SYNOPSIS

Title of the study: Double-blind, randomized, parallel-group, dose ranging, multi-center study to evaluate the efficacy and safety of 2.5, 10, 35 and 50 mg AVE7688 once daily, using 100 mg losartan-potassium once daily as calibrator, for 12 months treatment, in patients with mild to moderate hypertension. Study number: DFI6032 (RAVEL-1)
Sponsor's Responsible Medical Officer: [redacted]
Study center(s): 195 centers in 21 countries
Publications (reference): Not applicable
Study period: Date first patient enrolled: 6 Dec 2005 Date last patient completed: 20 Mar 2008
Phase of development: Dose-ranging (IIb)
Objectives: The primary objective of the study was to assess the efficacy of 2.5, 10, 35, and 50 mg AVE7688[1] (ilepatril) once daily on the change from baseline in trough seated diastolic blood pressure (SeDBP), at the end of 12 weeks of treatment in patients with mild to moderate essential hypertension. The secondary objectives, in the hierarchical order, were: • To assess the efficacy of 2.5, 10, 35, and 50 mg ilepatril once daily on the change from baseline in trough seated systolic blood pressure (SeSBP) at the end of 12 weeks of treatment; • To compare the percentages of responders after 12 weeks of treatment; and • To evaluate the long-term safety and tolerability of ilepatril at doses of 2.5, 10, 35, or 50 mg, with particular attention to angioedema.
Methodology: A prospective, multi-center multinational, randomized, double-blind, active-controlled, parallel-group, dose ranging study with 5 treatment groups (ilepatril at 4 different dosages and losartan-potassium 100 mg). There were 3 study phases: placebo lead-in, treatment, and follow-up. The treatment phase was divided in 12-week efficacy period and 40-week long-term safety period. During the long-term safety period, patients were allowed to take additional anti-hypertensive compounds except for angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). The follow-up period lasted for 2 weeks, during which patients continued taking antihypertensive medication, but not study medication.

[1] The International Nonproprietary Name (INN) “ilepatril” will be used hereafter to denote AVE7688.

Number of patients: Planned: 1730 (376 patients to be randomized to each of the 4 ilepatril groups and 226 patients to losartan)

Randomized: 1940 (ilepatril 2.5 mg – 418 patients, 10 mg – 429 patients, 35 mg – 430 patients, 50 mg – 408 patients; losartan – 255 patients)

Treated: 1940

Efficacy/pharmacodynamic: 1940

Safety: 1940

Pharmacokinetics: 146 (2.5 mg – 38 patients, 10 mg – 32 patients, 35 mg – 38 patients, 50 mg - 38 patients)

Diagnosis and criteria for inclusion: Patients, 18 years of age or older, with mild-to-moderate essential hypertension (treated or untreated), as defined by the guidelines of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of high blood pressure (JNC VII, 2003), who meet the following blood pressure (BP) eligibility criteria:

• At the first qualifying visit in the placebo lead-in phase (either visit P2 or P3), mean SeSBP ≥140 mm Hg and <180 mm Hg and mean SeDBP ≥90 mm Hg and <110 mm Hg (mean of 3 readings)

• At the second qualifying visit in the placebo lead-in phase (either visit P3 or P4, separated from the first qualifying visit by at least 1 week), mean SeSBP ≥140 mm Hg and <180 mm Hg and mean SeDBP ≥90 mm Hg and <110 mm Hg (mean of 3 readings). If the patient does not meet the criteria at the second qualifying visit, he or she will be excluded from randomization.

• The patient can be included in the study only when the variability between the mean BP measurements on the 2 consecutive qualifying visits, either P2 and P3 or P3 and P4 (if applicable), is less or equal 7 mm Hg for SeDBP.

Investigational product: Ilepatril, encapsulated tablets

Dose: 2.5, 10, 25, or 50 mg

Administration: Per os (PO)

Batch number(s): [redacted]

Duration of treatment: 52 weeks

Duration of observation: Efficacy – 12 weeks; safety (including follow-up) – 54 weeks.

Reference therapy:

Placebo capsules matching the appearance of encapsulated ilepatril and losartan-potassium tablets.

Dose: Not applicable

Administration: PO

Batch number(s): [redacted]

Losartan-potassium (calibrator), encapsulated tablets

Dose: 100 mg (2 x 50 mg)

Administration: PO

Batch number(s): [redacted]

Criteria for evaluation:

The primary efficacy variable was the change from baseline in trough SeDBP at Week 12.

Secondary efficacy variables, in a hierarchical order, were:

• The change from baseline in trough SeSBP at Week 12;

• The percentage of responders in each treatment group at Week 12, where responders are defined as follows:

- Patients with BP ≤140/90 mm Hg, or

- Patients with a reduction from baseline in SeDBP of ≥10 mm Hg or in SeSBP of ≥20 mm Hg.

The following safety criteria were evaluated and analyzed using descriptive statistics:

• Adverse events (AEs), including reports of angioedema;

• Vital signs (standing BP and heart rate);

• Clinical laboratory data (hematology, chemistry, and urinalysis);

• Electrocardiogram (ECG) (PR, QRS, QT, QT corrected by Fridericia's formula [QTcF], and RR intervals).

Statistical methods: Continuous variables were summarized by treatment group using number of observations, mean, standard deviation, median, minimum, and maximum. Categorical data were summarized by treatment group using counts and percentages. Efficacy analyses were implemented on the intent-to-treat population consisting of all randomized patients irrespective of whether the patient actually received the study drug and irrespective of the patient's compliance with the study Protocol (population "as randomized"). The population for safety analyses consisted of all randomized patients who actually took at least one dose of study medication (population "as treated").

Analysis of primary efficacy variable An analysis of covariance (ANCOVA) with appropriate contrasts was used on change from baseline in trough SeDBP at Week 12, to assess whether any of the high doses of ilepatril (10, 35 and 50 mg) differed significantly from the lowest dose of ilepatril (2.5 mg), using a stepdown procedure, at an overall alpha level of 5%. If the trough SeDBP value at the end of week 12 (visit T6) was missing, the last available post-baseline trough value was used (last observation carried forward [LOCF] method).
Analysis of secondary efficacy variables Once the null hypothesis concerning the primary objective was rejected (and the primary objective of the study established), further confirmatory statistical tests on secondary variables was performed. The same statistical model with the same missing value imputation strategies was used on the change from baseline in trough SeSBP at Week 12. The percentage of responders was compared between treatment groups using Pearson's X^2 test at Week 12.

Analyses of safety data The main safety endpoint was the incidence of treatment-emergent adverse events (TEAEs) and adjudicated angioedema. Other safety parameters included vital signs (standing BP and heart rate), clinical laboratory tests, and 12-lead ECGs at pre-specified time points. The statistical evaluation was descriptive only.

For laboratory analytes, vital signs, and ECG parameters, findings were flagged when values were out of normal ranges and/or corresponded to a potentially clinically significant abnormality (PCSA). PCSAs were to be detected in each patient during the on-treatment period, from the first drug intake to 14 days after the last drug intake. Both scheduled and unscheduled measurements were used for analyses of PCSAs.

All safety analyses were performed separately for each following period:

• For the efficacy evaluation period: data were analyzed from the first administration of the titration period (Day 1, visit T1) to visit T6 (end of Week 12) or 14 days after the last dose of study medication if premature permanent discontinuation, whichever came first.
• For the long-term safety evaluation period: data were analyzed from next day after visit T6 (end of Week 12) to visit F1 (end of Week 54) or 14 days after the last dose of study medication if premature permanent discontinuation, whichever came first.

• In this synopsized report, results of the safety analysis are reported for the entire study period.

Summary: Key efficacy results at Week 12 The primary efficacy analyses at endpoint (last available value at Week 12) demonstrated that change from baseline in trough SeDBP differed significantly between high doses of ilepatril (35 mg and 50 mg) and the lowest dose of ilepatril (2.5 mg), by -2.29 mm Hg and -3.06 mm Hg, respectively (**Table 1**).

Table 1 - ANCOVA on change from baseline in trough SeDBP at endpoint (last available value at Week 12), intent-to-treat (ITT) population

Seated Diastolic Blood Pressure (mm Hg)	AVE7688 2.5 mg (N=418)	AVE7688 10 mg (N=429)	AVE7688 35 mg (N=430)	AVE7688 50 mg (N=408)
SeDBP at baseline				
Number	414	427	424	407
Mean (SD)	96.7 (5.6)	96.8 (5.6)	97.4 (5.5)	96.2 (5.4)
Median	96.0	96.0	97.0	95.0
Min : Max	62 : 110	79 : 112	81 : 113	73 : 112
Change from baseline in SeDBP at endpoint				
Number	414	427	424	407
LS Mean (SE)	-9.82 (0.44)	-10.85 (0.43)	-12.11 (0.43)	-12.88 (0.44)
95% CI	(-10.68 to -8.96)	(-11.69 to -10.00)	(-12.96 to -11.27)	(-13.74 to -12.02)
LS Mean Difference (SE)		-1.02 (0.61)	-2.29 (0.61)	-3.06 (0.62)
95% CI		(-2.23 to 0.18)	(-3.50 to -1.09)	(-4.28 to -1.84)
p-value[(a)]		0.0944	0.0002	<.0001

Notes: The ANCOVA model includes corresponding baseline parameter as covariate and treatment as fixed effect.
Comparisons are performed between high doses of AVE7688 and the lowest dose of AVE7688.
LS Mean = least square mean ; SE = standard error; SeDBP = seated diastolic blood pressure
[(a)] p-value according the step down procedure controlling the multiplicity issue

The secondary efficacy analyses at endpoint (last available value at Week 12) demonstrated that high doses of ilepatril (35 mg and 50 mg) induced a significantly higher decrease from baseline than losartan 100 mg in trough SeDBP (LS mean difference of -2.20 mm Hg and -2.94 mm Hg, respectively) and in trough SeSBP (LS mean difference of -3.77 mm Hg and -5.76 mm Hg, respectively) (**Table 2**).

Table 2 - RAVEL-1 - Change from baseline in trough SeDBP and SeSBP at endpoint (last available value at Week 12). Secondary analyses versus losartan.

	AVE7688				Losartan
	2.5 mg (N=418)	10 mg (N=429)	35 mg (N=430)	50 mg (N=408)	100 mg (N=255)
Number	414	427	424	407	254
Change from baseline in SeDBP, LS Mean (SE)	-9.83 (0.43)	-10.85 (0.43)	-12.14 (0.43)	-12.88 (0.44)	-9.94 (0.55)
LS Mean Difference (SE)	0.11 (0.70)	-0.92 (0.70)	-2.20 (0.70)	-2.94 (0.71)	
p-value	0.8746	0.1891	0.0017	<.0001	
Change from baseline in SeSBP, LS Mean (SE)	-15.03 (0.70)	-16.60 (0.69)	-19.31 (0.69)	-21.30 (0.71)	-15.54 (0.89)
LS Mean Difference (SE)	0.51 (1.13)	-1.06 (1.13)	-3.77 (1.13)	-5.76 (1.14)	
p-value	0.6551	0.3473	0.0008	<.0001	

Notes: The ANCOVA model includes corresponding baseline parameter as covariate and treatment as fixed effect.
Comparisons are performed between high doses of AVE7688 and losartan.LS Mean = least square mean; SE = standard error; SeDBP = seated diastolic blood pressure; SeSBP = seated systolic blood pressure.

The percentage of responders at endpoint (last available value at Week 12) was higher with ilepatril 10 mg (72.7%), 35 mg (75.6%), and 50 mg (77.2%) than with losartan 100 mg (68.2%).

Key safety results over the entire 12-month treatment period

1. Overview

• Overall, the percentage of patients with TEAEs was slightly higher in ilepatril groups (ranging from 67.7% to 72.5%) than in the losartan group (65.9%) (**Table 3**).

• The percentage of patients experiencing a serious TEAE during the entire study period was slightly higher in ilepatril groups compared to the losartan group. Eighty-eight serious TEAEs (incidence of 5.2%) were reported in patients treated with ilepatril, led by events of the cardiac disorders system organ class and showing no dose dependency. Eleven serious TEAEs (incidence of 4.3%) were reported in patients treated with losartan.

• Seven on-treatment deaths occurred without causal relationship to the investigational products: 5 in ilepatril groups, without dose dependency, and 2 in the losartan group. Four more patients (3 on ilepatril an 1 on losartan) died in the post-treatment period, between 1 and 9 months.

• The percentage of patients who discontinued the study drug treatment prematurely and permanently was higher in ilepatril groups (10.7%) than in the losartan group (5.9%). The percentage of patients who stopped treatment was similar across ilepatril dose groups, ranging from 9.6% to 12.0%. Cough, headache, and dizziness were the most frequent TEAEs leading to permanent treatment discontinuation in ilepatril groups; hypotension as the cause of treatment discontinuation occurred with ilepatril and losartan with a similar frequency.

Table 3 - Overview of AVE7688 safety profile (TEAEs) during the entire study period, safety population

	AVE7688				
	2.5 mg (N=418)	10 mg (N=429)	35 mg (N=430)	50 mg (N=408)	Losartan (N=255)
Any TEAE	292 (69.9%)	303 (70.6%)	291 (67.7%)	296 (72.5%)	168 (65.9%)
Any serious TEAE	22 (5.3%)	24 (5.6%)	19 (4.4%)	23 (5.6%)	11 (4.3%)
Any TEAE leading to death	1 (0.2%)	2 (0.5%)	2 (0.5%)	0	2 (0.8%)
Any TEAE leading to permanent treatment discontinuation	47 (11.2%)	41 (9.6%)	43 (10.0%)	49 (12.0%)	15 (5.9%)

Notes: Entire study period = from the first administration of titration period (Day 1, Visit T1) to end of study.
Treatment emergent adverse event (TEAE) = adverse event that developed or worsened during the on-treatment phase in the period.
On-treatment phase = from the start of a specified period to 14 days after the date of the last study drug intake or end of the specifed period, whichever comes first.
n (%) = number and percentage of patients with at least one adverse event.
TEAE - treatment-emergent adverse event

2. Angioedema

Eighteen cases of treatment-emergent angioedema were confirmed by the Angioedema Assessment Board (AAB): 13 of them occurred during the efficacy evaluation period and 5 happened after Week 12. All events were categorized by the AAB as being of mild intensity, except for one hospitalization without airways compromise in the 35 mg dose group (**Table 4**).

Angioedema occurred only in patients treated with ilepatril (1.1%, exact 95% confidence interval [CI] of 0.63% to 1.68%).

Angioedema was observed at a higher rate in black patients. Overall, 9 cases of angioedema were reported in black patients (2.8%, exact 95% CI of 1.29% to 5.25%) and 9 cases in non-black patients (0.6%, exact 95% CI of 0.25% to 1.05%). The incidence of angioedema varied across ilepatril dose groups: 1.4 % to 5.1% in the black population, 0% to 5.4% in the Asian/Oriental population, and 0 to 0.9% in Caucasians.

Table 4 - Incidence of confirmed treatment-emergent angioedema by grade of severity and demographic characteristics during the entire study period, safety population

	AVE7688				
	2.5 mg (N=418)	10 mg (N=429)	35 mg (N=430)	50 mg (N=408)	Losartan (N=255)
Angioedema[(a)]	2 (0.5%)	3 (0.7%)	7 (1.6%)	6 (1.5%)	0
Exact confidence interval: LL(%) : UL(%)	0.06 : 1.72	0.14 : 2.03	0.66 : 3.33	0.54 : 3.17	0.00 : 1.17
Intensity category given by AAB					
No treatment administered or only antihistaminics	0	1 (0.2%)	5 (1.2%)	3 (0.7%)	0
Treatment with catecholamines or steroids	2 (0.5%)	2 (0.5%)	1 (0.2%)	3 (0.7%)	0
Treatment with both catecholamines and steroids	0	0	0	0	0
Hospitalization without airway compromise	0	0	1 (0.2%)	0	0
Hospitalization and airway compromise	0	0	0	0	0
Airway protection or death	0	0	0	0	0
Angioedema[(a)] by race					
Caucasian	0 / 252	0 / 245	1 / 237 (0.4%)	2 / 231 (0.9%)	0 / 152
Black	2 / 64 (3.1%)	1 / 71 (1.4%)	4 / 79 (5.1%)	2 / 67 (3.0%)	0 / 40
Asian, Oriental	0 / 32	2 / 41 (4.9%)	0 / 35	2 / 37 (5.4%)	0 / 19
Other	0 / 70	0 / 72	2 / 79 (2.5%)	0 / 73	0 / 44

Notes: Entire study period = from the first administration of titration period Day 1, Visit T1) to end of study.
Treatment-emergent event (TE event) = event that developed or worsened during the on-treatment phase in the period.
On-treatment phase = from the start of the specified period to 14 days after the date of the last study drug intake or end of the specifed period, whichever comes first.
n (%) = number and percentage of patients with at least one angioedema-like event
LL_{95} - lower limit of 95% confidence interval; UL_{95} - upper limit of 95% confidence interval

[(a)] angioedema-like event confirmed by Angioedema Assessment Board (AAB)

3. Liver tests

Liver enzyme elevations and simultaneous liver enzyme and bilirubin elevations were observed more frequently in ilepatril groups than in the losartan group (**Table 5**).

Alanine aminotransferase (ALT) ≥3 upper limits of the normal range (ULN) was observed in 27 patients (1.7%) of ilepatril groups and in 1 patient (0.4%) treated with losartan. ALT ≥5 ULN was observed in 10 patients (0.6%) and ALT ≥10 ULN in 2 patients (0.1%) on ilepatril and in none on losartan. The relation to dose in ilepatril groups remains uncertain.

Aspartate aminotransferase (AST) ≥3 ULN was observed in 19 patients (1.2%) of ilepatril groups and in 2 patients (0.8%) treated with losartan. AST ≥5 ULN was observed in 12 patients (0.7%) and AST ≥10 ULN in 1 patient (0.1%) on ilepatril and in none on losartan. The relation to dose in ilepatril groups remains uncertain.

Total bilirubin ≥1.5 ULN was observed in 19 patients (1.2%) of ilepatril groups and 3 patients (1.2%) of the losartan group. The relation to dose in ilepatril groups remains uncertain.

Two patients in the 50 mg ilepatril group, but none in the losartan group, showed a combined elevation of ALT ≥3 ULN and total bilirubin ≥2 ULN. The third patient stopped treatment at the time when ALT was 3 ULN and total bilirubin 1.7 ULN. In all patients, treatment was stopped and liver function tests went back to normal within 2 to 5 weeks.

Table 5 - Number of patients with at least one post-baseline PCSA on treatment during the entire study period: clinical chemistry, safety population

Laboratory Parameter / PCSA criteria	AVE7688				
	2.5 mg	10 mg	35 mg	50 mg	Losartan
n/N(%)	(N=418)	(N=429)	(N=430)	(N=408)	(N=255)
AST					
> 2 ULN	6/402 (1.5%)	7/417 (1.7%)	13/412 (3.2%)	11/396 (2.8%)	8/247 (3.2%)
≥ 3 ULN	5/402 (1.2%)	3/417 (0.7%)	4/412 (1.0%)	7/396 (1.8%)	2/247 (0.8%)
≥ 5 ULN	1/402 (0.2%)	1/417 (0.2%)	4/412 (1.0%)	6/396 (1.5%)	0/247
≥ 10 ULN	0/402	0/417	0/412	1/396 (0.3%)	0/247
≥ 20 ULN	0/402	0/417	0/412	0/396	0/247
ALT					
> 2 ULN	7/402 (1.7%)	11/417 (2.6%)	16/412 (3.9%)	18/396 (4.5%)	6/247 (2.4%)
≥ 3 ULN	5/402 (1.2%)	5/417 (1.2%)	6/412 (1.5%)	11/396 (2.8%)	1/247 (0.4%)
≥ 5 ULN	1/402 (0.2%)	2/417 (0.5%)	3/412 (0.7%)	4/396 (1.0%)	0/247
≥ 10 ULN	0/402	0/417	1/412 (0.2%)	1/396 (0.3%)	0/247
≥ 20 ULN	0/402	0/417	0/412	0/396	0/247
Total Bilirubin					
≥ 1.5 ULN	3/401 (0.7%)	2/417 (0.5%)	6/412 (1.5%)	8/396 (2.0%)	3/246 (1.2%)
ALT and Total Bilirubin					
ALT ≥ 3 ULN and Total Bilirubin ≥ 2 ULN	0/412	0/426	0/424	2/408 (0.5%)	0/253

Notes: Entire study period = from the first administration of titration period (Day 1, Visit T1) to end of study
PCSA = Potentially Clinically Significant Abnormality
On-treatment phase = from the start of the specified period to 14 days after the date of last study drug intake or end of the specifed period whichever comes first.
% calculated using the number of patients with at least one event (n) over the number of patients having at least one post-baseline value (N)

4. Other safety observations

• During the entire study period, 31 patients (2%) of ilepatril groups showed an abnormal neutrophil count (< 1Giga/L in black patients or <1.5 Giga/L in non-black), without dose dependency. No such abnormalities were observed in the losartan group.

NOTE
This is a synopsized report for the terminated project AVE7688, and as such, results are not being presented in full. Additional information on safety and pharmacokinetics is available in Appendices or upon request.

Date of report: 21-Oct-2008