

# The ONTARGET<sup>®</sup> Trial Programme

(Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial)

## Medical media backgrounder

### What is The ONTARGET<sup>®</sup> Trial Programme?

- ▶ The ONTARGET<sup>®</sup> Trial Programme includes two parallel studies, the landmark ONTARGET<sup>®</sup> Trial (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial)<sup>1</sup> and a parallel trial TRANSCEND (Telmisartan Randomised Assessment Study in ACE-I-iNtolerant subjects with cardiovascular Disease). The ONTARGET<sup>®</sup> Trial Programme is primarily sponsored by Boehringer Ingelheim.



ONTARGET/TRANSCEND study centres worldwide

### ONTARGET<sup>®</sup> - the largest ARB outcomes trial

- ▶ ONTARGET<sup>®</sup> is the largest outcomes-led cardiovascular (CV) trial undertaken with an angiotensin receptor blocker (ARB) and has the broadest population ever included in a study of this type – high-risk CV patients with a history of coronary heart disease, stroke, transient ischaemic attack, peripheral vascular disease or diabetes with target-organ damage.<sup>1</sup>
- ▶ The wide range of high-risk cardiovascular patients included in ONTARGET<sup>®</sup> reflects everyday clinical practice.
- ▶ The ONTARGET<sup>®</sup> Trial<sup>1</sup> investigated:
  - whether the ARB MICARDIS<sup>®</sup> (telmisartan) 80mg is at least as effective as, and better tolerated than, 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 MICARDIS<sup>®</sup> 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.

### What did the ONTARGET<sup>®</sup> Trial show?

- ▶ MICARDIS<sup>®</sup> – the first ARB shown to be as protective as ramipril<sup>2</sup>
  - The results of ONTARGET<sup>®</sup> show that MICARDIS<sup>®</sup> is as protective as the current gold standard ramipril in reducing the risk of cardiovascular death, heart attack, stroke and hospitalisation for congestive heart failure in high-risk CV patients already receiving optimal baseline care.<sup>2</sup>
  - These events occurred in 16.66% of patients treated with MICARDIS<sup>®</sup> and 16.46% of patients treated with ramipril.<sup>2</sup>
  - 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.<sup>2</sup>
- ▶ MICARDIS<sup>®</sup> – increased tolerability and treatment compliance
  - The ONTARGET<sup>®</sup> results also show that MICARDIS<sup>®</sup> 80mg is markedly better tolerated than ramipril 10mg in high-risk CV patients,<sup>2</sup> an important consideration as many patients are unable to tolerate treatment with ACEis.<sup>3-5</sup>
  - Increased tolerability also resulted in greater compliance with treatment – an essential factor for effective long-term treatment and protection against CV events.<sup>2</sup>

- ▶ The ONTARGET<sup>®</sup> Trial also showed that combining an ACEi (ramipril) and an ARB (MICARDIS) (i.e. dual blockade of the renin-angiotensin system, RAS) provides no additional protective benefit for the overall patient population studied, answering an important question for the clinical community.<sup>2</sup>

### What do the results of the ONTARGET<sup>®</sup> Trial mean for physicians and patients?

- ▶ Current treatment for hypertensive high-risk cardiovascular patients could be further improved by including MICARDIS<sup>®</sup> in the treatment regimen.
- ▶ In addition to already proven powerful 24-hour blood pressure reductions, the ONTARGET<sup>®</sup> Trial has now proven that MICARDIS<sup>®</sup> provides cardio and vascular protection for high-risk CV patients, which improves their long-term outcomes.<sup>2</sup>
- ▶ The ONTARGET<sup>®</sup> Trial Programme provides further evidence for the benefits of MICARDIS<sup>®</sup> beyond those of blood pressure lowering alone.<sup>2</sup> Previously, the AMADEO trial showed that MICARDIS<sup>®</sup> has the potential to provide renal protection as demonstrated by a significantly greater reduction in proteinuria compared to the ARB losartan.<sup>6</sup>

### What is cardio and vascular protection?

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

- ▶ MICARDIS<sup>®</sup> provides powerful and consistent blood pressure reductions over a full 24-hour period,<sup>7-11</sup> particularly in the risky early morning hours when blood pressure surges<sup>11,12</sup> and the risk of cardiovascular events is at its highest.<sup>12,13</sup>
- ▶ The ONTARGET<sup>®</sup> Trial has also proven that in addition to providing effective 24-hour blood pressure control, MICARDIS<sup>®</sup> also provides cardio and vascular protection for high-risk cardiovascular patients, which has led to the to improved clinical outcomes in these patients.<sup>2</sup>

### Unique characteristics of MICARDIS<sup>®</sup>

- ▶ The benefits of MICARDIS<sup>®</sup> seen in the ONTARGET<sup>®</sup> Trial could be attributed to the specific molecular structure that is demonstrably different from other ARBs and leads to pharmacological properties that make it unique amongst ARBs:
  - MICARDIS<sup>®</sup> has a longer duration of action than many other members of the ARB class; it takes 24 hours for half the dose of MICARDIS to be eliminated from the body compared with 6 to 15 hours for other ARBs.<sup>10,14</sup>
  - MICARDIS also has a higher lipophilicity and volume of distribution compared with other ARBs. This means that it extensively penetrates membranes including the blood-brain barrier and is available throughout the body, tissue and cellular spaces.<sup>15,16</sup>
- ▶ MICARDIS<sup>®</sup> has been shown to achieve superior blood pressure lowering to losartan and valsartan.<sup>17,18</sup> It has also been shown to achieve blood pressure lowering at least as effectively as enalapril, lisinopril, ramipril, amlodipine and atenolol, leading medicines in other classes.<sup>19-23</sup>
- ▶ The ONTARGET<sup>®</sup> Trial Programme provides additional evidence for the cardio and vascular protective benefits of MICARDIS<sup>®</sup> beyond those of blood pressure lowering alone.<sup>2</sup>

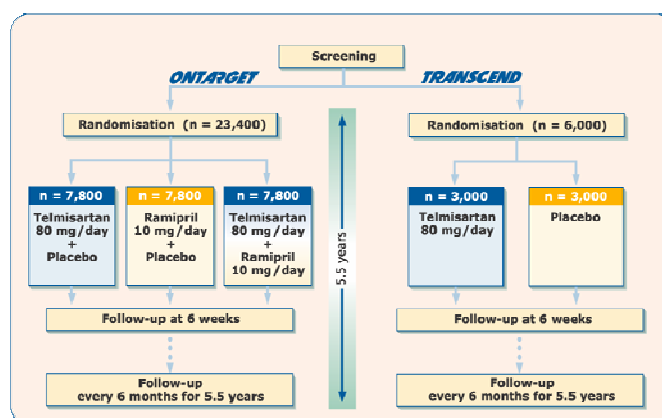
## ONTARGET® Trial design

- ▶ ONTARGET® is a randomised, double-blind clinical trial which evaluated over 25,600 high-risk cardiovascular patients with normal or controlled blood pressure. The ONTARGET® Trial Programme including ONTARGET® and TRANSCEND® (Telmisartan Randomized Assessment Study in ACE-I Intolerant subjects with cardiovascular Disease) was a long-term programme that took place over 5.5 years in over 700 centres across 40 countries.<sup>1</sup>
- ▶ ONTARGET® and TRANSCEND® were not hypertension studies: patients with blood pressure >160/100 mmHg were excluded. Patients were included in ONTARGET® if they met the following criteria:<sup>1</sup>
  - Male or female aged 55 years or older
  - At high risk of developing a major cardiovascular event, with a history of:
    - Coronary artery disease
    - Peripheral arterial occlusive disease
    - Stroke or transient ischaemic attacks
    - Diabetes mellitus with end-organ disease
  - In addition to the above criteria, TRANSCEND patients needed to be intolerant to treatment with ACE inhibitors.

- ▶ The ONTARGET® primary endpoints investigated:
  - Whether MICARDIS® 80mg daily was at least as effective as ramipril 10mg daily in reducing the combined risk of MI, stroke, hospitalisation for CHF, and cardiovascular death compared with ramipril 10mg alone<sup>1</sup>
  - Whether the combination of MICARDIS® 80mg and ramipril 10mg daily was more effective in reducing the combined risk of MI, stroke, hospitalisation for CHF, and cardiovascular death compared with ramipril 10mg alone.<sup>1</sup>
- ▶ The ONTARGET® secondary endpoints investigated:
  - the incidence of newly diagnosed CHF, revascularisation procedures, newly diagnosed diabetes mellitus, cognitive decline and dementia, and new onset of atrial fibrillation.<sup>1</sup>

## TRANSCEND – a first trial in cardiovascular protection

- ▶ TRANSCEND is the first trial to test the cardiovascular protective effect of MICARDIS® compared with placebo on top of standard therapy (including antihypertensives, anti-platelets and statins) in individuals who are intolerant to ACE inhibitors. The first results from TRANSCEND are expected later in 2008.<sup>1</sup>



## References

1. The ONTARGET/TRANSCEND Investigators (2004) 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
2. The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Eng J Med*. Published online 31 Mar 2008.
3. Israeli ZH, et al. *Ann Intern Med* 1992; **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. Bakris G et al. Poster presented at 22nd Ann Sci Mtg of the American Society of Hypertension, Chicago, 19 - 22 May 2007; Abstr P-65
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 Monit* 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. Brunner HR. *J Hum Hypertens* 2002; **16**(suppl 2):S13-S16.
15. Costa FV. *High Blood Press Cardiovasc Prev* 2006; **13**:85-94.
16. Kakuta H, et al. *Int J Clin Pharmacol Res* 2005; **25**:41-46.
17. Lacourcière Y et al. *Blood Press Monit* 2004; **9**:203-10.
18. Mallion JM. *J Hum Hypertens* 1999; **13**:657-64.
19. Parati, et al. Presented at the Annual Meeting of the European Society of Hypertension. June 2006, Madrid, Spain.
20. Neutel JM et al. *Am J Ther* 1999; **6**:161-6.
21. Freytag F et al. *Clin Ther* 2001; **23**:108-23.
22. Lacourcière Y et al. *Blood Press Monit* 1998; **3**:295-302.
23. Williams B et al. *Br J Hypertens* 2006; **24**:193-200.