



**Backgrounder – including initial findings presented at ESH 2010**

## **TALENT – A Multicentre Study Evaluating the Efficacy of Nifedipine GITS – Telmisartan Combination in Blood Pressure Control and Beyond: comparison of two strategies**

### **What is TALENT?**

- TALENT is the first trial to examine combination treatment with the calcium channel blocker (CCB) nifedipine (Adalat<sup>®</sup>) Gastrointestinal Therapeutic System (GITS) and angiotensin receptor blocker (ARB) telmisartan (Pritor<sup>®</sup>/Kinzal<sup>®</sup>) compared with starting with one drug and then adding the second, in patients with hypertension and additional risk factors for cardiovascular (CV) disease.
- The aim of the trial was to evaluate blood pressure (BP) control when antihypertensive therapy was initiated with a combination of Adalat<sup>®</sup> GITS 20mg daily and Pritor<sup>®</sup>/Kinzal<sup>®</sup> 80mg daily, compared with a regimen starting with one drug and then adding the second.<sup>1</sup>
- TALENT examined the quality of BP control.
- TALENT was also designed to examine the potential effects of treatment on metabolic and inflammatory indicators of CV risk.<sup>1</sup>
- The trial enrolled 405 patients and was carried out in 40 centres in Italy (30) and Spain (10). The principle investigators were Professor Giuseppe Mancia, Milan, Italy and Professor Luis Ruilope, Madrid, Spain.
- Initial findings of TALENT were presented at the 20th European Meeting on Hypertension, 18–21 June 2010, Oslo, Norway

### **Rationale for TALENT**

- Current hypertension management guidelines from the European Society of Hypertension/European Society of Cardiology<sup>2</sup> recognise the importance of using combination antihypertensive therapies. In particular, the guidelines recommend that patients with grade 2 (moderate) or 3 (severe) hypertension or with high or very high total CV risk should be given a 2-drug combination as initial treatment.
- Adalat<sup>®</sup> GITS is widely recognised as an ideal combination therapy partner to several classes of antihypertensive drugs. Several studies have already demonstrated that Adalat<sup>®</sup> GITS is effective as initial monotherapy,<sup>3,4</sup> as well as in combination with other antihypertensive agents for achieving target BP and reducing CV risk in hypertensive patients.<sup>5</sup>
- Pritor<sup>®</sup>/Kinzal<sup>®</sup> has demonstrated strong reduction of both systolic and diastolic BP, maintained over 24 hours.<sup>6</sup> The landmark ONTARGET<sup>®</sup> trial demonstrated that Pritor<sup>®</sup>/Kinzal<sup>®</sup> provides a high level of cardio and vascular protection with better efficacy/tolerability than the gold standard ACE inhibitor, ramipril in a broad range of CV risk patients.<sup>7,8</sup>
- The combination of a CCB such as Adalat<sup>®</sup> GITS with an ARB can provide synergistic BP-lowering and improved side-effects.<sup>9</sup> The simultaneous blockade of two different pathways leading to BP control offered by a CCB/ARB combination has been shown to result in significantly greater BP reductions and improved BP control compared with its monotherapy components.<sup>10</sup>
- By using a low dose of Adalat<sup>®</sup> GITS (20mg) in combination with Pritor<sup>®</sup>/Kinzal<sup>®</sup> in TALENT, the potential side effects of each drug can be ameliorated while still providing efficacious antihypertensive therapy.<sup>5</sup>



- TALENT assessed how to best administer Adalat® GITS and Pritor®/Kinzal® to patients whose BP was uncontrolled, or not treated to target, and who had additional CV risk factors. It also assessed the effects of the two treatment strategies on a number of indicators of CV risk.

### TALENT Study Design<sup>1</sup>

- TALENT was a 16-week study with an optional 8-week extension, which evaluated two treatment strategies: initiating therapy with the combination of nifedipine GITS 20mg/telmisartan 80mg versus starting therapy with one drug and then adding the second (Figure 1).
- The first 8-week double-blind treatment period consisted of three arms (all treatments given once daily):
  - Group A: nifedipine GITS 20mg/telmisartan 80mg combination
  - Group B: nifedipine GITS 20mg monotherapy
  - Group C: telmisartan 80mg monotherapy.
- The subsequent 8-week double-blind treatment period consisted of once-daily nifedipine GITS 20mg/telmisartan 80mg combination for all patients.
- The optional 8-week extension period consisted of nifedipine GITS 20mg/telmisartan 80mg combination for all patients, or treatment adjustment (optional open-label extension) with up-titration of nifedipine GITS to 30mg, or concomitant add-on medication (e.g. diuretic), at the discretion of the investigator and based on the patient's needs.
- Up-titration of nifedipine GITS or addition of another concomitant antihypertensive drug was not performed if SBP<120mmHg.

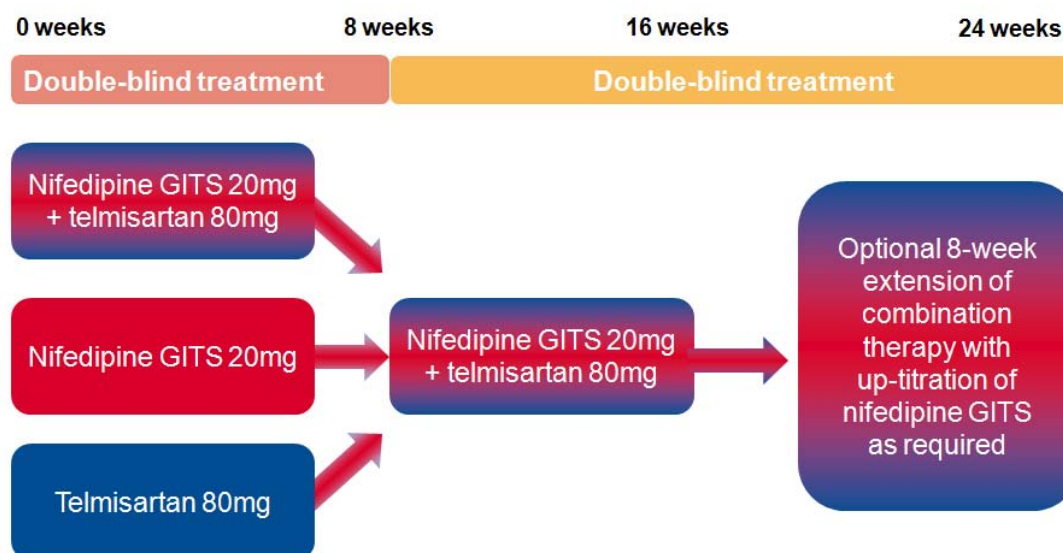


Figure 1. TALENT study design

### TALENT Participants

#### Main inclusion criteria<sup>11</sup>

- Age 18–75 years.
- Untreated or poorly controlled hypertension (office SBP >135mmHg) but stable antihypertensive regimen for ≥4 weeks.



- Presence of type 2 diabetes mellitus or target-organ damage (echocardiographic or electrocardiographic left ventricular hypertrophy or microalbuminuria).
- Presence of the metabolic syndrome, regardless of the concomitant use of lipid-lowering drugs such as statins, i.e. at least two of the following:
  - a. Impaired glucose tolerance (fasting plasma glucose 110–125mg/dL)
  - b. Raised serum triglycerides ( $\geq 150$ mg/dL)
  - c. Low HDL cholesterol (males:  $< 40$ mg/dL, females:  $< 50$ mg/dL)
  - d. Waist circumference of  $> 102$ cm (men) or  $> 88$ cm (women).
- Negative pregnancy test in women.
- Written informed consent.

**Main exclusion criteria<sup>11</sup>**

- Ongoing treatment with the following drugs: ACE-inhibitors (e.g. captopril, benazepril, enalapril, lisinopril, fosinopril, ramipril, perindopril, quinapril, moexipril, andtrandolapril), AT1-antagonists (e.g. losartan, candesartan, eprosartan, telmisartan) or calcium-antagonists (e.g. amlodipine, felodipine, isradipine, nifedipine, nimodipine) that could not be withdrawn.
- Concomitant treatment with other antihypertensive medication that could not be safely withdrawn at entry.
- Concomitant treatment with known cytochrome P450-3A4 inhibitors (e.g. cimetidine, anti-HIV protease inhibitors e.g. ritonavir, azole anti-mycotics e.g. ketoconazole, digoxin, quinidine, tacrolimus) or inducers such as anti-epileptic drugs (e.g. phenytoin, carbamazepine and phenobarbitone) or rifampicin.

**TALENT Endpoints**

**Primary endpoint**

- The primary efficacy parameter was 24-hour mean SBP on ambulatory BP monitoring (ABPM) at 16 weeks of treatment versus baseline. ABPM correlates more closely with hypertension-related organ damage and CV events than office BP.

**Secondary endpoints<sup>11</sup>**

- Safety parameters (adverse events, vital signs, routine laboratory blood tests and urinalysis, ECG).
- Response rate ( $\geq 10$ mmHg decrease in office SBP) at 8 and 16 weeks of treatment.
- Control rate ( $\leq 130/80$ mmHg of office BP) at 8 and 16 weeks of treatment.
- Mean SBP (office BP).
- Mean DBP (office BP).
- Percentage of patients achieving BP  $< 125/80$ mmHg (ABPM).
- Morning BP increase/surge (ABPM).
- 24-hour mean DBP (ABPM).
- Day average BP (ABPM).
- Night average BP (ABPM).
- BP variability (ABPM).
- Pulse pressure (difference between SBP and DBP).
- Trough-to-peak ratio.



- Smoothness index (ratio between the average of 24-hour hourly changes from baseline and the corresponding standard deviation).
- Dipping or non-dipping (nocturnal BP fall >10% or <10% of the daytime values).
- Reduction of microalbuminuria (in subgroup of patients).
- Metabolic parameters (fasting blood glucose, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides).
- Markers of inflammation:
  - Soluble receptors for advanced glycation end products [sRAGE] pg/mL – a low level of which implies higher risk
  - Eotaxin-3 pg/mL – a low level of which implies higher risk
  - C-reactive protein mg/dL – a high level of which implies higher risk.

### Initial findings of TALENT<sup>12</sup>

- Combination therapy with nifedipine GITS/telmisartan in TALENT lowered office and 24h BP in hypertensive patients at high CV risk
  - Office and 24h BP were reduced by 14.2/7.3mmHg and 10.0/4.7mmHg, respectively
- BP reduction with the combination of nifedipine GITS/telmisartan in TALENT was consistent throughout the 24h period
- Initiating antihypertensive treatment with the combination of nifedipine GITS/telmisartan allowed BP control to be achieved earlier compared with starting with one drug and then adding a second
- Optimum BP reduction was achieved as early as two weeks and was maintained throughout the study

### References

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