



What is the ONTARGET® Trial Program?

- The ONTARGET® (**ON**going **T**elmisartan **A**lone and in combination with **R**amipril **G**lobal **E**ndpoint **T**rial) program is the largest, most ambitious ARB clinical study program ever undertaken and was designed to clarify whether telmisartan, marketed by Bayer Schering Pharma as Pritor®/Kinzalmono®, or ramipril, or a combination of the two confers blood-pressure-independent cardio & vascular protection in high-risk patients whose blood pressure is well controlled. The trial was an academically-led study managed by the trials center at McMaster University, Hamilton, Canada.

ONTARGET® Trial Design

- ONTARGET® is a randomized, double-blind, double-dummy clinical trial outcomes-led study. It investigated the role of the angiotensin II receptor blocker telmisartan in cardio & vascular protection.
- ONTARGET® included the broadest population ever in a study of this type: high-risk cardiovascular patients with a history of coronary heart disease, stroke, transient ischaemic attack, peripheral vascular disease or diabetes with target organ damage.
- A high proportion of patients had previously received proven therapies:
 - Statins (61.6% at baseline, increasing to 70.6% by the end of the study)
 - Antiplatelet therapy (80.9% and 77.5%, respectively)
 - Beta-blockers (56.9% and 56.9%, respectively) and
 - Diuretics (28.0% and 32.5%, respectively)
 - The wide range of high-risk cardiovascular patients included in ONTARGET® reflects everyday clinical practice.

The ONTARGET[®] Trial Investigated

- Whether the ARB Pritor[®]/Kinzalmono[®] (telmisartan) 80mg is at least as effective as the current gold standard ramipril 10mg (an angiotensin converting enzyme inhibitor, ACEI) in reducing the risk of CV-related events and death in high-risk CV patients.
- Whether the combination of Pritor[®]/Kinzalmono[®] 80mg and ramipril 10mg (i.e. dual blockade of the renin-angiotensin-system, RAS) could provide a greater reduction in CV-related death and events than either treatment alone.
- ONTARGET[®] secondary endpoints:
 - Main secondary outcome: composite of death from cardiovascular causes, myocardial infarction, or stroke (primary endpoint of HOPE trial)
 - Newly diagnosed congestive heart failure
 - Cardiovascular revascularisation procedure
 - Newly diagnosed diabetes
 - Cognitive decline/dementia
 - New onset of atrial fibrillation

Results

Pritor[®]/Kinzalmono[®] – the only angiotensin II receptor blocker (ARB) demonstrated to be as effective as ramipril in providing cardio & vascular protection¹

- The results of ONTARGET[®] show that Pritor[®]/Kinzalmono[®] is as effective as the current gold standard ramipril in reducing the risk of cardiovascular death, myocardial infarction, stroke and hospitalization for congestive heart failure (combined primary endpoint) in high-risk CV patients already receiving optimal baseline care.¹
- These events occurred in 16.66% of patients treated with Pritor[®]/Kinzalmono[®] and 16.46% of patients treated with ramipril.¹

- The relative risk - the ratio of the probability of an event occurring in the telmisartan group versus the ramipril group - was 1.01, 95% CI 0.94-1.09.^{1,2}
- The combination of the two drugs was associated with more adverse events without an increase in benefit. As compared with the ramipril group, there was an increased risk of hypotensive symptoms (4.8% vs. 1.7%, $P<0.001$), syncope (0.3% vs. 0.2%, $P=0.03$), and renal dysfunction (13.5% vs. 10.2%, $P<0.001$).¹
- The relative risk – the ratio of the probability of an primary outcome in the telmisartan/Ramipril combination group – was 16.3%.¹
- There was no significant difference in the total number of deaths between the ramipril group and the telmisartan group regarding the secondary outcome. Death from cardiovascular causes, myocardial infarction, or stroke — occurred in 14.1% in the ramipril group and in 13.9% in the telmisartan group.¹

Pritor[®]/Kinzalmono[®] showed better tolerability

- The ONTARGET[®] results also show that Pritor[®]/Kinzalmono[®] is markedly better tolerated than ramipril 10mg in high-risk CV patients,¹ an important consideration as many patients are unable to tolerate treatment with ACE inhibitors.²⁻⁴
- More discontinuations in the ramipril group than in the Pritor[®]/Kinzalmono[®] group were due to
 - angioedema ($p=0.01$)
 - cough ($p<0.001$)
- More patients in the Pritor[®]/Kinzalmono[®] group discontinued because of hypotensive symptoms ($p<0.001$). This however did not result in more syncope ($p=0.49$).
- Increased tolerability also resulted in greater compliance with treatment – an essential factor for effective long-term treatment and protection against CV events.¹
- The ONTARGET[®] trial also showed that combining ramipril and telmisartan (i.e. dual blockade of the renin-angiotensin system, RAS) provides no additional

protective benefit for the overall patient population studied but revealed added side effects, answering an important question for the clinical community.¹

- The combination of Pritor[®]/Kinzalmono[®] 80mg and ramipril 10mg (i.e. dual blockade of the renin-angiotensin-system, RAS) was associated with more adverse events without an increase in benefit.

What do the results of the ONTARGET[®] trial mean for physicians and patients?

- Current treatment for hypertensive high-risk cardiovascular patients could be further improved by including Pritor[®]/Kinzalmono[®] in the treatment regimen.
- In addition to already demonstrated powerful 24-hour blood pressure reductions, the ONTARGET[®] trial has now demonstrated that Pritor[®]/Kinzalmono[®] provides cardio & vascular protection for high-risk patients as effectively as ramipril, and is also better tolerated and associated with better compliance.¹
- Together with its demonstrated renal protective effect demonstrated in the PROTECTION[®] program, Pritor[®]/ Kinzalmono[®] provides effective protection for patients at high CV risk.
- Dual blockade of the renin-angiotensin-aldosterone system (e.g. by adding an ACE-inhibitor to an angiotensin II receptor antagonist) is not recommended in patients with already controlled blood pressure and should be limited to individually defined cases with close monitoring of renal function.

What is cardio & vascular protection?

- Cardio & vascular protection means protection of the heart, other target organs and of the vascular system against damage which can cause a cardiovascular event including myocardial infarction (MI), stroke, congestive heart failure (CHF) and renal failure. Providing cardio & vascular protection is an important objective of patient management in cardiovascular disease. Providing cardio &

vascular protection benefits patients by reducing cardiovascular morbidity and mortality as a result of preventing cardiovascular events.

- Cardiovascular disease (CVD) is the term given to a wide range of disorders affecting the heart and blood vessels including coronary heart disease (CHD), cerebrovascular disease, hypertension (high blood pressure) and peripheral vascular disease (PVD).
- Pritor[®]/Kinzalmono[®] provides powerful and consistent blood pressure reductions over a full 24-hour period,⁷⁻¹¹ particularly in the risky early morning hours when blood pressure surges^{11,12} and the risk of cardiovascular events is at its highest.^{12,13}
- The ONTARGET[®] trial has also demonstrated that Pritor[®]/Kinzalmono[®] provides cardio & vascular protection for high-risk cardiovascular patients, which has led to the improved clinical outcomes in these patients.¹



What is the TRANSCEND[®] trial?

- TRANSCEND[®] (Telmisartan **R**andomised **A**ssessme**Nt** **S**tudy in **A**CEI **i**ntolerant subjects with cardiovascular **D**isease) is the first trial in cardio & vascular protection and the second arm of ONTARGET[®] and uses the identical treatment protocol as well as identical outcome measures, however, randomization is to telmisartan or placebo.
- TRANSCEND[®] is the first trial to test the cardiovascular protective effect of Pritor[®]/Kinzalmono[®] compared with placebo on top of standard therapy

(including antihypertensives, anti-platelets and statins) in individuals who are intolerant to ACE inhibitors.

- TRANSCEND is also the first cardiovascular trial to study a gender-balanced population, with 43% female participants.¹⁴

TRANSCEND® Trial Design

- TRANSCEND® is the first placebo controlled trial investigating the effect of an ARB on CV risk on top of standard care.
- The trial was conducted over 5 years with very high quality (only 0.32% of patients lost to follow-up).
- Contrary to previous trials investigating the effect on CV risk, TRANSCEND® is a trial with almost equal representation of both genders (43% women).
- The primary endpoint was a 4-fold composite endpoint of CV death, MI, stroke, and hospitalisation for CHF.
- The main secondary endpoint was a 3-fold composite endpoint of CV death, MI, and stroke, identical to the primary endpoint in HOPE.

Results:

- In the Pritor®/Kinzalmono® (telmisartan 80mg) arm of TRANSCEND® in the main secondary endpoint the risk of CV death, MI and stroke (HOPE primary endpoint) in ACE inhibitor-intolerant, high CV risk patients already on best practice therapy was reduced markedly by 13% ($p < 0.05$).
- The primary endpoint (cardiovascular death, myocardial infarction, stroke, or heart failure hospitalization) had a tendency which was not significant to occur more often in patients of the control group. The treatment with telmisartan 80mg in patients receiving current standard of care resulted in an 8% reduction in the composite endpoint of cardiovascular death, myocardial infarction, stroke and hospitalization for congestive heart failure.¹⁵

- TRANSCEND[®] has substantiated the protective benefits seen with Pritor[®]/Kinzalmono[®] (telmisartan 80mg) in the ONTARGET[®] trial, where Pritor[®]/Kinzalmono[®] (telmisartan 80mg) was as effective as the gold-standard ACE-inhibitor ramipril, but better tolerated.
- Thus, the evidence from both, ONTARGET[®] and TRANSCEND[®], establishes Pritor[®]/Kinzalmono[®] (telmisartan 80mg) as an ideal option for the broadest cross-section of CV high-risk patients.
- Pritor[®]/Kinzalmono[®] (telmisartan 80mg) is well tolerated and associated with less discontinuations and higher compliance than the control group.

Unique Properties of Pritor[®]/Kinzalmono[®]

- The benefits of Pritor[®]/Kinzalmono[®] seen in the ONTARGET[®] trial could be attributed to its specific molecular structure that is clearly different from other ARBs and leads to pharmacological properties that make it unique among the ARB class:
 - Insurmountable blockade of AT1-receptor
 - Slow rate of dissociation from the receptor
 - Highest volume of distribution of ARBs
 - Longest half-life of ARBs: effect maintained over 24 hours with single dose
 - High lipophilicity
 - High level of tissue penetration
 - Unique Selective PPAR- γ Modulations (SPPARM) that translate into a favorable glycaemic and lipid metabolism effect
- Pritor[®]/Kinzalmono[®] has been shown to achieve superior blood pressure lowering to losartan and valsartan.^{16,22} It has also been shown to achieve blood pressure lowering at least as effectively as enalapril, lisinopril, ramipril, amlodipine and atenolol, leading drugs in other classes.¹⁷⁻²¹
- It should be kept in mind that the combination of Pritor[®]/Kinzalmono[®] 80mg and ramipril 10mg (i.e. dual blockade of the renin-angiotensin-system, RAS) was

associated with more adverse events without an increase in benefit and is therefore not recommended mostly.

References

1. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Eng J Med*. Published online 31 Mar 2008.
2. Mancia M, et al. *J Hypertension* 2007;25:1105–87.
3. Israeli ZH et al. *Ann Intern Med* 1992 1; 117(3):234-42.
4. Matchar D et al. *Ann Intern Med* 2008;148:16-29.
5. Macaulay TE, Dunn SP. *US Pharmacist* 2007; 32 (2).
6. Volpe, M; Tocci, G. – Hot Topics in Hypertension n.1-2007, Renal protection with telmisartan: a key target when managing hypertension and diabetes.
7. Parati G et al. Presented at the Annual Meeting of the European Society of Hypertension. June 2007, Milan, Italy.
8. Redon J et al. Presented at the Annual Meeting of the European Society of Hypertension. June 2007, Milan, Italy.
9. Neutel JM Smith HG. *J Clin Hypertens* 2003; 5(1):58-63.
10. Burnier M Brunner HR. *Lancet* 2000; 355:637-45.
11. Gosse P et al. *Blood Press Mont* 2007 12(3):141-7.
12. Millar-Craig MW et al. *Lancet* 1978; 1:795-97.
13. Elliott WJ. *Stroke* 1998; 29:992-6.
14. The TRANSCEND Investigators. *Lancet*, published online August 31, 2008.
15. Yusuf, S et al. “Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. *The Lancet*. Published Online, August 31, 2008
16. Mallion JM. *J Hum Hypertens* 1999;13:657-64.
17. Parati G et al. Presented at the Annual Meeting of the European Society of Hypertension. June 2006, Madrid, Spain.
18. Neutel JM et al. *Am J Ther* 1999; 6:161-6.
19. Freytag F et al. *Clin Ther* 2001; 23:108-23.
20. Lacourcière Y et al. *Blood Press Monit* 1998; 3:295-302.
21. Williams B et al. *Br J Hypertens* 2006; 24:193-200.
22. Lacourcière Y et al. *Blood Press Monit* 2004;9:203-10.