136	(4.6)
Events per 100 patient years	2.90		3.33	
Hazard ratio2 vs. placebo; 95% CI	0.87 (0.76, 1.00)			
p-value[4]	0.049			

[1] First occurrence, if simultaneous events, all individual events were considered, so the sum of the individual outcomes may exceed the overall number of patients.
[2] Cox regression
[3] To address multiciplicty, the 97.5 CI (one-sided) was used for determining p-value.
[4] 3- and 4-fold endpoints are 2-sided p-value. The 3-fold is a nominal p-value with no adjustment.
Source: Adapted from ONTARGET CTR Table 11.4.1.1.1: 1 and Table 11.4.1.2.1.1 and TRANSCEND CTR Table 11.4.1.1: 1

Analyses showed consistency of effect for the 3- and 4-fold endpoints for telmisartan compared to ramipril for virtually all subgroups (i.e., age, gender, race, geographical region, concomitant medications, presence of hypertension, and presence of diabetes). Reductions by telmisartan therapy of non-fatal stroke and non-fatal MI had the largest contribution to the benefit of telmisartan. As was done in ONTARGET sensitivity analyses were performed to assess the affect of blood pressure on outcomes and the results showed a modest impact similar in magnitude to ONTARGET. Analyses on the effects of statin and beta blocker use also showed no treatment interaction, although as expected these agents reduced the occurrence of heart attacks and hospitalization for CHF, respectively

1.4 DISCUSSION AND SUMMARY OF EFFICACY RESULTS

The telmisartan/ramipril combination was not superior to telmisartan or ramipril alone and had a worse safety profile. For example there were increased incidences of hypotensive symptoms, syncope, hyperkalaemia, and renal dysfunction in patients treated with the combination.

The point estimate of the hazard ratio (telmisartan/ramipril) in ONTARGET was extremely close to 1.00 and it was concluded that telmisartan was non-inferior to ramipril for the 4-fold (HR 1.01; 97.5% CI 0.93, 1.10) and 3-fold (HR 0.99; 97.5% CI 0.90, 1.08) endpoints because the protocol-specified non-inferiority margin for the hazard ratio (1.13) was met. Similar to VALIANT, the design of ONTARGET guaranteed that if the NI margin was met for the primary endpoint, at least 51% of the estimated effect of ramipril was preserved (based on an imputed placebo effect of ramipril from the HOPE trial). Of interest, FDA recommended a non-inferiority margin of 1.085. The 3-fold endpoint, with an upper bound of 1.08 for the 97.5% confidence limit met that margin; however, the 4-fold endpoint narrowly missed it with an upper bound limit of 1.10. Further supporting the protocol specified non-inferiority margin, the estimate of the effect of ramipril (based on a pooled analysis of 3 recent studies of ACE-I in patients not required to have LV dysfunction) was similar to that from the HOPE study alone (see Section 4.2), which supports the correctness of the point estimate of the effect of ramipril observed in HOPE and used to develop the protocol specified NI margin in ONTARGET.

The results from ONTARGET demonstrate that telmisartan preserved about 95% (95% CI, 66, 124) of the benefits of ramipril over placebo with respect to the 4-fold endpoint, and preserved 105% (95% CI, 74 to 137) of the benefits with respect to the 3-fold outcome based on a 'putative' placebo comparison using the point estimate (Hasselblad et al., 2001) from the HOPE study. Thus, according to the CI from this calculation, telmisartan preserves at least 2/3 of ramipril's effect for the 4-fold endpoint and 3/4 for the 3-fold endpoint.

Two pieces of additional evidence support the use of telmisartan for CV risk reduction:

1. TRANSCEND demonstrated telmisartan resulted in fewer adverse CV outcomes than placebo for the 3-fold endpoint with a 13% risk reduction and a nominal p-value below 0.05. These effects were limited to reducing stroke and MI in a population different from ONTARGET. The modest benefit of telmisartan in TRANSCEND, conducted in a different population than ONTARGET and HOPE, is supportive of the demonstration of non-inferiority of telmisartan compared to ramipril in ONTARGET and indicates that the drug provides some clinical benefit even in the ACE-I intolerant population.

The effect of telmisartan on CHF may have been masked by an increased use of diuretics in the placebo group. The analysis of the combined outcome "New CHF or addition of diuretics" revealed a clear difference between patients treated with telmisartan and placebo (HR = 0.80, 95% CI 0.72, 0.89; p = 0.0001) which impacted the primary endpoint results.

2. A pooled analysis (patients not using ACE-Is in PRoFESS and TRANSCEND) of placebo-controlled data was performed in patients not at risk of worse safety outcomes because of dual RAAS blockade. In this population at high-risk of the occurrence of stroke and MI, the 3-fold endpoint showed a 10% risk reduction by telmisartan compared to placebo. An Investigator generated analysis of these pooled data suggested greater benefit for observations beyond 6 months. Details of the pooled analysis are described in greater detail in the body of the Briefing Document.

The data from this well designed and executed clinical research program demonstrates that telmisartan reduces the occurrence of CV events in high risk patients, predominantly strokes and MIs. The data showed consistency of telmisartan's effects across all major subgroups in all studies and no treatment by subgroup interaction in virtually all subgroups. Specifically, analyses were performed demonstrating the use of statins and beta blockers, which have been shown to improve CV outcomes, did not affect the ability to demonstrate non-inferiority. Results for the 3-fold endpoint are consistent across both populations, those tolerant of ACE-I and those intolerant of ACE-I. High-risk ACE-I intolerant patients without overt heart failure have no available proven therapeutic alternative RAAS blocking agent.

In conclusion, this well designed and conducted clinical research program of contemporaneous trials generated data from over 50,000 patients assessed the effects of telmisartan in reducing CV outcomes in patients at high risk for their occurrence. The results demonstrated that telmisartan provides incremental benefit for the reduction of CV events (i.e., MI and stroke) in contemporary medical practice. Telmisartan can provide an alternative therapy that preserves the benefit of the current standard of care (ramipril) in high risk patients

1.5 SAFETY

Data from these outcome studies showed the safety profile of telmisartan was consistent with the product label for telmisartan and that known for this class of drug.

Over 99% of patients in the outcome studies were followed until either completion of the trials or death occurred. The study treatments in these trials were given on top of standard of care medications.

Safety data of the combination therapy of telmisartan and ramipril are not presented in detail because this treatment was associated with a less favorable safety profile than both monotherapies without any additional efficacy benefits. For example there were increased incidences of hypotensive symptoms, syncope, hyperkalaemia, and renal dysfunction in patients treated with the combination.

In ONTARGET, telmisartan was better tolerated than ramipril. Permanent discontinuation of active telmisartan was significantly less than active ramipril, with a hazard ratio of 0.90 (p=0.0008). For permanent discontinuations of active treatment due to AEs, the hazard ratio was 0.79 (p <0.0001). Cough and angioedema more frequently resulted in treatment

discontinuation for ramipril, despite the fact that 58% of ONTARGET patients had previously regularly taken ACE-Is before study entry and there was a run-in period which screened out more ACE-I intolerant patients.

Dry cough (up to 39%) and potentially life-threatening angioedema (0.1-1.0%) occur in patients on ACE-Is (Israili et al., 1992). CV outcome studies comparing ACE-Is and ARBs (ELITE II, OPTIMAAL and VALIANT) have consistently demonstrated significantly fewer patients on ARBs discontinue treatment due to AEs. During the run-in period of ONTARGET, cough (1.08%) and angioedema (0.14%) as well as during the randomized period were reported as reasons for study discontinuation. These rates are much lower than would be expected in practice because 58% of the ONTARGET patients were previous regular users of ACE-I. Published literature reports that compliance rates diminish over time. Notably, non-compliance with ACE-I in patients with coronary artery disease has been shown in an HMO setting to be associated with more deaths and CV events (Ho et al., 2008).

Patients with lower baseline blood pressures were more susceptible to developing hypotensive symptoms or syncope. Hypotension is listed in telmisartan's label.

The renal findings are consistent with inhibition of the RAAS. In ONTARGET, dual RAAS blockade led to a higher frequency of adverse events. As a result, a precaution has been added (pending FDA approval) to the prescribing information for telmisartan.

An unexpected increased incidence of sepsis events was observed across the three outcome trials. Analyses revealed that known risk factors for sepsis were observed and predictive in these studies. Treatment was not identified as a significant predictive factor in ONTARGET and TRANSCEND, although it was in PRoFESS. It is not clear whether the increase in sepsis is real or occurred by chance, as a review of the literature does not indicate an excess of sepsis in other trials of ARBs or ACE-Is or identify a likely mechanism. Despite this, the Sponsor has taken the decision to add the risk of sepsis with possibly fatal outcomes to the prescribing information for telmisartan.

There was an increased incidence of malignancies in the telmisartan/ramipril combination arm in ONTARGET. There was an inconsistent pattern in the malignancy data in the other two trials. In the larger PRoFESS study, malignancies occurred more frequently in the placebo arm, while in TRANSCEND the reverse was the case. Clinical and preclinical data with telmisartan and other ARBs do not support mutagenic or carcinogenic potential of ARBs. The Sponsor does not believe that telmisartan leads to an increased risk of malignancies.

In conclusion, the safety profile of telmisartan is consistent with the current label as well as with earlier clinical and post-marketing experience.

1.6 RISK/BENEFIT

The clear demonstration of non-inferiority of telmisartan to ramipril in ONTARGET and the nominally significant reduction relative to placebo in the composite of CV death, MI and stroke in TRANSCEND establish the benefit of telmisartan in patients at high risk for CV events. Telmisartan is effective as it unequivocally preserved at least 51% on the 4-fold and 68% on the 3-fold endpoints of ramipril's effect. The other secondary endpoints were

consistent with this conclusion. The data suggest that telmisartan reduces the rate of MI and stroke, but it has no effect on hospitalization for heart failure.

The risk-benefit for telmisartan in reducing the risk of stroke and MI in high risk patients is favorable and compares well to the risk-benefit of the gold standard ramipril. In the clinical practice setting it has been demonstrated that adherence to ARBs is much better than ACE-Is. In ONTARGET medication adherence to telmisartan was better than ramipril despite the exclusion of ACE-I intolerant patients and the use of a run-in period which eliminated many patients who could not tolerate ramipril. Importantly, excess mortality (hazard ratio 1.74) has been reported from a retrospective cohort study in a HMO setting using data from patients with known coronary-artery disease who were not adherent to ACE-Is (median follow up 4.1 years, comparable to ONTARGET). The better tolerability and adherence of telmisartan compared to ramipril can provide a greater benefit in clinical practice and provide public health benefits. Inclusion of this information in the telmisartan label could provide an additional option for improved individualized therapy within current guideline-driven US clinical practice.

In conclusion, the aggregate data demonstrate that telmisartan provides incremental benefit for patients at high risk of CV events (i.e., MI and stroke) in contemporary medical practice. Telmisartan provides a better tolerated treatment option that also preserves the benefit of the current standard of care (ramipril) in high risk patients.

TABLE OF CONTENTS

Page

LIST OF ABBREVIATIONS

AAC	Adjudication and Assessment Committee (PRoFESS)
ACE	Angiotensin Converting Enzyme
ACE-I	Angiotensin Converting Enzyme Inhibitor
AE	Adverse Event
AF	Atrial Fibrillation
ANCOVA	Analysis of Covariance
ARB	Angiotensin Receptor Blocker
ARISg	BI Adverse Reaction Information System, global
ASA	Acetylsalicylic Acid/ Aspirin
AUC	Area Under the plasma Concentration curve
BI	Boehringer Ingelheim
BIPI-DSI	Boehringer Ingelheim Pharmaceuticals Inc - Department of Drug Safety and Information
BMI	Body Mass Index
BL	Baseline
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CHARM	Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity trial
CAD	Coronary artery disease
CHF	Congestive Heart Failure
CCB	Calcium Channel Blocker
CI	Confidence Interval
CK-MB	Plasma Creatine Kinase Muscle-Brain fraction
C_{max}	Maximum measured concentration
Cr	Creatinine
CRF	Case Report Form
CPMP	Committee for Proprietary Medicinal Products
CT	Computerised Tomography
CTD	Common Technical Document
CV	Cardiovascular
CVA	Cerebral Vascular Accident
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DCRP	The Division of Cardiovascular and Renal Products
Del	Delix®
DMC	Data Monitoring Committee (PRoFESS)
DSMB	Data Safety Monitoring Board
EAC	Event Adjudication Committee
ECG	Electrocardiogram
EOT	End Of Trial
ESRD	End Stage Renal Disease
EU	European Union
FAS	Full Analysis Set
FDA	US Food and Drug Administration
FDC	Fixed Dose Combination
FPC	Final Patient Contact
FPI	First Patient In
eGFR	Estimated Glomerular Filtration Rate
GI	Gastrointestinal
gMean	Geometric mean
Hb1Ac	Haemoglobin 1Ac
HDL	High Density Lipoprotein
HOPE	Heart Outcomes Prevention Evaluation study

HR	Hazard Ratio
ICH	International Conference on Harmonisation
IEOVC	International External Outcome Validation Committee
IND	Investigational New Drug
ISF	Investigator Site File
ITT	Intent to Treat
JNC VI	The Sixth Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure
LBBB	Left Bundle Branch Block
LDL	Low Density Lipoprotein
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LPO	Last Patient Out
LV	Left Ventricle / Ventricular
LVEF	Left Ventricular Ejection Fraction
LVH	Left Ventricular Hypertrophy
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MI	Myocardial Infarction
Mic	Micardis®
MRI	Magnetic Resonance Imaging
N.A	Not Applicable
NI.	Non inferiority
NSAID	Non-Steroidal Anti-Inflammatory Drug
ODVE	Other Designated Vascular Events
OGTT	Oral Glucose Tolerance Test
ONTARGET	Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PBO	Placebo
PCSA	Possibly Clinically Significant Abnormalities
Pat. No(s).	Patient Number(s)
PCI	Percutaneous Coronary Intervention
PEN	PENultimate visit
PHRI	Population Health Research Institute
p.o.	Per os (by mouth)
PPS	Per Protocol Set
PR	Pulse Rate
PRoFESS	Prevention Regimen For Effectively avoiding Second Strokes
PT	Preferred Term
PTCA	Percutaneous Transluminal Coronary Angioplasty
PY	Patients with event per 100 patient years
R	Ramipril
RAAS	Renin-Angiotensin-Aldosterone System
RAN	Randomized Set
RBBB	Right Bundle Branch Block
RIS	Run-In Set
RR	Risk ratio
SAE	Serious Adverse Event
SAVE	Survival And Ventricular Enlargement trial
SBP	Systolic Blood Pressure
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard Deviation
SGOT (AST)	Serum Glutamate-Oxaloacetate-Transaminase (Aspartate Aminotransferase)
SGOT (ALT)	Serum Glutamate-Pyruvate-Transaminase (Alanine Aminotransferase)
SOLVD	Study of Left Ventricular Dysfunction
sNDA	Supplemental New Drug Application

SOC	System Organ Class
SRE	Sepsis Related Event
T	Telmisartan
TDC	Trial Data Center
TIA	Transient Ischemic Attack
T/R	Telmisartan + Ramipril
TRANSCEND	Telmisartan Randomized AssessmeNt Study in aCE iNtolerant patients with cardiovascular Disease
TS-B	Treated set B (patients who received at least 1 dose of telmisartan in PRoFESS)
UACR	Urine Albumin Creatinine Ratio
ULN	Upper Limit of Normal
VF	Ventricular Fraction
WBC	White blood cell count

2.0 INTRODUCTION

Micardis (telmisartan) was approved for the treatment of hypertension in the European Union (EU) and in the United States in 1998. Currently telmisartan is approved for this indication in more than 80 countries.

Boehringer Ingelheim Pharmaceuticals, Inc. has conducted a large clinical research program evaluating the effects of telmisartan in preventing cardiovascular morbidity and mortality, which is recognized as a major public health burden throughout the world (Lopez et al, 2006).

The totality of the data from a clinical research program in over 50,000 patients with approximately 180,000 years of exposure supports a modification of labeling, which can provide health care providers an additional option in their therapeutic armamentarium to reduce the risk of stroke and myocardial infarction.

The renin-angiotensin-aldosterone system (RAAS) plays an important role in all phases of the cardiovascular disease continuum (Dzau et al, 2006; Stoll et al, 1995)]. 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 that are involved in the development of atherosclerosis and the occurrence of acute coronary syndromes (Ohkubo el al, 1997; Navalkar et al, 2001). The effects of angiotensin II can be attenuated by blocking the angiotensin II subtype 1-receptors using an angiotensin receptor blocker (ARB) or by inhibiting the angiotensin converting enzyme using an angiotensin converting enzyme inhibitor (ACE-I).

Multiple trials in the 1980s and 1990s examined the cardiovascular protective effects of ACE-Is in patients with LV dysfunction and/or overt heart failure. The ACE-Inhibitor Myocardial Infarction Collaboration Group performed an overview of individual data from the 12,763 patients in the SAVE, AIRE, TRACE and SOLVD trials. Significant cardiovascular outcome benefits for ACE-I on mortality, myocardial infarction and hospitalization for CHF were demonstrated in patients with LV dysfunction and/or heart failure, with or without a previous myocardial infarction (Flather et al., 2000). The Heart Outcomes Prevention Evaluation (HOPE) was a landmark study conducted in the 1990s that showed CV outcomes could be prevented in a broader population of patients. In the HOPE study, the angiotensin converting enzyme inhibitor (ACE-I) ramipril reduced the incidence of a 3-fold composite endpoint of MI, stroke, and death due to cardiovascular causes (CV death) by 22% compared to placebo in patients at least 55 years of age with a history of either coronary artery disease, stroke, peripheral vascular disease or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated cholesterol, low HDL cholesterol, smoking or documented microalbuminuria). The results of this study supported a new indication for ramipril tablets, specifically; reduction in the risk of myocardial infarction, stroke, and death from cardiovascular causes and resulted in changes in guidelines for the treatment of at risk patients.

Despite the well established cardioprotective benefits of ACE-Is, their use is limited by the frequent occurrence of treatment-related adverse drug reactions. As many as 39% of patients receiving ACE-Is have reported dry cough, and 0.1% to 1.0% of ACE-I exposed patients

have reported angioedema (Israili et al, 1992). Cardiovascular outcome studies comparing ACE-Is and ARBs (ELITE II, OPTIMAAL and VALIANT) have consistently demonstrated significantly fewer patients in the ARB group compared to the ACE-I group discontinue treatment because of AEs. In clinical practice, the adherence to ACE-I and other antihypertensives is worse than that observed in trials, and similarly in this setting adherence to ARBs is better than ACE-I (Wogen et al., 2003; Siiskonen et al., 2007). Finally, in an HMO setting (Ho et al., 2007), non-adherence to ACE-I and other medications was evaluated over a median 4.1 year observation time in patients with prior PCI, myocardial infarction or coronary artery bypass graft surgery. Non-adherence to ACE-I was present in about 25% of such patients and was associated with significantly increased risks for all-cause mortality, cardiovascular mortality, hospitalization for myocardial infarction or heart failure and coronary revascularization procedures (hazard rations between 1.32 and 1.74). Although ACE-I have proven cardiovascular benefits, their potential liabilities, especially in the clinical practice setting, prompted Boehringer Ingelheim to plan a clinical research program with telmisartan, an ARB with placebo-like tolerability.

Several outcome studies with ACE-Is and ARBs have consistently demonstrated benefit in preventing cardiovascular outcomes, including stroke and MI. The results of these studies led to the inclusion of labeling for cardiovascular risk reduction.

3.0 TELMISARTAN

3.1 OVERVIEW

The approval of telmisartan for the treatment of hypertension was based on multiple placebo-controlled studies with doses ranging from 20 mg to 160 mg in patients with mild to moderate hypertension. The trials for the initial indication assess safety in more than 3700 patients.

3.2 PHARMACOLOGIC CLASS AND MECHANISM OF ACTION

Telmisartan is an orally active, non-peptide angiotensin II receptor blocker (ARB) that blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II. It selectively blocks the binding of angiotensin II to the AT1 receptor in many tissues.

3.3 PHARMACOKINETICS AND PHARMACODYNAMICS

Following oral administration, peak concentrations (Cmax) of telmisartan are reached in 0.5 to 1 hour after dosing. The absolute bioavailability of telmisartan is dose dependent. At 40 and 160 mg, the bioavailability is 48% and 58%, respectively. The pharmacokinetics of orally administered telmisartan are nonlinear over the dose range of 20 mg to 160 mg, with greater than proportional increases of plasma concentrations (Cmax and AUC) with increasing doses. Telmisartan has a terminal elimination half life of approximately 24 hours.

3.4 CLINICAL EXPERIENCE IN HYPERTENSION

Telmisartan reduces blood pressure after the first dose, with a maximum reduction observed by approximately 4 weeks. This effect of telmisartan is not influenced by patient age, gender, weight, or body mass index. Consistent with data on other ACE-Is and ARBs, blacks experience less blood pressure lowering than whites.

The magnitude of blood pressure reduction from baseline after placebo subtraction is approximately (SBP/DBP) 6-8/6 mmHg for 20 mg, 9-13/6-8 mmHg for 40 mg, and 12-13/7-8 mmHg for 80 mg. Studies have shown that the antihypertensive effect is maintained for the full 24 hour dose interval.

In placebo-controlled studies of doses of 20 to 160 mg of telmisartan, the overall incidence of AEs was similar to that of placebo. Adverse events (AEs) were generally mild to moderate in severity and only infrequently led to discontinuation of therapy. The incidence of cough occurring with telmisartan in was the same as reported in patients in the placebo group (1.6%).

AEs that occurred at ≥1% of telmisartan (T) patients and at a higher rate than among patients on placebo (P) included upper respiratory tract infection (T 7%; P 6%), back pain (T 3%; P 1%), sinusitis (T 3%; P 2%), diarrhea (T 3%; P 2%), and pharyngitis (T 1%; P 0%). The following other events occurred at a rate of 1% but were at least as frequent in the placebo group: influenza-like symptoms, dyspepsia, myalgia, urinary tract infection, abdominal pain, headache, dizziness, pain, fatigue, coughing, hypertension, chest pain, nausea, and peripheral edema.

Post-marketing adverse reactions described in the US prescribing information for telmisartan include hypotension (including postural hypotension), hyperkalemia, syncope, and renal impairment including acute renal failure. Similar types of reactions have been seen with other ACEIs and ARBs. BI has made additional label modifications, based on the results of the clinical research program; these are under review by the FDA and are discussed later in this document.

4.0 CLINICAL DEVELOPMENT PROGRAM FOR CARDIOVASCULAR RISK REDUCTION

4.1 BACKGROUND

4.1.1 Evidence-based medicine up to 2000 (prior to start of ONTARGET)

ACE-Is had shown improved cardiovascular outcomes in a series of studies starting in 1987. Patients with severe heart failure treated with enalapril lived longer than placebo- treated patients (CONSENSUS [Swedberg K, 1987]). Subsequently, a series of studies with similar methodology evaluated the effects of multiple ACE-Is in patients with systolic dysfunction (LVEF ≤ 0.40) following myocardial infarctions. All studies demonstrated benefit on CV outcomes (enalapril – (SOLVD) (The SOLVD Investigators, 1992), captopril - (SAVE) (Pfeffer et al., 1992), ramipril - (AIRE) (AIRE study Investigators, 1993), trandolapril - (TRACE) (Kober et al., 1995), and zofenopril - (SMILE) (Ambrosioni et al., 1995).

The ACE-Inhibitor Myocardial Infarction Collaboration Group performed an analysis of the individual 12,763 patient data from the SAVE, AIRE, TRACE and SOLVD trials. Significant cardiovascular outcome benefits for ACE-I on mortality, myocardial infarction and hospitalization for CHF were demonstrated in patients with LV dysfunction and/or heart failure, with or without a previous myocardial infarction (Table 4.1.1: 1) (Flather et al., 2000).

Table 4.1.1: 1 Pooled results of ACE inhibitor trials in patients with systolic dysfunction*

	EVENTS		OR (95% CI)	p-value
	ACE Inhibitor (N=6,391)	Placebo (N= 6,372)		
Death	1467 (23.0%)	1710 (26.8%)	0.80 (0.74-0.87)	<0.0001
Reinfarction**	571 (8.9%)	703 (11.0%)	0.79 (0.70-0.89)	0.0001
Readmission for CHF	876 (13.7%)	1202 (18.9%)	0.67 (0.61-0.74)	<0.0001
Stroke	239 (3.7%)	249 (3.9%)	0.96 (0.80-1.15)	0.63
Death or reinfarction	1725 (27.0%)	2043 (32.1%)	0.77 (0.72-0.84)	<0.0001
Death or readmission for CHF	1962 (30.7%)	2354 (36.9%)	0.74 (0.69-0.80)	<0.0001
Death/MI/or readmission for CHF	2161 (33.8%)	2610 (41.0%)	0.72 (0.67-0.78)	<0.0001
Death/MI/Stroke/readmission for CHF***	2285 (35.8%)	2705 (42.5%)	0.74 (0.69-0.80)	<0.0001

*(SAVE, AIRE, TRACE, SOLVD). CHF = congestive heart failure; MI - myocardial infarction.
**If only the adjudicated MI events from SAVE are included, the odds ratio is 0.83 (95% CI 0.71-0.98) for SAVE, AIRE, and TRACE and 0.81 (0.72-0.91) for all trials.
***Additional analysis, not in original paper.
Source: Adapted from Flather et al., 2000

The HOPE (**H**eart **O**utcomes **P**revention **E**valuation) study, conducted in the late 1990s, compared ramipril to placebo in 9,927 patients at high risk for the occurrence of major cardiac outcome events. HOPE, the first prospective large scale outcome study in this patient

population, demonstrated that ramipril could prevent cardiovascular outcome events in a high risk population both with and without antecedent cardiovascular events. The trial showed clinical benefit in patients with no heart failure at baseline (The HOPE Study Investigators, 1996; 2000a; 2000b; Sleight P., 2000). In this study, ramipril demonstrated a statistically significant 22% risk reduction on the primary 3-fold composite endpoint of CV death, MI or stroke. These results are very consistent with the results from the earlier ACE inhibitor trials of patients with CHF or LV dysfunction, as summarized in Table 4.1.1: 2; however, HOPE should less benefit on hospitalization for heart failure when an ACE-I was studied in patients without documented low LVEF or symptomatic heart failure at study entry. It should be noted that in HOPE publication, the CHF endpoint was adjudicated in a somewhat different manner than primary efficacy endpoint.

Table 4.1.1: 2 Summary of Results from Early Major ACE-I Clinical Trials

Variables	SAVE, AIRE, TRACE, SOLVD			HOPE			ALL TRIALS		
	Active n=6,391	Control n=6,372	OR (95% CI) p-value	Active n=4,645	Control n=4,652	OR (95% CI) p-value	Active n=11,036	Control n=11,024	OR (95% CI) p-value
Death	1467 (23.0%)	1710 (26.8%)	0.80 (0.74-0.87) <0.0001	482 (10.4%)	569 (12.2%)	0.83 (0.73-0.95) 0.0047	1949 (17.7%)	2279 (20.7%)	0.81 (0.70-0.87) <0.0001
MI	571 (8.9%)	703 (11.0%)	0.79 (0.70-0.89) <0.0001	459 (9.9%)	570 (12.3%)	0.79 (0.69-0.89) 0.0003	1030 (9.3%)	1273 (11.5%)	0.79 (0.72-0.86) <0.0001
Stroke	239 (3.9%)	249 (3.9%)	0.96 (0.80-1.15) 0.63	156 (3.4%)	226 (4.9%)	0.68 (0.55-0.84) 0.0003	395 (3.6%)	475 (4.3%)	0.83 (0.72-0.95) 0.0055
CHF Hosp*	876 (13.7%)	1202 (18.9%)	0.67 (0.61-0.74) <0.0001	141 (3.0%)	161 (3.5%)	0.87 (0.69-1.10) 0.2474	1017 (9.2%)	1363 (12.4%)	0.70 (0.64-0.76) <0.0001
Death/MI/Stroke	1869 (29.2%)	2174 (34.1%)	0.79 (0.73-0.85) <0.0001	822 (17.7%)	992 (21.3%)	0.79 (0.72-0.88) <0.0001	2691 (24.4%)	3166 (28.7%)	0.79 (0.74-0.84) <0.0001
Death/MI/Stroke/ CHF Hosp*	2285 (35.8%)	2705 (42.5%)	0.74 (0.69-0.80) <0.0001	887 (19.1%)	1076 (23.1%)	0.78 (0.71-0.87) <0.0001	3172 (28.7%)	3781 (34.3%)	0.76 (0.71-0.80) <0.0001

Unpublished results from updated analysis of data from ACE inhibitor trials.
* For HOPE this is a component of the overall CHF endpoint
Source: ONTARGET Protocol, Table 2

In summary, ACE-Is prevented cardiac events in patients with systolic dysfunction, although beneficial effects on preventing the occurrence of heart failure were less marked in patients without decreased LVEFs.

4.1.2 Evidence-based medicine since 2000 (during and after ONTARGET)

Several major ACE-I and ARB outcome studies have reported results after the start of ONTARGET and TRANSCEND. For ACE-Is, the studies examined whether their use by patients at high risk of CV events, but without heart failure or left ventricular dysfunction, lessens the probability of major atherosclerotic events. The EUROPA study showed a 20% risk reduction for the primary endpoint of CV death, MI, and cardiac arrest for perindopril compared with placebo (The EUROPA Investigators, 2003). In EUROPA, use of perindopril led to a marked reduction in HF, which has led to the approval of perindopril in several countries. The PEACE trial was a double-blind, placebo controlled study of 8290 patients which tested the hypothesis that patients with stable coronary artery disease and normal or near normal left ventricular function would benefit from the addition of the ACE-I trandolapril to standard medical therapy. In the final analysis, this trial was underpowered for the primary endpoint and could not demonstrate a benefit from the active therapy.

Several clinical outcome trials have investigated whether ARBs, or a combination of ARBs and ACE-Is, prevents CV events, including heart failure. Table 4.1.2: 1 provides an overview of outcome trials with ARBs. With the exception of CHARM-preserved and I-PRESERVE, patients had systolic dysfunction and/or heart failure. Note that concomitant therapy use (e.g., statins, beta blockers, and diuretics) changed during ONTARGET and these trials. Use of these medications has improved the cardiovascular outcomes of patients as treatment guidelines have been updated, although the relative risk reductions observed in the more recent studies of ACE-Is and ARBs do not appear to have been affected by these changes in clinical practice patterns.

Table 4.1.2: 1 Results from selected large ARB outcome trials

Name of trial (year reported)	Total No. patients	Inclusion criteria	Drugs tested	Median follow-up	Primary endpoint
ELITE II (Pitt et al., 2000)	3152	- New York Heart Association functional class II-IV CHF - LVEF ≤40% - No previous treatment with ACE-Is or ARBs[3] - ≥60 years of age	Losartan vs. captopril[2]	18 mths	All-cause mortality: Losartan: 280 patients (17.7%) Captopril: 250 patients (15.9%) HR (Losartan/Captopril): 1.13 [95% CI 0.95 to 1.35] p-value: 0.16
CHARM-added (McMurray et al., 2003)	2548	- New York Heart Association functional class II-IV CHF[1] - LVEF ≤40% - Prior treatment with ACE-I at a constant dose (≥30 days) - ≥18 years of age	Candesartan/ACE-Is vs. placebo/ACE-Is[2]	41 mths	Composite of CV death and hospitalization for CHF Candesartan: 438 patients (38%) Placebo: 538 patients (42%) HR (Candesartan/Placebo): 0.85 [95% CI 0.75 to 0.96] p-value: 0.011
CHARM-alternative (Granger et al., 2003)	2028	- New York Heart Association functional class II-IV CHF[1] - LVEF ≤40% - ACE-I-intolerance - ≥18 years of age	Candesartan vs. placebo (no ACE-Is)[2]	33.7 mths	Composite of CV death and hospitalization for CHF Candesartan: 334 patients (33%) Placebo: 406 patients (40%) HR (Candesartan/Placebo): 0.77 [95% CI 0.67 to 0.89] p-value: 0.0004
CHARM-preserved (Yusuf et al., 2003)	3023	- New York Heart Association functional class II-IV CHF[1] - LVEF >40% - History of hospital admission for a cardiac reason - ≥18 years of age	Candesartan vs. placebo [2]	36.6 mths	Composite of CV death and hospitalization for CHF Candesartan: 333 patients (22%) Placebo: 366 patients (24%) HR (Candesartan/Placebo): 0.89 [95% CI 0.77 to 1.03] p-value: 0.118

Table 4.1.2: 1 (continued) Results from selected ARB outcome trials

Name of trial (year reported)	Total No. patients	Inclusion criteria	Drugs tested	Median Follow-up	Primary endpoint
I Preserve (Massie et al., 2008)	4128	New York Heart Association functional class II-IV CHF plus "corroborating evidence" LVEF ≥ 45 ACE-I allowed if "essential" therapy -Age ≥ 60	Irbesartan vs. placebo	49.5 mths	All cause mortality or CV hospitalization Irbesartan: 742 patients (36%) Placebo: 763 patients (37%) HR (Irbesartan: placebo) 0.95 [95% CI 0.86 to 1.05] p-value 0.35
Val-HeFT (Cohn and Tognoni, 2001)	5010	- History and clinical findings of heart failure for ≥3 months before screening - New York Heart Association functional class II-IV CHF - LVEF <40% - Treatment for ≥2 weeks with a fixed dose regimen that could include ACE-Is, diuretics, digoxin, and beta blockers - ≥18 years of age	Valsartan vs. placebo (concomitant therapy with ACE-I or beta blockers)[1]	23 mths	All-cause mortality Valsartan: 495 patients (19.7%) Placebo: 484 patients (19.4%) RR (Valsartan/Placebo): 1.02 [95% CI 0.88 to 1.18] p-value: 0.80 Composite of mortality and CV morbidity (cardiac arrest with resuscitations, hospitalization for CHF, or intravenous inotropic or vasodilator drug for ≥4h without hospitalization) Valsartan: 723 patients (28.8%) Placebo: 801 patients (32.1%) RR (Valsartan/Placebo): 0.87 [95% CI 0.77 to 0.97] p-value: 0.009

Name of trial (year reported)	Total No. patients	Inclusion criteria	Drugs tested	Median Follow-up	Primary endpoint	
VALIANT (Pfeffer et al., 2003)	14703	- MI (between 0.5 and 10 days prior to the study) - Heart failure or left ventricular systolic dysfunction[2], or both - Baseline SPB >100 mmHg - Baseline serum creatinine <2.5mg/dL - ≥18 years of age	Valsartan vs. valsartan+captopril vs. captopril[1]	24.7 mths	All-cause mortality Valsartan: Valsartan+Captopril: Captopril: HR (Valsartan/Captopril): p-value: HR (Valsartan+Captopril /Captopril): p-value: p-value (non-inferiority):	 979 patients (19.9%) 941 patients (19.3%) 958 patients (19.5%) 1.00 [97.5% CI 0.90 to 1.11] 0.98 0.98 [97.5% CI 0.89 to 1.09] 0.73 0.004
OPTIMAAL (Dickstein and Kjekshus, 2002)	5477	- Acute MI and heart failure during the acute phase, or an ejection fraction of ≥0.35, or a new Q-wave anterior infarction or reinfarction - ≥50 years of age	Losartan vs. captopril[1]	32.4 mths	All-cause mortality Losartan: Captopril: RR (Losartan/Captopril): p-value:	 499 patients (18%) 447 patients (16%) 1.13 [95% CI 0.99 to 1.28] 0.07

LVEF = left ventricular ejection fraction, RR = risk reduction

[1]For ≥4 weeks before randomization; if class II, patients had to have been hospitalised for a cardiac reason in the previous 6 months.

[2]Patients were allowed to take background medical treatment, e.g. diuretics, beta blockers, CCBs, lipid-lowering agents, antiarrhythmic agents, oral anticoagulants, other vasodilators, or antiplatelet agents.

[3]An exemption was made for some patients who had recently started treatment with ARBs or ACE-Is with an exposure period of ≤7 days within the last 3 months as an impact on long-term clinical outcomes appeared unlikely.

[1]Patients were allowed to take background medical treatment, e.g. diuretics, beta blockers, CCBs, lipid-lowering agents, antiarrhythmic agents, oral anticoagulants, other vasodilators, or antiplatelet agents.

[2]Ejection fraction ≤0.35 on echocardiography or contrast angiography and ≤0.40 on radionuclide ventriculography

Source: Table 1.3.1: 1 in Summary of Clinical Efficacy

Two major clinical trials evaluated the use of ARBs in patients with preserved left ventricular function. CHARM-preserved investigated the effect of candesartan in patients with preserved LVEF; no difference was seen between candesartan and placebo for the composite primary endpoint (unadjusted HR = 0.89; [95% CI 0.77–1.03]; p=0.118). In I-PRESERVE (Massie et al., 2008), a study comparing irbesartan and placebo in patients with left ventricular ejection fractions greater than 40%, demonstrated no benefit of the ARB. In I-PRESERVE, among patients with preserved left ventricular function, irbesartan did not show evidence of reducing hospitalization for cardiovascular causes (HR = 0.95; 95% CI, 0.85 to 1.08; P = 0.44).

Patients in CHARM-preserved and I-PRESERVE did not have systolic dysfunction, in contrast to earlier studies such as SOLVD (The SOLVD Investigators, 1992) and SAVE (Pfeffer et al., 1992). The absence of a benefit in CHARM-preserved and I-PRESERVE on their primary efficacy endpoints suggests that ARBs may not have benefit in preventing the development of new, overt, symptomatic heart failure in patients without systolic dysfunction.

4.1.3 FDA interactions

BI had a number of interactions with the FDA during the design of ONTARGET and TRANSCEND focusing on the non-inferiority analysis, selection of the primary endpoint, and safety reporting. Details will be discussed in relevant sections in this document.

4.2 CV RISK REDUCTION STUDIES WITH TELMISARTAN

The aim of a non-inferiority trial is to show the therapeutic similarity of two treatments, usually a test drug and an existing proven drug for the same disease used as a standard active comparator (Jones et al, 1996). Major characteristics of such studies include:

1. The design should mirror the characteristics of earlier successful trials as closely as possible.
2. Loss to follow-up and protocol deviations should be minimized.
3. Avoidance of biases in allocation, endpoint ascertainment, and analysis. .
4. Independent assessment of outcomes.
5. Results should be consistent across different analysis strategies (Intent To Treat [ITT], Per Protocol [PP]).
6. Prespecified statistical definition of non-inferiority.
7. The standard care at the time of the non-inferiority study should be similar to the standard of care in the earlier trials.

For ONTARGET, the design and analyses were consistent with respect to the established characteristics of a non-inferiority study. Similar properties were inherent to the supportive studies, even though assessment of non-inferiority was not their target. The study had sufficient power to confirm the effect of statins.

1. Mirroring of the previous relevant trials. The inclusion and exclusion criteria in ONTARGET were similar to those in HOPE. In both ONTARGET and HOPE, adherence to evidence-based concomitant therapy was encouraged.

2. Patient loss and protocol deviations were minimized as evidenced by the high compliance rate and the number of patients who completed the trials. For example, 99.8 % of the patients completed the trial in ONTARGET and compliance was approximately 84% for telmisartan and 81% for ramipril. Further, only 0.1 % of patients did not meet the inclusion criteria in ONTARGET.
3. Protection against bias.

    a. ONTARGET, like the successful HOPE study, had an independent Steering Committee comprised of academic researchers who had operational oversight for the trial conduct. The publications resulting from these studies were the responsibility of the academic physicians. Further, the data base for ONTARGET was managed at the same academic site (PHRI) that managed HOPE, and the data were only later transferred to the Sponsor for preparation of health regulatory submissions.

    b. ONTARGET, TRANSCEND, and PRoFESS were randomized, double-blind, multicenter trials.
4. Primary endpoints were centrally adjudicated by independent adjudication committees that were blinded to individual treatment allocations. Data Safety Monitoring Committees, independent of the Sponsor and of the Steering Committees, oversaw the safety of the patients.
5. The estimated effect sizes were consistent across the different analysis populations (ITT and PP). This briefing document presents only the ITT analysis and the results of the PP analysis were in line with those presented in this briefing document.
6. Statistical definition of the non-inferiority hypothesis with pre-specified margin

A non-inferiority design requires ruling out unacceptable excess risk of the test treatment compared to the reference treatment. Many quite different approaches for defining non-inferiority margins have been utilized in the literature and there is no clear consensus on how to choose an appropriate margin. During the last decade or so, methods have been proposed; some have been rejected; some have been modified. The following list presents five of the commonly used methods.

1. a margin based upon judgment by clinical experts of a minimally important clinical difference
2. a statistically derived margin of relative difference derived from the point estimate of an effect size of a reference product or series of products
3. a margin derived from the lower bound of a confidence interval around a point estimate of a reference product or series of products
4. a margin derived from method (2) or (3) above, but incorporating some degree of preservation of the effect size observed in the studies of the referenced product,

5. combinations of the above, such as the use of an absolute margin for a certain range of outcome events and the use of a hazard ratio for another range of outcome events.

When the ONTARGET program was being developed, a number of possible statistical approaches were available for selecting a non-inferiority margin. The Investigators chose to base the margin on the second method described above. The source for the estimate of the effect of ramipril was the HOPE study, in which ramipril 10 mg was compared to placebo on top of standard care. The HOPE study had shown consistent risk reductions not only in its primary 3-fold endpoint (CV death, MI and stroke) with a HR of 0.78 and 95%-CI of (0.70 - 0.86), but also in most secondary endpoints and subgroup analyses. Furthermore, the effect size of ramipril observed in HOPE was consistent with the risk reduction of other ACE-Is in placebo-controlled studies of patients after MI (for example, SAVE, TRACE, and AIRE). The Investigators of ONTARGET and the FDA agreed that HOPE was a suitable basis for the statistical calculation of the NI margin. The Investigators and FDA discussed how to best assure that telmisartan would preserve at least 50% of ramipril's effect.

In the HOPE study, the estimated hazard ratio for ramipril 10 mg relative to placebo for the 4-fold composite endpoint as planned for ONTARGET was 0.78 with a 95%CI of (0.70 - 0.85). This result was provided by PHRI, which had been the data center for the HOPE study and would be the data management center for ONTARGET. For the derivation of a NI margin in ONTARGET the relative risk decrease of ramipril compared to placebo was converted into a relative risk increase of placebo compared to ramipril. Inversion of the hazard ratio and its confidence limits translated from HOPE resulted in a hazard ratio of excess risk of placebo over ramipril of 1.29 (=1/0.78) with a 95%-CI of (1.17 - 1.42).

The ONTARGET protocol developed by its Investigators and the Sponsor used a discounted estimate of the central tendency of the estimated risk increase as the reference for the calculation of the NI margin. Rather than the point estimate of 1.29, a value of 1.26 (which is roughly equivalent to the lower bound of a 66% one-side CI around the point estimate) was chosen to reflect the variability in the estimate and to discount the possibility that there could be a change in the relative risk reduction of ramipril, the reference product, over time. This selection insured that two thirds of all possible risk ratios of ramipril versus placebo in line with the HOPE data were covered. By dividing the assumed excess risk of 26% by 2, to protect against certain situations wherein ramipril could have been less effective in ONTARGET than it was in HOPE. By convention, this led to a margin of 1.13 for the hazard ratio; that is, telmisartan would be judged non-inferior to ramipril if the upper bound of the 97.5% confidence interval for the hazard ratio was less than 1.13, provided an adjustment for multiplicity was required. The calculation of a non-inferiority margin for the 3-fold endpoint resulted in an identical outcome as with the 4-fold endpoint and a NI margin of 1.13. While the ONTARGET Investigators and the Sponsor arrived at a NI margin of 1.13 during a discussion in 2001, the FDA recommended a margin of 1.085. The FDA's recommendation was based on using half the lower limit of the 95% CI (i.e. 1.17) as the reference, thereby covering

97.5% of risk increases consistent with the HOPE data. Given the state of flux in methodology for selecting non-inferiority margins at the time of the design of ONTARGET, coupled with the consensus of the Investigators that a margin of 1.13 was clinically acceptable, BI and the Investigators opted not to change the design of ONTARGET but to keep the prespecified margin of 1.13, which was also the margin specified in the VALIANT protocol.

The VALIANT study, some of whose Investigators were members of the Steering Committee for ONTARGET had, in designing VALIANT chosen the same margin of 1.13. VALIANT was a 3-arm study comparing valsartan, captopril, and the combination of both, to establish non-inferiority of valsartan vs. captopril regarding the primary endpoint of overall mortality. The results of VALIANT led to the additional indication for valsartan: reduction of cardiovascular mortality following MI. Other development programs calculated their non-inferiority margins from estimate of the comparator's effect using the lower bound of the 2-sided 90% CI (for example the NI study involving pemetrexed in 2004). Had ONTARGET adopted the method used for pemetrexed, the resulting NI margin would have been 1.095.

ONTARGET was sized to attain at least 90% power to demonstrate non-inferiority at the Investigator and Sponsor-defined margin of 1.13 assuming that telmisartan and ramipril have equal effect sizes. The sample size of 25,000, calculated from a 1.13 non-inferiority margin, had roughly 60% power to demonstrate non-inferiority at the FDA's recommended margin of 1.085. To conduct the trial with a design using a non-inferiority margin of 1.085, a sample size of 55,000 patients would have been necessary.

An aspect of the ONTARGET program that differed from HOPE was the addition of hospitalization for CHF to the 3 component HOPE endpoint. The Investigators added hospitalization for heart failure because they believed that ACE-Is, and by extension ARBs, could prevent the development of symptomatic heart failure as had been seen in SAVE, AIRE, TRACE, and SOLVD. These four trials had included patients with diminished LVEF and or/symptomatic heart failure. However, the ONTARGET Investigators expected a similar benefit in patients without symptomatic heart failure, with most presumably having preserved LV function. Further, the HOPE Investigators reported a statistically significant reduction in the rate of development of heart failure not requiring hospitalization, although the reduction in HF hosp was not statistically significant on its own.

5.0 EXPERIENCE FROM OUTCOME CLINICAL TRIALS

5.1 ONTARGET - TRIAL DESIGN AND EFFICACY

5.1.1 Trial Design

The design of ONTARGET was similar to HOPE. Because of the labeling of ramipril, it was necessary to slowly up-titrate the drug and therefore a run-in period of up to 4 weeks was necessary, which excluded the vast majority of patients that would not tolerate ramipril. The ONTARGET study was designed to determine if (a) the combination of telmisartan 80 mg and ramipril 10 mg (T/R) is superior to ramipril 10 mg (R) and (b) telmisartan 80 mg (T) is non-inferior to ramipril 10 mg in reducing the 4-fold composite endpoint of CV death, MI, stroke, or hospitalization for CHF. The key secondary endpoint was the 3-fold composite of CV death, non-fatal MI, and non-fatal stroke (primary endpoint of the HOPE study). ONTARGET had additional secondary endpoints, including the individual components of the 4-fold endpoint (i.e. CV death, MI, stroke, or hospitalization for CHF).

In ONTARGET, a total of 25,620 patients 55 years of age or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes (with end organ damage) were randomized for treatment with ramipril (n=8576), telmisartan (n=8542) or telmisartan and ramipril (n=8502). Fifty eight percent of patients had regular ACE-I use prior to study entry. Patients were treated for a mean duration of 4.6 years (range 4.5-4.6 years).

Figure 5.1: 1 below presents a schematic of the overall trial design of the ONTARGET study.

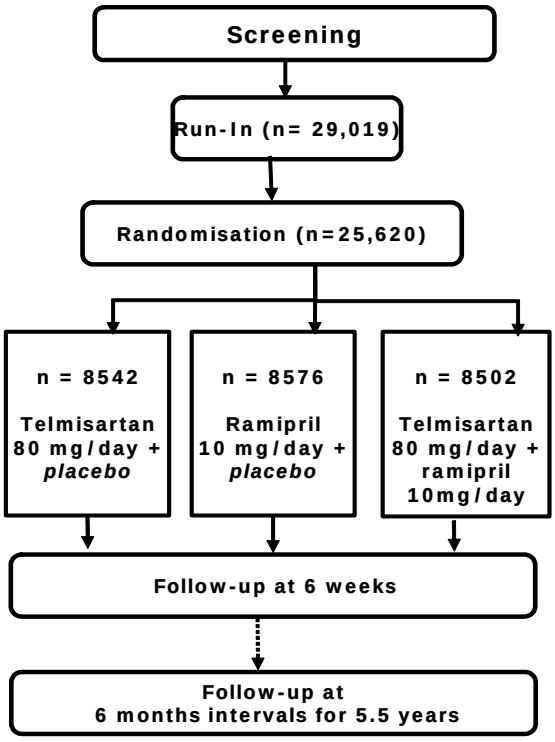


Figure 5.1: 1 ONTARGET flow chart

Patients who were known to be ACE-I intolerant based on their medical history (cough and angioedema etc) or were found to be intolerant to ACE-Is during the ONTARGET run-in period were not eligible for ONTARGET but could be enrolled into the TRANSCEND trial, which was conducted in parallel and had the same study endpoints. For example, during the run-in period of ONTARGET, 1.08% and 0.14% of patients permanently discontinued due to cough and angioedema, respectively. These discontinuations were low, since 58% of patients were regular users of ACE-Is and were tolerant to this medication class. All reasons for discontinuation during the run-in period of ONTARGET are summarized in Section 6.3.1. The two studies (ONTARGET and TRANSCEND) were conducted at predominantly the same study centers.

During the ONTARGET run-in period, patients received the following single-blind treatment to determine their tolerance to ramipril and telmisartan. Figure 5.1.:2 shows the trial drugs administered during the different study periods.

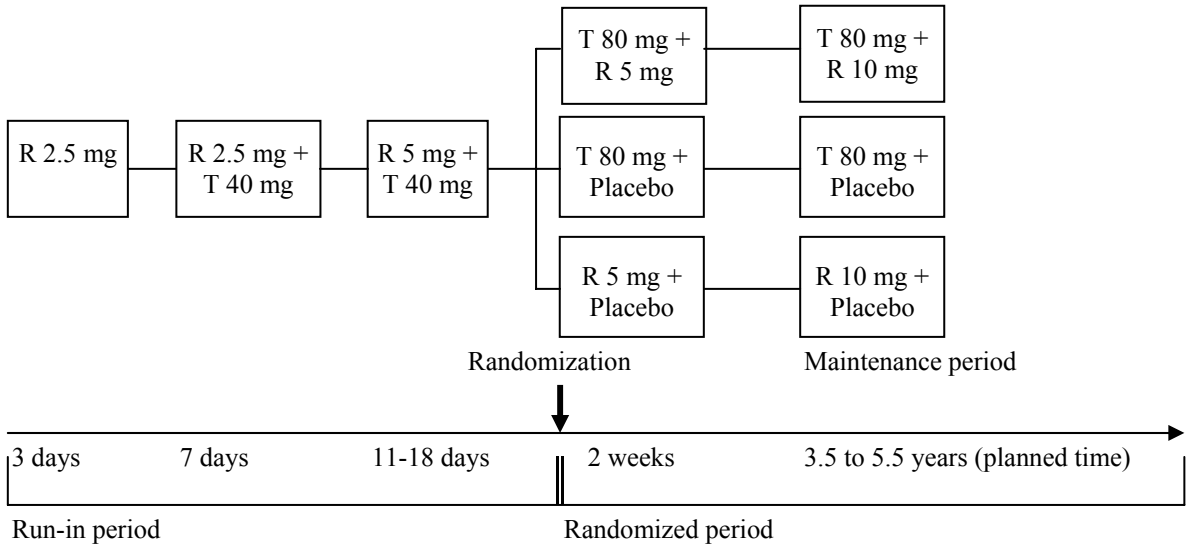


Figure 5.1:2 ONTARGET Run-in period.

5.1.2 Key Inclusion Criteria

Male or female patients, 55 years of age or older, who were at high risk of developing a major CV event were eligible for the study. Patients were eligible if they had any of the following: coronary artery disease (CAD), peripheral arterial disease (PAD), previous stroke, transient ischemic attack (TIA) or high risk diabetes with evidence of end organ damage. Patients were excluded from the ONTARGET trial if they were unable to discontinue ACE-Is or ARBs or had hypersensitivity or intolerance to ACE-Is or ARBs, or uncontrolled hypertension on treatment.

5.1.3 Trial Endpoints

The primary endpoint of ONTARGET was the 4-fold composite of time to first occurrence of either CV death, non-fatal MI, non-fatal stroke, or hospitalization for CHF. All events that contributed to this 4-fold endpoint were centrally adjudicated by an independent committee that was blinded regarding the treatment allocation.

Key secondary endpoints for ONTARGET were:

- Composite of CV death, non-fatal MI, and non-fatal stroke (3-fold HOPE endpoint - this was specified for consistency with HOPE).
- Individual components of the primary and secondary composite endpoints (i.e. CV death, MI, non-fatal stroke, and hospitalization for CHF - this was specified in order to examine the consistency of the effects on each of the components of the composites).

5.1.4 Safety Analyses

Only SAEs (excluding study outcome events) and adverse events leading to discontinuation of study medication were collected in ONTARGET and TRANSCEND. Standard non-serious AEs were not recorded. An independent DSMB monitored the safety data during the course of the study. The safety reporting plan was submitted to the FDA in 2001. Following a pre-NDA meeting in 2007, reporting of safety data in the supplemental NDA was clarified.

5.1.5 Planned Statistical Analysis

For primary and secondary outcome events, time to event analysis (Kaplan Meier curves) and hazard ratios based on the intention-to-treat principle and using the proportional hazard model (Cox regression) were to be calculated.

5.1.6 Baseline Characteristics and Results

5.1.6.1 Patient Disposition

A total of 29019 patients were enrolled by 732 centers worldwide. The first patient was enrolled in December 2001; patient recruitment ended in July 2003, and the last formal patient observation was in February 2008.

Table 5.1.6.1:1 presents an overview on the number of patients in the single-blind run-in period [Run-In Set (RIS)] and the randomized period [Full Analysis Set (FAS)]. The RIS included all patients enrolled in the run-in period irrespective of whether they were randomized. The FAS was created according to the ITT principle; it included all patients who were randomized and had follow up information available.

Table 5.1.6.1:1 ONTARGET analysis sets for all enrolled and randomized patients

	T/R		T		R		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Run-in set (RIS)							29019	(100.0)
Randomized	8502	(100.0)	8542	(100.0)	8576	(100.0)	25620	(100.0)
Full analysis set (FAS)	8502	(100.0)	8542	(100.0)	8576	(100.0)	25620	(100.0)

Source: ONTARGET CTR Table 11.1: 1

Of the 29019 patients who participated in the single-blind run-in period 3399 (11.7%) were not randomized (Table 5.1.6.1:2). A total of 943 (3.2%) patients discontinued because of adverse events, which included the following known possible side of effects of ramipril and/or telmisartan: persistent symptomatic hypotension (1.7%), hyperkalaemia (0.8%), and azotaemia (0.2%).

Table 5.1.6.1:2 ONTARGET Disposition of patients for the run-in period / RIS

	Total[5]	
	n	(%)
Enrolled/screened	29019	(100.0)
Not randomized[1]	3399	(11.7)
Insufficient compliance with study medication (<75%)[2]	1345	(4.6)
Elevation/increase in creatinine[3]	64	(0.2)
Elevation in potassium to >5.5 mmol/L	245	(0.8)
Persistent symptomatic hypotension[4]	507	(1.7)
Patient request	1587	(5.5)
Other reasons	1328	(4.6)
Death	29	(0.1)
AEs	943	(3.2)
Administrative reasons	397	(1.4)

[1] A patient can be counted in more than 1 category.
[2] As assessed by pill count
[3] Elevation in creatinine to >3.75 mg/dL (330 µmol/L) or greater or increase of 0.8 mg/dL (100 µmol/L) during the run-in period
[4] Unexplained syncopal episode or any episode of dizziness or lightheadedness experienced in the upright position, regardless of the availability of a BP measurement taken at that time
[5] Numbers differ from those published since the publication prioritized reason for discontinuation and counted each patient only once.
Source: ONTARGET CTR Table 10.1:2

Overall and in all 3 treatment groups, 99.8% of the randomized patients completed the trial (Table 5.1.6.1:3).

Table 5.1.6.1:3 ONTARGET Disposition of patients for the randomized period / FAS

	T/R		T		R		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Randomized	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: ONTARGET CTR Table 10.1: 3

The regional distribution of patients was similar across all treatment groups, with Europe/South Africa and North America representing about 70% of all enrolled patients (Table 5.1.6.1:4).

Table 5.1.6.1:4 ONTARGET enrolment by geographic region / FAS

	T/R		T		R		Total	
Randomized, n (%)	8502	(100.0)	8542	(100.0)	8576	(100.0)	25620	(100.0)
Geographical region, %								
Europe/South Africa[1]	48.2		48.1		48.2		48.2	
North America[2]	21.2		21.2		21.3		21.2	
Asia/Middle East[3]	14.1		14.2		14.1		14.1	
Latin America[4]	9.4		9.3		9.3		9.3	
Australia/New Zealand	7.2		7.1		7.1		7.1	

[1] Denmark, Finland, Norway, Sweden, Austria, Belgium, France, Germany, Ireland, The Netherlands, Switzerland, United Kingdom, Greece, Italy, Portugal, Spain, Czech Republic, Hungary, Poland, Russia, Slovakia, Ukraine, South Africa
[2] Canada, USA
[3] China, Hong Kong, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand, Turkey, UAE
[4] Argentina, Brazil, Mexico
Source: ONTARGET CTR Table 11.2.2: 1

5.1.6.2. Demographics

Demographics are summarized in Table 5.1.6.2:1. Most patients were male (73.3%) and of white ethnicity (74.2%).

Table 5.1.6.2:1 ONTARGET demographics by randomized treatment / FAS

	T/R	T	R	Total
Randomized, 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)

[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: ONTARGET CTR Table 11.2: 1

5.1.6.3 Diagnosis for study entry

For the majority of patients, the primary diagnosis for study entry was coronary artery disease (66.1%), followed by high-risk diabetes (14.8%) and previous stroke (11.4%). The treatment groups were balanced with respect to primary reason for inclusion in the study (Table 5.1.6.3:1).

Table 5.1.6.3: 1 ONTARGET diagnosis for study entry as recorded at the run-in visit / FAS

	T/R	T	R	Total
Randomized, 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: ONTARGET CTR Table11.2.5: 1

5.1.6.4 Previous and concomitant regular use of medications

Commonly used concomitant medications, reported with regular use (defined as at least 3 times per week) at baseline were acetylsalicylic acid (ASA 75.7%), statins (61.6%), beta-blockers (56.9%), nitrates (29.4%), diuretics (28.0%), and oral hypoglycemic agents (25.1%). Table 5.1.6.4:1 summarizes the previous medication use and regular concomitant use of medications in the FAS.

Regular ACE-I use was present in 57.6% of patients while regular use of ARBs occurred for only 8.6% of patients. This difference increased the likelihood of patients remaining on ramipril compared to ACE-I naïve patients. Other than this major discrepancy, the use of previous or concomitant medications was similar across the 3 treatment groups.

Table 5.1.6.4: 1 ONTARGET previous and concomitant medications taken at a regular basis as recorded at the run-in visit / FAS

	T/R	T	R	Total
Randomized, n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)	25620 (100.0)
Previous regular use of ACE-Is or ARBs[1], %				
Previous regular use of ACE-Is	57.2	58.5	56.9	57.6
Previous regular use of ARBs	9.0	8.5	8.5	8.6
Previous regular use of both ACE-Is and ARBs[2]	2.9	3.0	2.7	2.9
Concomitant regular use[3], %				
ASA	76.0	75.7	75.5	75.7
Statins	61.8	62.0	61.0	61.6
Beta-blockers	57.4	56.9	56.5	56.9
Nitrates	29.4	29.7	29.0	29.4
Diuretics	27.7	27.6	28.6	28.0
Oral hypoglycemic agents	25.3	25.1	25.0	25.1
Calcium channel blockers excl diltiazem/verapamil	24.2	23.7	23.5	23.8
Insulin	10.1	11.0	10.0	10.4
Diltiazem/verapamil	10.0	9.4	9.9	9.8
Clopidogrel	8.6	8.7	8.4	8.6
Oral anticoagulants	7.4	7.5	7.7	7.6
Fibrates	4.5	4.3	4.5	4.5
Alpha-blockers	4.3	4.1	4.4	4.3
Ticlopidine	2.4	2.6	2.5	2.5
Other medication[4]	45.4	44.5	45.9	45.2
Gender-specific				
Estrogen replacement[5]	8.6	8.5	8.4	8.5
Estrogen + progesterone replacement[5]	2.3	2.6	2.1	2.4
Viagra/Sildenafil[6]	1.8	1.7	1.6	1.7

[1] No definition provided in the CRF for regular use of previous medications
[2] Use of both ACE-Is and ARBs includes concomitant and sequential use.
[3] Regular use of concomitant medications refers to at least 3 times per week.
[4] If a medication was not specifically listed in the CRF, the Investigator was to check the tick box 'other medication'.
[5] Percentage refers to female patients.
[6] Percentage refers to male patients.
Source: Adapted from ONTARGET CTR Table11.2.7: 1

5.1.6.5 ONTARGET - EFFICACY

Kaplan-Meier survival curves were used to summarize time-to-event data were for each treatment group. The treatments were compared using Cox regression (with SBP at baseline or all SBP values as a covariate). For all outcomes, hazard ratios were calculated together

with the 2-sided 95% CIs. For the non-inferiority comparison between T and R also 2-sided 97.5% CIs, to adjust for multiplicity, are given.

Since an ideal method for adjusting for blood pressure is not available, several sensitivity analyses were performed. Adjustments for baseline SBP and changes in SBP during the study were performed to assess if the treatment differences persisted after correction for BP changes. In addition, a post-hoc analysis was performed to adjust for the most recent SBP before an event (for patients with events) or the SBP before the last date of follow-up (for patients without event) as performed for the ONTARGET publication.

5.1.6.5.1 Key endpoints

5.1.6.5.1.1 Composite 4-fold and 3-fold endpoint of CV death, non-fatal MI, non-fatal stroke, with (4-fold) and without (3-fold) hospitalization for CHF

Table 5.1.6.5.1.1: 1 presents the results of the analysis on the 4-fold composite endpoint consisting of CV death, non-fatal MI, non-fatal stroke, and hospitalization for CHF and the 3-fold composite endpoint of CV death, non-fatal MI and non-fatal stroke. For patients who experienced more than one of these events, the first event was used to calculate hazard ratios, to create Kaplan-Meier curves, and to perform similar analyses. If multiple simultaneous events occurred, all such individual events were used in these analyses and are presented.

The hazard ratio for the 4-fold endpoint for T/R vs. R was 0.99 (95% CI 0.92, 1.07; p=0.85, for superiority). Thus, the trial demonstrated that adding telmisartan to ramipril provided no additional benefit to telmisartan or ramipril treatment. Since the first hypothesis testing failed, an adjustment for multiplicity was made for testing of the co-primary endpoint. Therefore, since T/R was not shown superior to R, non-inferiority of T vs. R was only to be concluded if the 2-sided 97.5% CI excluded the pre-specified margin of 1.13 and the one-sided p-value for non-inferiority was <0.0125 (adjustment for multiple testing).

Telmisartan was non-inferior to ramipril in ONTARGET for the 4-fold endpoint comparing telmisartan to full dose ramipril, when using the protocol-specified criterion with a non-inferiority margin of 1.13. The point estimate of the HR was 1.01 (97.5% CI of 0.93 to 1.10) for the 4-fold composite endpoint and 0.99 (97.5% CI 0.90 to 1.08) for the 3-fold endpoint. The upper bound of 1.10 (for the 4-fold endpoint), exceeded the NI margin of 1.085 proposed by FDA. For the 3-fold endpoint, the upper bound was less than the protocol-specified margin of 1.13 and the FDA recommended margin of 1.085.

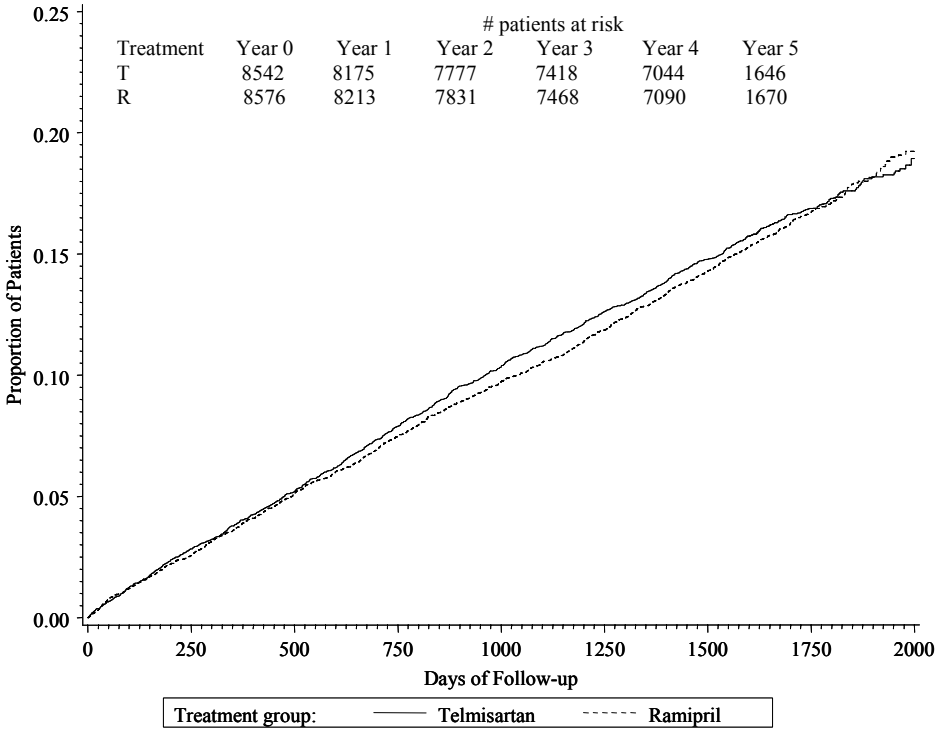
All components of the composite endpoint contributed to the results and no single component endpoint predominated.

Table 5.1.6.5.1.1: 1 ONTARGET incidence and ITT analysis of the 4-fold and 3-fold endpoint - first event.

	T		R	
Randomized, n (%)	8542	(100.0)	8576	(100.0)
4-fold endpoint[1], n (%)	1423	(16.7)	1412	(16.5)
CV death	367	(4.3)	373	(4.3)
Non-fatal MI	399	(4.7)	372	(4.3)
Non-fatal stroke	322	(3.8)	377	(4.4)
Hospitalization for CHF	353	(4.1)	312	(3.6)
Events per 100 patient years	3.87		3.82	
Hazard ratio[2] vs. ramipril	1.01			
95% CI	(0.94, 1.09)			
97.5% CI	(0.93, 1.10)			
p-value (non-inferiority, one-sided)	0.0019			
3-fold endpoint, n (%)[1]	1190	(13.9)	1210	(14.1)
CV death	438	(5.1)	448	(5.2)
Non-fatal MI	419	(4.9)	389	(4.5)
Non-fatal stroke	347	(4.1)	389	(4.5)
Events per 100 patient years	3.18		3.23	
Hazard ratio[2] vs. ramipril	0.99			
95% CI	(0.91, 1.07)			
97.5% CI	(0.90, 1.08)			
p-value (non-inferiority, one-sided)	0.0004			

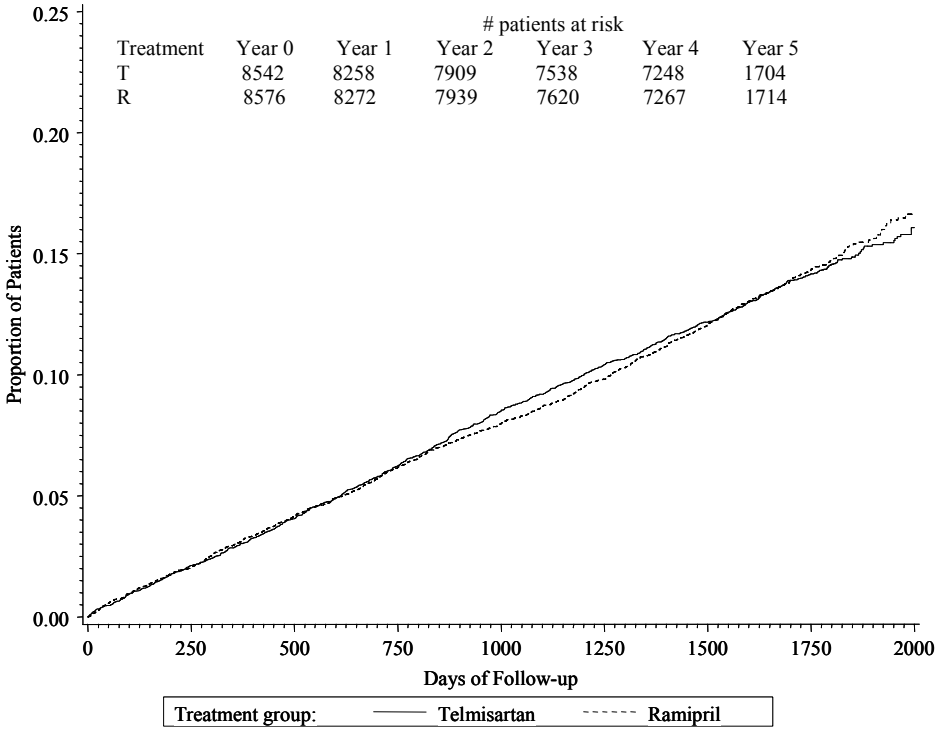
[1] The 3-fold and 4-fold endpoints were defined as the time to first event. In case of multiple simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcomes.
[2] Cox regression
Source: Adapted from ONTARGET CTR Table 11.4.1.1.1: 1 and Table 11.4.1.2.1.1

The Kaplan-Meier curves for the 4-fold endpoint are presented in Figure 5.1.6.5.1.1: 1 and the 3-fold endpoint in Figure 5.1.6.5.1.1: 2. The curves for the 3 treatment groups were indistinguishable over the entire observation period. The number of patients who were at risk, had an event, or were censored by year is given in Appendix E2, Table 1.



Source: ONTARGET CTR

Figure 5.1.6.5.1.1: 1 ONTARGET Kaplan-Meier estimates of the 4-fold endpoint.



Source: ONTARGET CTR:

Figure 5.1.6.5.1.1: 2 ONTARGET Kaplan-Meier estimates of the 3-fold endpoint.

5.1.6.5.1.2. Sensitivity analyses for changes in blood pressure effect

The individual mean change in sitting systolic blood pressure (SBP) from post randomization baseline to last observation was −6.7 mmHg in the telmisartan group, and −5.6 mmHg in the ramipril group. To investigate the influence of blood pressure, a Cox regression analysis with baseline SBP and time-dependent SBP measurements as covariates was performed. The results suggest that the risk of experiencing a 4-fold endpoint event rose only slightly with increasing SBP (Table 5.1.6.5.1.2: 1). The relative hazard for a patient with a 10 mmHg higher SBP at baseline was 1.03 (95% CI 1.01, 1.05). An increase of 10 mmHg in SBP during the trial was associated with a hazard ratio of 1.04 (95% CI 1.02, 1.06).

The relatively low increase in risk with rising blood pressure observed in ONTARGET may be explained by the comparatively large proportion of patients with optimal, normal, or high-normal (i.e., <140/90 mmHg) blood pressure (40.1%) at baseline, the rather low mean baseline SBP/DBP of 141.8/82.1 mmHg, and the substantial use of other antihypertensive medications during the trial

Table 5.1.6.5.1.2: 1 ONTARGET sensitivity analysis of the 4-fold composite endpoint using baseline SBP and changes of SBP over time as covariates.

	T	R
Impact of SBP on composite outcome[1], hazard ratio (95% CI)		
SBP at baseline	1.03 (1.01, 1.05)	
SBP time-dependent	1.04 (1.02, 1.06)	
Hazard ratio[2] vs. ramipril	1.02	
95% CI	(0.95, 1.10)	
97.5% CI	(0.94, 1.11)	
p-value (conventional, 2-sided)	0.60	
p-value (non-inferiority, one-sided)	0.0066	

[1] Per 10 mmHg
[2] Adjusted for all other factors in the Cox regression model
Source: Adapted from ONTARGET CTR: Table 11.4.1.1.1: 6

5.1.6.5.2 Other endpoints

5.1.6.5.2.1 Individual components of the 4-fold endpoint

Table 5.1.6.5.2.1: 1 presents results of analyses of the first occurrence of CV death, MI, stroke, and hospitalization for CHF (e.g. for the analysis of MI, only the first MI experienced by a patient was considered). Hazard ratios and Kaplan-Meier estimates were calculated for the first event in each category. For MI and stroke, these were determined (a) considering only non-fatal events according to the assessment of the EAC and (b) considering non-fatal and fatal events.

For each component, slight differences in incidences were observed between treatment groups. There were no meaningful differences in risk reduction between treatments (Table 5.1.6.5.2.1: 1).

Table 5.1.6.5.2.1: 1 ONTARGET incidence and analyses of the components of efficacy endpoints - first event in each category.

	T	R
Randomized, n (%)	8542 (100.0)	8576 (100.0)
CV death, n (%)	598 (7.0)	603 (7.0)
Events per 100 patient years	1.54	1.54
Hazard ratio[1] vs. ramipril (95% CI)	1.00 (0.89, 1.12)	
Non-fatal MI, n (%)	431 (5.0)	400 (4.7)
Events per 100 patient years	1.13	1.05
Hazard ratio[1] vs. ramipril (95% CI)	1.08 (0.94, 1.24)	
MI (non-fatal and fatal)[2], n (%)	438 (5.1)	409 (4.8)
Events per 100 patient years	1.15	1.07
Hazard ratio[1] vs. ramipril (95% CI)	1.08 (0.94, 1.23)	
Non-fatal stroke, n (%)	364 (4.3)	402 (4.7)
Events per 100 patient years	0.95	1.05
Hazard ratio[1] vs. ramipril (95% CI)	0.91 (0.79, 1.05)	
Stroke (non-fatal and fatal)[2], n (%)	369 (4.3)	405 (4.7)
Events per 100 patient years	0.97	1.06
Hazard ratio[1] vs. ramipril (95% CI)	0.91 (0.79, 1.05)	
Hospitalization for CHF, n (%)	394 (4.6)	354 (4.1)
Events per 100 patient years	1.03	0.92
Hazard ratio[1] vs. ramipril (95% CI)	1.12 (0.97, 1.29)	
Hospitalization for CHF confirmed by X-ray, n (%)	285 (3.3)	269 (3.1)
Events per 100 patient years	0.74	0.70
Hazard ratio[1] vs. ramipril (95% CI)	1.06 (0.90, 1.26)	
Hazard ratio[1] vs. telmisartan (95% CI)		

[1] Cox regression
Source: Adapted from ONTARGET CTR: Table 11.4.1.2.2: 1

Numerous patients experienced more than 1 outcome event during the trial. The table below presents an overview for the 4-fold endpoint.

Table 5.1.6.5.2.1: 2 ONTARGET: Distribution of patients by number of outcome events – 4-fold endpoint.

	T	**R**
1st event	1423	1412
2nd event	393	393
3rd event	116	112
4th event	37	56
5th event	21	28
6th event	11	14
> 7th event	16	18
Total number of events	2017	2033
CV death	598	603
MI	474	451
Stroke	389	434
CHF hospitalization	556	545

Source: ONTARGET database

The proportional means model with sandwich variance estimate according to Lin et al (2000) was used to analyse these data. The resulting HR comparing T vs. R was 1.00 (95% CI 0.92, 1.08; p = 0.93). The analysis of the number of events within the 4-fold composite using Poisson regression revealed a similar result although with a tighter CI (RR=1.00, 95% CI 0.94, 1.06; p = 0.90). Most of the recurrent events were CV deaths and hospitalizations for CHF.

For the 3-fold endpoint the number of patients with recurrent events, i.e. MIs or strokes, is displayed in Table 5.1.6.5.2.1: 3.

Table 5.1.6.5.2.1: 3 ONTARGET: Distribution of patients by number of outcome events – 3-fold endpoint

	T	**R**
1st event	1190	1210
2nd event	228	225
3rd event	31	35
4th event	6	7
5th event	1	5
6th event	1	2
> 7th event	4	4
Total number of events	1461	1488
CV death	598	603
MI	474	451
Stroke	389	434

Source: ONTARGET database

The resulting HR of a comparison of T vs. R was 0.99 (95% CI 0.91, 1.07; p = 0.75). Using Poisson regression the RR was 0.99 (95% CI 0.92, 1.06; p = 0.67).

5.1.6.5.2.2 All-cause mortality in all patients

Overall, 3068 randomized patients (12.0%) died during the study (Table 5.1.6.5.2.2: 1).

Table 5.1.6.5.2.2: 1 ONTARGET incidence of all-cause mortality

	T		R	
Randomized, n (%)	8542	(100.0)	8576	(100.0)
Patients who died, n (%)	989	(11.6)	1014	(11.8)
CV death	598	(7.0)	603	(7.0)
Non-CV death	391	(4.6)	411	(4.8)
Malignancy	205	(2.4)	208	(2.4)
Other causes	186	(2.2)	203	(2.4)
Events per 100 patient years	2.54		2.60	
Hazard ratio[1] vs. ramipril (95%CI)	0.98 (0.90, 1.07)			

[1] Cox regression

Source: Adapted from ONTARGET CTR: Table 11.4.1.2.5: 1

In conclusion, the protocol-specified non-inferiority margin for ONTARGET was a hazard ratio of 1.13. The upper bounds of the 97.5% confidence intervals for ONTARGET were 1.10 and 1.08 for the 4-fold and 3-fold endpoints, respectively, thus meeting the protocol-specified non-inferiority margin and demonstrating that telmisartan was non-inferior to ramipril for both endpoints. An estimate of the effect of ramipril (based on a pooled analysis of 3 studies of ACE-I in patients not required to have left ventricular dysfunction) was similar to that from the HOPE study alone. Telmisartan is considered effective as it unequivocally preserved 51% of the estimated effect of ramipril. The other secondary endpoints were consistent with this conclusion

5.2 TRANSCEND – TRIAL DESIGN AND EFFICACY

5.2.1 Trial Design

TRANSCEND included a total of 5926 patients who were intolerant to ACE-Is randomized for treatment with telmisartan (n=2954) or placebo (n=2972).Although the trial endpoints, safety analysis, and planned statistical analysis were similar to ONTARGET, the patient population differed due to the requirement that patients be ACE-I intolerant, did not need regular ACE-I and/or ARB use (prevented inclusion of diabetics with renal disease) among other factors such as concomitant medication use. There was a run-in period and a double-blind randomized treatment period. All TRANSCEND patients initiated treatment with telmisartan 80 mg/day or placebo.

Figure 5.2.1: 1 presents a schematic of the overall trial design of TRANSCEND.

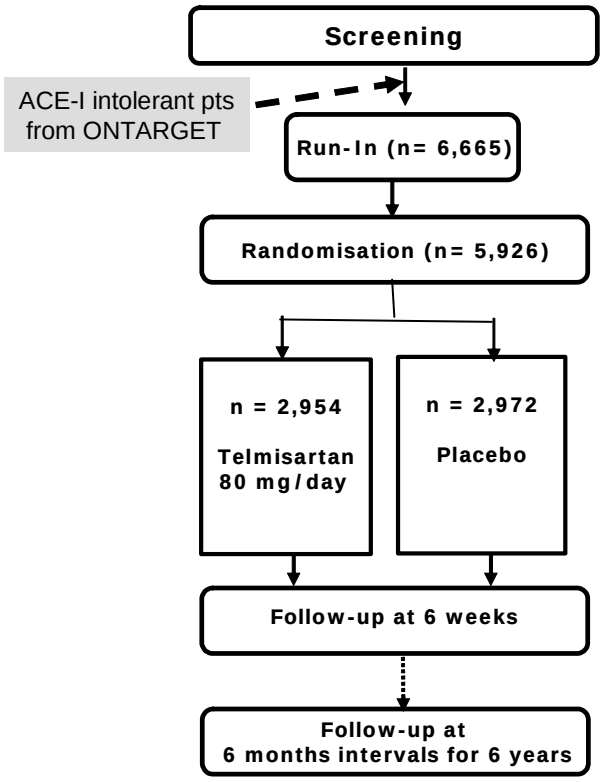


Figure 5.2.1:1 TRANSCEND flow chart

5.2.2 Baseline characteristics and results

5.2.2.1 Patient Disposition

A total of 6665 patients were enrolled by 650 centers worldwide. The first patient was enrolled in November 2001; patient recruitment ended in May 2004, and the last formal patient observation was in June 2008.

A total of 739 patients (11.1%) were not randomized. A total of 173 patients (2.6%) discontinued because of adverse events; of these, 55 discontinued because of symptomatic hypotension. Table 5.2.2.1: 1 shows patient disposition for the RIS. All randomized patients were included in the FAS.

Table 5.2.2.1: 1 TRANSCEND disposition of patients for the run-in period / RIS

	Total	
	n	(%)
Enrolled/screened	6665	(100.0)
Not randomized[1]	739	(11.1)
Insufficient compliance with study medication (<75%)[2]	342	(5.1)
Elevation/increase in creatinine[3]	11	(0.2)
Elevation in potassium to >5.5 mmol/L	27	(0.4)
Persistent symptomatic hypotension[4]	55	(0.8)
Patient request	406	(6.1)
Other reasons	281	(4.2)
Death	3	(0.0)
AEs	173	(2.6)
Administrative reasons	113	(1.7)

[1] A patient can be counted in more than 1 category.
[2] As assessed by pill count
[3] Elevation in creatinine to >3.75 mg/dL (330 µmol/L) or greater or increase of 0.8 mg/dL (100 µmol/L) during the run-in period
[4] Unexplained syncopal episode or any episode of dizziness or lightheadedness experienced in the upright position, regardless of a BP measurement taken at the time
Source: TRANSCEND CTR: Table 10.1: 2

Overall and in both treatment groups, 99.7% of the randomized patients completed the trial (Table 5.2.2.1: 2).

Table 5.2.2.1: 2 TRANSCEND disposition of patients for the randomized period / FAS

	T		PBO		Total	
	N	(%)	n	(%)	N	(%)
Randomized	2954	(100.0)	2972	(100.0)	5926	(100.0)
Completed[1]	2946	(99.7)	2962	(99.7)	5908	(99.7)
Deaths	364	(12.3)	349	(11.7)	713	(12.0)
Not completed	8	(0.3)	10	(0.3)	18	(0.3)

[1] Completed was defined as final visit performed or vital status confirmed (including death) at the end of the trial.
Source: TRANSCEND CTR: Table 10.1: 3

The regional distribution of patients was similar across all treatment groups, with Europe/South Africa and North America representing about 45.5% of all patients enrolled.(Table 5.2.2.1: 3).

Table 5.2.2.1: 3 TRANSCEND enrollment by geographic region

	T	PBO	Total
Randomized, n (%)	2954 (100.0)	2972 (100.0)	5926 (100.0)
Geographical region, %			
Europe/South Africa[1]	45.4	45.6	45.5
Asia/Middle East[2]	20.2	20.1	20.1
Latin America[3]	15.4	15.7	15.5
North America[4]	13.8	13.5	13.7
Australia/New Zealand	5.2	5.0	5.1

[1] Denmark, Finland, Norway, Sweden, Austria, Belgium, France, Germany, Ireland, The Netherlands, Switzerland, United Kingdom, Greece, Italy, Portugal, Spain, Czech Republic, Hungary, Poland, Russia, Slovakia, Ukraine, South Africa
[2] China, Hong Kong, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand, Turkey, UAE
[3] Argentina, Brazil, Mexico
[4] Canada, USA
Source: TRANSCEND CTR Table 11.2.2: 1

5.2.2.2 Demographics

Demographics are summarized in Table 5.2.2.2.1: 1. Most patients were male (57.0%) and white (62.4%).

Table 5.2.2.2.1: 1 TRANSCEND demographics by randomized treatment.

	T	PBO
Randomized, n (%)	2954 (100.0)	2972 (100.0)
Mean age (SD) [years]	66.9 (7.3)	66.9 (7.4)
Age group, %		
<65 years	39.8	40.3
≥65 to <75 years	43.6	43.3
≥75 years	16.5	16.4
Sex, %		
Male	56.7	57.4
Female	43.3	42.6
Ethnicity[1], %		
White	62.2	62.6
Black	1.7	1.9
Asian	21.6	21.0
Other	14.5	14.6
Mean BMI (SD) [kg/m^2]	28.25 (4.87)	28.14 (4.77)
Mean weight (SD) [kg]	77.3 (15.2)	77.2 (15.5)

[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.
Source: TRANSCEND CTR Table 11.2.1: 1

5.2.2.3 Diagnosis for study entry

The qualifying criterion for increased CV risk for study entry for most patients (66.8%) was coronary artery disease (Table 5.2.2.3: 1).

Table 5.2.2.3: 1 TRANSCEND: qualifying criterion for increased CV risk for study entry

	T	PBO
Randomized, n (%)	2954 (100.0)	2972 (100.0)
Primary reason for study entry, (%)		
CAD	67.0	66.5
High-risk diabetes[1]	13.1	13.3
Previous stroke	12.2	12.7
PAD	5.0	4.8
TIA (>7 days and <1 year)	2.5	2.6

[1] Patients with an entry diagnosis of diabetes had to have another relevant complication such as retinopathy, LVH, or any evidence of previous cardiac or vascular disease at run-in.
Source: TRANSCEND CTR Table 11.2.5: 1

5.2.2.4 Previous and concomitant regular use of medications

Patients were asked at the run-in visit which medications they currently used on a regular basis (defined as at least 3 times per week). The use of concomitant medications by trial patients was different to that seen in ONTARGET. For example, there was more regular diuretic (54% vs. 45%) and dihydropyridine (51% vs 31%) use in TRANSCEND compared to ONTARGET. Further, more than half of the patients (58.6%) had previously taken ACE-Is on a regular basis; 29.9% of patients reported the previous regular use of ARBs in contrast to 8.6% in ONTARGET. Table 5.2.2.4: 1 summarizes the previous medication use and regular concomitant use of medications in the FAS. The use of previous or concomitant medications was similar across both treatment groups in TRANSCEND.

Table 5.2.2.4: 1 TRANSCEND: concomitant medications at run-in.

	T n (%)	PBO n (%)	HOPE n (%)
Randomized, n (%)	2954 (100.0)	2972 (100.0)	9297 (100)
Previous regular use of ACE-Is or ARBs[1], %			
Previous regular use of ACE-Is	58.9	58.3	-[7]
Previous regular use of ARBs	29.6	30.2	-
Previous regular use of both ACE-Is and ARBs	16.5	16.5	-
Concomitant regular use[2], %			
ASA	75.0	74.4	73.3
Beta blockers	59.3	57.2	39.5
Statins	55.7	54.7	28.6[8]
Nitrates	34.6	33.6	31.0
Diuretics	33.2	32.8	15.2
CCBs excl. diltiazem / verapamil	30.9	31.3	20.6
Oral hypoglycaemic agents	23.5	24.2	21.9
Diltiazem / verapamil	9.7	9.9	27.1
Clopidogrel	7.8	8.5	-
Oral anticoagulants	7.0	7.2	-
Insulin	7.3	6.8	11.7
NSAIDs	6.1	6.0	6.8
Alpha blockers	4.1	3.9	-
Fibrates	3.6	4.2	-
Ticlopidine	3.1	2.2	-
Other[3]	42.8	43.3	-
Gender-specific, %			
Estrogen replacement[5]	6.9	7.4	10.8
Estrogen and progesterone replacement[4]	2.0	2.1	2.6
Viagra / sildenafil[5]	1.7	0.9	-

[1] No definition provided in the CRF for regular use of previous medications
[3] Regular use of concomitant medications refers to at last 3 times per week.
[4] If a regular medication was not specifically listed in the CRF, the Investigator was to check the tick box 'other medication'.
[5] Percentage refers to female patients.
[6] Percentage refers to male patients.
[7] Information not available
[8] Lipid lowering agents
Source: Adapted from TRANSCEND CTR Table 11.2.7: 2

5.2.2.5 TRANSCEND - EFFICACY

5.2.2.5.1. Composite 4-fold and 3-fold endpoint of CV death, non-fatal MI, non-fatal stroke, with (4-fold) and without (3-fold) hospitalization for CHF

Table 5.2.2.5.1: 1 shows the results of the analysis on the 4-fold composite endpoint consisting of CV death, non-fatal MI, non-fatal stroke, and hospitalization for CHF and the 3-fold composite endpoint of CV death, non-fatal MI and non-fatal stroke. For patients who experienced several of these events, the first event was used for the calculation of hazard

ratios, the preparation of Kaplan-Meier curves, and other similar analyses. If multiple simultaneous events occurred, all the individual events were presented in tables

The primary 4-fold endpoint showed an 8% reduction vs. placebo (p=0.22). For the 3-fold endpoint telmisartan resulted in fewer adverse CV outcomes compared to placebo with a risk reduction of 13%, with a nominal p-value below 0.05 (HR 0.87 [0.76 – 1.0]). These effects were limited to reducing stroke and myocardial infarction in a different population from ONTARGET, and who were also taking different proportions of cardiovascular medications.

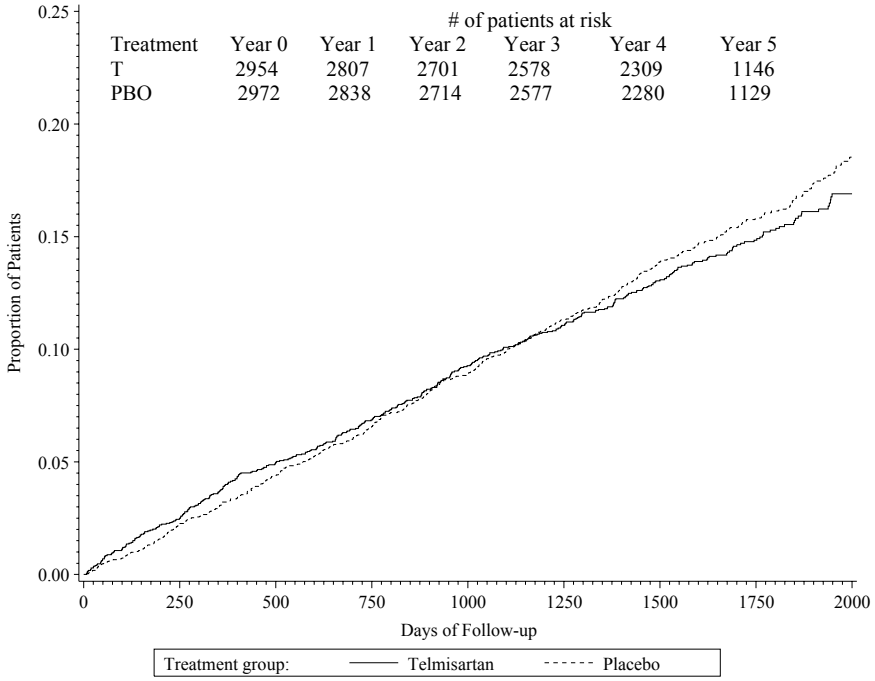
All 4 components of the composite endpoint contributed to the result with none of the individual components predominating.

Table 5.2.2.5.1: 1 TRANSCEND - incidence and ITT analysis of the 4-fold and 3-fold endpoint - first event.

	T	PBO
Randomized, n	2954 (100.0)	2972 (100.0)
4-fold endpoint[1], n (%)	465 (15.7)	504 (17.0)
CV death	140 (4.7)	137 (4.6)
Non-fatal MI	106 (3.6)	136 (4.6)
Non-fatal stroke	106 (3.6)	127 (4.3)
Hospitalization for CHF	123 (4.2)	112 (3.8)
Events per 100 patient years	3.58	3.87
Hazard ratio[2] vs. placebo (95% CI)	0.92 (0.81, 1.05)	
p-value	0.22	
3-fold endpoint[1], n (%)	384 (13.0)	440 (14.8)
CV death	169 (5.7)	170 (5.7)
Non-fatal MI	111 (3.8)	138 (4.6)
Non-fatal stroke	111 (3.8)	136 (4.6)
Events per 100 patient years	2.90	3.33
Hazard ratio[2] vs. placebo	0.87	
95% CI	(0.76, 1.00)	
p-value	0.0483	

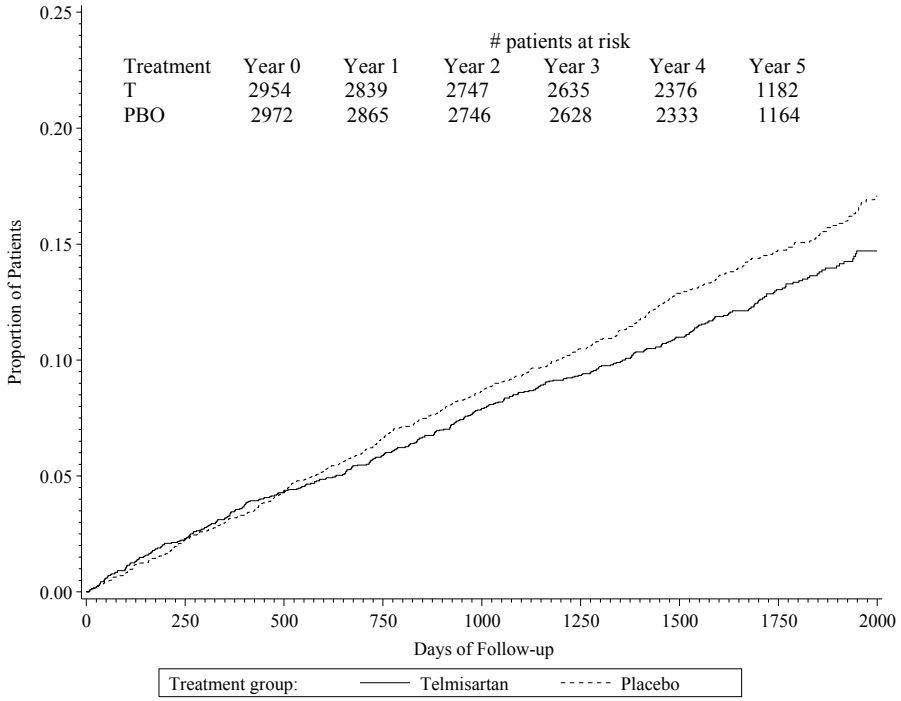
[1] The 4-fold endpoint was defined as the time to first event. In case of multiple simultaneous events, all individual events were considered; the sum of patients with individual outcomes may exceed the number of patients with primary outcomes.
[2] Cox regression
Source: Adapted from TRANSCEND CTR Table 11.4.1.1: 1

The Kaplan-Meier curves for the 4-fold and 3-fold composite endpoints are shown in Figure 5.2.2.5.1: 1 and Figure 5.2.2.5.1: 2, respectively. While the telmisartan curve is above placebo in the beginning of the trial, both curves cross at about 2 years and subsequently the telmisartan curve is below. The numbers of patients who were at risk, had an event, or were censored are given in Appendix E2, Table 2.



Source: TRANSCEND CTR Figure 11.4.1.1: 1

Figure 5.2.2.5.1: 1 TRANSCEND Kaplan-Meier estimates of the 4-fold endpoint.



Source: TRANSCEND CTR Figure 11.4.1.2.1: 1

Figure 5.2.2.5.1: 2 TRANSCEND Kaplan-Meier estimates of the 3-fold endpoint

5.2.2.5.2 Sensitivity Analyses for changes in blood pressure effect

As expected, patients who had received telmisartan in addition to standard treatment had a more pronounced BP reduction than patients in the placebo group. The individual mean change in sitting systolic blood pressure (SBP) post-randomization from baseline to last observation was −6.5 mmHg in the telmisartan group and −2.3 mmHg in the placebo group. To investigate the influence of blood pressure on the 4-fold endpoint, a Cox regression analysis with baseline SBP and time-dependent SBP measurements as covariate was performed. All available SBP values were taken into account as long as the patients were at risk. The results of this analysis are shown in Table 5.2.2.5.2: 1.

The relative hazard for a patient with a 10 mmHg-higher SBP at baseline to experience a primary outcome event was 1.02 (95% CI 0.98, 1.06). The relative hazard for a patient with a 10 mmHg-increase of the SBP during the study to experience a primary outcome event was 1.03 (95% CI 1.00, 1.07).

When adjusting for SBP, the hazard ratio of telmisartan vs. placebo was 0.94 (95% CI 0.83, 1.07; p = 0.3638). The adjusted hazard ratio was nearly identical to the unadjusted hazard ratio (HR 0.92; 95% CI 0.81, 1.05).

Table 5.2.2.5.2: 1 TRANSCEND Sensitivity ITT analysis of the 4-fold composite endpoint using baseline SBP and changes of SBP over time as covariates

	T	PBO
Impact of SBP on composite outcome[1], hazard ratio (95% CI)		
SBP at baseline	1.02 (0.98, 1.06)	
SBP time-dependent	1.03 (1.00, 1.07)	
Hazard ratio[2] vs. placebo (95% CI)	0.94 (0.83, 1.07)	
p-value	0.36	

[1] Per 10 mmHg
[2] Adjusted for all other factors in the Cox regression model
Source: Adapted from TRANSCEND CTR Table 11.4.1.1: 6

5.2.2.5.3 Other endpoints

5.2.2.5.3.1 Individual components of the 4-fold endpoint

Table 5.2.2.5.3.1: 1 presents results of analyses of the first occurrence of CV death, MI, stroke, and hospitalization for CHF (e.g. for the analysis of MI, only the first MI experienced by a patient was considered). Hazard ratios and Kaplan-Meier estimates were calculated for the first event in each category. For MI and stroke, these were determined (a) considering only non-fatal events according to the assessment of the Event Adjudication Committee (EAC) and (b) considering non-fatal and fatal events.

For the components CV death and hospitalization for CHF, the incidences in the 2 treatment groups were almost identical. For non-fatal MI, all MIs (fatal and non-fatal), non-fatal

strokes, and all strokes (fatal and non-fatal), the incidences were numerically lower in the telmisartan group than in the placebo group.

Table 5.2.2.5.3.1: 1 TRANSCEND Incidence and ITT analyses of the individual components of the 4-fold composite endpoint - first event in each category

	T	PBO
Randomized, n	2954 (100.0)	2972 (100.0)
CV death, n (%)	227 (7.7)	223 (7.5)
Events per 100 patient years	1.66	1.61
Hazard ratio[1] vs. placebo (95% CI)	1.03 (0.85, 1.24)	
Non-fatal MI, n (%)	114 (3.9)	145 (4.9)
Events per 100 patient years	0.85	1.07
Hazard ratio[1] vs. placebo (95% CI)	0.79 (0.62, 1.01)	
MI (non-fatal and fatal)[2], n (%)	115 (3.9)	147 (4.9)
Events per 100 patient years	0.85	1.09
Hazard ratio[1] vs. placebo (95% CI)	0.78 (0.61, 1.00)	
Non-fatal stroke, n (%)	112 (3.8)	136 (4.6)
Events per 100 patient years	0.83	1.01
Hazard ratio[1] vs. placebo (95% CI)	0.83 (0.64, 1.06)	
Stroke (fatal and non-fatal)[2], n (%)	112 (3.8)	136 (4.6)
Events per 100 patient years	0.83	1.01
Hazard ratio[1] vs. placebo (95% CI)	0.83 (0.64, 1.06)	
Hospitalization for CHF, n (%)	134 (4.5)	129 (4.3)
Events per 100 patient years	1.00	0.95
Hazard ratio[1] vs. placebo (95% CI)	1.05 (0.82, 1.34)	
Hospitalization for CHF confirmed by X-ray, n (%)	91 (3.1)	96 (3.2)
Events per 100 patient years	0.67	0.70
Hazard ratio[1] vs. placebo (95% CI)	0.96 (0.72, 1.27)	

[1] Cox regression
[2] Only those fatal events which were not adjudicated as CV death.
Source: Adapted from TRANSCEND CTR Table 11.4.1.2.2:1

Numerous patients experienced more than 1 outcome event during the trial. The table below (Table 5.2.2.5.3.1: 2) presents an overview for the 4-fold endpoint.

Table 5.2.2.5.3.1: 2 TRANSCEND: Distribution of patients by number of outcome events – 4-fold endpoint.

	T	**PBO**
1st event	465	504
2nd event	123	152
3rd event	35	47
4th event	12	23
5th event and more	5	19
Total number of events	640	745
CV death	228	223
MI	113	156
Stroke	124	156
CHF hospitalization	175	210

Source: TRANSCEND database

The proportional means model with sandwich variance estimate (cf. 5.1.6.5.2.1) was used to analyse these data. The resulting HR was 0.87 (95% CI 0.75, 1.00; p = 0.048). The majority of recurrent events were hospitalization for CHF.

For the 3-fold endpoint the number of patients with recurrent events, i.e. MIs or strokes, is displayed in Table 5.2.2.5.3.1: 3.

Table 5.2.2.5.3.1: 3 TRANSCEND: Distribution of patients by number of outcome events – 3-fold endpoint.

	T	**PBO**
1st event	384	440
2nd event	74	81
3rd event	7	12
4th event	-	2
Total number of events	465	535
CV death	228	223
MI	113	156
Stroke	124	156

Source: TRANSCEND database

The proportional means model with sandwich variance estimate (cf. section 4.2.1.6.5.2.1 was used to analyse these data. The resulting HR was 0.88 (95% CI 0.76, 1.01; p = 0.071).

5.2.2.5.4 All-cause mortality in all patients

A total of 713 (24.0%) patients died in the course of this study, including 364 patients (12.3%) in the telmisartan group and 349 (11.7%) in the placebo group (Table 5.2.2.5.4: 1).

Table 5.2.2.5.4: 1 TRANSCEND Incidence and ITT analysis of all-cause mortality

	T	PBO
Randomized, n	2954 (100.0)	2972 (100.0)
Patients 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)
Missing	0 (0.0)	1 (0.0)
Malignancy	66 (2.2)	67 (2.3)
Other causes	71 (2.4)	58 (2.0)
Events per 100 patient years	2.66	2.53
Hazard ratio1 vs. placebo (95% CI)	1.05 (0.91, 1.22)	

[1] Cox regression
Source: Adapted from TRANSCEND CTR Table 11.4.1.2.4: 1

5.2.2.5.5 Non-CV death

To complement the analysis of CV death, the occurrence of non-CV death was explored. The results are shown in Table 5.2.2.5.5: 1.

Table 5.2.2.5.5: 1 TRANSCEND Incidence of non-CV death / FAS

	T	PBO
Randomized, n	2954 (100.0)	2972 (100.0)
Non-CV death, n (%)	137 (4.6)	126 (4.2)
Events per 100 patient years	1.00	0.91
Hazard ratio[1] vs. placebo (95% CI)	1.10 (0.86, 1.40)	

[1] Cox regression
Source: Adapted from TRANSCEND CTR Table 11.4.1.2.4: 2

As noted the baseline medication use differed between the placebo and telmisartan groups cardiovascular medications including calcium channel blockers and diuretics. A further increased use in diuretics in placebo treated patients during the trial is presented in elsewhere in this document.

5.3 PROFESS - TRIAL DESIGN AND EFFICACY

5.3.1 Trial Design

PRoFESS was a 2x2 factorial study testing whether telmisartan was superior to placebo for reducing the risk of recurrent stroke in patients on anti-platelet therapy (either a fixed dose combination of ASA and dipyridamole ER or Clopidogrel). PRoFESS enrolled a different population than ONTARGET and TRANSCEND. A theoretical consideration was that early blood pressure reduction could be beneficial for these patients who are at higher risk of recurrent stroke in the first days after their primary stroke. Patients were enrolled soon after a stroke (40% within 10 days and 69% within 30 days), which had not previously been done in other secondary stroke prevention studies and almost one third of the patients were Asian. There also was less beta blocker, statin and dihydropyridine use than in ONTARGET.

PRoFESS enrolled 20,332 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 randomized for treatment with telmisartan (n=10,146) or placebo (n=10,186). Patients were treated for 19 months to 4 years and 5 months (mean duration of only 2.0 years). The PRoFESS study aimed to determine if telmisartan 80 mg is superior to placebo in reducing the risk of secondary stroke. A secondary endpoint evaluating the reduction in risk of a composite endpoint of CV death, MI, stroke, or hospitalization for CHF was also evaluated. An additional endpoint was the composite of CV death, non-fatal MI, and non-fatal stroke (primary endpoint of the HOPE study

This document presents study objectives, endpoints and results for the telmisartan versus placebo arms only.

Figure 5.3.1: 1 presents a schematic of the overall trial design of PRoFESS

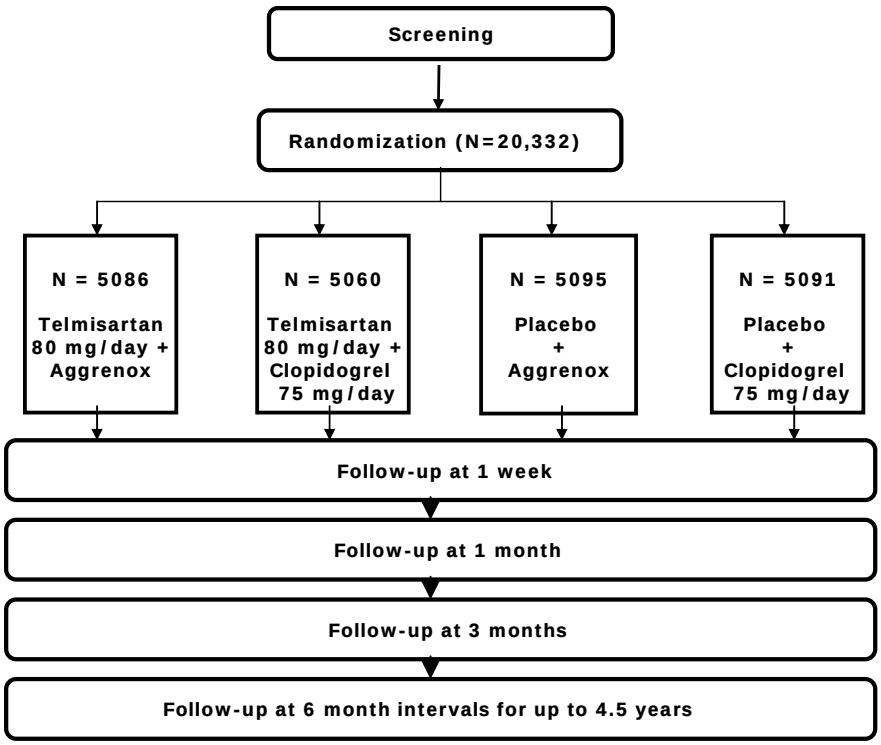


Figure 5.3.1: 1 PRoFESS flow chart.

5.3.2 Key Inclusion Criteria

Patients 55 years or older who had survived an ischemic stroke within the last 120 days or 50 to 54 years of age and/or 91 to 120 days after ischemic stroke, plus at least 2 additional risk factors (diabetes mellitus, hypertension (SBP ≥140 or DBP ≥90 mmHg), smoker at time of qualifying stroke, obesity (BMI ≥30 km/m^2), previous vascular disease (stroke, MI, or PAD prior to the qualifying stroke), end-organ damage (retinopathy, LVH, or microalbuminurea), and/or hyperlipidaemia).

5.3.3 Trial Endpoints

The primary endpoint was the time to the first recurrent stroke (ischemic, haemorrhagic, or of uncertain cause; fatal or non-fatal) over the course of the study.

Secondary endpoints for the telmisartan versus placebo comparison consisted of:

- Composite of CV death, MI, stroke, MI or new or worsening CHF (4-fold endpoint)
- Components of the 4-fold endpoint
- Three-fold endpoints (CV death, MI, or stroke), post-hoc

5.3.4 Safety Analyses

Only SAEs (excluding study outcome events) and adverse events leading to discontinuation of study medication were collected. Standard non-serious AEs were not recorded. Outcome events were analyzed solely as efficacy data and were not included in the safety analysis unless the Investigator reported them as SAEs. An independent DSMB monitored the safety data during the course of the study

5.3.5 Planned Statistical Analysis

In the telmisartan comparison, telmisartan was tested for superiority over placebo. The primary model used for analysis for both treatment comparisons was a Cox proportional hazards regression model with treatment as main effects and age, diabetes, baseline ACE-I use, and baseline modified Rankin score as covariates. In addition, the results for the primary and the composite endpoints are presented as Kaplan-Meier survival curves. The RAN was defined as including all patients who signed informed consent and were randomized following an ITT principle.

5.3.6 Baseline Characteristics and Results

Although the patient population is different, patients eligible to participate in PRoFESS would generally also have been eligible to participate in ONTARGET or TRANSCEND.

5.3.6.1 Patient Disposition

Eligible patients were randomized to either telmisartan (n=10,146) or placebo (n=10,186) and at the same time to either ASA+ER-DP or clopidogrel in a factorial design

Among the randomized patients, 67% of the patients were treated with ARB study medication until the end of their observation time (Table 5.3.6.1: 1). The frequencies of permanent premature discontinuations were 32.1% in the telmisartan group and 29.3% in the placebo group. The difference between the groups was primarily due to AEs (excluding outcome events); in the telmisartan group, 14.3% of the patients discontinued study medication because of AEs, compared to 11.1% in the placebo group.

Table 5.3.6.1: 1 Treatment disposition of patients at the end of the observation period (PRoFESS telmisartan comparison) / RAN

	T n (%)	PBO n (%)
Randomized patients	10 146 (100.0)	10 186 (100.0)
Not treated	127 (1.3)	133 (1.3)
Treated	10 019 (98.7)	10 053 (98.7)
Not prematurely discontinued from trial medication[1]	6756 (66.6)	7067 (69.4)
Prematurely discontinued from trial medication[1]	3255 (32.1)	2981 (29.3)
Adverse event[2]	1451 (14.3)	1128 (11.1)
Non-compliant with protocol[3]	815 (8.0)	830 (8.1)
Outcome event[4]	596 (5.9)	613 (6.0)
Consent withdrawn	114 (1.1)	137 (1.3)
Lost to follow-up	39 (0.4)	43 (0.4)
Other	237 (2.3)	229 (2.2)
Missing reason	3	1
No treatment disposition data available[3]	8 (0.1)	5

[1] Only refers to telmisartan or placebo, not to antiplatelet study medication. Percentages for 'not prematurely discontinued' and for 'prematurely discontinued' do not add up to 100% because of the patients not treated and the patients without treatment disposition data. Only permanent discontinuations are considered.
[2] Note that 28 patients had fatal AEs documented as reasons for premature discontinuation.
[3] The Investigators' comments were grouped into the following categories: 'Trial therapy stopped' (no further explanation given) in almost 50% of cases, 'Patient changed mind on trial' (about 16% of cases), 'Patient did not attend' (about 13% of cases), 'Other medical complications', 'Trial/medications too complex', 'Recommended to stop by 3rd party', 'Difficulties traveling to site', 'Patient moved', and 'Unknown' (4% or less for each of the latter 6 categories).
[3] Patients without data for the CRF page 'Permanent termination of trial medication'.
4 In total, 35% (approximately 420 patients) of these patients died within 7 days of the discontinuation.
Source: PRoFESS CTR Table 10.B.1: 2

Patients from the combined region of Europe, Israel and Australia represented the largest group at 38.3%, followed by Asia with 31.8% of patients, North America with 24.4%, and South America plus South Africa with 5.6%.

5.3.6.2 Description of Patient Population

The majority (64.0%) of patients were men (Table 5.3.6.2: 1). White patients made up 57.5% of patients, 32.8% were Asian, 4.0% black and 5.7% from other ethnic groups.

Table 5.3.6.2: 1 Demographic characteristics at baseline

	T		PBO	
Number of randomized patients, n (%)	10 146	(100.0)	10 186	(100.0)
Age, mean (SD) [years]	66.1	(8.6)	66.2	(8.6)
Age group, n (%)				
<65 years	4593	(45.3)	4539	(44.6)
≥65 to <75 years	3656	(36.0)	3746	(36.8)
≥75 years	1897	(18.7)	1901	(18.7)
Sex, n (%)				
Male	6527	(64.3)	6495	(63.8)
Female	3619	(35.7)	3691	(36.2)
Race, n (%)				
White	5827	(57.4)	5870	(57.6)
Asian	3332	(32.8)	3328	(32.7)
Black	407	(4.0)	409	(4.0)
Other	580	(5.7)	579	(5.7)
BMI, mean (SD) [kg/m^2]	26.8	(5.0)	26.8	(5.0)
Obesity[1], n (%)	2600	(25.6)	2607	(25.6)

Obesity status was not assessed for 86 patients (0.4% overall).
[1]Non-Asian patients with BMI ≥30 kg/m2 and Asian patients with BMI ≥27 kg/m2 were considered obese
Source: PRoFESS CTR Table 11.B.2.1: 1

Several baseline conditions were identified that could have had an influence on the incidence of outcome events, including systolic and diastolic BP, the characteristics of the qualifying ischemic stroke, the time from the qualifying stroke to randomization, and the severity of the qualifying stroke (measured using the modified Rankin scale and the NIHSS). Table 5.3.6.2: 2 summarizes this data.

Table 5.3.6.2: 2 Stroke risk factors at baseline

	T		PBO	
Number of randomized patients, n (%)	10 146	(100.0)	10 186	(100.0)
Seated DBP[1], mean (SD) [mmHg]	83.8	(10.5)	83.8	(10.6)
Seated SBP[1], mean (SD) [mmHg]	144.1	(16.4)	144.2	(16.7)
Pulse rate, mean (SD) [bpm]	73.2	(11.7)	73.1	(11.7)
Time from qualifying stroke to randomization, n (%)				
≤10 days	4021	(39.6)	4066	(39.9)
11 to 30 days	2959	(29.2)	2928	(28.7)
31 to 90 days	2785	(27.4)	2831	(27.8)
>90 days	360	(3.5)	338	(3.3)

[1] DBP and SBP were recorded in 20 325 patients
Source: PRoFESS CTR Table 11.B.2.3: 1

The most common concomitant medications recorded at baseline were antihypertensive medications (67.3%), followed by antithrombotics (65.8%), and lipid-modifying medications (48.5%). No relevant differences in the use of concomitant medications were detected between treatment groups at baseline (Table 5.3.6.2: 3).

Table 5.3.6.2: 3 Medications at baseline

	T		PBO	
	n (%)		n (%)	
Randomized patients	10 146	(100.0)	10 186	(100.0)
Antihypertensive medications	6809	(67.1)	6875	(67.5)
ACE-Is	3737	(36.8)	3782	(37.1)
CCBs other than Diltiazem/Verapamil	2257	(22.2)	2227	(21.9)
Beta-blockers	2096	(20.7)	2135	(21.0)
Thiazide diuretics	1721	(17.0)	1779	(17.5)
ARBs	513	(5.1)	546	(5.4)
Antithrombotic medications	6712	(66.2)	6669	(65.5)
Lipid-modifying agents	4867	(48.0)	4999	(49.1)
Anti-diabetic medications	2216	(21.8)	2251	(22.1)
Cardiac therapy	550	(5.4)	566	(5.6)

Note that antithrombotic medications and ARBs had to be stopped prior to randomization
[1] Percentages are based on female patients only

5.3.7 PRoFESS - EFFICACY

5.3.7.1 Primary endpoint

The primary objective of the telmisartan comparison was to test whether telmisartan was superior to placebo for the time to first recurrent stroke.

The incidence of the primary endpoint was slightly lower for telmisartan (8.7%) than for placebo (9.2%). The hazard ratio for telmisartan vs. placebo was 0.95 (95% CI 0.86, 1.04) with p = 0.23 as shown in Table 5.3.7.1: 1

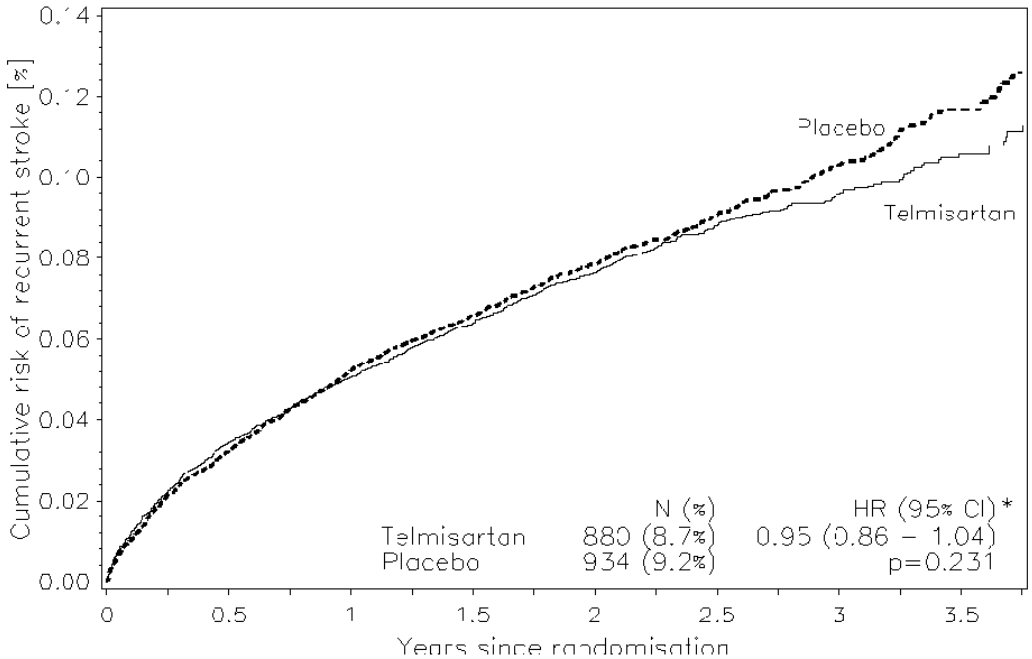
Table 5.3.7.1: 1 Cox proportional hazards analysis of recurrent stroke (PRoFESS telmisartan comparison) / RAN

	T	PBO
Patients randomized, n	10 146	10 186
Patients with recurrent stroke, n (%)	880 (8.7)	934 (9.2)
Hazard ratio[1] vs. placebo	0.95	-
95% Confidence interval	(0.86, 1.04)	-
p-value	0.23	-

The analysis is based on adjudicated results.

[1] Cox proportional hazards model with age, baseline diabetes status, baseline ACE-I use, and baseline Modified Rankin score as covariates. Source; PRoFESS CTR Table 11.B.4.1.1.2: 1

The results of the Kaplan-Meier analysis of the primary endpoint for the RAN are presented in Figure 5.3.7.1: 1. The curves appear to be diverging toward the end of the trial.



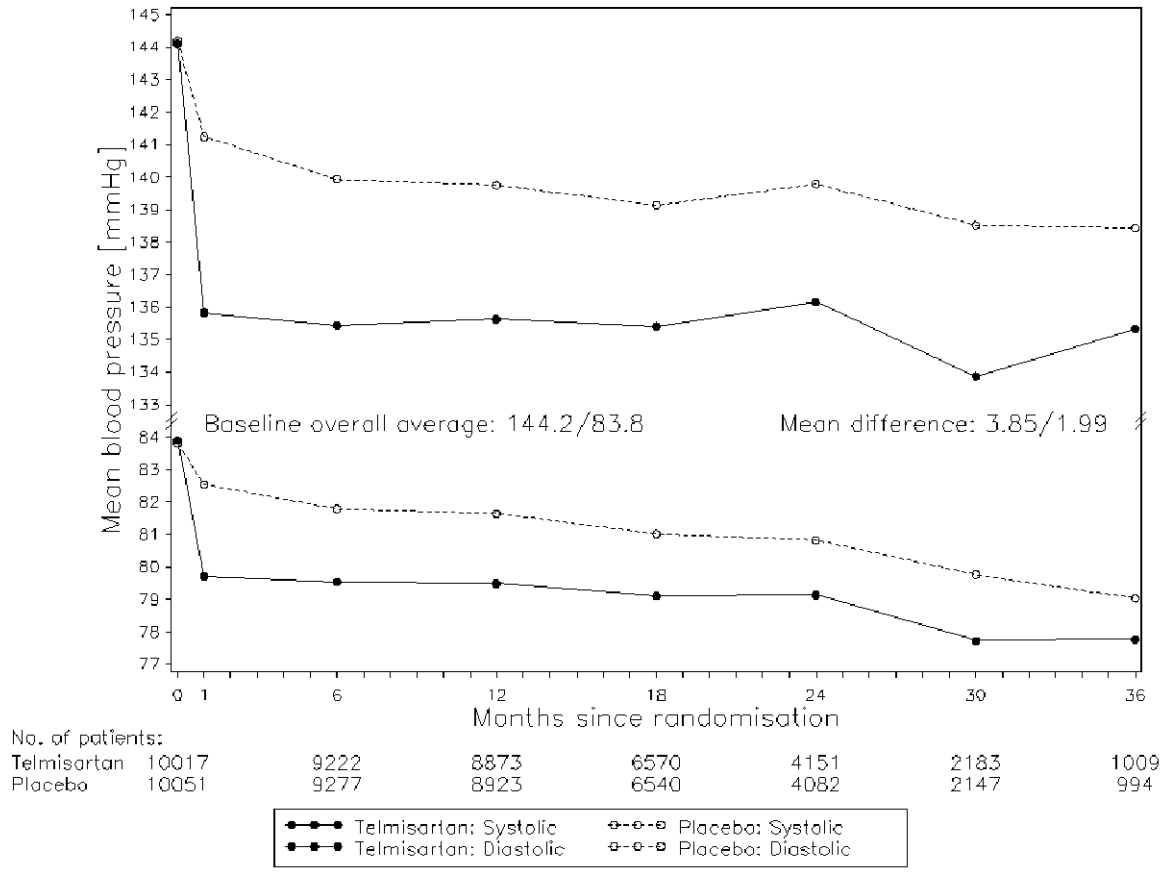
NOTE: Figure displays Kaplan–Meier probability of having an event.

* Covariates in the Cox model are age, baseline ACE–inhibitor use, modified Rankin score, and baseline diabetes status.

Source: PRoFESS CTR Figure 11.B.4.1.1.2: 1

Figure 5.3.7.1: 1 Kaplan-Meier estimates for the primary endpoint time to recurrent stroke (PRoFESS telmisartan comparison) / RAN

Management of blood pressure was recognized as an important factor in this trial. Therefore, irrespective of randomization, Figure 5.3.7.1: 2 presents mean SBP and DBP over time for the 2 treatment groups for the treated set of patients (TS-B). The mean BP at baseline was essentially identical in both treatment groups. Mean BP was lower in the telmisartan group compared to placebo at all subsequent visits.



BP was measured at each clinical visit (using standardised machines provided by the Sponsor). Blood pressure readings were taken after 5 min of sitting (or in the supine position, if patients could not sit). Recorded BP values consisted of 3 consecutive measurements taken approximately 2 min apart and rounded to the nearest whole number.
The standard deviations in the 2 treatment groups at the different time points ranged from 16.0 mmHg to 24.1 mmHg for SBP and from 10.5 mmHg to 11.6 mmHg for DBP.
The average BP was a weighted average of the in-trial BPs, weighted by the amount of time they account for (e.g. 1 month visit = 1/6, 3 month visit = 1/3, 6 month visit = 1/2, 1 year visit = 1). The mean difference is the difference between the means of the weighted averages.

Source: PRoFESS CTR Figure 11.B.4.1.1.4: 1

Figure 5.3.7.1: 2 Mean SBP and DBP by treatment group over time (PRoFESS telmisartan comparison) / TS-B

The influence of the amount of time each patient had controlled BP on the results of the primary analysis was investigated. The patient population was divided into 4 subgroups according to the proportion of visits at which patients had controlled BP: <25% of visits, 25% to <50% of visits, 50% to <75% of visits, and ≥75% of visits. This subgroup analysis revealed a trend at the $\alpha = 0.01$ level for a subgroup-by-treatment interaction ($p = 0.02$), indicating that patients who had BP control only for short periods were apparently at greater risk of stroke. For example, patients with BP control for <25% of visits had a HR for the primary endpoint of 1.07 (95% CI 0.90, 1.25), while those with BP control for ≥75% of visits had a HR of 0.81 (95% CI 0.68, 0.97).

5.3.7.2 Analysis of the 4-fold composite endpoint

The 4-fold composite of CV death, stroke, MI, or hospitalization for CHF (primary endpoint in ONTARGET and TRANSCEND) was a secondary endpoint in PRoFESS. According to the statistical analysis plan, secondary endpoints were to be tested sequentially for superiority

of telmisartan over placebo only if the primary endpoint had shown statistical superiority. As shown previously, telmisartan was not superior to placebo on the primary endpoint of time to first recurrent stroke. Thus, the results for this secondary endpoint are interpreted as exploratory only.

The same Cox regression model as for the primary analysis was used. The frequency of patients reaching the 4-fold composite outcome was slightly lower for telmisartan (13.5%) than for placebo (14.4%) (Table 5.3.7.2: 1).

Table 5.3.7.2: 1 Analysis of the composite secondary endpoint of recurrent stroke, MI, new or worsening CHF, and death due to vascular cause (PRoFESS telmisartan comparison) / RAN

	T		PBO	
Patients randomized, n	10 146		10 186	
Patients who reached composite outcome[1], n (%)	1367	(13.5)	1463	(14.4)
Recurrent stroke	855	(8.4)	914	(9.0)
MI	168	(1.7)	169	(1.7)
New or worsening CHF	121	(1.2)	117	(1.1)
Death due to vascular causes	223	(2.2)	263	(2.6)
Hazard ratio[2] vs. placebo	0.94		-	
95% Confidence interval	(0.87, 1.01)		-	
p-value	0.11		-	

The analysis is based on adjudicated results.
[1] For the composite outcome, only the first event of one of the components is counted per patient. Only these events contribute to the individual totals.
[2] Cox proportional hazards model with age, baseline diabetes status, baseline ACE-I use, and baseline modified Rankin score as covariates
Source: PRoFESS CTR Table 11.B.4.1.2.1: 1.

.
In the primary PRoFESS publication, the Investigators presented a number of analyses in addition to the primary endpoint result. Included in these analyses were: results of the 3-fold HOPE endpoint, and since the proportional hazards model was violated, results of the primary and HOPE endpoint before and after 6-months participation in the trial.

5.4 POOLED ANALYSES

Combination therapy in ONTARGET demonstrated that combining an ARB/ACE-I provided no additional benefit and a worse safety profile compared to monotherapy in this patient population (see Safety section). In clinical practice, the appropriate population for risk reduction by telmisartan monotherapy would be patients not prescribed ACE-Is at initial assessment. Thus, in order to better define the magnitude of the benefit of telmisartan for this ACE-I naïve population, the Sponsor performed a pooled analysis of the 2 placebo controlled trials. It has been speculated that the benefits of a number of cardioprotective treatments including ACE-I are not observed until after several months of exposure. This finding was further explored in the PRoFESS publication.

Pooling of data was considered reasonable since patients in PRoFESS were stratified by ACE-I use at baseline and the HOPE risk scores across trials were similar. This analysis was

specified by the Academic Investigators prior to unblinding TRANSCEND. Further information including, for example, patient demographics of the pooled population is provided in Appendix E3, Tables 1 and 2.

5.4.1 Efficacy analyses of pooled data

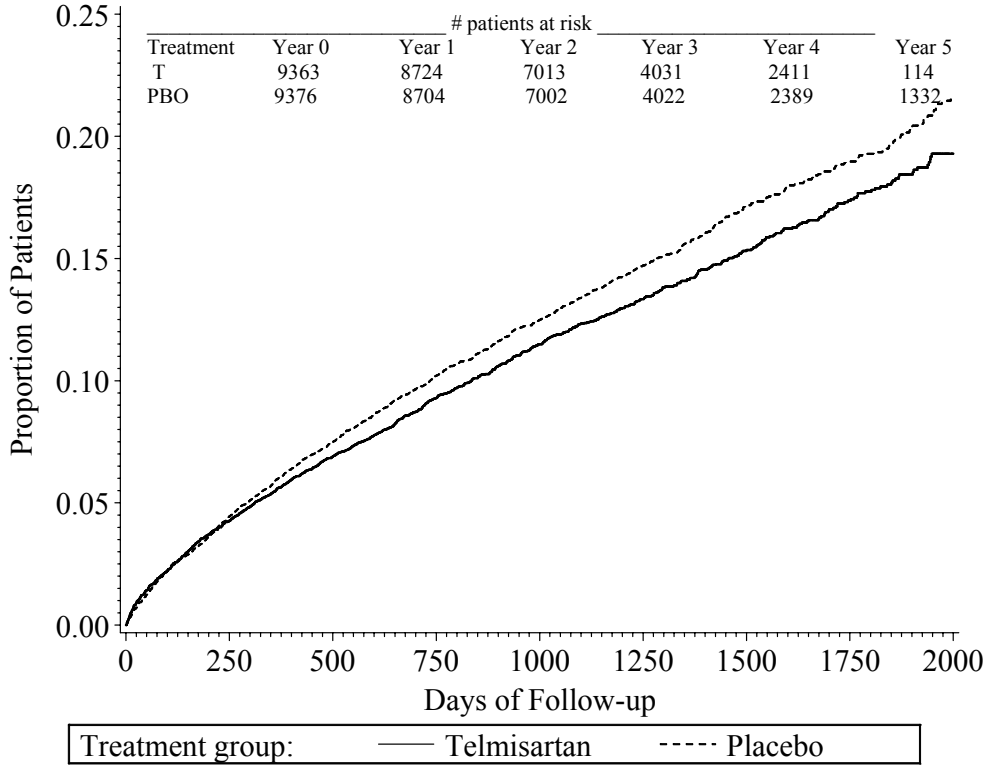
The incidence of the 4-fold endpoint and the event rate per 100 patient years were analyzed in the pooled analysis population (Table 5.4.1:1). The Kaplan-Meier estimates are also shown (Figure 5.4.1: 1). No study-by-treatment interaction was observed (p>0.99).

Non-fatal stroke was the outcome that had the highest contribution to the composite endpoint. The high rate of stroke is attributable to patients enrolled in PRoFESS since these patients had a qualifying stroke (median time from stroke to enrollment was 15 days in the PRoFESS study) and were therefore at a very high risk of having a second stroke.

Table 5.4.1: 1 Pooled analysis: incidence and ITT analysis of the 4-fold endpoint. - first event / Total/BL-NoACE-I)

	T		PBO	
Randomized, n (%)	9363	(100.0)	9376	(100.0)
Primary endpoint[1], n (%)	1284	(13.7)	1383	(14.8)
CV death	278	(3.0)	304	(3.2)
Non-fatal MI	202	(2.2)	231	(2.5)
Non-fatal stroke	642	(6.9)	694	(7.4)
Hospitalization for CHF	189	(2.0)	175	(1.9)
Events per 100 patient years	4.56		4.94	
Hazard ratio[2] vs. placebo	0.92			
95% CI	(0.86 – 1.00)			
Interaction between treatment and study	>0.99			

[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: Biostats output appSECT[1]



Source:SCE

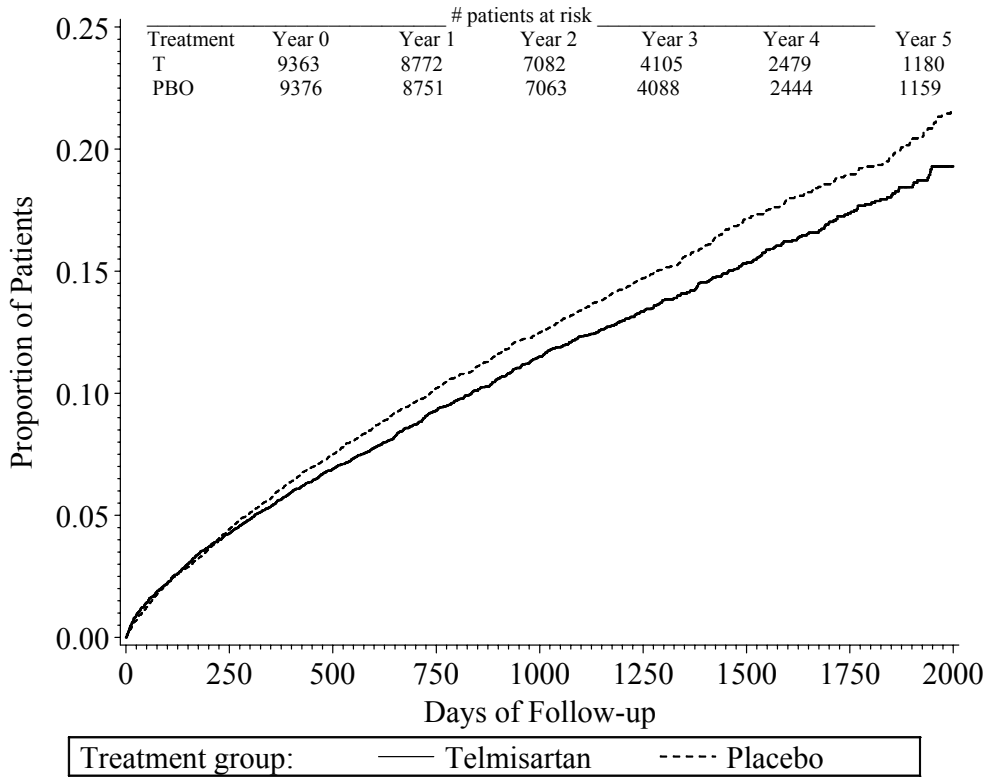
Figure 5.4.1: 1 Kaplan-Meier estimates of the 4-fold endpoint - Total/BL-No-ACE

The 3-fold endpoint was also analyzed for the pooled patient population of the TRANSCEND and PRoFESS trials (Table 5.4.1:2, Figure 5.4.1: 2). The incidence of the 3-fold composite endpoint as well as the event rate per 100 patient years were lower with T than with PBO. No study-by-treatment interaction was observed (p = 0.52).

Table 5.4.1:2 Pooled analysis incidence and analysis of the 3-fold endpoint - first event / Total/BL-NoACE-I)

	T		PBO	
Randomized, n (%)	9363	(100.0)	9376	(100.0)
3-fold endpoint, n (%)[1]	1163	(12.4)	1279	(13.6)
CV death	278	(3.0)	304	(3.2)
Non-fatal MI	202	(2.2)	231	(2.5)
Non-fatal stroke	642	(6.9)	694	(7.4)
Events per 100 patient years	4.09		4.52	
Hazard ratio[2] vs. placebo	0.90			
95% CI	(0.84 – 0.98)			
Interaction between treatment and study	0.52			

[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
Source: Biostats output appSECT[1]



Source: SCE

Figure 5.4.1:2 Kaplan-Meier estimates of the 3-fold endpoint - Total/BL-No-ACE)

The 3-fold endpoint was also analyzed for the pooled patient population who did not use ACE-I at any time during the studies. These results are presented in Appendix E3, Table 3 and Figure 1.

5.5 DISCUSSION OF EFFICACY RESULTS

5.5.1 ONTARGET

ONTARGET a 25,000 patient outcome trial with a mean 4.5 year follow-up had two clinically relevant findings:

1. The telmisartan/ramipril combination was not superior to telmisartan or ramipril alone and had a worse safety profile.

2. Telmisartan was non-inferior to ramipril.The protocol-specified non-inferiority margin for ONTARGET was a hazard ratio of 1.13. The upper bounds of the 97.5% confidence intervals (adjustment for multiple testing) for ONTARGET were 1.10 and 1.08 for the 4-fold and 3-fold endpoints, respectively, thus meeting the protocol-specified non-inferiority margin and demonstrating that telmisartan was non-inferior to ramipril for both endpoints. An estimate of the effect of ramipril (based on a pooled analysis of 3 studies of ACE-I in patients not required to have left ventricular dysfunction) was similar to that from the HOPE study alone. Telmisartan is considered effective as it unequivocally preserved 51% of the estimated effect of ramipril. The other secondary endpoints were consistent with this conclusion.

3. The results from ONTARGET demonstrate that telmisartan preserved about 95% (95% CI, 66, 124) of the benefits of ramipril over placebo with respect to the 4-fold endpoint, and preserved 105% (95% CI, 74 to 137) of the benefits with respect to the 3-fold outcome based on 'putative' placebo comparison of the point estimate (Hasselblad et al 2001) from the HOPE study. Thus, according to the CI from this calculation, telmisartan preserves at least 2/3 of ramipril's effect for the 4-fold endpoint and 3/4 for the 3-fold endpoint.

A series of studies (SAVE, AIRE, TRACE and SOLVD) conducted over a decade and half in the 1980s and early 1990s evaluated the effects of multiple ACE-Is in patients with systolic dysfunction (LVEF ≤ 0.40). Significant cardiovascular outcome benefits (approximately 20% relative risk reduction) on mortality, myocardial infarction and hospitalization for CHF were demonstrated in patients with LV dysfunction and/or heart failure, with or without a previous myocardial infarction The HOPE study, conducted in the late 1990s, showed clinical benefit in patients who did not have heart failure at baseline. Each component of the composite endpoint showed an approximate 20 % reduction in relative risk reduction (see Table 4.1.1: 2). There have been no large long-term outcome studies investigating the effect of ACE-Is on CV outcomes specifically in patients with relatively preserved LV function. The benefits have been consistently demonstrated in multiple trials over the last 2 decades, in patients well treated with evidence-based medications appropriate for the time.

For ARBs, results of several clinical outcome trials became available after ONTARGET was initiated. These trials evaluated patients with LV dysfunction and/or heart failure (ELITE-II, CHARM-added, CHARM-alternative, Val-HeFT, VALIANT, and OPTIMAAL). The relative risk reduction for CV death, stroke, and MI of these contemporary trials was generally less than those observed in the trials with ACE-Is in the 1980s and 1990s. These studies of ACE-Is and ARBs collectively changed treatment guidelines and reduced the occurrence of CV events in patients with LV dysfunction, with or without heart failure and in patients at high risk of CV events. ACE-Is and ARBs are now recommended (Class IIA) for patients at high risk for developing heart failure with a history of atherosclerotic vascular disease, diabetes, or hypertension with associated cardiovascular risk factors (AHA/ACC guidelines).

Several clinical outcome trials have investigated whether ARBs, or a combination of ARBs and ACE-Is, prevents CV events, including heart failure. Table 4.1.2: 1 provides an overview of outcome trials with ARBs. With the exception of CHARM-preserved and I-PRESERVE, patients had systolic dysfunction and/or heart failure. Note concomitant therapy use (e.g., statins, beta blockers, and diuretics) changed during ONTARGET and these trials. Use of these medications has improved the cardiovascular outcomes of patients as treatment guidelines have been updated, although the relative risk reductions observed in the more recent studies of ACE-Is and ARBs do not appear to have been affected by these changes in clinical practice patterns.

Two studies specifically evaluated patients with relatively preserved LV function (I-PRESERVE and CHARM-preserved). These studies did not demonstrate a benefit of ARBs in reducing heart failure hospitalizations in patients with relatively preserved LV function.

The results of ONTARGET are consistent with the body of evidence for trials of agents that block the RAAS. Telmisartan reduced the incidence of stroke and MI. This effect was seen in

all but one of the pre-specified subgroups supporting the clinical utility of these effects in a broad patient population.

The incidence of new CHF may also have been masked by an increased use of diuretics. The analysis of the combined outcome "New CHF or addition of diuretics" in ONTARGET revealed no difference between T and R (HR=1.00, 95% CI 0.94, 1.06).

Consistency of the ramipril effect when comparing HOPE and ONTARGET is suggested by the results of a 2-step analysis. In a first step, a Cox regression model for the ONTARGET data (4-fold endpoint) was built including all patient characteristics that are known as predictors of CV risk (e.g. patient history, concomitant medication). In a second step, this model was applied to a theoretical set of patients treated with ramipril assuming the distribution of the included covariates across patients would be the same as it was in the HOPE study. The resulting Kaplan-Meier curves (Figure 5.5.1: 1) for telmisartan and ramipril (from the 1st step) are displayed together with the theoretical curve for ramipril assuming an identical population as in HOPE had been included. In addition, the real curve for ramipril from HOPE is shown. Two conclusions can be drawn from this analysis: First, over the complete observation period the number of events is smaller in the real ramipril group than in the theoretical group, suggesting that the patients were at a higher risk and/or were less effectively treated with co-medication (especially statins). Second, the real curve of ramipril in HOPE is very similar to the theoretical curve of ramipril in ONTARGET, suggesting that the adjusted effect of ramipril was reasonably consistent in both studies.

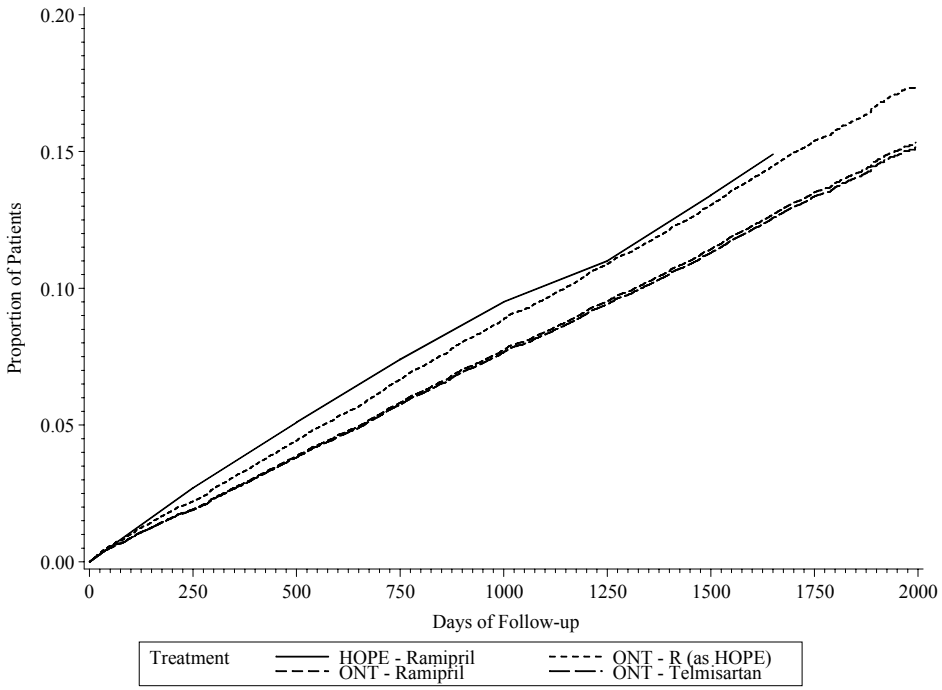


Figure 5.5.1: 1. Adjusted* Kaplan-Meier curves comparing ramipril in HOPE and ONTARGET

* Adjusted for sex, age, CAD, PAD, prior stroke/TIA, hypertension, diabetes, baseline SBP/DBP, pulse rate, current smoking, co-medication with beta-blockers, statins

Given the consistency of the ramipril effect across both studies, a 'putative' placebo comparison (Hasselblad et al 2001) was performed based on the historical data of the HOPE study.

The indirect comparison for the 4-fold endpoint revealed an HR vs. placebo of 0.79 (95% CI 0.70, 0.89). For the 3-fold endpoint the resulting HR was 0.77 (95% CI 0.68, 0.88). In terms of effect preservation, telmisartan preserved about 95% (95% CI, 66, 124) of the benefits of ramipril over placebo with respect to the 4-fold endpoint, and preserved 105% (95% CI, 74 to 137) of the benefits with respect to the 3-fold outcome. Thus, according to this calculations at least 2/3 of ramipril's effect are preserved for the 4-fold endpoint and 3/4 for the 3-fold endpoint.

5.5.2 Supportive Evidence

Two pieces of additional evidence further support the use of telmisartan for CV risk reduction:

1. TRANSCEND demonstrated that for the 3-fold endpoint telmisartan resulted in fewer adverse CV outcomes compared to placebo with a risk reduction of 13%, with a nominal p-value below 0.05. These effects were limited to reducing stroke and myocardial infarction in a population different from ONTARGET.

The effect of telmisartan on CHF may have been masked by an increased use of diuretics in the placebo group. The analysis of the combined outcome "New CHF or addition of diuretics" revealed a clear difference between patients treated with telmisartan and placebo (HR = 0.80, 95% CI 0.72, 0.89; p = 0.0001).

2. Data from an analysis of placebo-controlled studies for patients who would be appropriate for the use of telmisartan (i.e., not receiving an ACE-I when telmisartan is started) provides additional supportive information that telmisartan prevents the occurrence of myocardial infarction and stroke in high risk patients. Data for the 3-fold endpoint from this analysis identified a 10% reduction by telmisartan compared to placebo. The Investigator generated analysis for both PRoFESS and TRANSCEND highlighted a greater effect size when time-points beyond 6 months of observation were evaluated.

5.5.3 Discussion

The data from this clinical research program in over 50,000 patients demonstrates that telmisartan reduces the occurrence of CV events in high risk patients, predominantly strokes and myocardial infarctions. The data showed consistency of telmisartan’s effects across all major subgroups in all studies and no treatment by subgroup interaction in virtually all subgroups. Specifically, analyses were performed demonstrating the use of statins and beta blockers, which have been shown to improve cardiovascular outcomes, did not affect the ability to demonstrate non-inferiority. Statin use more than doubled from 29% at the beginning of HOPE to 71% at the end of the ONTARGET. Similarly, there was an approximate 50% increase in the use of beta blockers.

Results for the 3-fold endpoint are consistent across both populations who tolerate ACE-I and those intolerant of ACE-I. The latter group presently has no available proven therapeutic alternative RAAS blocking agent. Similar results were obtained when comparing the results

of ONTARGET and TRANSCEND with an Investigator pre-specified pooled analysis of placebo controlled studies in patients not receiving ACE-I at study entry.

Telmisartan provided benefit comparable to ramipril on top of the current evidence-based standard of care (high use of statins, aspirin, beta-blockers, etc). The protocol-specified non-inferiority margin for ONTARGET was a hazard ratio of 1.13. The upper bounds of the 95% confidence intervals for ONTARGET were 1.09 and 1.07 for the 4-fold and 3-fold endpoints, respectively, thus meeting the protocol-specified non-inferiority margin and demonstrating that telmisartan was non-inferior to ramipril for both endpoints. In terms of effect preservation, telmisartan preserved about 95% (95% CI, 66, 124) of the benefits of ramipril over placebo with respect to the 4-fold endpoint, and preserved 105% (95% CI, 74 to 137) of the benefits with respect to the 3-fold outcome. The other secondary endpoints were consistent with this conclusion.

An additional analysis simulating the effect of ramipril in ONTARGET based upon the characteristics of the patients in HOPE supported that there was constancy of ramipril's effect in the 2 studies. This supports the continued clinical relevance of the landmark HOPE study results despite changes in treatment paradigms and guidelines.

Placebo-controlled studies cannot be run except in limited, and clinically distinct, patient populations (i.e., ACE-I intolerant) because of the demonstrated benefit of current cardiovascular therapies. Looking at the pooled analysis of placebo controlled trials, telmisartan had a 10% relative risk reduction compared to placebo in patients not taking ACE-Is. This magnitude of effect is comparable with other contemporary clinical trials (for example the CHARM program).

A non-inferiority margin for ONTARGET was selected that was identical to the margin selected for VALIANT (1.13), which resulted in an FDA approval for valsartan to reduce cardiovascular mortality in post-myocardial infarction patients with left ventricular dysfunction. Similar to VALIANT, this margin preserved at least 66% for the 4-fold and 74% for the 3-fold endpoints of the effect of ramipril on cardiovascular outcomes.

In conclusion, this clinical research program of contemporaneously conducted trials generated data from over 50,000 patients to assess the effects of telmisartan in reducing cardiovascular outcomes in patients at high risk for their occurrence. These data demonstrate that telmisartan provides incremental benefit for patients at high risk for the occurrence of cardiovascular events (i.e., MI and stroke) in contemporary medical practice.

6. SAFETY

6.1 INTRODUCTION

This briefing document summarizes data from more than 50,000 patients randomized in ONTARGET, TRANSCEND and PRoFESS with approximately 180,000 years of observation time. Information from other sources is also provided for the special topics discussed in this section.

The safety profiles for ramipril and other ACE-Is were well characterized at the time these outcome studies were designed. The recording of safety data was limited to serious adverse events (SAE) and adverse events (AE) that resulted in treatment discontinuation; this approach was discussed with FDA.

Because of a higher incidence of adverse events in patients receiving the combination of T/R in ONTARGET but without additional efficacy, data for this treatment group will generally not be presented in this document. Some of the safety data for T/R are included in Appendix S1.

Safety data during the randomized period were collected differently in ONTARGET / TRANSCEND compared with PRoFESS. The differences are presented in Appendix S2.

6.2 OVERALL EXTENT OF EXPOSURE

In all 3 studies, patients were strongly encouraged to remain in the study even if they were no longer taking study medication. In ONTARGET and TRANSCEND, every attempt was made to restart study medication if it was medically appropriate. Because of differences in observation time (from several days up to 6 years), the data are presented as percentage of patients and where applicable per 100 patient years (100PY) of exposure duration. Ninety-nine percent of patients were followed until trial completion or death. Adherence to study medication was assessed by inspection of returned medication.

6.2.1 Overall observation time during the run-in period

6.2.1.1 ONTARGET

In ONTARGET, 29,019 patients were enrolled in the run-in period. The mean observation time during the run-in period was 25.2 days. For more details refer to Table 6.2.1.1: 1.

Table 6.2.1.1: 1 Observation time in the run-in period / ONTARGET RIS

	Run-in
Number of patients enrolled	29019
Observation time [days]	
Mean (SD)	25.2 (5.9)
Median	24.0
Observation categories, n (%)	
1 to ≤11 days	272 (0.9)
12 to ≤29 days	26969 (93.0)
≥ 30 days	1770 (6.1)
Missing	8 (0.0)
Overall patient years	1998

Source: Adapted from ONTARGET CTR Table 12.1.1: 1

6.2.1.2 TRANSCEND

In TRANSCEND, 6665 patients were enrolled in the run-in period. The mean observation time during the run-in period was 25.2 days. For more details refer to Table 6.2.1.2: 1.

Table 6.2.1.2: 1 Observation time during the run-in period / TRANSCEND RIS

	Run-in
Number of patients enrolled	6665
Observation time [days]	
Mean (SD)	25.2 (5.6)
Median	24.0
Observation categories, n (%)	
1 to ≤15 days	98 (1.5)
16 to ≤29 days	6136 (92.1)
≥30 days	428 (6.6)
Missing	3 (0.0)
Overall patient years	460

Source: Adapted from TRANSCEND CTR Table 12.1.1:

6.2.2 Overall observation time during the randomized period

6.2.2.1 ONTARGET

Mean observation time on treatment was comparable in the T group (1507 days) and the R group (1499 days). In both treatment groups, about 70% of patients were on treatment between 4 and 5 years and about 20% were on treatment more than 5 years. An overview of the observation time on treatment is provided in Table 6.2.2.1: 1.

Table 6.2.2.1: 1 Observation time on treatment in the randomised period of the trial / ONTARGET FAS

	T/R	T	R
Number of patients randomised n (%)	8502 (100.0)	8542 (100.0)	8576 (100.0)
Observation time [days]			
Mean (SD)	1444.2 (564.9)	1507.2 (505.5)	1499.4 (516.2)
Median	1635.0	1641.0	1640.0
Observation categories, n (%)			
≤3 years	607 (7.2)	552 (6.4)	563 (6.6)
3 to ≤4 years	271 (3.2)	253 (3.0)	261 (3.0)
4 to ≤5 years	5863 (69.0)	6019 (70.5)	5991 (69.9)
>5 years	1761 (20.7)	1718 (20.1)	1761 (20.5)
Overall patient years	33616	35249	35207

Note: 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 documented and the date of randomisation +1 day.
Source: Adapted from ONTARGET CTR Table 12.1.2: 1

Dose reduction in the randomised period

In ONTARGET, a down-titration of the ramipril dose from R10 to R5 (either active or matching placebo) was allowed for patients who experienced an AE. Dose-reduction of telmisartan to 40 mg was allowed from the 2-year visit (Visit 7) on. Only permanent treatment discontinuations were recorded. Owing to the double dummy design in ONTARGET it was possible that patients discontinued telmisartan, ramipril, or the respective matching placebo.

At year 4, the percentage of patients taking the full study dose of ramipril was much higher in ONTARGET than HOPE. In addition, a greater percentage of patients in the R group had reduced their dose or had discontinued ramipril (Table 6.2.2.1: 2) as compared to patients in the T group.

Table 6.2.2.1: 2 Comparison of dosing at year 4 in ONTARGET and HOPE

	ONTARGET		HOPE
	Telmisartan	Ramipril	Ramipril
Use of full study dose (%)	83.4	77.7	62.4
Dose reduction (%)	0.6	3.9	--
Discontinuation of study medication (%)	16.0	18.3	--

Source: Adapted from ONTARGET CTR Tables 15.1.5.1: 5; 15.1.5.1: 6; The HOPE Study Investigators, 2000a

In ONTARGET, telmisartan was better tolerated than ramipril. Permanent discontinuation of active telmisartan was significantly less than active ramipril, with a hazard ratio of 0.90 (p=0.0008). For permanent discontinuations of active treatment due to AEs, the hazard ratio was 0.79 (p <0.0001). Cough and angioedema more frequently resulted in treatment discontinuation for ramipril, despite the fact that 58% of ONTARGET patients had previously regularly taken ACE-Is before study entry and there was a run-in period which screened out more ACE-I intolerant patients.

6.2.2.2 TRANSCEND

The mean observation time on treatment was comparable between the T group (1527 days) and the PBO group (1515 days). In both treatment groups, about 40% of the patients were on treatment between 4 and 5 years; a similar percentage of patients were on treatment between 5 and 6 years. This between-group difference is consistent with fewer patients who permanently discontinued treatment in the T group than in the PBO group. An overview of the observation time on treatment is provided in Table 6.2.2.2: 1.

Table 6.2.2.2: 1 Observation time on treatment in the randomised period of the trial / TRANSCEND FAS

	Telmisartan		**Placebo**	
Number of patients randomised n (%)	2954	(100.0)	2972	(100.0)
Observation time [days]				
Mean (SD)	1526.9	(544.4)	1515.2	(548.2)
Median	1651.5		1644.0	
Observation categories, n (%)				
≤3 years	208	(7.0)	206	(7.0)
3 to ≤4 years	246	(8.3)	263	(8.8)
4 to ≤5 years	1239	(41.9)	1211	(40.7)
>5 years	1261	(42.7)	1292	(43.4)
Overall patient years	12349		12329	

Note: 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 medication was documented and the date of randomisation +1 day
Source: Adapted from TRANSCEND CTR Table 12.1.2: 1.

Dose reduction of telmisartan in the randomised period

The percentage of patients who reduced the dose of telmisartan was low at all visits. At the 4 year visit, 1.1% of patients in the T group and 0.5% of patients in the PBO group had reduced the dose to 40 mg. At year 4, 17.6% of patients in the T group and 18.1% of patients in the PBO group had permanently discontinued study medication.

6.2.2.3 PRoFESS/NoACE-I

The ONTARGET study unequivocally demonstrated that T should not be used with R in this patient population. Data from PRoFESS for patients taking ACE-I other than R showed similar safety findings. Therefore, in this document in general PRoFESS data will be presented for patient not receiving ACE-I (NoACE-I). The observation times on treatment for this population are presented in Table 6.2.2.3: 1.

Table 6.2.2.3: 1 Observation time on treatment in the randomised period of the PRoFESS trial / treated set (PRoFESS/NoACE-I)

	T	PBO
Patients treated	5589	5277
Time of observation [days]		
Mean (SD)	715.9 (398.1)	733.7 (386.5)
Median	764	775
Time categories, n (%)		
1 to ≤2 years	1240 (22.2)	1046 (19.8)
>2 to ≤3 years	1376 (24.6)	1336 (25.3)
>3 to ≤4 years	2067 (37.0)	2010 (38.1)
>4 years	906 (16.2)	885 (16.8)
Overall patient years	10955	10600

Source: Adapted from Summary of Clinical Safety Table 12.3.2:1

6.3 SAFETY ANALYSIS

Table 6.3: 1 and Table 6.3: 2 detail the analysis sets used in the analysis of safety during the run-in and randomized periods, respectively.

Table 6.3:1 Numbers of patients included in the safety sets during the run-in period

Study	Name of analysis set	Total	T	PBO	R
Run-in periods					
ONTARGET	ONTARGET RIS	29019	N.A.	N.A.	N.A.
TRANSCEND	TRANSCEND RIS	6665	N.A.	N.A.	N.A.

RIS: run-in set, comprising all patients enrolled;
Source: Adapted from Summary of Clinical Safety Table 1.1.4.: 1

Table 6.3: 2 Numbers of patients included in the different safety sets during the randomized period

Study	Name of analysis set	Total	T/R	T	PBO	R
Randomized periods						
ONTARGET	ONTARGET FAS	17118	8502	8542	N.A.	8576
TRANSCEND, all patients	TRANSCEND FAS	5926	N.A	2954	2972	N.A.
PRoFESS, all patients	RAN (PRoFESS)	20332	N.A	10146	10186	N.A.
PRoFESS, no ACE-I use[1, 2]	RAN (PRoFESS/NoACE-I)	11011	N.A.	5661	5350	N.A.
PRoFESS, ACE-I use[1]	RAN (PRoFESS/ACE-I)	9321	N.A.	4485	4836	N.A.

FAS: full analysis set, comprising all patients randomized irrespective of treatment; TS: treated set, comprising all patients who received at least one dose of telmisartan/matching placebo

[1] ACE-I use recorded at baseline or at any time during the PRoFESS trial. This analysis focuses on patients who did not receive ACE-Is in PRoFESS, however, an additional report on the safety of these patients also includes the safety analyses for the patients who received ACE-Is. Both analysis sets are mutually exclusive.

[2]No ACE-I use at any time

Source: Adapted from Summary of Clinical Safety Table 1.1.4: 1

A number of subgroups were analyzed as part of the safety analyses in ONTARGET, TRANSCEND, and PRoFESS. The core subgroups with defining criteria are presented in Table 6.3: 3.

Table 6.3: 3 Core subgroups analyzed for the evaluation of safety

Subgroup with defining criteria
Age (<65, ≥65 to <75 years, ≥75 years)
Sex (male, female)
Ethnicity (white, black, Asian, others)
Obesity (BMI ≥30 kg/m2) 1
Presence of hypertension2
Presence of diabetes3
Impaired renal function4 (eGFR <60 mL/min/1.73 m2)
Geographical region5 (North America, Europe/South Africa, Asia/Middle East, Latin America, and Australia/New Zealand)

[1] In Asian patients, the cut-off was 27 kg/m^2

[2] As given in patient history and/or seated SBP ≥140 mmHg or DBP ≥90 mmHg at start of run-in; in PRoFESS, only the patient history was evaluated

[3] As given in patient history and/or fasting plasma glucose level ≥125 mg/dL (7 mmol/L) at start of run-in; in PRoFESS, only the patient history was evaluated

[4] At baseline

[5] Geographical regions were not analyzed for the clinical laboratory evaluations in the ONTARGET and TRANSCEND trials.

Source: Summary of Clinical Safety Table 1.1.4: 3

6.3.1 Adverse Events during run-in period

Table 6.3.1:1 presents the overall summary of AEs leading to treatment discontinuation during the run-in period of ONTARGET. This should be viewed in the context that 57.6%

and 8.6% of patients, respectively, reported previous regular use of ACE-Is and ARBs at study entry.

Table 6.3.1: 1 Overview of the most common reasons leading to permanent treatment discontinuation during the run-in period (in at least 0.1% of any treatment group) / ONTARGET RIS

	Total	
	n	**(%)**
Enrolled	29019	(100.00)
Deaths	29	(0.10)
Patients with permanent treatment discontinuation	1120	(3.86)
Patients with reasons for permanent treatment discontinuation considered as AEs	1067	(3.68)
Cough	313	(1.08)
Dizziness / vertigo / light headedness	212	(0.73)
Hypotension / low BP	192	(0.66)
Eczema / rash / itch / allergies / dermatitis	76	(0.26)
Fatigue / weakness / lethargy / hypotonia	74	(0.26)
Cephalgia / headache	71	(0.24)
Nausea / vomiting	70	(0.24)
Diarrhea	62	(0.21)
Abdominal discomfort; pain, upset / GI irritation / GI syndrome	48	(0.17)
Angioedema	40	(0.14)
Increase in laboratory values (general, not specified)	37	(0.13)
Other pain / myalgia / arthritis pain / back pain / joint pain	37	(0.13)
Unwell / malaise / discomfort / flu symptoms / cold	34	(0.12)
Patients with other reasons for permanent treatment discontinuation	119	(0.41)
Patient refusal / withdrawn / decision / patient reasons	59	(0.20)
Other reasons	52	(0.18)

Reasons for permanent treatment discontinuation are based on PHRI coding. Note that patient frequencies are given and multiple entries are possible. GI: gastrointestinal, BP: Blood pressure
Source: Summary of Clinical Safety Table 2.1.1.3: 1

Adverse events leading to permanent treatment discontinuation during the Run-in Period of the TRANSCEND trial are presented in Table 6.3.1: 2. Of note, cough was responsible for a greater rate of study discontinuation during the run-in period of ONTARGET (1.08%) in patients receiving active R and/or T than TRANSCEND (0.29%) in patients receiving only active T. In addition, 40 patients developed angioedema during the run-in period.

Table 6.3.1:2 Overview of the most common reasons leading to permanent treatment discontinuation during the run-in period (in at least 0.1% of patients) / TRANSCEND RIS

	Total	
	n	**(%)**
Enrolled	6665	(100.00)
Deaths	3	(0.05)
Patients with permanent treatment discontinuation	175	(2.63)
Patients with reasons for permanent treatment discontinuation considered as AEs	169	(2.54)
Dizziness / vertigo / light headedness	45	(0.68)
Fatigue / weakness / lethargy / hypotonia	21	(0.32)
Nausea / vomiting	20	(0.30)
Cough	19	(0.29)
Eczema / rash / itch / allergies / dermatitis	19	(0.29)
Cephalgia / headache	18	(0.27)
Hypotension / low BP	16	(0.24)
Diarrhea	16	(0.24)
Abdominal discomfort; pain, upset / GI irritation / GI syndrome	15	(0.23)
Unwell / malaise / discomfort / flu symptoms / cold	12	(0.18)
Other pain / myalgia / arthritis pain / back pain / joint pain	7	(0.11)
Patients with other reasons leading to permanent treatment discontinuation	24	(0.36)
Other reasons	14	(0.21)
Patient refusal / withdrawn / decision / patient reasons	8	(0.12)

Reasons for permanent treatment discontinuation are based on PHRI coding. Note that patient frequencies are given and multiple entries are possible. GI: gastrointestinal, BP: Blood pressure
Source: Summary of Clinical Safety Table 2.1.1.3: 3

6.3.2 Adverse Events during the randomized period

Table 6.3.2: 1 and Table 6.3.2: 2 present an overview of AEs in the randomized periods of ONTARGET and TRANSCEND, and PRoFESS/NoACE-I at any time, respectively. Note that in PRoFESS, outcome events were only analyzed as efficacy data and, thus, are not included in the tabulations of SAEs.

Table 6.3.2: 1 Overall summary of SAEs and deaths reported during the randomized period / ONTARGET FAS and TRANSCEND FAS

	ONTARGET			TRANSCEND								
				R			T			PBO		
	n	(%)	PY[1]	n	(%)	PY[1]	n	(%)	PY[1]	n	(%)	PY[1]
Randomized	8542	(100)		8576	(100)		2954	(100.0)		2972	(100.0)	
Total Deaths[4]	989	(11.58)	2.54	1014	(11.82)	2.60	364	(12.32)	2.66	349	(11.74)	2.53
Deaths on Treatment	750	(8.78)	2.13	759	(8.85)	2.16	284	(9.61)	2.30	266	(8.95)	2.16
Non-CV deaths	267	(3.13)	0.76	274	(3.19)	0.78	94	(3.18)	0.76	94	(3.16)	0.76
Deaths Post Treatment	239	(2.80)	6.54	255	(2.97)	6.60	80	(2.71)	5.91	83	(2.79)	5.59
Non-CV deaths	124	(1.45)	3.40	137	(1.60)	3.55	43	(1.46)	3.18	32	(1.08)	2.15
Patients w SAEs[2]	5537	(64.82)	14.23	5416	(63.15)	13.86	1802	(61.00)	13.15	1825	(61.41)	13.21
Patients w SAEs on treatment[2,3,5]	5282	(61.84)	14.98	5158	(60.14)	14.65	1691	(57.24)	13.69	1739	(58.51)	14.11
Patients w SAEs post treatment[2,3,6]	666	(7.80)	18.24	653	(7.61)	16.91	237	(8.02)	17.50	243	(8.18)	16.36

[1] Adjusted for observation time (patients per 100 patient years).
[2] Excluding deaths. Non-fatal SAEs that occurred in patients who later died are included. All information is based on the information provided by the Investigators.
[3] SAEs with an onset date before the date of the visit at which permanent discontinuation was documented +1 day were considered to have occurred 'on treatment', SAEs with an onset date thereafter until the final visit +1day 'post-treatment'. Note that 25 patients with SAEs were also reported after the final visit +1 day for ONTARGET and 7 patients for Transcend. These SAEs are described in the text.
[4] All causes comprises all deaths reported, i.e. reported as outcome event or SAE. Deaths were generally to be reported as outcome events, except for deaths occurring later than 14 days after the final patient contact; these were to be reported as SAEs. In addition, SAEs could have had the information 'fatal' on the SAE report form; these are presented as 'fatal SAEs' in this table.
[5] Patients were considered on treatment from randomization up to permanent treatment discontinuation +28 days and post-treatment from permanent treatment discontinuation +28 days up to the last patient contact +28 days; 21 SAEs reported after the last patient contact +28 days ('post final visit') are described in the text.
Source: Adapted from ONTARGET CTR Table 12.2.1: 2; TRANSCEND CTR Table 12.2.1: 2

Table 6.3.2: 2 Overall summary of SAEs and deaths reported during the randomized period / PRoFESS/NoACE-I (treated set)

	T			PBO		
	n	**(%)**	**PY1**	**n**	**(%)**	**PY1**
Randomized	5589	(100.0)		5277	(100.0)	
Total Deaths2	417	(7.46)	3.81	389	(7.37)	3.67
Patients w SAEs on treatment3	1277	(22.85)	11.66	1107	(20.98)	10.44
Patients w SAEs post-treatment3	376	(6.73)	3.43	316	(5.99)	2.98

[1] Adjusted for observation time (patients per 100 patient years).
[2] All causes comprises all deaths reported, i.e. reported as outcome event or SAE. Deaths were generally to be reported as outcome events, except for deaths occurring later than 14 days after the final patient contact; these were to be reported as SAEs.
[3] Patients were considered on treatment from randomization up to permanent treatment discontinuation +28 days and post-treatment from permanent treatment discontinuation +28 days up to the last patient contact.
Source: Adapted from Summary of Clinical Safety Table 2.1.2: 3

6.3.2.1 ONTARGET

6.3.2.1.1 AEs leading to permanent treatment discontinuation

Adverse events leading to permanent treatment discontinuation were reported at comparable frequencies in the T group and the R group (Table 6.3.2.1.1: 1). As expected, cough, and angioedema occurred more commonly with R and hypotension/low blood pressure occurred more frequently with T.

Table 6.3.2.1.1: 1 Overview of AEs leading to permanent treatment discontinuation during the randomized period (in at least 0.2% of patients in any treatment group) / ONTARGET FAS

	T n=8542		R n=8576	
	%	PY[1]	%	PY[1]
Patients with AE leading to permanent treatment discontinuation	8.19	1.99	8.73	2.13
Hypotension / low blood pressure	1.53	0.37	1.13	0.28
Cough	0.56	0.14	1.67	0.41
Dizziness / vertigo / light headedness	0.73	0.18	0.50	0.12
Hospitalization	0.76	0.18	0.69	0.17
Renal impairment / renal failure / renal artery stenosis / nephropathy / kidney disease / haemodialysis /nephrosclerosis	0.61	0.15	0.58	0.14
Increase in K (Potassium) / hyperkalaemia	0.35	0.09	0.33	0.08
Hypertension / higher blood pressure / uncontrolled high BP	0.59	0.14	0.48	0.12
Increase in creatinine	0.39	0.09	0.27	0.07
Fatigue / weakness / lethargy / hypotonia	0.41	0.10	0.27	0.07
Cancer	0.26	0.06	0.48	0.12
Eczema / rash / itch / allergies / dermatitis	0.25	0.06	0.38	0.09
Other pain / myalgia / arthritis pain / back pain / joint pain	0.30	0.07	0.33	0.08
Unwell / malaise / discomfort / flu symptoms / cold	0.18	0.04	0.24	0.06
Stroke / TIA / CVA	0.25	0.06	0.27	0.07
Nausea / vomiting	0.20	0.05	0.20	0.05
CHF / heart failure / heart insufficiency / cardiac insufficiency	0.26	0.06	0.15	0.04
MI	0.29	0.07	0.12	0.03
Angioedema	0.07	0.02	0.23	0.06

AEs leading to permanent treatment discontinuation are based on PHRI coding. Multiple entries are possible.
GI: gastrointestinal.
1 Adjusted for observation time (patients per 100 patient years).
Source: ONTARGET CTR Table 12.3.2.3.2.1: 1

6.3.2.1.2 Serious adverse events

The incidences of SAEs while on treatment were generally comparable in the T and R treatment groups in the ONTARGET trial (Table 6.3.2.1.2: 1).

Table 6.3.2.1.2: 1 Frequencies of patients with SAEs while on treatment during the randomized period by SOC and PT (PT in at least 1% of patients in any treatment group) / ONTARGET FAS

	T		R	
	N = 8542		N = 8576	
	%	PY[1]	%	PY[1]
Patients with SAEs	64.46	15.62	62.67	15.27
Surgical and medical procedures	28.38	6.88	27.66	6.74
Coronary angioplasty	7.55	1.83	7.19	1.75
Cataract operation	6.61	1.60	6.70	1.63
Angioplasty	3.90	0.94	3.70	0.90
Coronary artery bypass	3.04	0.74	3.16	0.77
Retinal laser coagulation	2.21	0.54	2.34	0.57
Knee arthroplasty	1.14	0.28	0.93	0.23
Hip arthroplasty	1.07	0.26	0.72	0.18
Cardiac disorders	26.75	6.48	25.45	6.20
Angina pectoris	15.17	3.68	14.51	3.53
Atrial fibrillation	5.84	1.42	5.94	1.45
Myocardial infarction	5.62	1.36	5.33	1.30
Cardiac failure[2]	5.74	1.39	5.52	1.34
Vascular disorders	10.96	2.66	10.95	2.67
Intermittent claudication	8.03	1.95	7.66	1.87
Hypertension	0.98	0.24	1.10	0.27
Nervous system disorders	9.79	2.37	9.93	2.42
Cerebral infarction	3.03	0.73	3.16	0.77
Transient ischaemic attack	2.14	0.52	2.32	0.57
Cerebrovascular accident	1.65	0.40	1.89	0.46
Syncope	1.56	0.38	1.48	0.36
Neoplasms benign, malignant and unspecified[3]	8.51	2.06	8.22	2.00
Prostate cancer	1.59	0.39	1.39	0.34
Lung neoplasm malignant	1.19	0.29	1.27	0.31
Skin cancer	1.17	0.28	1.19	0.29
Infections and infestations	8.10	1.96	8.52	2.08
Pneumonia	3.63	0.88	3.24	0.79
Metabolism and nutrition disorders	7.63	1.85	7.25	1.77
Diabetes mellitus	4.61	1.12	4.21	1.03
Hyperglycaemia	1.56	0.38	1.54	0.37
Renal and urinary disorders	4.89	1.19	4.63	1.13
Diabetic nephropathy	2.12	0.51	2.10	0.51
Renal failure	1.35	0.33	1.25	0.30
General disorders and administration site conditions	4.95	1.20	4.71	1.15
Sudden cardiac death	1.81	0.44	1.64	0.40

	T		R	
	N = 8542		N = 8576	
	%	PY[1]	%	PY[1]
Chest pain	1.12	0.27	1.20	0.29
Skin and subcutaneous tissue disorders	4.23	1.02	4.47	1.09
Skin ulcer	3.68	0.89	3.74	0.91
Diabetic ulcer	1.42	0.34	1.33	0.32
Injury, poisoning and procedural complications	3.99	0.97	3.86	0.94
Fall	1.16	0.28	1.14	0.28
Blood and lymphatic system disorders	2.07	0.50	1.82	0.44
Anaemia	1.83	0.44	1.53	0.37

Note that frequencies of patients are presented and patients could have experienced SAEs of different preferred terms (PTs).
[1] Adjusted for observation time (patients per 100 patient years).
[2] Reported PTs: cardiac failure, cardiac failure acute, cardiac failure congestive, and cardiac failure chronic
[3] Including cysts and polyps.
Source: ONTARGET CTR Table 12.3.2.2.1: 1

6.3.2.1.3 Deaths

Overall the percentage of patients who died during the randomized period was comparable between the T group (11.58%) and the R group (11.82%; Table 6.3.2: 1). The percentage of randomized patients who died while on treatment was also comparable between the T group (8.78%) and the R group (8.85%). In the following subsections, the primary causes of death and SAEs reported in association with death are presented separately.

Primary causes of death during the randomized period

The most frequently reported primary causes of death were other sudden cardiac death (T: 1.80%; R: 1.61%) and cancer (T: 1.53%; R: 1.56%) while on treatment. Other sudden cardiac death excludes MI, stroke, and ventricular tachyarrhythmia. Other causes were observed in 1.88% of patients in the T group and in 1.66% of patients in the R group. Similar to the primary causes of death reported while on treatment, cancer and other sudden cardiac death were also the most frequently primary causes of death reported post-treatment.

Primary causes of death while on treatment and post-treatment were comparable between treatment groups, also after adjustment for observation time. Worsening of heart failure as the primary cause of death was reported less frequently in the T group (0.29%) than in the R group (0.59%), a between-treatment difference that was also seen after adjustment for observation time.

6.3.2.1.4 Adverse events of special interest

Cough, angioedema, renal failure, and signs of renal dysfunction are adverse events commonly associated with RAAS blockade. Hypotensive symptoms and syncope are adverse events commonly associated with anti-hypertensive medications. These adverse events were defined post-hoc as AEs of special interest.

Table 6.3.2.1.4: 1 compares the treatment groups with respect to the incidence of these events. Statistically significant differences in cough (p = <0.0001) and angioedema (p = 0.007) were reported with the event occurring more frequently in the R group compared to

the T group. Hypotensive symptoms were reported more frequently in the T group than the R group (p = 0.0003). All other events, including syncope, occurred at similar rates in the two groups.

Table 6.3.2.1.4: 1 Overview of analysis of AEs of special interest – ONTARGET / FAS

	T	**R**
	N = 8542	**N = 8576**
Cough, n (%)	99 (1.16)	365 (4.26)
RR1 vs. ramipril (95% CI)	0.27 (0.22, 0.34)	
p-value	<0.0001	
Angioedema, n (%)	11 (0.13)	28 (0.33)
RR1 vs. ramipril (95% CI)	0.39 (0.20, 0.79)	
p-value	0.007	
Hypotensive symptoms, n (%)	408 (4.78)	315 (3.67)
RR1 vs. ramipril (95% CI)	1.30 (1.13, 1.50)	
p-value	0.0003	
Syncope, n (%)	167 (1.96)	159 (1.85)
RR1 vs. ramipril (95% CI)	1.05 (0.85, 1.31)	
p-value	0.63	
Renal failure, n (%)	239 (2.80)	222 (2.59)
RR1 vs. ramipril (95% CI)	1.08 (0.90, 1.29)	
p-value	0.40	
Signs of renal dysfunction, n (%)2	796 (9.32)	744 (8.68)
RR1 vs. ramipril (95% CI)	1.07 (0.98, 1.18)	
p-value	0.14	

[1]Risk ratio, χ^2 test.
[2]Signs of renal dysfunction are listed in Appendix S3, Table 1.
Source: Adapted from ONTARGET CTR Table 12.3.2.4.2: 1

6.3.2.2 TRANSCEND

6.3.2.2.1 Adverse events leading to permanent treatment discontinuation

Adverse events leading to permanent treatment discontinuation were reported in slightly more patients in the T group than in the PBO group (Table 6.3.2.2.1: 1). This difference between treatment groups was also seen after adjustment for observation time. As expected, the types of AEs commonly associated with T were more frequently reported.

Table 6.3.2.2.1: 1 Overview of AEs leading to permanent treatment discontinuation during the randomized period (in at least 0.2% in either treatment group) / TRANSCEND FAS

	T N = 2954		PBO N = 2972	
	%	PY[1]	%	PY[1]
Patients with AE leading to permanent treatment discontinuation	8.36	2.00	7.57	1.82
Hypertension / higher blood pressure / uncontrolled high BP	0.61	0.15	1.01	0.24
Hospitalization	0.64	0.15	0.71	0.17
CHF / heart failure / heart insufficiency / cardiac insufficiency	0.51	0.12	0.61	0.15
Hypotension / low blood pressure	0.71	0.17	0.37	0.09
Dizziness / vertigo / light headedness	0.74	0.18	0.30	0.07
Renal impairment / renal failure / renal artery stenosis / nephropathy / kidney disease / haemodialysis / nephrosclerosis	0.64	0.15	0.37	0.09
Eczema / rash / itch / allergies / dermatitis	0.44	0.11	0.54	0.13
Cough	0.44	0.11	0.40	0.10
Proteinuria / microalbuminuria	0.37	0.09	0.44	0.11
Other Pain / myalgia / arthritis pain / back pain / joint pain	0.37	0.09	0.30	0.07
Unwell / malaise / discomfort / flu symptoms / cold	0.30	0.07	0.34	0.08
Cancer	0.34	0.08	0.30	0.07
Abdominal discomfort; pain, upset / GI irritation / GI syndrome	0.44	0.11	0.13	0.03
MI	0.24	0.06	0.27	0.06
Fatigue / weakness / lethargy / hypotonia	0.17	0.04	0.27	0.06
Increase in creatinine	0.30	0.07	0.07	0.02
Nausea / vomiting	0.20	0.05	0.17	0.04
Increase in K (Potassium) / hyperkalaemia	0.34	0.08	0.00	0.00
Diarrhea	0.24	0.06	0.07	0.02

AEs leading to permanent treatment discontinuation are based on PHRI coding. Multiple entries are possible. GI: gastrointestinal.
[1] Adjusted for observation time (patients per 100 patient years).
Source: Adapted from TRANSCEND CTR Table 12.3.2.3.2.1: 1

6.3.2.2.2 Serious adverse events

The incidence of SAEs was comparable between the treatment groups (Table 6.3.2.2.2: 1). Diabetes mellitus was more frequently reported in the PBO group than in the T group.

Table 6.3.2.2.2: 1 Frequencies of patients with SAEs while on treatment during the randomized period by SOC and PT (PT in at least 1% in either treatment group) / TRANSCEND FAS

	T		**PBO**	
	N = 2954		**N = 2972**	
	%	**PY[1]**	**%**	**PY[1]**
Patients with SAEs	60.29	14.42	61.57	14.84
Cardiac disorders	24.51	5.86	26.62	6.42
Angina pectoris	14.15	3.38	15.31	3.69
Cardiac failure[2]	5.96	1.43	5.82	1.40
Myocardial infarction	4.67	1.12	5.42	1.31
Atrial fibrillation	4.94	1.18	5.01	1.21
Surgical and medical procedures	22.27	5.33	24.09	5.81
Coronary angioplasty	6.70	1.60	7.10	1.71
Cataract operation	4.91	1.17	5.32	1.28
Coronary artery bypass	2.67	0.64	2.79	0.67
Angioplasty	2.40	0.57	2.29	0.55
Retinal laser coagulation	1.32	0.32	1.21	0.29
Knee arthroplasty	0.95	0.23	1.01	0.24
Metabolism and nutrition disorders	9.34	2.24	10.46	2.52
Diabetes mellitus	6.60	1.58	8.04	1.94
Hyperglycaemia	1.35	0.32	1.58	0.38
Vascular disorders	9.68	2.32	8.65	2.08
Intermittent claudication	6.70	1.60	5.65	1.36
Hypertension	1.12	0.27	1.41	0.34
Nervous system disorders	8.97	2.15	8.95	2.16
Cerebral infarction	2.78	0.66	3.13	0.75
Transient ischaemic attack	1.93	0.46	2.02	0.49
Cerebrovascular accident	1.73	0.41	1.78	0.43
Syncope	1.05	0.25	0.64	0.15
Infections and infestations	8.97	2.15	7.97	1.92
Pneumonia	3.35	0.80	3.26	0.79
Urinary tract infection	1.05	0.25	0.87	0.21
Neoplasms benign, malignant and unspecified[3]	7.41	1.77	6.43	1.55
Prostate cancer	1.15	0.28	0.81	0.19
Lung neoplasm malignant	1.02	0.24	0.77	0.19
General disorders and administration site conditions	5.08	1.21	4.74	1.14
Sudden cardiac death	2.34	0.56	2.29	0.55
Chest pain	1.29	0.31	0.87	0.21
Injury, poisoning and procedural complications	4.16	1.00	3.80	0.92
Fall	1.29	0.31	1.24	0.30
Renal and urinary disorders	4.10	0.98	3.84	0.92
Diabetic nephropathy	1.93	0.46	2.05	0.49

	T		PBO	
	N = 2954		N = 2972	
	%	PY[1]	%	PY[1]
Investigations	3.35	0.80	3.26	0.79
Angiogram	1.18	0.28	0.74	0.18
Skin and subcutaneous tissue disorders	2.91	0.70	2.46	0.59
Skin ulcer	2.51	0.60	1.99	0.48
Blood and lymphatic system disorders	1.79	0.43	1.41	0.34
Anaemia	1.46	0.35	1.21	0.29

Note that frequencies of patients are presented and patients could have experienced SAEs of different preferred terms (PTs).
1 Adjusted for observation time (patients per 100 patient years).
2 Reported PTs: cardiac failure, cardiac failure acute, cardiac failure congestive, and cardiac failure hronic
3 Including cysts and polyps.
Source: TRANSCEND CTR Table 12.3.2.2.1: 1

6.3.2.2.3 Deaths

All-cause mortality was analyzed as a secondary efficacy endpoint. Overall, 713 randomized patients (12.03%) died during the randomized period. Mortality overall and on treatment was slightly higher in the T group than in the PBO group (overall: 12.32% vs. 11.74%; on treatment: 9.61% vs. 8.95%); a slight numerical difference was also seen after adjustment for observation time. The estimated hazard ratio was 1.05 with 95% CI 0.91, 1.22.

Of the patients who discontinued treatment permanently (i.e., were post-treatment), 15.30% died in the T group and 14.41% in the PBO group. In the following subsections, the primary causes of death and SAEs reported in association with death are presented separately.

Primary causes of death during the randomized period

The most frequently reported primary causes of death reported on treatment were other sudden cardiac death (T: 2.27%; PBO: 2.22%), cancer (T: 1.59%; PBO: 1.51%), and MI (T: 1.18%; PBO: 1.18%). The primary cause of death 'other sudden cardiac death' excludes MI, stroke, and ventricular tachyarrhythmia, which were specified separately. Other causes were observed in 1.83% of patients in the T group and in 1.88% of patients in the PBO group.

Primary causes of death while on treatment and post-treatment were generally comparable between treatment groups, also after adjustment for observation time.

6.3.2.2.4 Adverse events of special interest

Cough, angioedema, renal failure, and signs of renal dysfunction are adverse events commonly associated with RAAS blockade. Hypotensive symptoms and syncope are adverse events commonly associated with anti-hypertensive medications. These adverse events were defined post-hoc as AEs of special interest. Table 6.3.2.2.4: 1 compares the incidence of these events in both treatment groups.

Table 6.3.2.2.4: 1 Overview of analysis of AEs of special interest – TRANSCEND / FAS

	T	PBO
	N = 2954	N = 2972
Cough, n (%)	16 (0.54)	21 (0.71)
RR[1] vs. placebo (95% CI)	0.77 (0.40, 1.47)	
p-value	0.42	
Angioedema, n (%)	2 (0.07)	3 (0.10)
RR1 vs. placebo (95% CI)	0.67 (0.11, 4.01)	
p-value	0.66	
Hypotensive symptoms, n (%)	85 (2.88)	57 (1.92)
RR1 vs. placebo (95% CI)	1.50 (1.08, 2.09)	
p-value	0.016	
Syncope, n (%)	43 (1.46)	21 (0.71)
RR1 vs. placebo (95% CI)	2.06 (1.23, 3.46)	
p-value	0.005	
Renal failure, n (%)	54 (1.83)	48 (1.62)
RR1 vs. placebo (95% CI)	1.13 (0.77, 1.66)	
p-value	0.53	
Signs of renal dysfunction, n (%)[2]	267 (9.04)	190 (6.39)
RR1 vs. placebo (95% CI)	1.41 (1.18, 1.69)	
p-value	0.0001	

1. Risk ratio, χ^2 test.
2. Signs of renal dysfunction are listed in Appendix S3, Table 1.

Source: Adapted from TRANSCEND CTR Table 12.3.2.4.2: 1

6.3.2.3 PRoFESS

6.3.2.3.1 Adverse events leading to permanent treatment discontinuation

Adverse events leading to permanent treatment discontinuation were reported for more patients in the T group (14.26%) than in the PBO group (10.74%; Table 6.3.2.3.1: 1). Differences were also observed after adjustment for observation time. Patients in the T group experienced more syncope, hypotension, angina pectoris, chest pain, chronic obstructive pulmonary disease, anaemia and diarrhea.

Table 6.3.2.3.1: 1 Overview of AEs leading to permanent treatment discontinuation during the randomized period (in at least 0.2% of patients in any treatment group) / treated set (PRoFESS/NoACE-I)

	T N = 5589		PBO N = 5277	
	%	PY[1]	%	PY[1]
Patients with AEs leading to permanent treatment discontinuation	14.26	5.75	10.74	4.36
Infections and infestations	1.68	0.68	1.57	0.64
Pneumonia	0.81	0.32	0.64	0.26
Urinary tract infection	0.27	0.11	0.23	0.09
Cardiac disorders	1.43	0.58	1.33	0.54
Atrial fibrillation	0.48	0.19	0.30	0.12
Angina unstable	0.18	0.07	0.30	0.12
Angina pectoris	0.23	0.09	0.09	0.04
Nervous system disorders	1.66	0.67	1.06	0.43
Headache	0.34	0.14	0.19	0.08
Syncope	0.30	0.12	0.08	0.03
Dizziness	0.23	0.09	0.17	0.07
Gastrointestinal disorders	1.15	0.46	1.10	0.45
Diarrhoea	0.21	0.09	0.09	0.04
Injury, poisoning and procedural complications	1.23	0.50	0.87	0.35
Fall	0.41	0.17	0.30	0.12
General disorders and administration site conditions	0.81	0.32	0.85	0.35
Death	0.14	0.06	0.28	0.12
Chest pain	0.21	0.09	0.08	0.03
Respiratory, thoracic and mediastinal disorders	0.86	0.35	0.72	0.29
Respiratory failure	0.20	0.08	0.19	0.08
Chronic obstructive pulmonary disease	0.20	0.08	0.02	0.01
Renal and urinary disorders	0.59	0.24	0.61	0.25
Renal failure acute	0.21	0.09	0.28	0.12
Vascular disorders	0.68	0.27	0.40	0.16
Hypotension	0.39	0.16	0.09	0.04
Blood and lymphatic system disorders	0.27	0.11	0.15	0.06
Anaemia	0.20	0.08	0.08	0.03

Note that outcome events were not reported as AEs in the PRoFESS trial.
[1] Adjusted for observation time (patients per 100 patient years).

Source: Abstracted from Biostats output ae_lt01a

6.3.2.3.2 Serious adverse events

The incidence of SAEs while on treatment was slightly higher in the T group (22.85%) than in the PBO group (20.98%; Appendix S4, Table 1). Overall, the incidences of SAEs were

generally comparable between the treatment groups except for some terms indicative of sepsis.

The between group differences were also observed after adjustment for observation time.

6.3.2.3.3 Deaths

Overall mortality (including deaths reported as outcome events and as fatal SAEs) on treatment was comparable between the T group (7.46%) and the PBO group (7.37%).

6.3.2.3.4 Adverse events of special interest

Cough, angioedema, and renal failure are adverse events commonly associated with RAAS blockade. Hypotensive symptoms and syncope are adverse events commonly associated with anti-hypertensive medications. The incidence of hyperkalemia was also analyzed. These adverse events were defined post-hoc as AEs of special interest. Angioedema and hyperkalemia were experienced by small numbers of patients, so the significance of the results could not be determined (Table 6.3.2.3.4: 1). Patients in the T group had a statistically higher incidence of hypotensive symptoms (p = 0.019) and syncope (p = 0.011) than patients in the PBO group.

Table 6.3.2.3.4: 1 Overview of analysis of AEs of special interest – PRoFESS NoACE-I / FAS

	T N = 5589	PBO N = 5277
Angioedema, n (%)	2 (0.04)	0
RR1 vs. placebo (95% CI)	Not determinable	
p-value	0.17	
Hypotensive symptoms, n (%)	70 (1.25)	42 (0.80)
RR1 vs. placebo (95% CI)	1.57 (1.08, 2.30)	
p-value	0.019	
Syncope, n (%)	46 (0.82)	23 (0.44)
RR1 vs. placebo (95% CI)	1.89 (1.15, 3.11)	
p-value	0.011	
Renal failure, n (%)	46 (0.82)	30 (0.57)
RR1 vs. placebo (95% CI)	1.45 (0.92, 2.29)	
p-value	0.11	
Hyperkalaemia, n (%)	8 (0.14)	0 (0.0)
RR1 vs. placebo (95% CI)	Not determinable	
p-value	0.0060	

Risk ratio, $\chi 2$ test.
Source: Adapted from Summary of Clinical Safety Table 2.1.2.4.2:

6.4 SPECIAL TOPICS

In contrast to the PRoFESS NoACE-I / FAS subgroup presented above in safety, this section includes all of the PRoFESS study population for the special topics presented below.

6.4.1 Hypotensive Symptoms

Hypotensive symptoms (pooled terms including dizziness, dizziness exertional, dizziness postural, hypotension, orthostatic hypotension, procedural hypotension, presyncope, syncope vasovagal, syncope and circulatory collapse) were analysed in each of the three studies by baseline blood pressure category. The majority of patients with these symptoms had lower baseline blood pressures as expected (Figures 6.4.1: 1 to 6.4.1: 2 provide the results from ONTARGET and TRANSCEND; similar results were observed in PRoFESS). These results are in line with the mechanism of action of telmisartan and both hypotension and syncope are listed events in its prescribing information.

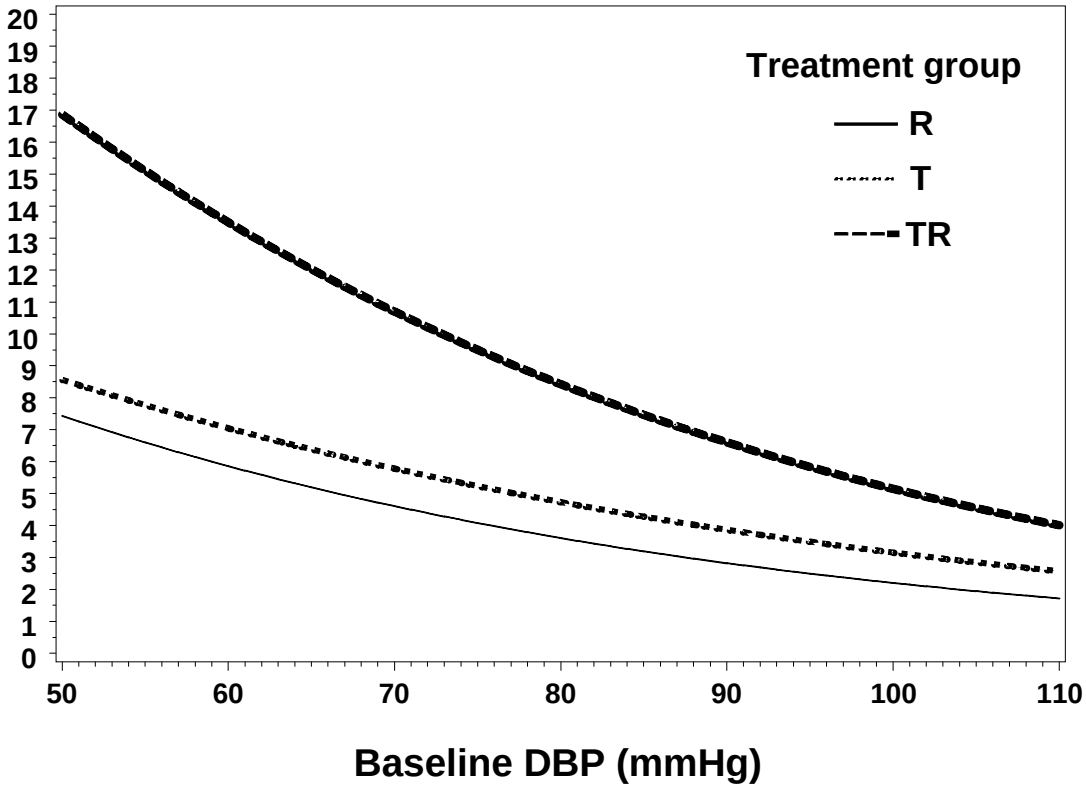


Figure 6.4.1: 1 Logistic regression curves for the probability of developing hypotensive symptoms in relation to baseline blood pressure and treatment from the ONTARGET study

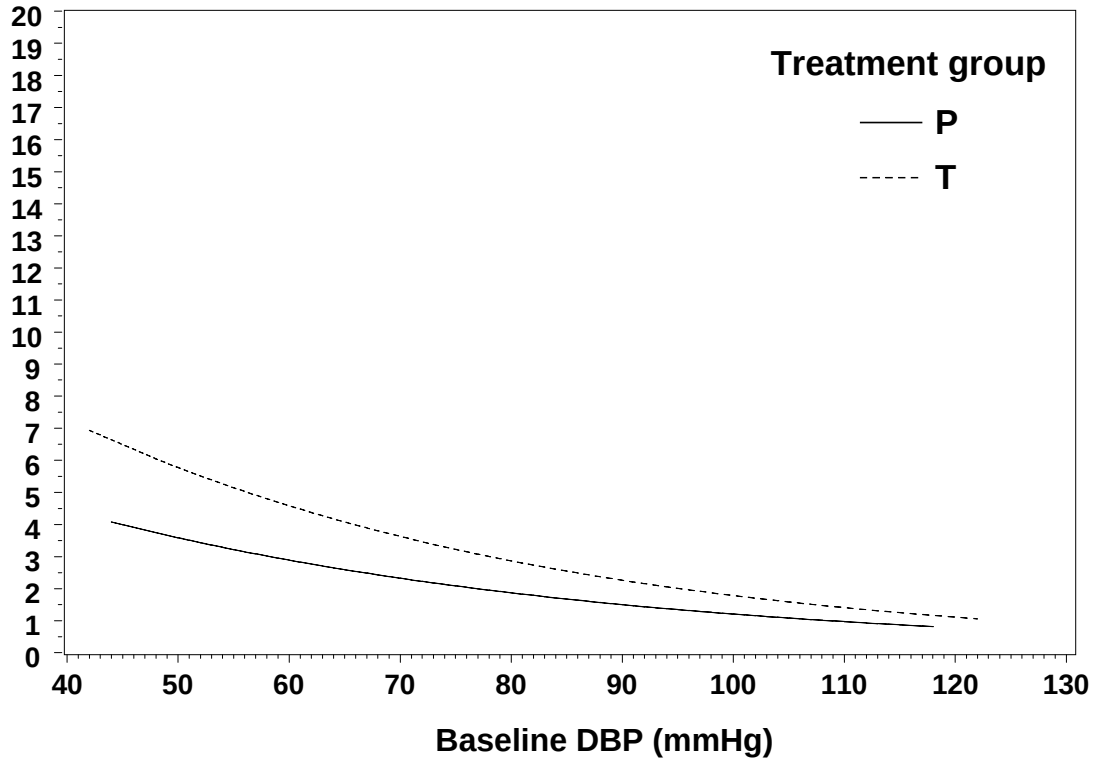


Figure 6.4.1: 2 Logistic regression curves for the probability of developing hypotensive symptoms in relation to baseline blood pressure and treatment from the TRANSCEND study

6.4.1.1 Spontaneous and other non-clinical trial adverse event reports

A review of the spontaneous and other non-clinical trial reports of "serious" hypotension with telmisartan in BI's Adverse Reaction Information System, global (ARISg) was undertaken. No additional information was derived from this review.

6.4.2 Renal observations

6.4.2.1 Introduction

This section presents information on serum creatinine, potassium and adverse events including the need for dialysis and renal failure.

6.4.2.2 Renal laboratory measurements

6.4.2.2.1 ONTARGET and TRANSCEND renal laboratory measurements

Serial measures of serum creatinine for ONTARGET and TRANSCEND are presented in Tables 6.4.2.2.1: 1. and 6.4.2.2.1: 2, respectively.

Table 6.4.2.2.1: 1 Serum Creatinine and Potassium over time /ONTARGET FAS

	T/R	T	R
Serum Creatinine (mg/dL)			
Start of run−in (baseline), mean (SD)	N = 8483 1.07 (0.28)	N = 8525 1.06 (0.28)	N = 8557 1.06 (0.27)
Final visit, N, mean (SD)	N = 6465 1.17 (0.46)	N = 6570 1.14 (0.42)	N = 6587 1.11 (0.42)
Change from baseline, mean (SD)	0.12 (0.38)	0.09 (0.35)	0.06 (0.36)
Serum Potassium (mmol/L)			
Start of run−in (baseline) , N, mean (SD)	N = 8480 4.39 (0.45)	N = 8510 4.39 (0.44)	N = 8556 4.39 (0.44)
Final visit, n, mean (SD)	N = 6422 4.50 (0.50)	N = 6535 4.45 (0.48)	N = 6562 4.42 (0.47)
Change from baseline, mean (SD)	0.11 (0.55)	0.06 (0.52)	0.03 (0.52)

Source: Adapted from Document ONTARGET CTR, Table 15.3.3.2: 1

Table 6.4.2.2.1: 2 Serum Creatinine and Potassium over time / TRANSCEND FAS

	T/R	T
Serum Creatinine (mg/dL)		
Start of run−in (baseline), mean (SD)	N = 2950 1.04 (0.29)	N = 2965 1.05 (0.28)
Final visit, N, mean (SD)	N = 2247 1.09 (0.39)	N = 2215 1.05 (0.37)
Change from baseline, mean (SD)	0.06 (0.36)	0.01 (0.33)
Serum Potassium (mmol/L)		
Start of run−in (baseline) , N, mean (SD)	N = 2947 4.38 (0.44)	N= 2965 4.37 (0.45)
Final visit, n, mean (SD)	N = 2231 4.42 (0.47)	N = 2197 4.29 (0.48)
Change from baseline, mean (SD)	0.05 (0.54)	-0.07 (0.54)

Source: Adapted from TRANSCEND CTR, Table 15.3.3.2: 1

There were small increases in serum creatinine and potassium in the RAAS blocking treatment groups in both studies.

6.4.2.2.2 Selected renal events

Co-administration of telmisartan and ramipril resulted in more doubling of serum creatinine, hyperkalemia, acute dialysis and renal failure than did either telmisartan or ramipril alone. The occurrence of these events in the telmisartan only and ramipril only groups were similar. The results are shown in Tables 6.4.2.2.2: 1 and 6.4.2.2.2: 2.

Table 6.4.2.2.2: 1 Selected renal events of special interest during the randomized period / ONTARGET

	T/R	**T**	**R**
	N (%/Per 100 PY	**N (%/Per 100 PY)**	**N (%/Per 100 PY)**
Randomized	8502	8542	8576
Doubling of serum creatinine	167 (1.96 / 0.36)	160 (1.87 /0.35)	149 (1.74 /0.33)
Potassium > 5.5 mmol/L	480 (5.65 / 1.04)	287 (3.36 /0.63)	283 (3.30 /0.62)
Need for dialysis	65 (0.76 / 0.14)	52 (0.61 /0.11)	50 (0.58 / 0.11)
Renal failure	227 (2.67 / 0.49)	187 (2.19 /0.41)	177 (2.06 / 0.39)

Source: Adapted from ONTARGET CTR, Table: 15.3.2.2: 29

Table 6.4.2.2.2: 2 Selected renal events of special interest during the randomized period / TRANSCEND

	T	**PBO**
	N (%/per 100 PY)	**N (%/per 100 PY)**
Randomized	2954	2972
Doubling of serum creatinine	62 (2.10 / 0.38)	40 (1.35 / 0.24)
Potassium > 5.5 mmol/L	114 (3.86 / 0.70)	51 (1.72 / 0.31)
Need for dialysis	7 (0.24 / 0.04)	10 (0.34 / 0.06)
Renal failure	37 (1.25 / 0.23)	36 (1.21 / 0.22)

Source: Adapted from TRANSCEND CTR, Table: 15.3.2.2: 23

For TRANSCEND, there was a greater frequency of doubling of serum creatinine, potassium levels greater than 5.5 mmol/L in the telmisartan treatment group than placebo. The frequencies of need for dialysis and renal failure were similar in the two treatment groups.

6.4.2.2.3 Renal Failure Events

T/R led to more serious renal adverse events than in the monotherapy treatment groups. There were no differences in chronic renal failure between T and R in ONTARGET and T and PBO in TRANSCEND and PRoFESS. (Appendix S5, Tables 1 - 3).

6.4.2.2.4 Renal Dialysis Adverse Events

Table 6.4.2.2.4: 1 and Table 6.4.2.2.4: 2 present the causes of dialysis in ONTARGET and TRANSCEND, respectively.

Table 6.4.2.2.4: 1 Patients with dialysis during the randomized period in ONTARGET

	T/R N = 8502 %	T N = 8542 %	R N = 8576
Patients w/any dialysis	0.76	0.61	0.58
Acute dialysis (<2 months)	0.35	0.23	0.15
Chronic dialysis (>= 2 months)	0.40	0.36	0.38
Dialysis type missing	0.01	0.01	0.05
Recovery of renal function	0.20	0.19	0.07
Primary reason for dialysis*			
Post-surgery or trauma	0.05	0.06	0.01
Severe infection	0.14	0.12	0.03
Volume depletion	0.04	0.01	0.05
Specific renal disease	0.21	0.15	0.14
Drugs	0.06	0.01	0.02
NSAID	0.00	0.00	0.00
Contrast media	0.01	0.00	0.01
Other	0.04	0.01	0.01
Other reason	0.32	0.28	0.34

* Multiple reasons for dialysis possible
Source: Adapted from ONTARGET CTR, Table 15.3.2.2: 32

Table 6.4.2.2.4: 2 Patients with dialysis during the randomized period in TRANSCEND

	T N = 2954 %	PBO N = 2972 %
Patients w/any dialysis	0.2	0.3
Acute dialysis (<2 months)	0.1	0.1
Chronic dialysis (>= 2 months)	0.1	0.2
Dialysis type missing	0.0	0.0
Recovery of renal function	0.1	0.0
Primary reason for dialysis*		
Post-surgery or trauma	0.0	0.0
Severe infection	0.0	0.0
Volume depletion	0.0	0.0
Specific renal disease	0.1	0.2
Drugs	0.0	0.0
NSAID	0.0	0.0
Contrast media	0.0	0.0
Other	0.0	0.0
Other reason	0.1	0.1

* Multiple reasons for dialysis possible
Source: Adapted from TRANSCEND CTR

In ONTARGET, there was more acute dialysis in the T/R combination treatment group than in T or R alone. In TRANSCEND, the frequency of acute and chronic dialysis was low, and similar between T and PBO. The incidence of chronic dialysis did not differ between the treatment groups in each of the outcome studies.

6.4.2.2.5 Spontaneous and other non-clinical trial adverse event reports

No additional safety signals were or useful information was identified from a search of all reports of Renal Failure, Acute Renal Failure and Chronic Renal Failure in ARISg.

6.4.2.2.6 Summary of Renal Observations

Dual RAAS Blockade

Co-administration of telmisartan and ramipril resulted in more doubling of serum creatinine, hyperkalemia, acute dialysis and renal failure than those receiving either telmisartan or ramipril alone. These findings are consistent with the known mechanism of drugs that block the RAAS. As a result, the following precaution has been added (pending FDA approval) to the prescribing information for telmisartan:

Dual Blockade of the Renin-angiotensin-aldosterone System*: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should be used with caution and should include close monitoring of renal function.*

Telmisartan

In ONTARGET, potassium levels greater than 5.5 mmol/L, doubling of serum creatinine, and renal failure were similar when comparing telmisartan to ramipril. Acute dialysis was more frequent with telmisartan than ramipril.

In TRANSCEND, doubling of serum creatinine and potassium levels > 5.5 mmol/L was more frequent with telmisartan than placebo. The need for dialysis and renal failure was similar in the two treatment groups.

6.4.3 Sepsis

During the preparation process for this sNDA, the Sponsor noted an unexpected increased incidence in the number of sepsis reports across the three trials (Table 6.4.3: 1). The sepsis events were recorded "as reported" by the Investigators, and were not adjudicated using the standard definition of sepsis as per ACCP/SCCM Consensus Conference, 1992 (Levy et al, 1992). Therefore, the Sponsor conducted additional analyses using a collection of 84 MedDRA preferred terms related to sepsis [sepsis-related events (SREs); Appendix S6; Table 1].

Table 6.4.3: 1 Overall summary of the special search category of sepsis related events (SREs) during the randomized period in ONTARGET, TRANSCEND and PRoFESS FAS

	ONTARGET						TRANSCEND				PRoFESS			
	T/R		T		R		T		PBO		T		PBO	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Randomized	8502	100	8542	100	8576	100	2954	100	2972	100	10019	100	10053	100
Patients with sepsis	73	0.86	70	0.82	60	0.7	25	0.85	17	0.57	70	0.7	49	0.49
Risk ratio vs. comparator (95% CI)	1.23 (0.87, 1.72)		1.17 (0.83, 1.65) ♣				1.48 (0.80, 2.73)§				1.43 (1.00, 2.06)§			
Risk ratio vs. telmisartan (95% CI)	1.05 (0.76, 1.45)													
Patients with fatal sepsis	31	0.4	26	0.30	27	0.3	15	0.5	9	0.3	33	0.3	16	0.2
Risk ratio vs. comparator (95% CI)	1.16 (0.69, 1.94) ♣		0.97 (0.56, 1.66) ♣				1.68 (0.73, 3.83)§				2.07 (1.14, 3.76) §			
Risk ratio vs. telmisartan (95% CI)	1.20 (0.71, 2.02)													

♣ Ramipril, §Placebo

SOURCE: Adapted from Addendum to Clinical Overview Tables 2.5.5.3.1:3 and 2.5.5.3.2:3 (U08-2183)

6.4.3.1 Other data and analyses

To better understand the sepsis finding, the Sponsor conducted several additional analyses. These analyses focused on occurrences while on treatment.

a) Time to onset analysis compared the timing of the first occurrence of SREs in the three outcome trials: the separation between treatment arms occurred at inconsistent times in the three outcome trials. In ONTARGET, the temporal occurrence of SREs was similar between treatment arms (Figure 6.4.3.1: 1). In PRoFESS, between-treatment separation of SREs occurred within the first months of treatment (Figure 6.4.3.1: 2), whereas in TRANSCEND, separation occurred after a year of treatment (Figure 6.4.3.1: 3).

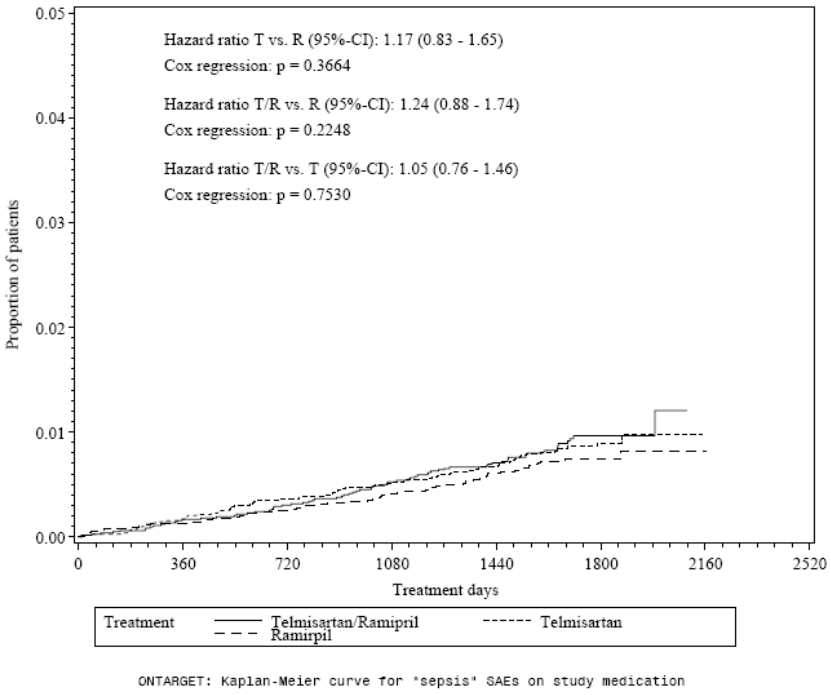


Figure 6.4.3.1: 1 Kaplan-Meier curve for sepsis-related events on study medication in ONTARGET

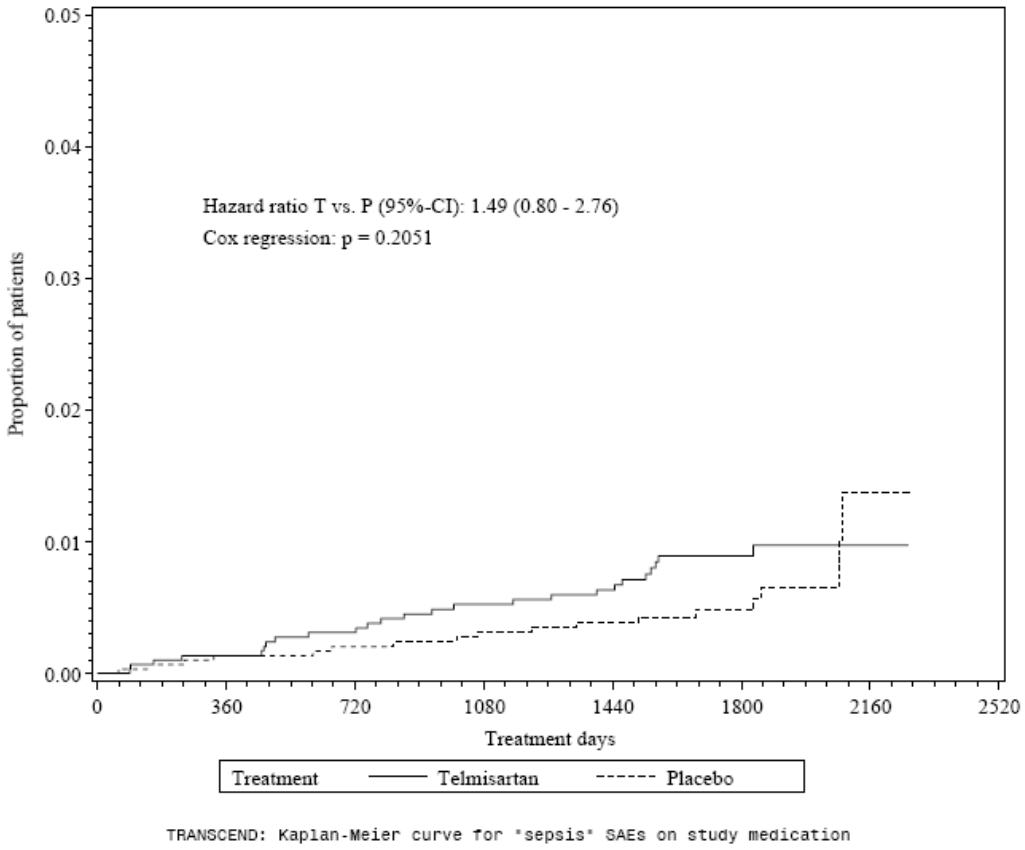


Figure 6.4.3.1: 2 Kaplan-Meier curve for sepsis-related events on study medication in TRANSCEND

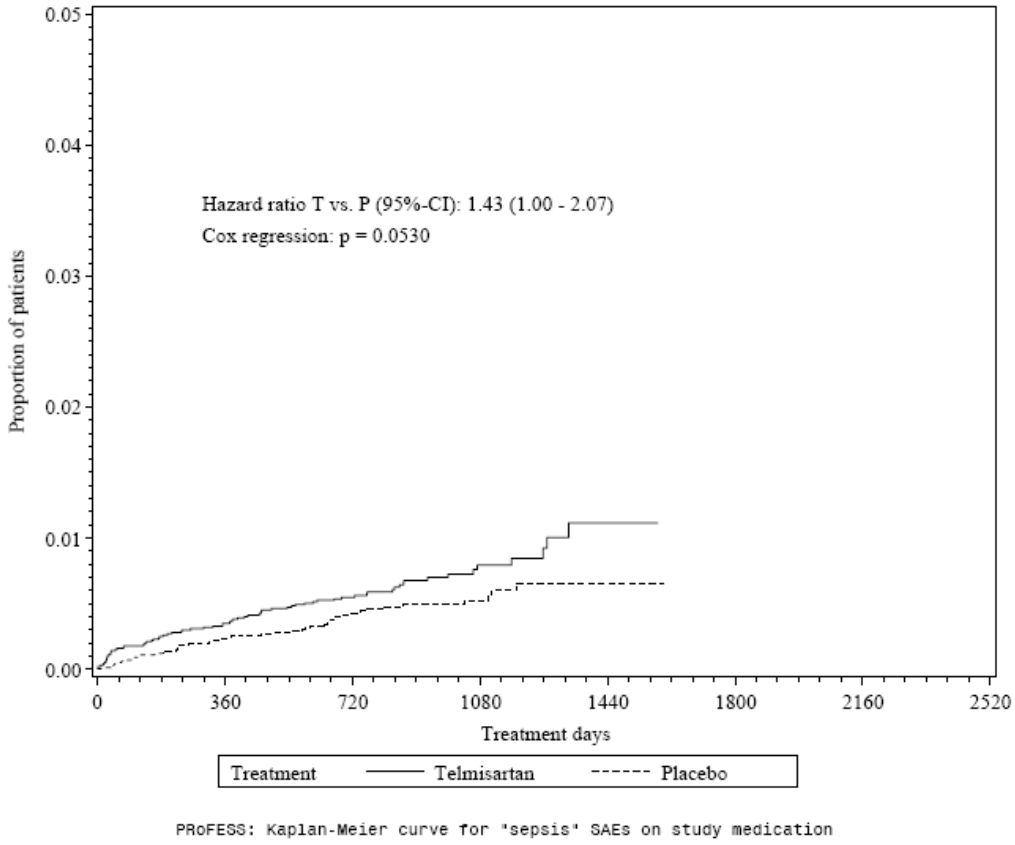


Figure 6.4.3.1: 3 Kaplan-Meier curve for sepsis-related events on study medication in PRoFESS

b) A multi-factorial regression analysis assessed the predictive association between 17 potential risk factors (predictors) as defined by Hodgin and Moss, 2008 in the three outcome trials. The model included study treatments (Appendix S6, Table 2).

A model selection procedure was used to assess the impact of predictors on the occurrence of SREs. This procedure first selected the explanatory variable with the best fit (according to the score chi2 statistic), and then subsequently selected the best model with 2, 3 or more variables. All variables with significant impact on the occurrence of SREs were identified, and also ordered by their predictive value.

A total of 364 patients with SREs were identified across the three trials. In ONTARGET, predictors with statistical impact on SRE occurrence in decreasing order were: infections, age, diabetes, number of hospitalizations, socioeconomic condition, Asian ethnicity, smoking status, and gender. In TRANSCEND, the predictors with statistical impact in decreasing order were: infections, age, and number of hospitalizations. In ONTARGET and TRANSCEND, treatment was not a predictor. In PRoFESS, significant predictors in decreasing order were: infections, diabetes, age, and Asian ethnicity, and treatment. Treatment was the weakest predictor for the occurrence of SREs.

c) A treatment - subgroup interaction analysis assessed the interaction between trial treatments and significant predictors with the highest impact on occurrence of SREs as identified in the multi-factorial regression analysis in the three outcome trials.

This analysis did not reveal any interaction between previous infection, diabetes, age, ethnicity, and trial treatments. There was no subgroup at high risk of developing SREs in presence of trial treatments.

d) Adverse event reports of SREs were evaluated to determine the temporal sequence of known predictors of sepsis prior to the onset of SREs in PRoFESS. Detailed information was available in 22 (31.4%) patients on telmisartan and 23 (46.9%) patients on placebo. Cancer and diabetes preceded SREs in the majority of these patients. (Appendix S6; Table 3). Reported infections occurred prior to SREs in 59 (84.3%) patients on telmisartan and 33 (67.3%) patients on placebo. When available, the leading infection sites were pulmonary and urinary tract (Appendix S6; Table 4).

e) Seventeen pre-clinical studies (animal models of sepsis, inflammation, immune modulation, and toxicological) revealed an anti-inflammatory effect of telmisartan. Telmisartan increased survival in presence of systemic bacterial/fungal infection, and did not have any immunosuppressive effect.

6.4.3.2 Sepsis in hypertension clinical trials

The Sponsor conducted a search for all reports of sepsis in the AE database for hypertension trials using a pre-defined list of sepsis-related events (SREs; Appendix S6; Table 5). This search identified reports of SREs in 15 patients (telmisartan: n = 10, comparator: n = 5). All patients presented with multiple risk factors for sepsis.

6.4.3.3 Spontaneous and other non-clinical trial adverse event reports of sepsis-related events

Using the pre-defined list of SREs, the Sponsor identified a small number of cases all of whom had predisposing factors for sepsis.

6.4.3.4 Summary

Incidence of sepsis in US ranges between 240 (Martin et al., 2003) and 300 (Angus et al., 2001) per 100,000. The incidence increases with age (Angus et al., 2001), is slightly higher for women (Martin et al., 2003), and is associated with a mortality rate of approximately 30%. The most common site of the infection is lung (Silva et al., 2004; Dremiszov et al., 2006).

In the outcome trials, unexpected small differences in incidence rates of SREs were observed between treatment arms. The prevalence of predictors in the three trial populations was similar to the general population (Alberti et al., 2002, Moss et al., 2000, Danai et al., 2006). Current literature does not support an association between sepsis and use of ARBs. In a retrospective study of 8,652 subjects using the Department of Veterans Affairs Administrative database, ARB use was associated with reduced mortality from sepsis (Mortensen et al., 2007). Animal studies evaluating potential benefit of ARBs in treatment of sepsis are inconclusive (e.g. Nitescu et al., 2008). Preliminary preclinical and toxicological

studies with telmisartan do not provide any mechanistic explanation for this association. It is not clear whether the increase in sepsis is real or a chance finding. The Sponsor has added (pending FDA approval) the following language to the telmisartan label, and is continuing its pharmacovigilance monitoring:

Cardiovascular Risk Reduction Trials

In clinical studies with patients at high risk of developing major cardiovascular events, cases of sepsis, including some with fatal outcomes, have been reported.

6.4.4 Malignancies

The Sponsor noted an imbalance in malignancies in ONTARGET and TRANSCEND.

There was a nonsignificant difference in the numbers of individuals with malignancy in the HOPE trial, and consequently, information on the occurrence of malignancies was prospectively collected in ONTARGET and TRANSCEND in more detail than usually done in cardiovascular outcome trials. Following the last patient last visit in ONTARGET, the steering and operations committees requested the collection of detailed information for each report of cancer in both ONTARGET and TRANSCEND. This information, collected through specific case report forms, allowed adjudication of malignancy reports by the adjudication committee.

In PRoFESS, cancer information was collected as SAEs per routine pharmacovigilance monitoring. To attempt to perform similar analyses for PRoFESS as was done in ONTARGET and TRANSCEND, the Sponsor categorized SAE MedDRA preferred terms representing site-specific malignancies.

6.4.4.1 ONTARGET

During the trial, malignancies were recorded in 2,321 randomized patients (9.1%). The hazard ratio for malignancies in the randomized patients was higher for telmisartan/ramipril than ramipril regardless of the presence of malignancies at baseline. In the subset of fatal malignancies, hazard ratios were higher for telmisartan/ramipril vs. ramipril and vs. telmisartan. Hazard ratios were similar for telmisartan vs. ramipril (Table 6.4.4.1: 1). For the randomized patients, malignancy sites were generally comparable across the 3 treatment groups (Table 6.4.4.1: 2).

Table 6.4.4.1: 1 Incidence of malignancies reported during the trial / ONTARGET FAS***

	T/R	T	R
Fatal and non-fatal malignancies[1]			
Randomised, n (%)	8502 100	8542 100	8576 100
Patients with fatal and non-fatal malignancies, n (%)	824 9.7	762 8.9	735 8.6
Total time to event/censoring [years]	37022	37405	37709
Events per 100 patient years	2.23	2.04	1.95
Hazard ratio[2] vs. ramipril (95% CI)	1.14 (1.03, 1.26)	1.05 (0.94, 1.16)	
Hazard ratio[2] vs. telmisartan (95% CI)	1.09 (0.99, 1.21)		
Patients without cancer at baseline n (%)	7968 100	8001 100	8032 100
Patients with fatal and non-fatal malignancies, n (%)	690 8.7	645 8.1	625 7.8
Total time to event/censoring [years]	34902	35212	35476
Events per 100 patient years	1.98	1.83	1.76
Hazard ratio[2] vs. ramipril (95% CI)	1.12 (1.01, 1.25)	1.04 (0.93, 1.16)	
Hazard ratio[2] vs. telmisartan (95% CI)	1.08 (0.97, 1.20)		
Fatal malignancies			
Randomised, n (%)	8502 100	8542 100	8576 100
Patients with fatal malignancies, n (%)	242 2.8	200 2.3	204 2.4
Total time to event/censoring [years]	38320	38707	38880
Events per 100 patient years	0.63	0.52	0.52
Hazard ratio[2] vs. ramipril (95% CI)	1.2 (1.00, 1.45)	0.99 (0.81, 1.20)	
Hazard ratio[2] vs. telmisartan (95% CI)	1.22 (1.01, 1.47)		
Patients without cancer at baseline n (%)	7968 100	8001 100	8032 100
Patients with fatal malignancies, n (%)	212 2.7	181 2.3	182 2.3
Total time to event/censoring [years]	35940	36253	36447
Events per 100 patient years	0.59	0.5	0.5
Hazard ratio[2] vs. ramipril (95% CI)	1.18 (0.97, 1.44)	1 (0.81, 1.23)	
Hazard ratio[2] vs. telmisartan (95% CI)	1.18 (0.97, 1.44)		

[1] Excluding cases which were adjudicated as 'no cancer'
[2] Cox regression
***Malignancy was defined as the first diagnosis of cancer
SOURCE : Adapted from ONTARGET CTR Table 11.4.1.2.10:1 (U08-1821)

Table 6.4.4.1: 2 Frequency of fatal and non-fatal malignancy subcategories in the study population /ONTARGET (FAS)***

Site	T/R		R		T	
	N	%	N	%	N	%
Randomized	8502		8542		8576	
Male	6252		6292		6245	
Female	2250		2250		2331	
Other sites	284	3.3	265	3.1	238	2.8
Prostate*	141	1.7	134	1.6	128	1.5
Breast**	33	0.4	27	0.3	34	0.4
Lung	129	1.5	100	1.2	101	1.2
Skin	112	1.3	102	1.2	112	1.3
Gastrointestinal	79	0.9	76	0.9	65	0.8
Genito-urinary	38	0.4	50	0.6	43	0.5
Brain	7	0.1	8	0.1	14	0.2
Multi site	1	0.0	0	0.0	0	0.0

Source: ONTARGET CTR Table 15.2.3: 9 (U08-1821)
Adjustments made in consideration of gender specific malignancies:
*For Males: T/R 2.3%; T 2.1%; R 2.0%.
**For Females: T/R 1.4%; T 1.2%; R 1.4%
***Malignancy was defined as the first diagnosis of cancer

6.4.4.2 TRANSCEND

During the trial, malignancies were recorded in 440 randomized patients (7.4%). The hazard ratio for malignancies in the randomized patients without cancer at baseline was higher for telmisartan than placebo. (Table 6.4.4.2: 1). For the randomized patients, malignancy sites were generally comparable across the treatment groups (Table 6.4.4.2: 2).

Table 6.4.4.2: 1 Incidence of malignancies reported during the trial / TRANSCEND FAS***

	Telmisartan		Placebo	
	N	%	N	%
Fatal and non-fatal malignancies[1]				
Randomised, n (%)	2954	100	2972	100
Patients with fatal and non-fatal malignancies, n (%)	236	8	204	6.9
Total time to event/censoring [years]	13248		13437	
Events per 100 patient years	1.78		1.52	
Hazard ratio[2] vs. Placebo (95% CI)	1.17	(0.97, 1.41)		
Patients without cancer at baseline n (%)	2809	100	2827	100
Patients with fatal and non-fatal malignancies, n (%)	206		169	6
Total time to event/censoring [years]	12640		12827	
Events per 100 patient years	1.63		1.32	
Hazard ratio[2] vs. Placebo (95% CI)	1.24	(1.01, 1.52)		
Fatal malignancies				
Randomised, n (%)	2954	100	2972	100
Patients with fatal and non-fatal malignancies, n (%)	66	2.2	65	2.2
Total time to event/censoring [years]	13638		13772	
Events per 100 patient years	0.48		0.47	
Hazard ratio[2] vs. Placebo (95% CI)	1.02	(0.73, 1.44)		
Patients without cancer at baseline n (%)	2809	100	2827	100
Patients with fatal and non-fatal malignancies, n (%)	57	2	56	2
Total time to event/censoring [years]	12966		13090	
Events per 100 patient years	0.44		0.43	
Hazard ratio[2] vs. Placebo (95% CI)	1.03	(0.71, 1.49)		

[1] Excluding cases which were adjudicated as 'no cancer'
[2] Cox regression
***Malignancy was defined as the first diagnosis of cancer
Source: Adapted from TRANSCEND CTR Table 11.4.1.2.9: 1

Table 6.4.4.2: 2 Frequency of fatal and non-fatal malignancy subcategories / TRANSCEND (FAS)***

Site	T		PBO	
Randomised	2954		2972	
Male	1674		1705	
Female	1280		1267	
Prostate*	35	1.2	27	0.9
Breast**	20	0.7	17	0.6
Lung	35	1.2	27	0.9
Skin	25	0.8	23	0.8
Gastrointestinal	24	0.8	24	0.8
Genito-urinary	11	0.4	12	0.4
Brain	3	0.1	2	0.1
Other sites	83	2.8	72	2.4

Source: TRANSCEND CTR - Table 15.2.3: 9 (U08-1959)
Adjustments made in consideration of gender specific malignancies:
*For Males: T 2.1%; PBO 1.6%
**For Females: T 1.5%; PBO 1.3%
*** Malignancy was defined as the first diagnosis of cancer

6.4.4.3 PRoFESS

During the trial, a total of 666 patients (Table 6.4.4.3: 1) presented with SAE MedDRA preferred terms representing malignancies. The frequencies of malignancies and fatal malignancies were similar between the treatment groups. Information on the presence of a malignancy at baseline was not requested. Malignancy sites were generally similar between treatment groups (Table 6.4.4.3: 2).

Table 6.4.4.3: 1 Incidence and analysis of fatal and non-fatal SAE preferred terms representing malignancies / PRoFESS**

Fatal and non-fatal malignancy	**Telmisartan**	**Placebo**
Randomized	10016	10048
Patients with fatal and non-fatal malignancies, N (%)	326 (3.3)	340 (3.4)
Time to event / censoring [years]	33387	32771
Events per 100 patient yrs	0.98	1.04
Hazard ratio* vs. Placebo	0.92	
95% CI	(0.79, 1.05)	
p-value	0.2313	
Fatal malignancies		
Patients with fatal malignancies N (%)	71 (0.7)	73 (0.7)
Time to event / censoring [years]	33787	33189
Events per 100 patient yrs	0.21	0.22
Hazard ratio* vs. Placebo	0.95	
95% CI	(0.83, 1.08)	
p-value	0.4278	

*Cox regression
Sponsor post-hoc analysis PRoFESS – Malignancy status was not available at baseline
**Malignancy was defined as any report of cancer SAE, i.e. one patient could have multiple reports.

Table 6.4.4.3: 2 Frequency of fatal and non-fatal SAE preferred terms representing malignancy subcategories as defined by the Sponsor / PRoFESS***

Site	**T**		**PBO**	
Randomized	10016		10048	
Male	6455		6418	
Female	3561		3630	
Breast**	20	0.2	15	0.1
Lung	37	0.4	30	0.3
Gastrointestinal	33	0.3	43	0.4
Prostate*	36	0.4	32	0.3
Other sites	137	1.4	145	1.4

Source: Additional analyses – Malignancy status was not available at baseline
Adjustments made in consideration of gender specific malignancies:
*For Males: T = 0.3%; PBO = 0.3%
**For Females: T = 0.5%; PBO = 0.4%
*** Malignancy was defined as any report of cancer SAE, i.e. one patient could have multiple reports.

6.4.4.4 Other data and analyses

The Sponsor conducted several exploratory analyses to better understand the findings:

a) Fatality analyses in patients with cancer at baseline in ONTARGET and TRANSCEND were performed and no significant differences between treatment groups were observed (Table 6.4.4.4: 1 and Table 6.4.4.4: 2).

Table 6.4.4.4: 1 ONTARGET Incidence and analysis of fatal malignancies** / FAS***

	T/R	**T**	**R**
Patients with cancer at baseline, n	534	541	544
Fatal malignancy, n (%)	30 (5.6)	19 (3.5)	22 (4.0)
Total time to event/censoring (years)	2381	2454	2433
Events per 100 patient years	1.26	0.77	0.90
Hazard ratio* vs. Ramipril	1.39	0.86	
95% confidence interval	(0.80 – 2.41)	(0.47 – 1.59)	
p-value	0.2403	0.6282	
Hazard ratio* vs. Telmisartan	1.62		
95% confidence interval	(0.91 – 2.87)		
p-value	0.1007		

*Cox regression
** Excluding case which have been adjudicated as "no cancer"
*** Malignancy was defined as the first diagnosis of cancer
Source: Adapted from ONTARGET CTR: Table 15.2.3: 8

Table 6.4.4.4: 2 TRANSCEND Incidence and analysis of fatal malignancies** / FAS***

	T	PBO
Patients with cancer at baseline, n	145	145
Fatal malignancy, n (%)	9 (6.2)	9 (6.2)
Total time to event/censoring (years)	673	682
Events per 100 patient years	1.34	1.34
Hazard ratio* vs. placebo	1.0	
95% confidence interval	(0.40 – 2.53)	
p-value	0.9940	

*Cox regression
** Excluding case which have been adjudicated as "no cancer"
*** Malignancy was defined as the first diagnosis of cancer
Source: Adapted from TRANSCEND CTR: Table 15.2.3: 8

b) To evaluate the potential for diagnostic detection bias, a multi-factorial regression model (as described above for sepsis) was used to assess the impact of predictors on the occurrence of lung malignancies (Appendix S7; Table 1). A total of 438 patients with reports of malignancies were identified in ONTARGET and TRANSCEND. In ONTARGET, smoking status (current and former), baseline lung malignancy, and age were the significant predictors of on-treatment onset of lung malignancies. In TRANSCEND, smoking status (current and former) and age were significantly associated with lung malignancies. Treatment group was not found to be a predictor of lung malignancies. Occurrence of respiratory conditions as defined by "Cough, cluster of Shortness of breath / breathing difficulties / Respiratory Insufficiency and the MedDRA system organ class Respiratory, thoracic and mediastinal disorders, prior to the onset of lung malignancies did not lead to a diagnostic bias. This analysis as not performed in PRoFESS due to methodological differences in reporting adverse events.

c) Preclinical studies with telmisartan have not demonstrated evidence of mutagenicity or carcinogenicity

d) A database analysis of malignancy adverse event reports in controlled clinical trials of one or more years in duration was conducted using the Standardized MedDRA Query for malignancies (SMQ, code 20000090) to review the frequencies of malignancies by treatment groups. Overall, the numbers of malignancies by preferred terms were small between treatment groups. There was no suggestion of an increased frequency of malignancies overall, for patients treated with telmisartan compared to placebo, and other comparator treatments, which included valsartan, losartan, lisinopril and enalapril (telmisartan groups combined: n = 31 patients (1.8%); comparator groups combined: n = 26 patients (2.1%); placebo: n = 2 patients (1.1%) – Appendix S7, Table 2.

6.4.4.5 Spontaneous and other non-clinical trial adverse event reports

A search for all non-CT reports involving malignancy using a pre-defined Standardized MedDRA Query (SMQ, code 20000090) for malignancies was conducted in ARISg.

Upon review, key information regarding malignancy risk factors for the reported events was often lacking. However, time to onset was generally well documented. The majority of events occurred less than a year after start of the drug and therefore there appears to be no causal relationship.

6.4.4.6 Summary

The imbalance in malignancies was seen primarily in the telmisartan/ramipril combination arm in ONTARGET. Malignancy data was inconsistent in the other two trials. In the larger PRoFESS study, malignancies occurred more frequently in the placebo arm, while in TRANSCEND the reverse was the case. The preclinical data do not indicate mutagenicity or carcinogenicity of telmisartan. The literature does not indicate an association between ARBs and malignancies (Coleman et al., 2008). The outcome trials were not of sufficient duration or designed to study the development of solid human tumors (Friberg and Mattson, 1997).

The inconsistent findings and the numerous exploratory analyses do not provide evidence of a causal association. The Sponsor does not believe that telmisartan leads to an increased risk of malignancies.

6.5 SAFETY IN SPECIAL POPULATIONS

6.5.1 Drug-demographic interactions

Drug-demographic interactions were assessed for the following demographic parameters: age, gender, ethnicity, and obesity. There were no interactions observed in any of the demographic parameters.

6.5.2 Drug-disease interaction

SAEs are summarised by presence of hypertension, presence of diabetes, and impaired renal function. Note that because of different collection of baseline data, presence of hypertension and diabetes are evaluated on the basis of both the patient history and baseline measurements in ONTARGET and TRANSCEND, whereas patients who did not receive ACE-Is in PRoFESS were based solely on the patient history.

In ONTARGET and TRANSCEND, the incidence of SAEs was evaluated in the following subgroups to investigate drug-disease interactions: patients categorised for baseline SBP tertiles, patients with previous CAD, previous PAD, previous stroke/TIA, high risk diabetes, albuminuria, patients with diabetic nephropathy, and patients post newly diagnosed CHF. In these subgroups, no unexpected differences from the overall study population results were observed and no relevant differences occurred between the treatment groups.

There were no drug-disease interactions observed for hypertension, diabetes, or impaired renal function.

6.5.3 Interactions by Geographic Region

No interactions between drug and geographical regions were observed. Between the regions, incidences of SAEs differed numerically; in Australia/New Zealand, the incidences of SAEs were generally higher than in the other regions. In ONTARGET, the incidences of SAEs in the different geographical regions were generally comparable between the T and R group; in TRANSCEND, the incidences were comparable between the T and PBO group. In PRoFESS/NoACE-I, the incidences of SAEs (excluding outcome events) were slightly higher in the T than in the PBO group in all geographical regions. Similarly, the incidences of AEs leading to permanent treatment discontinuation by geographical region were generally higher in the T group than in the PBO group.

6.6 SAFETY DISCUSSION

Data from these outcome studies showed the safety profile of telmisartan was consistent with the product label for telmisartan and that known for this class of drug.

In total, more than 50,000 patients were randomized in the three cardiovascular outcome studies discussed herein. Over 99% of patients were followed until either completion of the trials or death occurred.

Safety data of the combination therapy of telmisartan and ramipril are not presented in detail because this treatment was associated with a less favorable safety profile than both monotherapies without any additional efficacy benefits. For example there were increased incidences of hypotensive symptoms, syncope, hyperkalaemia, and renal dysfunction in patients treated with the combination.

The study treatments in these trials were given on top of standard of care medications. PRoFESS safety data were generally evaluated for patients who did not receive ACE-Is at anytime during the study.

In ONTARGET, telmisartan was better tolerated than ramipril. Permanent discontinuation of active telmisartan was significantly less than active ramipril, with a hazard ratio of 0.90 (p=0.0008). For permanent discontinuations of active treatment due to AEs, the hazard ratio was 0.79 (p <0.0001). Cough and angioedema more frequently resulted in treatment discontinuation for ramipril, despite the fact that 58% of ONTARGET patients had previously regularly taken ACE-Is before study entry and there was a run-in period which screened out more ACE-I intolerant patients.

As many as 39% of patients receiving ACE-Is have reported dry cough, and 0.1% to 1.0% of ACE-I have reported angioedema (Israili et al, 1992). During the run-in period of ONTARGET, cough (1.08%) and angioedema (0.14%) were reported as reasons for study discontinuation. Cough and angioedema were also responsible for treatment discontinuation during the randomized period. These rates are much lower than what would be expected in the community setting because 57.6% of the ONTARGET patients were previous regular users of ACE-I. Published literature reports that compliance rates diminish over time and non-compliance of prescribed medications leads to an increase in CV events (Ho et al., 2008).

Patients with lower baseline blood pressures were more susceptible to developing hypotensive symptoms or syncope. Hypotension is a listed event in the telmisartan prescribing information.

The renal findings are consistent with the known mechanism of action of angiotensin receptor blockade and interrupting the renin-angiotensin-aldosterone system (RAAS). In ONTARGET, dual RAAS blockade with telmisartan and ramipril led to a higher frequency of RAAS blockade-related events. As a result, the following precaution has been added (pending FDA approval) to the prescribing information for telmisartan:

Dual Blockade of the Renin-angiotensin-aldosterone System*: As a consequence of inhibiting the renin angiotensin-aldosterone system, changes in renal function (including acute renal failure) have been reported. Dual blockade of the renin-angiotensin-aldosterone*

system (e.g., by adding an ACE-inhibitor to an angiotensin II receptor antagonist) should be used with caution and should include close monitoring of renal function.

An unexpected increased incidence of sepsis events was observed across the three outcome trials. Analyses revealed that known risk factors for sepsis were observed and predictive in these studies. Treatment was not identified as a significant predictive factor in ONTARGET and TRANSCEND, although it was in PRoFESS. It is not clear whether the increase in sepsis is real or occurred by chance, as a review of the literature does not indicate an excess of sepsis in other trials of ARBs or ACE-Is or identify a likely mechanism Despite this, the Sponsor has taken the decision to add the risk of sepsis with possibly fatal outcomes to the prescribing information for telmisartan.

There was an increased incidence of malignancies in the telmisartan/ramipril combination arm in ONTARGET. There was an inconsistent pattern in the malignancy data in the other two trials. In the larger PRoFESS study, malignancies occurred more frequently in the placebo arm, while in TRANSCEND the reverse was the case. Clinical and preclinical data with telmisartan and other ARBs do not support mutagenic or carcinogenic potential of ARBs. The Sponsor does not believe that telmisartan leads to an increased risk of malignancies.

In conclusion, data from these outcome studies showed the safety profile of telmisartan was consistent with the product label for telmisartan and that known for this class of drug.

7. SUMMARY OF RISK-BENEFIT

In ONTARGET, both the 4-fold and 3-fold endpoint met the protocol-specified non-inferiority margin. In TRANSCEND, the 3-fold endpoint achieved a nominal p value of <0.05. The totality of evidence from the placebo-controlled comparisons demonstrates that telmisartan reduces the risk of the occurrence of cardiovascular events, in particular, stroke and MI. The safety profile is entirely consistent with telmisartan's labeling and with the profile of agents in this class. This clinical research program demonstrates that telmisartan can provide incremental benefit for patients at high risk for the occurrence of cardiovascular events (i.e., MI and stroke) in contemporary medical practice.

7.1 LIMITATIONS OF EXISTING THERAPY

Although ramipril is approved for reducing the risk of CV death, non-fatal MI, and non-fatal stroke, a number of adverse events associated with ramipril may limit its use in clinical practice, potentially leading to stopping of an effective therapy in high risk patients (Conlin et al., 2001 and Delgi et al., 2002). In the HOPE study, 9.8% of patients discontinued ramipril during the run-in period and 28.9% during the randomized period. Additionally, in the randomized period, the incidence of cough and angioedema was higher in the ramipril treated patients than in the placebo treated patients; 7.3% vs. 1.8% for cough and 0.4% vs. 0.2% for angioedema, for ramipril vs. placebo, respectively (HOPE Study Investigators, 2001a). Further, the incidence of cough and angioedema has been reported to be causally associated with the use of ACE-Is, due to the mechanism of action of these RAAS agents (for example increase in bradykinin).

Despite the well established cardioprotective benefits of ACE-Is, their use is limited by the frequent occurrence of treatment-related adverse drug reactions. As many as 39% of patients receiving ACE-Is have reported dry cough, and 0.1% to 1.0% of ACE-I exposed patients have reported angioedema (Israili et al, 1992). Cardiovascular outcome studies comparing ACE-Is and ARBs (ELITE II, OPTIMAAL and VALIANT) have consistently demonstrated significantly fewer patients in the ARB group compared to the ACE-I group discontinue treatment because of AEs. In clinical practice, the adherence to ACE-I and other antihypertensives is worse than that observed in trials, and similarly in this setting adherence to ARBs is better than ACE-I (Wogen et al., 2003; Siiskonen et al., 2007). Finally, in an HMO setting (Ho et al., 2007), non-adherence to ACE-I and other medications was evaluated over a median 4.1 year observation time in patients with prior PCI, myocardial infarction or coronary artery bypass graft surgery. Non-adherence to ACE-I was present in about 25% of such patients and was associated with significantly increased risks for all-cause mortality, cardiovascular mortality, hospitalization for myocardial infarction or heart failure and coronary revascularization procedures (hazard rations between 1.32 and 1.74).

Another limitation of current therapy is that ramipril is the only RAAS blocking agent approved for a broad CV risk reduction indication. For example, only losartan is indicated to reduce the risk of stroke, and this only in patients with hypertension and left ventricular hypertrophy (Losartan Prescribing Information). There is still a need to have new agents offering incremental benefit with better long-term adherence to medication use in the setting of contemporary medical practice.

7.2 RISKS OF TELMISARTAN

As expected telmisartan use was associated with an increased incidence of hypotensive episodes; especially in normotensive patients. Hypotension is already a listed adverse event for telmisartan and other anti-hypertensive agents. Blood pressure is easy to monitor either by a health care provider or even by patients themselves, so that this risk can be well managed also in a real life setting .

The comparison of telmisartan to placebo showed an imbalance of renal adverse events, with the imbalance being driven by more instances of hyperkalaemia (mean change 0.1-0.2 mmol/L), although there was also an increase in the need for acute dialysis. There was no increased need for chronic dialysis comparing telmisartan to placebo or ramipril. The more frequent renal adverse events in the telmisartan group are expected consequences of RAAS blockade and consistent with the current safety labeling for telmisartan and other RAAS blocking agents. Modest increases (approximately 0.1 mg/dL) in mean serum creatinine levels were greater with telmisartan than for ramipril and placebo in these outcome studies.

An unexpected observation in the outcome studies was an increased incidence of sepsis with telmisartan compared to placebo, but this was comparable for telmisartan vs. ramipril (0.20/100 PY vs. 0.17/100 PY for telmisartan and ramipril, respectively). There is currently no plausible scientific mechanism or hypothesis to explain this observation. The majority of patients had concurrent risk factors for developing sepsis. A post-hoc analysis of the outcomes studies was performed; only in the PRoFESS study did telmisartan treatment have a small but significant predictive value for the occurrence of sepsis. Even though the observation has no plausible explanation, the Sponsor has added (pending FDA approval) the risk of sepsis with possibly fatal outcomes to the US prescribing information for telmisartan. This proposed labeling change was submitted to the FDA prior to the submission of the sNDA.

There was an increased incidence of malignancies in the telmisartan/ramipril combination arm in ONTARGET. Malignancy data was inconsistent in the other two trials. In the larger PRoFESS study, malignancies occurred more frequently in the placebo arm, while in TRANSCEND the reverse was the case. Clinical and preclinical data with telmisartan and other ARBs do not support mutagenic or carcinogenic potential of ARBs. The Sponsor does not believe that telmisartan leads to an increased risk of malignancies.

Overall, safety data from these outcome studies showed a safety profile consistent with the product label for telmisartan and that known for the class.

7.3 BENEFITS OF TELMISARTAN

For the 3 fold endpoint (CV death, non-fatal myocardial infarction, and non-fatal stroke, i.e., the HOPE primary endpoint), for any of the proposed non-inferiority margins, telmisartan was non-inferior to ramipril. For the 4-fold endpoint (CV death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for heart failure) telmisartan was non-inferior to ramipril for the protocol-specified non-inferiority margin. In terms of effect preservation, telmisartan preserved about 95% (95% CI, 66, 124) of the benefits of ramipril over placebo with respect to the 4-fold endpoint, and preserved 105% (95% CI, 74 to 137) of the benefits with respect to the 3-fold outcome. The other secondary endpoints were consistent with this conclusion.

In the TRANSCEND study, the superiority of telmisartan over placebo was demonstrated for the 3-fold endpoint as evidenced by a nominal p value below 0.05 with an approximately 13% risk reduction mainly for the stroke and myocardial infarction components of the endpoint. Additionally, a pooled analysis of placebo controlled outcome study data for patients not receiving ACE-I at baseline demonstrated an approximate 10% reduction in the 3-fold endpoint.

Data on the clinically important 3-fold endpoint comprises a body of evidence that demonstrates telmisartan reduces stroke and MI in patients at high risk for their occurrence. This conclusion is supported by the consistency of effect across numerous prespecified subgroups (i.e., diabetics, elderly, women, etc.).

The totality of information from these outcome studies, in the context of current scientific knowledge and medical practice, shows that telmisartan has a benefit similar to ramipril. The data from the outcome studies were obtained with guideline-driven current background cardiovascular therapies, supporting the conclusion that telmisartan can provide incremental benefit in the US clinical practice setting.

7.4 RISK-BENEFIT CONCLUSIONS

The clear demonstration of non-inferiority of telmisartan to ramipril in ONTARGET and the nominally significant reduction relative to placebo in the composite of CV death, MI and stroke in TRANSCEND establish the benefit of telmisartan in patients at high risk for cardiovascular events. Telmisartan is considered effective as it unequivocally preserved at least 66% on the 4-fold and 74% on the 3-fold endpoints of ramipril's effect. The other secondary endpoints were consistent with this conclusion. The data suggest that telmisartan reduces the rate of MI and stroke, but it has no effect on hospitalization for heart failure.

The risk-benefit for telmisartan in reducing the risk of stroke and myocardial infarction in high risk patients is favorable and compares well to the benefit risk of the gold standard ramipril. In clinical practice it has been shown that adherence to ARBs is much better than ACE-Is. In ONTARGET medication adherence to telmisartan was better than ramipril despite the exclusion of ACE-I intolerant patients and the use of a run-in period which eliminated many patients that could not tolerate ramipril. Importantly, excess mortality (hazard ratio 1.74) has been reported from a retrospective cohort study in a HMO setting using data from patients with known coronary-artery disease who were not adherent to ACE-Is (median follow up 4.1 years, comparable to ONTARGET). The better tolerability and adherence of telmisartan compared to ramipril will provide a greater benefit in clinical practice and provide public health benefits. Inclusion of information from this clinical research program in the label of telmisartan would provide an additional option for improved individualized therapy within current guideline-driven US clinical practice.

8. REFERENCES

Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, et al. Epidemiology of sepsis and infection in ICU patients from an international multicenter cohort study. Intensive Care Med 2002; 28(2): 108-21.

Ambrosioni E, Borghi C, Magnani B.The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. N Engl J Med 1995; 332(2): 80-85.

Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001; 29(7):1303-10.

Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. Mtg of the American Heart Association, New Orleans, 12 - 15 Nov 2000, N Engl J Med 2001; 345 (23): 1667–1675.

Coleman CI, Baker WL, Kluger J, White CM Antihypertensive medication and their impact on cancer incidence: a mixed treatment comparison meta-analysis of randomized controlled trials. J Hypertens 2008; 26(4), 622-629.

Conlin PR, Gerth WC, Fox J. Roehm JB. et al. Four-Year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other artihypertensive drug classes. Clinical Therapeutics 2001; 23(12): 1999-2010.

Danai PA, Moss M, Mannino DM, Martin GS. The epidemiology of sepsis in patients with malignancy. Chest 2006 Jun; 129(6): 1432-40.

Delgi EE, Sturani A, Di Martino M, et al. Long-term persistence with antihypertensive drugs in new patients. J. Hum. Hypertens 2002; 16(6): 439-444

Dickstein K, Kjekshus J, OPTIMAAL Steering Committee, OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Lancet 2002; 360:752-760.

Dremsizov T, Clermont G, Kellum JA, Kalassian KG, Fine MJ, Angus DC. Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course? Chest. 2006 ;129(4):968-78

Dzau VJ, Antman EM, Black HR, Hayes DL, Manson JE, Plutzky J, Popma JJ, Stevenson W. The cardiovascular disease continuum validated: clinical evidence of improved patient outcomes: part I: pathophysiology and clinical trial evidence (risk factors through stable coronary artery disease). Circulation 2006; 114(25): 2850-2870.

EURopean Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet 2003; 362: 782-788.

Flather MD, Yusuf S, Kober L, et al. Long-term ACE-Inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet 2000; 355: 1575-1581.

Friberg S. and Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. J Surg Oncol 1997; 65(4): 284-97.

Granger CB, McMurray JJ, Yusuf S, et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 2003; 362(9386): 772-776.

Hasselblad V, Kong DF. Statistical methods for comparison to placebo in active-control trials. Drug Inf J 2001; 35:435-449.

Ho PM, Magid DJ, Shetterly SM, Olson KL, Maddox TM, Peterson PN, Masoudi FA, Rumsfeld JS. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. American Heart Journal 2008; 155(4): 772-779.

Hodgin KE, Moss M. The epidemiology of sepsis. Curr Pharm Des 2008;14(19): 1833-1839.

Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. Ann Intern Med 1992; 117(3): 234-242.

Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. BMJ 1996; 313: 36-39.

Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995; 333(25): 1670-1676.

Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G; International Sepsis Definitions Conference. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003 Apr;29(4):530-8.

Lin, D., Wei, L., Yang, I., and Ying, Z. Semiparametric Regression for the Mean and Rate Functions of Recurrent Events. Journal of the Royal Statistical Society, Series B, 2000; 62: 711-730.

Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 2006; 367: 1747-1757.

Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, editors. Global burden of disease and risk factors. New York: Oxford University Press 2006.

Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348(16):1546-54

Massie BM, Carson PE, McMurray JJ et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008; 359: 2456–2467.

McMurray JJV, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003; 362(9386): 767-771.
Mortensen EM, Restrepo MI, Copeland LA, Pugh JA, Anzueto A, Cornell JE, Pugh MJV Impact of previous statin and angiotensin II receptor blocker use on mortality in patients hospitalized with sepsis. Pharmacotherapy 2007; 27 (12): 1619–1626.

Mortensen EM, Restrepo MI, Copeland LA, Pugh JA, Anzueto A, Cornell JE, Pugh MJV Impact of previous statin and angiotensin II receptor blocker use on mortality in patients hospitalized with sepsis. Pharmacotherapy 2007; 27(12), 1619–1626.

Moss M, Guidot DM, Steinberg KP, Duhon GF, Treece P, Wolken R, et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Crit Care Med 2000 Jul; 28(7): 2187-92.

Navalkar S, Parthasarathy S, Santanam N, Khan BV, Irbesartan, an Angiotensin Type I Receptor Inhibitor, regulates markers of inflammation in patients with premature atherosclerosis. J .Am. Coll Cardiol 2001; 37: 440-444.

Nitescu N, Grimberg E, Guron G Low-dose candesartan improves renal blood flow and kidney oxygen tension in rats with endotoxin-induced acute kidney dysfunction. Shock 2008; 30 (2), 166–172.

Ohkubo N, Matsubara H, Nozawa Y, Mori Y, Murasawa S, Kijima K, et al. Angiotensin Type 2 Receptors Are Reexpressed by Cardiac Fibroblasts From Failing Myopathic Hamster Hearts and Inhibit Cell Growth and Fibrillar Collagen Metabolism. Circulation 1997; 96: 3954-3962.

ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008; 358(15): 1547-1559.

ONTARGET/TRANSCEND Investigators. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: the ongoing telmisartan alone and in combination with ramipril global endpoint trial/telmisartan randomized assessment study in ACE intolerant subjects with cardiovascular disease (ONTARGET/TRANSCEND) trials. Am Heart J 2004; 148(1): 52–61.

Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ Jr, Cuddy TE, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: Results of the Survival and Ventricular Enlargement Trial. N Engl J Med 1992; 327(10): 669-677.

Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II. Lancet 2000; 355: 1582-1587.

Siiskonen SJ, Breekveldt- Postma NS, Vincze G, Khan ZM, Erkens JA, Herings R. Higher persistence with valsartan compared with enalapril in daily practice. Vascular Health and Risk Management 2007; 3(6): 1039-1044.

Silva E, Pedro Mde A, Sogayar AC, Mohovic T, Silva CL, Janiszewski M, Cal RG, de Sousa EF, Abe TP, de Andrade J, de Matos JD, Rezende E, Assunção M, Avezum A, Rocha PC, de Matos GF, Bento AM, Corrêa AD, Vieira PC, Knobel E; Brazilian Sepsis Epidemiological Study. Brazilian Sepsis Epidemiological Study (BASES study). Crit Care. 2004;8(4):R251-60.

Sleight P. The HOPE study (Heart Outcomes Prevention Evaluation). J Renin Angiotensin Aldosterone Syst 2000; 1: 18-20.

Stoll M, Steckelings UM, Paul M, Bottari SP, Metzger R, Unger T. The Angiotensin AT2-Receptor Mediates Inhibition of Cell Proliferation in Coronary Endothelial Cells. J Clin Invest 1995; 95: 651-657.

Swedberg K. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987; 316(23): 1429–1435.

Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet 2008; 372 (9644): 1174–1183.

The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342: 821-828.

The HOPE Study Investigators. The HOPE (Heart Outcomes Prevention Evaluation) Study: The design of a large, simple randomized trial of an angiotensin-converting enzyme inhibitor (ramipril) and vitamin E in patients at high risk of CV events. Can J Cardiol 1996; 12(2): 127-137.

The HOPE Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on CV events in high-risk patients. N Engl J Med 2000a; 342(3): 145-153.

The HOPE Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000b; 355: 253-259.

The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992; 327: 685-691.

Wogen J, Kreilick C, Livornese R, Yokoyama K, Frech F. Patient adherence with amlodipine, lisinopril or valsartan therapy in a usual-care setting. JMCP 2003; 9: 424-429.

Yusuf S, Pfeffer MA, Swedberg K, et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003; 362(9386): 777-81.

Yusuf S, et al, PRoFESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. N Engl J Med 2008; 359 (12): 1225–1237.

APPENDIX E1

CRITERIA FOR THE INDIVIDUAL COMPONENTS OF THE PRIMARY COMPOSITE ENDPOINT

1.0 Cardiovascular Death

1.1 Unexpected death: unexpected death presumed to be due to ischemic CV disease, occurring within 24 hours of the onset of symptoms without confirmation of CV cause, and without clinical or post mortem evidence of other etiology.

1.2 MI: death within 7 days of the onset of documented MI. (see Section 2, Non-fatal MI).

1.3 CHF: death due to clinical, radiological or post mortem evidence of CHF without clinical or post mortem evidence of other cause such as ischaemia, infection, dysrhythmia (cardiogenic shock to be included).

1.4 Post CV invasive interventions: death associated with the following intervention: within 30 days of CV surgery, or within 7 days of cardiac catheterisation, or angioplasty, atherectomy, stent deployment or other invasive coronary or peripheral vascular interventions.

1.5 Documented arrhythmia: death due to bradyarrhythmias or tachyarrhythmias not induced by an acute ischemic heart disease event.

1.6 Post non-CV surgery: death due to CV causes as defined in 1.1-1.5, 1.7, and 1.8 and within 30 days of surgery.

1.7 Stroke: death due to stroke occurring within 7 days of the signs and symptoms of a stroke

1.8 Death due to other CVD such as pulmonary embolism and abdominal aortic aneurysm rupture

1.9 Presumed CV death: Suspicion of CV death with clinically supporting evidence that may not have fulfilled criteria otherwise stated. Example: Patient admitted with typical chest pain of 3 hours duration and treated as an MI but without ECG and enzymes documentation to meet normal criteria. A patient without available supporting documentation who had been found dead was adjudicated as having had a presumed CV death; the date on which the patient was found dead was regarded as the date of death.

Accidental death qualified as a CV event unless clear evidence of extraneous disease or reason is known. Cardiac transplantation was not considered a cardiac death.

2.0 Non-fatal MI

2.1 'Q-Wave MI' or 'ST elevation MI': Q-wave MI was defined as the presence of new significant Q waves (≥0.04 s duration or 3 mm in depth and loss in height of ensuing R wave or new significant R waves in V1-V2) in at least 2 leads on the standard 12-lead ECG, ST elevation MI was defined as 1 mm new ST elevation of 1 mm in limb leads or 2 mm in precordial leads. (Development of new left bundle branch block [LBBB] in the clinical context of MI was considered as a 'Q-Wave MI').
In addition to the ECG characteristics of 'Q-Wave MI' or 'ST elevation MI', there should have been observed at least one of the following:

1. Typical symptoms (e.g., chest pain) and/or
2. Significant elevation with serial changes of cardiac enzymes/markers, i.e. presence of any one of the following criteria:

a) Elevation of creatine kinase isoenzyme MB (CK-MB) above the ULN within 36 hours of onset of acute symptoms of MI; if CK-MB was not available, total creatine kinase at least twice the laboratory specific ULN and with characteristic pattern
b) Serum glutamate-oxaloacetate-transaminase/aspartate aminotransferase (SGOT/AST), lactate dehydrogenase at least twice the laboratory specific ULN and with characteristic pattern
c) Elevated troponin T or I level above the definite abnormal level for the laboratory (necrosis range)

2.2 Silent Q-wave MI: was defined as development of new Q waves in at least 2 adjacent leads (Minnesota Code 1.11)

2.3 'Non Q-wave MI' or 'non ST elevation MI': was defined as the presence of new and persistent (>24 hours) ST changes or T wave changes, defined as ST depression ≥2 mm or T wave inversion ≥3 mm on the ECG with significant cardiac enzymes/markers elevation (see above under 2.1(2) and/ or typical symptoms of chest pain)

2.4 MI without significant ECG changes: was defined as a patient with characteristic symptoms plus significant elevation of cardiac enzymes/markers (see Section 2.1(2)). ECG changes could be minimal, transient, or non-diagnostic.

2.5 Diagnosis of periprocedural MI:
2.51 For percutaneous coronary intervention (PCI): (within 7 days), new Q-wave MI in ECG as defined for new MI, or CK-MB 3 times ULN, or troponin 3 times above the definite abnormal level for the laboratory (necrosis range).
2.52 For CABG: (within 30 days), new Q-wave MI in ECG as defined for new MI, or CK-MB 10 times ULN.
2.53 For non-CV surgical interventions: (within 30 days), new Q-wave MI in ECG as defined for new MI, or CK-MB 3 times ULN.

3.0 Non-fatal stroke

Stroke was defined as the presence of acute focal neurological deficit thought to be of vascular origin with signs or symptoms lasting longer than 24 hours (it was noted in the definition that subarachnoid haemorrhage may not involve neurological deficit).

On the basis of clinical symptoms, autopsy and/or computed tomography (CT)/magnetic resonance imaging (MRI), strokes were classified as:

a) Definite or probable ischemic stroke (confirmed by CT, MRI scan or autopsy), or
b) Definite haemorrhagic stroke, (confirmed by CT, MRI scan or autopsy), or
c) Subarachnoid haemorrhage, or
d) Uncertain or unknown stroke.

3.1 Cerebral infarction: stroke with CT scan performed within 3 weeks that was either normal or showed infarct in the clinically expected area.

3.11 Lacunar infarct – cerebral infarction with:
- consciousness and higher mental functions maintained
- one of the typical lacunar syndromes such as pure motor stroke, pure sensory stroke, sensori-motor stroke or ataxic hemiparesis.
- CT performed within 3 weeks that was either normal or showed a small infarct in the basal ganglia, internal capsule, medulla or pons.

3.12 Cardioembolic infarct – Cerebral infarction with:
- absence of lacunar characteristics
- no definite evidence of large artery disease in the neck
- major cardioembolic source present (e.g. atrial fibrillation, MI in the last 6 weeks, cardiomyopathy, endocarditis or prosthetic heart valve)

3.13 Large artery infarct:
- absence of lacunar characteristics
- no major cardioembolic source present
- evidence of large artery disease in the neck (e.g., a bruit or duplex scan evidence of a stenosis of more than 50%)

3.14 Unclassified infarct: cerebral infarction without lacunar characteristics, cardioembolic source or large artery disease; this category also included patients who had more than one potential cause for stroke (e.g., atrial fibrillation and large artery disease) if it was not possible to determine which mechanism was the cause of the stroke.

3.2 Intracerebral haemorrhage: definite stroke with CT evidence of cerebral haemorrhage; this did not include haemorrhage secondary to cerebral infarct, post-traumatic intracerebral haemorrhage, haemorrhage into a tumour, and haemorrhage into a vascular malformation.

3.3 Stroke, type uncertain: definite stroke that did not meet the above criteria for cerebral infarction or haemorrhage.

3.4 Subarachnoid haemorrhage: typical clinical syndrome of sudden onset headache, with or without focal signs, and CT or cerebrospinal fluid evidence of bleeding primarily in the subarachnoid space.

4.0 Hospitalization for CHF

Hospitalization for CHF was defined as hospitalization for CHF or attendance in an acute care setting (emergency room) for administration of intravenous diuretic, escalation of diuretic doses and/or inotropes, and/or evidence of heart failure from chest X-rays.

The definition for CHF was revised on 08 November 2005 to account for changes in practice patterns, which had been observed over the last few years and since the HOPE trial. In the previous definition the evidence of heart failure from chest X-rays was mandatory. However, chest X-rays are nowadays not routinely obtained by physicians before treating patients with CHF with the appropriate intravenous diuretic, escalation of diuretic doses and/or inotropes. By insisting on confirmation of CHF by chest X-rays for this outcome, the incidence of this event would have been underestimated in the trial. The revised definition was added to Protocol Amendment 3.1, dated 14 February 2006. All cases of CHF adjudicated before 08 November 2005 were re-adjudicated according to the new definition.

Source: ONTARGET CTR, Section 9.5

APPENDIX E2

Table 1 ONTARGET Frequency of the CV composite endpoint by year / FAS

	Telmisartan / Ramipril			Telmisartan			Ramipril		
Year	At risk[1]	With event	Censored[2]	At risk[1]	With event	Censored[2]	At risk[1]	With event	Censored[2]
1	8502	327	43	8542	335	32	8576	321	42
2	8132	320	72	8175	316	82	8213	303	79
3	7740	270	95	7777	297	62	7831	265	98
4	7375	250	107	7418	274	100	7468	286	92
5	7018	204	5133	7044	186	5212	7090	211	5209
>5	1681	15	1666	1646	15	1631	1670	26	1644

[1] Number of patients entering the respective time interval
[2] All effort was made to collect information about the primary outcome events for those patients lost to follow-up. In case of no contact, the patient was censored on the last day of available contact during the study.

Table 2 TRANSCEND frequency of the CV composite endpoint by year / FAS

	Telmisartan			Placebo		
Year	At risk[1]	With event	Censored[2]	At risk[1]	With event	Censored[2]
1	2954	133	14	2972	121	13
2	2807	85	21	2838	100	24
3	2701	93	30	2714	105	32
4	2578	76	193	2577	98	199
5	2309	60	1103	2280	55	1096
6	1146	18	1099	1129	25	1066
>6	29	0	29	38	0	38

[1] Number of patients entering the respective time interval
[2] All effort was made to collect information about the primary outcome events for those patients lost to follow-up. In case of no contact, the patient was censored on the last day of available contact during the study

APPENDIX E3

POST-HOC POOLED DATA FROM TRANSCEND AND PROFESS

Pooling of TRANSCEND and PRoFESS data to produce a large body of placebo-controlled data to better understand the effects of telmisartan seems reasonable since the 2 studies showed many similarities and shared design elements. Both studies were large CV outcome trials conducted during the same time period and all outcome events were centrally adjudicated by independent committees. The study populations were overlapping and constitute a representative cross section of patients at the moderately-high to very-high risk stages of the cardiovascular disease spectrum.

The PRoFESS trial was performed almost in parallel to TRANSCEND, and was comprised of patients at high cardiovascular risk. The Sponsor considered the pooled analysis of both trials suitable to substantiate the effect size of telmisartan compared with placebo, both given on top of standard of care. The additional supportive analyses provide clinically relevant information on approximately 16,000 patients at high cardiovascular risk, including 9363 patients treated with telmisartan from PRoFESS and 9376 treated with placebo.

The primary endpoint of TRANSCEND was included as a secondary endpoint in the PRoFESS trial. Despite these similarities in design and conduct, a study effect was observed, which was attributed to different inclusion criteria. PRoFESS enrolled patients with a recent stroke, with the median time to enrolment in PRoFESS of 15 days. In contrast, in TRANSCEND, patients could have had a stroke much earlier before study entry and still qualified for inclusion in the study. TRANSCEND patient enrollment also allowed coronary artery disease (CAD), peripheral artery disease (PAD), or high-risk diabetes as risk factors. To account for this study-to-study heterogeneity, the study effect was included in the Cox regression model. It should be noted that all PRoFESS patients over age 55 could have been enrolled in the TRANSCEND study as they met this inclusion criterion.

The pooled analysis involved all patients from the TRANSCEND and PRoFESS trials who did not use ACE-Is at baseline (total / BL NoACE-I population), as this was the most relevant population for consideration, given the negative benefit/risk balance seen in the telmisartan/ramipril arm of ONTARGET.

Table 1 Pooled analysis demographic characteristics at baseline / Total/BL-NoACE-I

	T		PBO		Total	
Number of randomized patients, n (%)	9363	(100.0)	9376	(100.0)	18739	(100.0)
Age, mean (SD) [years]	66.5	(8.2)	66.5	(8.2)	66.5	(8.2)
Age group, n (%)						
<65 years	4020	(42.9)	3998	(42.6)	8018	(42.8)
≥65 to <75 years	3617	(38.6)	3662	(39.1)	7279	(38.8)
≥75 years	1726	(18.5)	1716	(18.3)	3442	(18.4)
Sex, n (%)						
Male	5779	(61.7)	5745	(61.3)	11524	(61.5)
Female	3584	(38.3)	3631	(38.7)	7215	(38.5)
Race, n (%)						
White	5073	(54.2)	5102	(54.4)	10175	(54.3)
Asian	3300	(35.2)	3287	(35.1)	6587	(35.2)
Black	292	(3.1)	269	(2.9)	561	(3.0)
Other	698	(7.5)	718	(7.7)	1416	(7.6)
Weight mean (SD) [kg]	74.1	(15.9)	74.0	(15.8)	74.0	(15.8)
Height mean (SD) [cm]	165.7	(9.9)	165.7	(10.0)	165.7	(10.0)
BMI, mean (SD) [kg/m^2]	26.89	(4.93)	26.86	(4.88)	26.87.	(4.90)

Table 2 Pooled analysis disposition of patients / Total/BL-NoACE-I

	T n (%)	PBO n (%)	Total n (%)
Randomized patients	13100	13258	26258
Received ACE-I at baseline	3737 (28.5)	3782 (28.7)	7519 (28.6)
No ACE-I at baseline	9363 (100.0)	9376 (100.0)	18739 (100.0)
Completed[1]	9311 (99.4)	9313 (99.3)	18624 (100.0)
Deaths	830 (8.9)	796 (8.5)	1626 (8.7)
Not completed	52 (0.6)	63 (0.7)	115 (0.6)
Lost to follow-up	20 (0.2)	26 (0.3)	46 (0.2)
Consent withdrawn	31 (0.3)	34 (0.4)	65 (0.3)
Other	0 (0.0)	2 (0.0)	2 (0.0)
Permanently discontinued study medication[2]	2547 (27.2)	2421 (25.8)	1968 (26.5)
Serious adverse events[3]	862 (9.2)	740 (7.9)	1602 (8.5)
Patient request[4]	576 (6.2)	650 (6.9)	1226 (6.5)
Adverse event	693 (7.4)	565 (6.0)	1258 (6.7)
Other reasons	462 (4.9)	523 (5.6)	985 (5.3)

[1] Final visit performed or vital status confirmed (including death)
[2] Multiple reasons possible
[3] Includes outcome events in PRoFESS
[4] Did not withdraw consent followed-up but did not want to be further treated with study medication

Table 3 Pooled analysis incidence and analysis of the composite of CV death, non-fatal MI, or non-fatal stroke in analogy to the HOPE study - first event / FAS (Total/NoACE-I)

	T	PBO
Randomized, n (%)	8587 (100.0)	8290 (100.0)
3-fold endpoint, n (%)[1]	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	(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

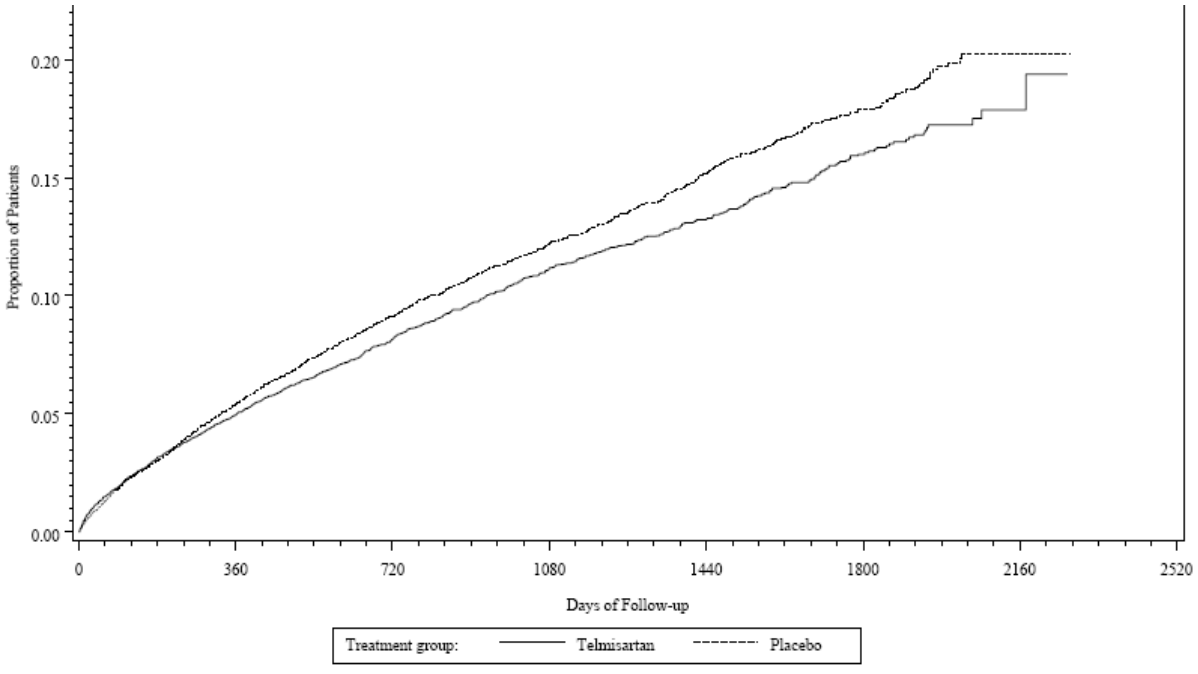


Figure 1 Pooled analysis Kaplan-Meier estimates of the composite outcome of CV death, non-fatal MI, or non-fatal stroke, by treatment group / FAS (Total/NoACE-I)

Similar to what was observed for the primary endpoint, the cumulative proportion of patients experiencing the primary event was comparable with T than with PBO until approximately 6

months after randomization. An analysis investigating the effect of time (≤6 months vs. >6 months) was performed and reported in the PRoFESS study. There was a statistically significant interaction between treatment and time period (p = 0.0178). There was no relevant treatment difference in the first 6 months after randomization. In the period >6 months, significantly fewer (p = 0.0002) patients in the T group than in the PBO group experienced a primary event.

APPENDIX S1

The majority of known adverse events related to inhibition of the RAAS were observed at higher frequencies in the T/R group than in the T or R alone (Table 1 below).

Table 1 Renal safety issues in ONTARGET

	T/R n=8502	T n=8542	R n=8576
	%	%	%
Creatinine			
Patients with changes in creatinine from low or normal to high	22.6	18.4	16.1
Clinically significant increases in creatinine	18.5	15.7	13.0
Mean increases in creatinine (mg/dL)	0.12	0.09	0.06
Adverse events leading to permanent treatment discontinuation	12.39	8.19	8.73
Renal failure as SAE	1.65	1.35	1.25
Renal failure with death	0.19	0.09	0.13

Source: Adapted from ONTARGET CTR Tables 12.2.1: 2, 12.2.1: 3 and 12.3.1.2: 1

Due to the higher incidence of these and other adverse events in patients receiving the combination of T/R but without additional efficacy, the Sponsor updated the US prescribing information for telmisartan to include the following statement:

"Dual blockade of the renin-angiotensin-aldosterone system should be used with caution and should include close monitoring of renal function."

APPENDIX S2

Safety data collection and reporting in ONTARGET / TRANSCEND and PRoFESS

	ONTARGET/TRANSCEND	PRoFESS
Definition of 'on treatment' and 'post-treatment'	'On treatment': time between visit date at which the permanent stop of study medications was documented and the date of randomization +1 day; 'Post-treatment': time between date last seen (or vital status confirmed via telephone) and the date of the visit at which the permanent stop of study medications was documented +1 day	'On treatment': time between date of last intake of study medication and the date of randomization +28 days; 'Post-treatment': time after the date of last intake of study medication +28 days (including temporary interruptions longer than 28 days)
Categories of events that required reporting to authorities	CC0: outcome events and hospitalizations CC1: unexpected SAEs considered study drug-related CC2: expected SAEs considered study drug-related Exempt: serious, expected not study drug related events	ICH category 0: SAEs not considered study drug-related, excluding outcome events ICH category 1: unexpected SAEs considered study drug-related ICH category 2: expected SAEs considered study drug-related Exempt: non study drug-related events expected to occur in the patient population
Evaluation of primary causes of death (pre-specified categories on CRF)	MI, stroke, ventricular tachyarrhythmia, other sudden cardiac death, worsening heart failure, pulmonary embolism, other vascular, embolism, other, amputation related, ketoacidosis, nephropathy/renal failure, cancer, other non-vascular	Ischemic stroke, haemorrhagic stroke, stroke of uncertain cause, MI, haemorrhage (excluding intracranial bleeding), other vascular causes, asystole, CHF, ventricular tachycardia, ventricular fibrillation, pneumonia, other infection, cancer, trauma, other non-vascular
Evaluation of SAEs reported in association with death or fatal SAEs	Evaluated as SAEs reported in association with death	Evaluated as outcome events, except for deaths that occurred later than 14 days after last patient contact
Evaluation of outcome events as AEs	All evaluated as SAEs based on Investigators' information	Outcome events analyzed for efficacy; not evaluated as SAEs except for deaths that occurred later than 14 days after last patient contact[1]
Recording of AEs leading to permanent treatment discontinuation	Events leading to permanent treatment discontinuation were recorded as SAEs and reasons leading to permanent treatment discontinuation. The SAEs were MedDRA coded, the reasons were coded internally by PHRI. Reasons could have been considered as AEs, but also as other reasons.	AEs leading to permanent treatment discontinuation were recorded irrespective of seriousness (no information on seriousness recorded); all were MedDRA coded based on Investigators' information
AEs of special interest	Cough, angioedema, hypotensive symptoms, syncope, renal failure, signs of renal dysfunction, and diarrhea.	Angioedema, hypotensive symptoms, syncope, renal failure, diarrhea, and hyperkalemia.
Clinical laboratory parameters	Selected clinical laboratory parameters were determined at run-in, in a defined time-window before randomization, and at 3 time points during the randomization period	Serum creatinine and potassium were determined at run-in and 1 month after randomization.

1 Outcome events in PRoFESS: death, stroke, MI, TIA, new onset diabetes, new or worsening of CHF, major and minor haemorrhagic events, pulmonary embolism, retinal vascular accidents, deep venous thrombosis, peripheral artery occlusion, central (cerebral) venous thrombosis, thrombotic thrombocytopenic purpura, central post-stroke pain, neutropenia. Source: Adapted from Summary of Clinical Safety Table 1.1.4: 2

APPENDIX S3

Table 1 Adverse Event coding for signs of renal dysfunction

	MedDRA preferred terms for SAEs	**PHRI code for AEs leading to treatment discontinuation[1]**	**Clinical laboratory parameters**
Renal failure	Renal failure	Renal impairment	
	Acute pre-renal failure	Renal failure	
	Renal failure acute	Renal artery stenosis	
	Renal failure chronic	Nephropathy	
	Hemodialysis	Kidney disease	
	Peritoneal dialysis	Hemodialysis	
	Dialysis	Nephrosclerosis	
Signs of renal dysfunction[2]	Renal failure Acute prerenale failure Renale failure acute Renal failure chronic Diabetic nephropathy Diabetic end stage renal disease Glomerulonephropathy Azotaemia Hypertensive nephropathy Microalbuminuria Nephropathy Nephropathy toxic Nephrotic syndrome Proteinuria Renal disorder Renal impairment Urate nephropathy Haemodialysis Peritoneal dialysis Dialysis	Increase in K (potassium) / hyperkalaemia Increase in creatinine Increase in urea Azotaemia Renal impairment / renal failure / renal artery stenosis / nephropathy / kidney disease / haemodialysis / nephrosclerosis Proteinuria / microalbuminuria	Doubling of serum creatinine Potassium >5.5 mmol/L eGFR <15 mL/min/1.73[2]

[1] For the analysis of AEs of special interest, AEs leading to temporary or permanent treatment discontinuations were included. Adverse events leading to temporary or permanent treatment discontinuation were derived from the reasons for temporary and permanent treatment discontinuations which had been provided by the Investigators on the CRFs and had been internally coded by PRHI.

[2] This AE of special interest was only analysed for the randomised period, because the clinical laboratory parameters serum creatinine and potassium were not available for the run-in set (RIS), but only for the patients who had been randomised.

Source: Summary of Clinical Safety Table 1.1.3.1.3: 1

APPENDIX S4

Table 1 Frequencies of patients with SAEs while on treatment during the randomized period by SOC and PT (PT in at least 0.2% of patients in any treatment group / treated set (PRoFESS/NoACE-I)

	T n=5589		PBO n=5277	
	%	PY[1]	%	PY[1]
Patients with SAEs	22.85	11.66	20.98	10.44
Infections and infestations	4.42	2.25	4.02	2.00
Pneumonia	1.13	0.58	1.46	0.73
Urinary tract infection	0.61	0.31	0.53	0.26
Sepsis	0.38	0.19	0.23	0.11
Gastroenteritis	0.25	0.13	0.11	0.06
Cellulitis	0.20	0.10	0.11	0.03
Bronchitis	0.20	0.10	0.13	0.07
Appendicitis	0.13	0.06	0.13	0.07
Cardiac disorders	3.63	1.85	2.79	1.39
Atrial fibrillation	0.88	0.45	0.59	0.29
Angina unstable	0.66	0.34	0.42	0.21
Coronary artery disease	0.21	0.11	0.47	0.24
Angina pectoris	0.39	0.20	0.28	0.14
Cardiac arrest	0.32	0.16	0.17	0.08
Coronary artery stenosis	0.20	0.10	0.08	0.04
Nervous system disorders	4.03	2.05	3.66	1.82
Syncope	0.57	0.29	0.36	0.18
Convulsion	0.57	0.29	0.49	0.25
Carotid artery stenosis	0.48	0.25	0.38	0.19
Dizziness	0.29	0.15	0.36	0.18
Headache	0.45	0.23	0.27	0.13
Epilepsy	0.25	013	0.25	0.12
Injury, poisoning and procedural complications	3.17	1.62	2.77	1.38
Fall	0.93	0.47	0.95	0.47
Hip fracture	0.23	0.12	0.25	0.12
Femur fracture	0.27	0.14	0.21	0.10
Femoral neck fracture	0.25	0.13	0.32	0.16
Head injury	0.16	0.08	0.21	0.10
Road traffic accident	0.25	0.13	0.19	0.09
Gastrointestinal disorders	2.54	1.30	2.96	1.47
Vomiting	0.34	0.17	0.30	0.15
Diarrhoea	0.32	0.16	0.34	0.17
Inguinal hernia	0.07	0.04	0.36	0.18
Abdominal pain	0.21	0.11	0.17	0.08
Gastric ulcer	0.27	0.14	0.21	0.10
Nausea	0.23	0.12	0.08	0.04
Neoplasms benign, malignant and unspecified (incl cysts and polyps	2.92	1.49	2.86	1.42
Lung neoplasm malignant	0.47	0.24	0.34	0.17
Prostate cancer	0.30	0.16	0.30	0.15
Colon cancer	0.23	0.12	0.25	0.12
General disorders and administration site conditions	2.72	1.39	2.33	1.16
Death	0.84	0.43	0.83	0.42
Chest pain	0.59	0.30	0.47	0.24
Pyrexia	0.32	0.16	0.28	0.14
Musculoskeletal and connective tissue disorders	1.84	0.94	1.55	0.77

	T n=5589		PBO n=5277	
	%	PY[1]	%	PY[1]
Osteoarthritis	0.61	0.31	0.47	0.24
Back pain	0.25	0.13	0.23	0.11
Metabolism and nutrition disorders	1.22	0.62	1.25	0.62
Dehydration	0.25	0.13	0.25	0.12
Hyponatraemia	0.21	0.11	0.25	0.12
Hypoglycaemia	0.21	0.11	0.19	0.09
Respiratory, thoracic and mediastinal disorders	1.59	0.81	1.35	0.67
Chronic obstructive pulmonary disease	0.47	0.24	0.25	0.12
Dyspnoea	0.29	0.15	0.17	0.08
Respiratory failure	0.21	0.11	0.17	0.08
Vascular disorders	1.27	0.65	1.08	0.54
Hypotension	0.48	0.25	0.15	0.08
Renal and urinary disorders	1.22	0.62	1.08	0.54
Renal failure acute	0.48	0.25	0.28	0.14
Psychiatric disorders	0.86	0.44	0.97	0.48
Depression	0.27	0.14	0.27	0.13
Hepatobiliary disorders	0.47	0.24	0.63	0.31
Cholelithiasis	0.20	0.10	0.19	0.09
Blood and lymphatic system disorders	0.61	0.31	0.51	0.25
Anaemia	0.36	0.18	0.30	0.15
Ear and labyrinth disorders	0.55	0.28	0.36	0.18
Vertigo	0.34	0.17	0.21	0.10
Reproductive system and breast disorders	0.50	0.26	0.44	0.22
Benign prostatic hyperplasia	0.29	0.15	0.23	0.11
Eye disorders	0.38	0.19	0.38	0.19
Cataract	0.16	0.08	0.21	0.10

Note that frequencies of patients are presented and patients could have experienced SAEs of different preferred terms (PTs).
Note that outcome events were not reported as AEs in the PRoFESS trial.
[1] Adjusted for observation time (patients per 100 patient years).

Source: Abstracted from Biostats output ae_lt01a2.doc

APPENDIX S5

Table 1 ONTARGET renal failure SAEs (MedDRA preferred terms)

	T/R n = 8502			T = 8542			R n=8576	
	%	PY[1]		%	PY[1]		%	PY[1]
Renal failure [unspecified]	1.65	0.42		1.35	0.33		1.25	0.30
Renal failure acute	0.72	0.18		0.42	0.10		0.34	0.08
Renal failure chronic	0.29	0.07		0.13	0.03		0.12	0.03

[1] Adjusted for observation time (patients per 100 patient years);
Source: Adapted from ONATRGET CTR, Table 15.3.2.2: 4:

Table 2 TRANSCEND renal failure SAEs (MedDRA preferred terms)

	T n=2954			PBO n=2972	
	%	PY[1]		%	PY[1]
Renal failure[unspecified]	0.78	0.19		0.64	0.15
Renal failure acute	0.24	0.06		0.37	0.09
Renal failure chronic	0.17	0.04		0.20	0.05

[1] Adjusted for observation time (patients per 100 patient years),
Source: Adapted from TRANSCEND CTR , Table 15.3.2.2: 4

Table 3 PRoFESS renal failure SAEs (MedDRA preferred terms)

	T n=10019		PBO n=10053
	%		%
Renal failure [unspecified]	0.2		0.2
Renal failure acute	0.7		0.4
Renal failure chronic	0.1		0.1

Source: Adapted from PRoFESS CTR,Table 15.2.3.2: 19

APPENDIX S6

Table 1 MedDRA Sepsis-related Preferred Terms

HLT sepsis, bacteraemia, viraemia and fungaemia NEC	**Other sepsis potential related terms**	
Preferred Term	**Preferred Term**	**Preferred Term**
Abdominal sepsis	Group B streptococcus neonatal sepsis	Sepsis neonatal
Acinetobacter bacteraemia	Haemophilus bacteraemia	Sepsis pasteurella
Amniotic infection syndrome of Blane	Haemophilus sepsis	Sepsis syndrome
Anthrax sepsis	Helicobacter sepsis	Septic arthritis gonococcal
Bacteraemia	Herpes sepsis	Septic arthritis haemophilus
Bacterial sepsis	Infantile septic granulomatosis	Septic arthritis neisserial
Bacterial toxaemia	Klebsiella bacteraemia	Septic arthritis staphylococcal
Bacteroides bacteraemia	Klebsiella sepsis	Septic arthritis streptobacillus
Biliary sepsis	Listeria sepsis	Septic arthritis streptococcal
Brucella sepsis	Meningococcal bacteraemia	Septic embolus
Candida sepsis	Meningococcal sepsis	Septic necrosis
Catheter bacteraemia	Micrococcal sepsis	Septic phlebitis
Catheter sepsis	Myocarditis septic	Septic rash
Citrobacter sepsis	Neutropenic sepsis	Septic shock
Clostridium bacteraemia	Nocardia sepsis	Serratia bacteraemia
Clostridium difficile sepsis	Pelvic sepsis	Serratia sepsis
Corynebacterium sepsis	Plague sepsis	Staphylococcal bacteraemia
Cryptococcal fungaemia	Pneumococcal bacteraemia	Staphylococcal sepsis
Endotoxaemia	Pneumococcal sepsis	Staphylococcal toxaemia
Endotoxic shock	Postpartum sepsis	Stenotrophomonas sepsis
Enterobacter bacteraemia	Post procedural sepsis	Streptococcal bacteraemia
Enterobacter sepsis	Pseudallescheria sepsis	Streptococcal sepsis
Enterococcal bacteraemia	Pseudomonal bacteraemia	Thrombophlebitis septic
Enterococcal sepsis	Pseudomonal sepsis	Umbilical sepsis
Escherichia bacteraemia	Pulmonary sepsis	Urosepsis
Escherichia sepsis	Salmonella bacteraemia	Viraemia
Fungaemia	Salmonella sepsis	Wound sepsis
Fungal sepsis	Sepsis	Yersinia bacteraemia

NOTE: This list included the MedDRA Higher Level Term 'sepsis, bacteraemia, viraemia, and fungaemia NEC' and other sepsis-related preferred terms in order to minimize the difference of definition criteria by Investigator and country
Source: Adapted from Addendum to Clinical Overview (U08-2183-01), Annex 1

Table 2 Multifactorial Regression Analysis for sepsis in patients with sepsis-related events in ONTARGET (n: 213), TRANSCEND (n: 42) and PRoFESS (n: 119)

	ONTARGET				**TRANSCEND**				**PRoFESS**			
Variable[#]	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**Pr > ChiSq**
T vs R	1.172	0.829	1.66	0.3679								
TR vs R	1.236	0.878	1.74	0.2247								
T vs. P					1.559	0.839	2.897	0.16	1.504	1.043	2.17	0.029
Age (yrs)	1.063	1.043	1.08	<.0001	1.057	1.014	1.103	0.0093	1.049	1.026	1.07	<.0001
Gender: Male vs. Female	0.726	0.52	1.01	0.0587	0.677	0.335	1.368	0.2772	1.01	0.669	1.523	0.9633
Race: Black vs. White	0.845	0.341	2.09	0.7154	1.55	0.207	11.617	0.6695	1.154	0.415	3.209	0.7832
Race: Asian vs. White	1.82	1.246	2.66	0.002	1.252	0.564	2.777	0.5808	2.261	1.534	3.33	<.0001
Race: Other vs. White	2.019	1.356	3.01	0.0005	1.655	0.701	3.91	0.2506				
Diabetes mellitus (de novo or past)	1.97	1.472	2.64	<.0001	1.081	0.581	2.011	0.8053	2.523	1.741	3.66	<.0001
Any cancer	1.132	0.785	1.63	0.5057	1.211	0.52	2.821	0.6564	1.291	0.64	2.605	0.4757
Any infection	5.207	3.719	7.29	<.0001	6.686	3.228	13.85	<.0001	20.087	13.16	30.7	<.0001
Employment: Unemployed vs. Others*	1.015	0.446	2.31	0.9708	-	-	-	-	-	-	-	-
Social security or disability vs. Others*	2.034	1.284	3.22	0.0025	1.314	0.397	4.347	0.6551	-	-	-	-
Alcohol (number of drinks/d)	1.048	0.881	1.25	0.5959	0.84	0.468	1.511	0.5612	0.8	0.588	1.087	0.154
Current/former smoker vs. never smoker	1.625	1.162	2.27	0.0045	1.386	0.684	2.809	0.3656	1.028	0.684	1.546	0.8929
Creatinine (mg/dL)	1.041	0.814	1.33	0.7513	1.043	0.578	1.879	0.8898	-	-	-	-
Micro-albuminuria	0.54	0.314	0.93	0.0267	1.166	0.484	2.809	0.7327	-	-	-	-
Number of hospitalizations	1.08	1.03	1.13	0.0013	1.095	0.978	1.226	0.1137	1.023	0.918	1.139	0.684

This model used SAS procedure PHREG selecting the model with the highest score chi2 statistic for all possible model sizes ranging from one explanatory variable to the total number of explanatory variables. Variables were excluded if not available (PRoFESS) or the numbers were too small (TRANSCEND)

[#]All variables (with the exception of treatment) were recorded at study visits; *Surrogate for socioeconomic status

Table 3 Number (%) of risk factors for sepsis-related events in PRoFESS patients.

Risk Factors	T N (%Ψ)	PBO N (%♣)
Diabetes	6 (8.6)	3 (6.1)
Cancer	5 (7.1)	9 (18.4)
Renal Impairment	4 (5.7)	0 (0)
Indwelling Catheter	2 (2.9)	1 (2.0)
Other	8 (11.4)	11 (22.4)

Some patients presented with more than one risk factor for SRE, Ψ total = 70; ♣ total = 49

Table 4 Number (%) of infections preceding the onset of sepsis-related events in PRoFESS patients

Identified Potential Source for SRE	T N (%Ψ)	PBO N (%♣)
Pulmonary	25 (35.7)	11 (22.4)
Urinary tract	22 (31.4)	14 (28.6)
Skin/Soft Tissue	10 (14.3)	2 (4.1)
Bloodstream Infection	8 (11.4)	7 (14.3)
Gastrointestinal	4 (5.7)	5 (10.2)
Other	6 (8.6)	1 (2.0)

Some patients presented with more than one potential source for SRE, Ψ total = 70; ♣ total = 49

Table 5 Number of patients with sepsis-related events in hypertension trials with telmisartan

Trial	Telmisartan	Comparator
502.214	1	
502.216	1	
502.236	2	
502.396	5	1[1]
502.397	1	4[2]
Total	10	5

[1] Losartan
[2] Valsartan

APPENDIX S7

Table 1 Multi-factorial Regression Analysis of lung malignancies in ONTARGET and TRANSCEND.

	ONT				TRA			
	Hazard Ratio	**95% Hazard Ratio Confidence Limits**		**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**Pr > ChiSq**
Variable								
T vs. R	1.00	0.78	1.30	0.99				
T/R vs. R	1.23	0.96	1.57	0.11				
T vs. PBO					1.37	0.84	2.23	0.21
Latin-Am vs. North-America	0.77	0.39	1.55	0.47	0.35	0.09	1.34	0.12
Europe vs. North-America	0.78	0.61	1.00	0.05	0.63	0.33	1.19	0.15
Asia vs. North-America	0.61	0.31	1.22	0.16	1.08	0.28	4.20	0.91
Aus/NZL vs. North-America	1.03	0.70	1.52	0.89	1.03	0.42	2.52	0.94
Age	1.04	1.02	1.05	<.0001	1.07	1.04	1.11	<.0001
Female vs. Male	0.89	0.68	1.17	0.40	0.82	0.46	1.46	0.50
Black vs. White	0.97	0.53	1.79	0.92	0.00	0.00	.	0.98
Asian vs. White	1.01	0.52	1.95	0.98	0.46	0.12	1.76	0.25
Other vs. White	0.65	0.33	1.29	0.22	1.32	0.38	4.57	0.66
Ex smoker vs. Never smoked	3.12	2.20	4.41	<.0001	3.94	1.87	8.29	0.00
Smoker vs. Never smoked	9.10	6.32	13.09	<.0001	9.44	4.11	21.67	<.0001
Lung cancer at BL vs. No Cancer	9.25	4.74	18.06	<.0001	0.00	0.00	.	1.00
Respiratory Conditions* prior to diagnosis of lung malignancies	1.35	0.95	1.93	0.10	2.23	0.30	16.45	0.43

*Occurrence of respiratory conditions as defined by "Cough, cluster of Shortness of breath / breathing difficulties / Respiratory Insufficiency and the MedDRA system organ class Respiratory, thoracic and mediastinal disorders".

BL = baseline; NZL = New Zealand

Table 2 Database analysis of malignancy adverse event reports using Standardized MedDRA Query for malignancies (SMQ, code 20000090) in controlled clinical trials of one or more years in duration

	Telmisartan	Comparator	Placebo
Patients, N	1727	1214	176
Mean exposure (days)	426	433	475
Patient years	2015	1440	229
Mean age	59.1	59.6	61.1
% Female	33.9	34.7	27.3
% Black	8.2	6.6	0
Patients with SMQ Cancer	31	26	2
%	1.8	2.1	1.1
Per 100 PY	1.54	1.81	0.87