SYNOPSIS

Name of Sponsor:
Abbott Healthcare Products B.V.

Individual Study Table: **(For National Authority Use only)**

Name of Finished Product:
TBC

Name of Active Ingredient:
Eprosartan

Study Title:
A Prospective, Randomized, Double-Blind, Parallel-Group Study to Compare the Effect of Eprosartan and Eprosartan Mesylate on Blood Pressure in Subjects with Essential Hypertension

Investigator(s):
PPD (Coordinating Investigator)

Study Center(s):
The study was conducted in 38 study centers in Germany, the Russian Federation, and the United Kingdom.

Publication (Reference):
Not applicable.

Study Period:
29 JUN 2012 (first subject first visit) to
30 APR 2013 (last subject last visit)

Phase of Development:
III

Objectives:

Primary Objective
The primary objective of this study is to assess the therapeutic equivalence of eprosartan (a new formulation containing the active moiety eprosartan) with eprosartan mesylate (currently marketed formulation) on trough sitting diastolic blood pressure (DBP) in ambulatory subjects with mild to moderate essential hypertension after 8 weeks of treatment (monotherapy).

Secondary Objectives
The secondary objectives are to compare the effect of eprosartan with eprosartan mesylate on sitting systolic blood pressure (SBP), responder rate, and normalization rate after 8 weeks (monotherapy) and 12 weeks (add-on therapy) of treatment, and on sitting trough blood pressure (BP) at 12 weeks.

Safety Objectives
The safety objectives are to evaluate short-term safety and tolerability, as reflected by adverse events (AEs), clinical laboratory parameters, vital signs, physical examination findings, and 12-lead electrocardiogram (ECG).

Methodology:

This was a prospective, randomized, double-blind, double-dummy, parallel-group, multicenter study in subjects with mean sitting SBP ≥ 140 and ≤ 179 mmHg and mean sitting DBP ≥ 90 and ≤ 109 mmHg.

The study consists of the following periods:

- 3-week single-blind placebo washout period.
- 12-week double-blind treatment period, which consists of:
  - 8 weeks of randomized monotherapy (eprosartan or eprosartan mesylate).
  - 4 weeks of either continued randomized monotherapy in responders at Visit 4 (Week 8) or original randomized study medication plus add-on therapy (hydrochlorothiazide [HCTZ]) in non-responders at Visit 4 (Week 8).

After signing informed consent, subjects with mild to moderate hypertension, either treatment naïve or already on antihypertensive treatment, were screened for eligibility. Eligible subjects both treatment naïve and already on antihypertensive treatment, in whom current antihypertensive therapy could have been safely withdrawn for the duration of the washout period, entered a 3-week, single-blind placebo washout period (Visit 1). Subjects on triple combination of antihypertensive drugs were not considered suitable for withdrawal, subjects on dual combination were considered for withdrawal only if they had mild hypertension (SBP ≥ 140 to 159 mmHg and/or DBP ≥ 90 to 99 mmHg). During this washout period, all subjects received two double-dummy placebo tablets, one for each active tablet, once daily (OD). At Visit 1 blood samples were drawn for clinical laboratory evaluations which were used for screening at baseline and subjects were given a standard automated sphygmomanometer for routine BP self-monitoring. At Week -2 subjects were contacted by telephone (Visit 1.1) to collect safety information.

Subjects were instructed to take their study medication without food in the morning, at least 1 hour before or 2 hours after breakfast at about the same time of the day (± 90 minutes). They were also instructed to take the study medication after the study visit, so that trough BP (predose) could be determined. At screening all subjects received dietary (salt intake) and physical exercise recommendations, which they were asked to maintain for the duration of the study.

Blood pressure eligibility (mean sitting SBP ≥ 140 mmHg and ≤ 179 mmHg; and mean sitting DBP ≥ 90 mmHg and ≤ 109 mmHg) were to be confirmed for treatment naïve subjects and for subjects already on antihypertensive therapy at screening (Visit 1; Week -3) and at baseline (Visit 2; Week 0). Subject compliance with the study medication during the single-blind 3-week placebo washout period was considered for eligibility. If a subject took less than 80% or more than 120% of the study medication, he/she was considered noncompliant and thus not eligible.

Eligible subjects were randomized at a 1:1 ratio to either treatment A (eprosartan 450 mg OD) or treatment B (eprosartan mesylate equivalent to eprosartan 600 mg OD) at baseline (Visit 2), and entered a 12-week double-blind active treatment period with a double-dummy placebo. The planned number of subjects to be randomized was 596.

Trough sitting SBP and DBP were assessed at Visit 3 (Week 4) and Visit 4 (Week 8). Responders on monotherapy (SBP < 140 mmHg or a decrease in SBP ≥ 20 mmHg and/or

DBP < 90 mmHg or a decrease in DBP ≥ 10 mmHg and for subjects with diabetes mellitus or renal disease SBP < 130 mmHg or a decrease in SBP ≥ 20 mmHg and/or DBP < 80 mmHg or a decrease in DBP ≥ 10 mmHg) at Visit 4 (Week 8) continued on monotherapy up to Visit 5 (Week 12). Nonresponders on monotherapy at Visit 4 (Week 8) received HCTZ 12.5 mg as add-on therapy, and continued for an additional 4 weeks. At the end of Visit 5 (Week 12), active treatment was to be discontinued in all subjects, and safety and efficacy assessed. Subjects could have started their usual antihypertensive therapy after safety and efficacy assessments were completed.

Number of Subjects (Planned, Randomized and Analyzed):

Planned: 596 subjects

Randomized: 665 subjects

Analyzed: 665 subjects

Diagnosis and Main Criteria for Inclusion:

Male or female subjects aged ≥ 18 years with mild to moderate essential hypertension.

Test Product, Dose and Mode of Administration:

Eprosartan 450 mg orally, once daily as monotherapy, and HCTZ 12.5 mg orally, once daily as add-on therapy.

Duration of Treatment:

Approximately 15 weeks, including a 3-week single-blind placebo washout period and a 12-week double-blind active treatment period.

Reference Therapy, Dose and Mode of Administration:

Eprosartan mesylate equivalent to eprosartan 600 mg orally, once daily as monotherapy, and HCTZ 12.5 mg orally, once daily as add-on therapy.

Criteria for Evaluation

Efficacy:

Primary

The primary efficacy variable is the change in trough sitting mean DBP from baseline (Visit 2) to end of Visit 4 (Week 8).

Secondary

- Change in trough sitting mean SBP from baseline to end of Visit 4 (Week 8)
- Change in trough sitting mean SBP from baseline to end of Visit 5 (Week 12)
- Change in trough sitting mean DBP from baseline to end of Visit 5 (Week 12)
- Responder rate at Visit 4 (Week 8) and at Visit 5 (Week 12) on monotherapy
- Normalization rate at Visit 4 (Week 8) and Visit 5 (Week 12) on monotherapy
- Responder rate at Visit 5 (Week 12) in subjects with add-on HCTZ
- Normalization rate at Visit 5 (Week 12) in subjects with add-on HCTZ

Safety:

Safety and tolerability were to be assessed by the assessment of AEs, evaluation of vital

signs (SBP, DBP, and pulse rate), laboratory measurements (hematology and biochemistry), 12-lead ECGs, and concomitant medication. A urine pregnancy test was also to be performed on females of childbearing potential.

Statistical Methods:

The efficacy analysis was performed on the full analysis (FA) and the per protocol (PP) subject samples. The primary objective of this study was to assess the therapeutic equivalence of eprosartan (a new formulation containing only the active moiety eprosartan) with eprosartan mesylate (current marketed formulation) on sitting DBP in ambulatory subjects with mild to moderate essential hypertension after 8 weeks of treatment. The primary efficacy variable was the change in trough sitting DBP from baseline to Visit 4 (Week 8).

An analysis of covariance (ANCOVA) model was assumed for the primary efficacy variable with the treatment group as fixed factor and the sitting DBP at baseline as a covariate. From this ANCOVA model the following statistics are presented: least squares (LS) mean change from baseline, LS mean standard error (SE), and the point estimate of the difference of the LS mean change from baseline as well as the associated 95% confidence interval (CI).

To show that eprosartan was equivalent to eprosartan mesylate, the two-sided 95% CI has to lie entirely in the equivalence margin. An equivalence margin of 2.5 mmHg (DBP) is recommended by the Federal Institute for Drugs and Medical Devices in Germany (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM).

Analyses were performed on the FA subject sample (last observation carried forward [LOCF] ANCOVA) and the PP subject sample. In addition, further sensitivity analyses (e.g., mixed effect model for repeated measures [MMRM]) was performed.

Secondary efficacy parameters:

- Change in trough sitting SBP from baseline (Visit 2) to end of Visit 4 (Week 8)
- Change in trough sitting DBP and trough sitting SBP from baseline (Visit 2) to end of Visit 5 (Week 12)
- Responder rate at Visit 4 (Week 8) and at Visit 5 (Week 12) on monotherapy
- Normalization rate at Visit 4 (Week 8) and Visit 5 (Week 12) on monotherapy
- Responder rate at Visit 5 (Week 12) in subjects with add-on HCTZ
- Normalization rate at Visit 5 (Week 12) in subjects with add-on HCTZ

A responder is defined as:

- For subjects with diabetes mellitus or renal disease, a responder is defined as subjects with trough sitting mean SBP < 130 mmHg OR a decrease in SBP ≥ 20 mmHg AND/OR trough sitting mean DBP < 80 mmHg OR a decrease in DBP ≥ 10 mmHg.
- For subjects without diabetes mellitus and renal disease, trough sitting mean SBP < 140 mmHg OR a decrease in SBP ≥ 20 mmHg AND/OR trough sitting mean DBP < 90 mmHg OR a decrease in DBP ≥ 10 mmHg.

Normalization is defined as:

- For subjects with diabetes mellitus or renal disease, normalization is defined as trough sitting mean SBP < 130 mmHg AND trough sitting mean DBP < 80 mmHg.
- For subjects without diabetes mellitus and renal disease, trough sitting mean SBP < 140 mmHg AND trough sitting mean DBP < 90 mmHg.

Responder rate and normalization rate were analyzed using frequency tables and chi-square tests.

The safety subject sample was used for the analysis of the safety and tolerability data. Adverse events were reported on a per-subject basis, i.e., counting subjects rather than events. This meant that if a subject suffered the same AE repeatedly during the applicable study period, the event was counted only once for that period. Repeated events per subject were summarized according to the following rule: if a subject suffered the same AE more than once, the event was assigned the worst severity, the closest relationship to the study medication and the earliest starting date. Only treatment-emergent AEs (TEAEs) were summarized. In the listings, however, all occurrences of the AEs are presented.

For each unique treatment, TEAEs were summarized per primary system organ class (SOC), per high level term (HLT) by primary SOC, and per preferred term (PT) by HLT and primary SOC. Severity and drug-event relationship of TEAEs were summarized separately. Laboratory variables were summarized. A separate listing was made with all clinically relevant values. Vital signs and ECG data were summarized. Markedly abnormal values were listed.

Summary - Conclusions

Efficacy Results:

- The primary objective of this study was achieved in that eprosartan was found to be therapeutically equivalent to eprosartan mesylate in subjects with mild to moderate essential hypertension after 8 weeks of monotherapy using the FA subject sample (95% CI: -1.52; 0.80 [ANCOVA]) and the PP subject sample (95% CI: -1.52; 0.89 [ANCOVA]).
- Decreases in the trough sitting mean DBP and SBP from baseline to the end of Visit 4 (Week 8) for eprosartan (DBP -7.4 mmHg and SBP -11.4 mmHg) and eprosartan mesylate (DBP -7.2 mmHg and SBP -12.9 mmHg) were similar between the treatment groups.
- Decreases in the trough sitting mean DBP and SBP from baseline to the end of Visit 5 (Week 12) were similar for subjects who continued on monotherapy with eprosartan (DBP -11.4 mmHg and SBP -18.7 mmHg) and eprosartan mesylate (DBP -10.6 mmHg and SBP -18.7 mmHg) and for subjects who received add-on treatment with HCTZ from Week 8 in the eprosartan (DBP -7.5 mmHg and SBP -14.0 mmHg) and eprosartan mesylate (DBP -8.1 mmHg and SBP -15.8 mmHg) treatment groups.
- The response rate was similar between the treatment groups at Week 8 (61.4% in the eprosartan group and 62.2% in the eprosartan mesylate group) and at Week 12 (90.3% in the eprosartan group and 84.4% in the eprosartan mesylate group for subjects who continued on monotherapy; 65.7% in the eprosartan + HCTZ group and 67.2% in the

eprosartan mesylate + HCTZ group).

- The normalization rate was similar between the treatment groups at Week 8 (34.6% at Week 8 the eprosartan group and 33.3% in the eprosartan mesylate group) and at Week 12 (56.4% in the eprosartan group and 54.7% in the eprosartan mesylate group for subjects who continued on monotherapy; 27.6% in the eprosartan + HCTZ group and 26.4% in the eprosartan mesylate + HCTZ group).

Safety Results:

- None of the randomized subjects died during the study.
- The number of subjects with treatment-emergent serious adverse events (TESAEs) during monotherapy before Visit 4 (Week 8) was similar between the treatment groups (3 [0.9%] subjects in the eprosartan group; 7 [2.1%] subjects in the eprosartan mesylate group).
- Twenty subjects (2.7% in the eprosartan group and 3.3% in the eprosartan mesylate group) prematurely discontinued their study medication administration due to TEAEs and 19 subjects (2.4% in the eprosartan group and 3.3% in the eprosartan mesylate group) prematurely withdrew from the study due to AEs during monotherapy before Visit 4 (Week 8). No subjects reported TESAEs and TEAEs leading to discontinuation from the study medication or study after Visit 4 (Week 8).
- The number of TEAEs was similar between the treatment groups; before Visit 4 (Week 8) (30.7% in the eprosartan group; 31.0% in the eprosartan mesylate group), as well as after Visit 4 (Week 8) (16.0% in the eprosartan group; 12.1% in the eprosartan mesylate group) and add-on therapy (16.1% in the eprosartan + HCTZ group; 17.1% in the eprosartan mesylate + HCTZ group). The most frequently reported TEAEs were nasopharyngitis (Infections and infestations) and headache (Nervous system disorders), the incidence of these AEs was similar between the treatment groups.
- The number of subjects with at least one TEAE considered related to study medication was similar between the treatment groups before Visit 4 (Week 8) (8.1% in the eprosartan group; 5.4% in the eprosartan mesylate group), as well as after Visit 4 (Week 8) (3.0% in the eprosartan group; 1.6% in the eprosartan mesylate group) and add-on therapy (1.5% in the eprosartan + HCTZ group; 3.1% in the eprosartan mesylate + HCTZ group).
- No trends over time and between treatment groups were observed in any hematology and biochemistry variables.
- No trends of concern over time and between treatment groups were observed for vital signs.
- No trends over time and between treatment groups were observed in heart rate, PR interval, QRS interval, QT interval, QTcB interval, QTcF interval, and RR interval.

Conclusion:

- The primary objective of this study was achieved in that eprosartan was found to be therapeutically equivalent to eprosartan mesylate for change in trough sitting DBP from baseline to Week 8 in subjects with mild to moderate essential hypertension using the

FA subject sample (95% CI: -1.52; 0.80) and the PP subject sample (95% CI: -1.52; 0.89).

- Analyses of all secondary endpoints supported the results from the primary analysis.
- Eprosartan and eprosartan mesylate administered as monotherapy for 8 weeks, further monotherapy for 4 weeks in responders and combination treatment with HCTZ for 4 weeks in non-responders once daily over 8 to 12 weeks was safe and well tolerated in subjects with mild to moderate hypertension.