SYNOPSIS

Name of Sponsor/Company: Solvay Pharmaceuticals	**Individual Study Table**	**(For National Authority Use only)**
Name of Finished Product: Not applicable		
Name of Active Ingredient: Daglutril (SLV306-6)		

Title of Study:
A Randomized, Placebo-controlled, Double-blind, Six-arm, Dose Escalation, Multi-center Study to Evaluate the Efficacy and Safety of SLV306: 150, 300, 600 mg Once Daily, 150-300 mg Twice Daily and Amlodipine 5-10 mg Once Daily in Subjects with Hypertension

Investigator(s):
Principal investigators: four in Australia, eight in Bulgaria, three in Denmark, one in Estonia, 16 in Germany, three in Hungary, six in Israel, six in Latvia, three in Lithuania, eight in Slovakia, and 49 in the UK

Study Centers:
A total of 107 principal investigators and 109 outpatient clinics in Australia, Bulgaria, Denmark, Estonia, Germany, Hungary, Israel, Latvia, Lithuania, Slovakia and the UK

Publication (Reference):
None

Study Period:	**Phase of Development:**
07 JAN 2004 – 05 SEP 2006	II

Objectives:
Primary Objective
To determine the superiority of at least one dose of SLV306 (daglutril) compared to placebo on the change in office diastolic blood pressure (DBP) (measured at trough in mmHg) from baseline to endpoint in subjects with hypertension.
Secondary Objectives
- To investigate the effect of daglutril compared to placebo on the change in office systolic blood pressure (SBP) (measured at trough in mmHg) from baseline to the end of the 12-week treatment period in subjects with hypertension
- To investigate the change in mean systolic and diastolic blood pressure using 24-hour ambulatory blood pressure measurement (ABPM) (measured in mmHg) from baseline to the end of the 12-week treatment period of daglutril compared to placebo in subjects with hypertension
- To investigate the change in mean day-time and night-time blood pressure using 24-hour ABPM (measured in mmHg) from baseline to the end of the 12-week treatment period of daglutril compared to placebo in subjects with hypertension
- To investigate the change in office diastolic and systolic blood pressure measured at trough (in mmHg) from baseline to the end of the 4- and 12-week treatment periods of 5-10 mg amlodipine once daily (od) compared to placebo in subjects with hypertension
- To investigate the change in the neurohormones at trough: big endothelin (ET), cyclic guanidine monophosphate (cGMP), angiotensin II and aldosterone from baseline to the end of the 4- and 12-week treatment periods of daglutril compared to placebo in subjects with hypertension

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– To determine plasma concentrations of daglutril and its metabolite KC12615 as well as amlodipine.

Safety Objective

To obtain safety and tolerability data: vital signs, physical examination, laboratory data, 12-lead electrocardiogram (ECG), adverse events (AEs) and concomitant medication.

Methodology:

This was a double-blind, placebo-controlled, parallel group, randomized, dose escalation, multi-center study, comparing 150, 300, 600 mg daglutril od, 150-300 mg daglutril twice daily (bid) and 5-10 mg amlodipine od with placebo.

The study consisted of three dosing steps:

Dosing step 1: 150 mg daglutril od or placebo were administered

Dosing step 2: 300 mg daglutril od or placebo were administered

Dosing step 3: 600 mg daglutril od, 150-300 mg daglutril bid, 5-10 mg amlodipine od or placebo were administered

New cohorts of subjects were enrolled in each dosing step. The second and third dosing steps were initiated only after the last subject completed the first four weeks of randomized treatment and no safety concerns occurred (as evaluated by an independent safety monitoring board). In the 150-300 mg daglutril bid and 5-10 mg amlodipine od treatment groups the initial dose was 150 mg daglutril bid or 5 mg amlodipine od, respectively. After four weeks of randomized treatment the dose was doubled for subjects with office DBP ≥ 85 mmHg. Subjects with office DBP < 85 mmHg continued to receive 150 mg daglutril bid or 5 mg amlodipine od for the remaining eight weeks. The dose remained unchanged during the study for subjects in the 600 mg daglutril od treatment group. After four weeks of randomized treatment, subjects with office DBP ≥ 85 mmHg in the 600 mg daglutril od and placebo treatment groups underwent a fictitious titration step using the same dose in order to mimic the titration step in the amlodipine od and daglutril bid treatment groups and to maintain the blindness of the study. Subjects were kept under observation for two hours after the first study drug intake of each dosing step.

Number of Subjects (Planned, Consented, Randomized and Analyzed):

Planned: 522 randomized subjects (87 to each treatment group).

Consented: 1602 subjects.

Randomized: 552 subjects (150 mg daglutril od group: 95 subjects; 300 mg daglutril od group: 95 subjects; 150-300 mg daglutril bid group: 90 subjects; 600 mg daglutril od group: 90 subjects; 5-10 mg amlodipine od group: 89 subjects; placebo group: 93 subjects).

Analyzed safety: 548 subjects (150 mg daglutril od group: 95 subjects; 300 mg daglutril od group: 93 subjects; 150-300 mg daglutril bid group: 90 subjects; 600 mg daglutril od group: 88 subjects; 5-10 mg amlodipine od group: 89 subjects; placebo group: 93 subjects).

Analyzed intent-to-treat (ITT): 529 subjects (150 mg daglutril od group: 90 subjects; 300 mg daglutril od group: 88 subjects; 150-300 mg daglutril bid group: 87 subjects; 600 mg daglutril od group: 86 subjects; 5-10 mg amlodipine od group: 87 subjects; placebo group: 91 subjects).

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Analyzed per-protocol (PP): 469 subjects (150 mg daglutril od group: 80 subjects; 300 mg daglutril od group: 80 subjects; 150-300 mg daglutril bid group: 75 subjects; 600 mg daglutril od group: 75 subjects; 5-10 mg amlodipine od group: 74 subjects; placebo group: 85 subjects).

Diagnosis and Main Criteria for Inclusion:
Subjects signed an informed consent form before any screening procedures were performed. They were aged ≥ 18 years, males or females without child-bearing potential, with a sitting office DBP between 90 and 109 mmHg, office SBP between 140 and 179 mmHg and mean diastolic 24-h ABPM blood pressure ≥ 85 mmHg inclusive at baseline.

Test Product, Dose and Mode of Administration, Batch Number:
SLV306-6 in 150 mg and 300 mg oral tablets for doses of 150, 300 and 600 mg daglutril od and 150-300 mg daglutril bid. Batch numbers: 67443 (150 mg SLV306-6) and 67444 (300 mg SLV306-6).

Duration of Treatment:
Four-week placebo run-in period and 12-week randomized double-blind treatment period for each of three dosing steps.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Amlodipine in 5 mg oral tablets for a dose of 5-10 mg amlodipine od. Batch number: EPP2103A-G1.
SLV306-6 matching placebo oral tablets. Batch numbers: 67447 and 67446.
Amlodipine matching placebo oral tablets. Batch number: ED-O-093-402.

Criteria for Evaluation:
Efficacy:
Primary: the change from baseline to the end of the treatment period in office sitting DBP measured at trough.
Secondary: baseline-adjusted office sitting SBP measured at trough, mean 24-hour DBP and SBP, and day-time and night-time 24-hour DBP and SBP at the end of the randomized treatment period; and neurohormone concentrations of big ET, cGMP, angiotensin II and aldosterone.
Safety:
Adverse events, laboratory data, vital signs, 12-lead ECG, physical examination and concomitant medication.

Statistical Methods:
The primary objective was to determine the superiority of daglutril compared to placebo in the change from baseline in office DBP. The null hypothesis was that there was no difference in change from baseline between daglutril and placebo. The alternative hypothesis was that for at least one daglutril dose, the mean difference was not 0. To test the hypothesis of no difference in primary efficacy variable between daglutril versus placebo, an analysis of covariance (ANCOVA) with treatment, cohort, and country as fixed factors and baseline as covariate was performed on the ITT sample at the primary analysis time point, endpoint; where endpoint was the last available post baseline observation carried forward for all efficacy data. Dunnett's test

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was to be performed for multiple comparisons of each of the four daglutril doses against placebo. The treatment by country interaction was investigated as an exploratory factor and was separately checked. If the treatment-by-country interaction was significant at the 10% level ($p \leq 0.1$), then the treatment effect within each country was to be assessed to find an explanation.
As a separate exploratory analysis, differences between the placebo treatment groups for each cohort were estimated. If such a difference was significant at the 10% level ($p \leq 0.10$), then the primary analysis was to be supported by the presentation of estimates of the difference between active and placebo treatment groups within each cohort.
The underlying assumptions for statistical models were assessed. If the assumptions were substantially violated, appropriate non-parametric methods were to be considered. To examine the sensitivity of the primary analysis to these discontinuations, the primary analysis was repeated using only subjects who completed the study. As an additional sensitivity analysis, the primary analysis was repeated for the ITT sample, but with response imputed (other than last observation carried forward) for subjects who did not complete the study, using a model which included at least country and cohort as factors and baseline as covariate.
The dose-response relationship for the od daglutril regimes was described for the primary variable by linear regression with dose and dose squared as factors. This model was reduced sequentially, first eliminating dose squared if the factor was not statistically significant at the 10% significance level, and subsequently eliminating dose if this factor was not statistically significant at the 10% significance level. If the model did not fit, log(dose) was to be explored.
The ANCOVA analysis on the ITT sample based on the observed cases data at Weeks 4, 8 and 12, as well as on the PP sample at Weeks 4, 8, 12 and endpoint were a supportive analysis. Summary statistics were presented per visit.
For the change from baseline in secondary efficacy variables, a similar ANCOVA as for the primary efficacy analysis was used, except for the check of the assumptions and the sensitivity analysis. A dose-response relationship was assessed for the cardiovascular data only. If censoring occurred for neurohormone data, this was to be accounted for. To compare 5-10 mg amlodipine od to placebo in the change from baseline in office SBP and DBP at trough, a similar ANCOVA analysis for the ITT and PP samples was performed with an additional treatment arm (5-10 mg amlodipine od). All plasma concentration data for subjects receiving active study drug were listed per subject. The trough plasma concentrations of daglutril, KC12615 and amlodipine were summarized using descriptive statistics. All tests were significant (two-sided) at the p-value ≤ 0.05 level unless otherwise specified.
The safety analyses were performed on the safety sample and were assessed by AE data, laboratory tests, vital signs, 12-lead ECG data, physical examination and documented concomitant medications. All safety data were listed and summarized as appropriate.

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Summary – Conclusions

Efficacy Results:

Office Blood Pressure

The following table presents a summary of the change from baseline to endpoint in office sitting DBP (mmHg) for daglutril versus placebo for the ITT sample.

		Placebo (N = 91)	150 mg Daglutril od (N = 90)	300 mg Daglutril od (N = 88)	150-300 mg Daglutril bid (N = 87)	600 mg Daglutril od (N = 86)
	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	442	97.0 (6.4)	97.9 (7.0)	95.6 (7.5)	96.4 (7.2)	97.7 (7.1)
Endpoint - baseline	441	-3.7 (10.2)	-5.2 (9.9)	-4.9 (9.8)	-5.0 (9.2)	-7.4 (9.7)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint - baseline	428	-4.7 (0.95)	-4.8 (1.60)	-7.3 (1.60)	-7.2 (1.61)	-8.5 (1.61)
Estimate of the mean				Treatment contrast to placebo		
Endpoint - baseline			-0.1 (1.8)	-2.6 (1.8)	-2.5 (1.9)	-3.7 (1.9)
P-value			1.000	0.459	0.539	0.171
95% CI			(-4.7, 4.4)	(-7.0, 1.9)	(-7.1, 2.2)	(-8.4, 1.0)

CI = confidence interval; df = degrees of freedom; ITT = Intent-to-treat; LSmean = least square mean;
N = Number of subjects in ITT sample in the daglutril and placebo groups; n = total number of subjects with data in these groups; SD = Standard deviation; SE = standard error.

There was a decrease from baseline to endpoint in office sitting DBP which was greater for the daglutril groups than for placebo; this treatment difference was not statistically significant for any of the daglutril groups. Similar results were observed at the other time points. There was evidence of a linear relationship between daglutril dose and the decrease from baseline to endpoint in office sitting DBP ($p = 0.022$), indicating that blood pressure decreased with an increase in dose.

The following table presents a summary of the change from baseline to endpoint in office sitting SBP (mmHg) for daglutril versus placebo for the ITT sample.

		Placebo (N = 91)	150 mg Daglutril od (N = 90)	300 mg Daglutril od (N = 88)	150-300 mg Daglutril bid (N = 87)	600 mg Daglutril od (N = 86)
	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Baseline	442	155.2 (14.2)	157.3 (14.2)	155.2 (14.5)	153.5 (12.7)	159.2 (14.1)
Endpoint - baseline	441	-4.3 (14.9)	-5.4 (15.0)	-6.4 (14.2)	-7.9 (16.8)	-12.8 (15.5)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint - baseline	428	-6.3 (1.52)	-7.8 (2.58)	-7.4 (2.58)	-10.3 (2.59)	-12.3 (2.59)
Estimate of the mean				Treatment contrast to placebo		
Endpoint - baseline			-1.5 (3.0)	-1.1 (2.9)	-4.1 (3.1)	-6.3 (3.1)
P-value			0.968	0.991	0.506	0.141
95% CI			(-8.9, 5.9)	(-8.3, 6.2)	(-11.7, 3.4)	(-13.9, 1.3)

CI = confidence interval; df = degrees of freedom; ITT = Intent-to-treat; LSmean = least square mean;
N = Number of subjects in ITT sample in the daglutril and placebo groups; n = total number of subjects with data in these groups; SD = Standard deviation; SE = standard error.

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Analysis of the secondary efficacy parameters showed decreases in the mean change from baseline in office sitting SBP which were greater for the daglutril groups than for placebo; however, these treatment differences were only statistically significant at Weeks 4 and 8 for 600 mg od daglutril (estimate [SE]): -6.6 (2.7) and -7.9 (2.9); p = 0.049 and p = 0.032, respectively, and at Week 8 for 150-300 mg bid daglutril: -8.5 (3.0); p = 0.017. As with DBP, there was evidence for a dose response relationship for office sitting SBP (p = 0.040).

Ambulatory Blood Pressure Monitoring

The following table presents a summary of the change from baseline to endpoint in mean 24-hour DBP, SBP and MAP (mmHg).

		Placebo (N = 91)	150 mg Daglutril od (N = 90)	300 mg Daglutril od (N = 88)	150-300 mg Daglutril bid (N = 87)	600 mg Daglutril od (N = 86)
	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Mean 24-hour DBP						
Baseline	431	91.9 (7.1)	93.1 (7.6)	91.6 (7.0)	91.9 (6.5)	91.1 (8.1)
Endpoint - baseline	360	-0.6 (7.7)	-4.3 (4.9)	-2.5 (6.0)	-4.6 (7.1)	-5.6 (7.0)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint - baseline	347	-1.2 (0.76)	-6.4 (1.34)	-2.2 (1.27)	-3.7 (1.27)	-4.8 (1.28)
Estimate of the mean				Treatment contrast to placebo		
Endpoint - baseline			-5.2 (1.6)	-1.1 (1.4)	-2.6 (1.5)	-3.6 (1.5)
P-value			0.004	0.884	0.263	0.056
95% CI			(-9.0, -1.3)	(-4.6, 2.4)	(-6.3, 1.1)	(-7.3, 0.1)
Mean 24-hour SBP						
Baseline	431	146.0 (12.0)	148.5 (12.4)	146.9 (12.4)	144.9 (11.6)	147.4 (13.5)
Endpoint - baseline	360	-0.3 (10.0)	-6.3 (7.3)	-4.9 (9.0)	-8.5 (12.1)	-10.0 (10.5)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint - baseline	229	-1.5 (1.10)	-8.7 (1.94)	-5.9 (1.85)	-6.7 (1.83)	-7.5 (2.85)
Estimate of the mean				Treatment contrast to placebo		
Endpoint - baseline			-7.1 (2.3)	-4.4 (2.1)	-5.2 (2.1)	-6.1 (2.2)
P-value			0.007	0.113	0.057	0.018
95% CI			(-12.7, -1.5)	(-9.6, 0.7)	(-10.5, 0.1)	(-11.5, -0.8)
Mean 24-hour MAP						
Baseline	431	110.7 (8.3)	112.1 (8.6)	110.6 (7.9)	110.2 (7.8)	110.5 (9.5)
Endpoint - baseline	360	-0.7 (8.1)	-5.1 (5.5)	-3.5 (7.0)	-6.3 (8.7)	-7.2 (7.8)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint - baseline	347	-1.5 (0.84)	-7.3 (1.49)	-3.3 (1.42)	-5.1 (1.41)	-6.0 (1.42)
Estimate of the mean				Treatment contrast to placebo		
Endpoint - baseline			-5.7 (1.7)	-1.9 (1.6)	-3.7 (1.7)	-4.6 (1.7)
P-value			0.004	0.590	0.099	0.024
95% CI			(-10.0, -1.4)	(-5.9, 2.0)	(-7.8, 0.4)	(-8.7, -0.4)

CI = confidence interval; DBP = diastolic blood pressure; df = degrees of freedom; ITT = Intent-to-treat; LSmean = least square mean; MAP = mean arterial pressure; N = Number of subjects in ITT sample in the daglutril and placebo groups; n = total number of subjects with data in these groups; SBP = systolic blood pressure; SD = Standard deviation; SE = standard error.

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Similar results as for office blood pressure were observed with the 24-hour ABPM data: decreases in the mean change from baseline were observed for all groups and were greater for daglutril than for placebo. Statistically significant treatment differences in favor of daglutril were observed for 150 mg od daglutril on comparison with placebo in the mean decrease from baseline in 24-hour DBP, SBP and MAP at endpoint (see table) and also at Week 4 (p = 0.041, 0.020 and 0.018, respectively), Week 8 (p = 0.024, 0.006 and 0.014, respectively) and Week 12 (p = 0.025, 0.042 and 0.030, respectively). Statistically significant differences in favor of daglutril were also observed on comparison of 150-300 mg bid daglutril and placebo in the mean decrease from baseline in 24-hour SBP at Week 4 (-6.5 [2.5], p = 0.029) and on comparison of 600 mg od daglutril with placebo in the mean decrease from baseline in 24-hour SBP and MAP at endpoint and at Week 4 (-7.2 [2.5], p = 0.015; and -4.7 [1.9], p = 0.047). No other statistically significant treatment differences were observed.

As with office DBP and SBP, there was evidence for dose response relationships for the change from baseline to endpoint in mean 24-hour DBP (p = 0.002), SBP (p < 0.001) and MAP (p < 0.001).

The following table presents a summary of the change from baseline to endpoint in mean day-time DBP, SBP and MAP (mmHg).

		Placebo (N = 91)	150 mg Daglutril od (N = 90)	300 mg Daglutril od (N = 88)	150-300 mg Daglutril bid (N = 87)	600 mg Daglutril od (N = 86)
	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Mean Day-time DBP						
Baseline	431	94.7 (7.2)	96.1 (8.0)	94.4 (7.0)	94.8 (6.9)	94.2 (8.5)
Endpoint- baseline	360	-0.73 (8.1)	-4.4 (5.8)	-2.3 (6.4)	-5.1 (7.5)	-5.8 (7.3)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint – baseline	347	-1.4 (0.81)	-6.0 (1.43)	-2.4 (1.36)	-4.0 (1.35)	-4.7 (1.36)
Estimate of the mean				Treatment contrast to placebo		
Endpoint – baseline			-4.5 (1.7)	-1.1 (1.5)	-2.6 (1.6)	-3.4 (1.6)
P-value			0.026	0.894	0.307	0.124
95% CI			(-8.7, -0.4)	(-4.9, 2.6)	(-6.6, 1.3)	(-7.3, 0.6)
Mean Day-time SBP						
Baseline	431	149.3 (12.1)	152.2 (12.7)	150.2 (12.1)	148.4 (11.9)	150.9 (13.8)
Endpoint – baseline	360	-0.60 (10.5)	-6.7 (8.2)	-4.5 (9.0)	-9.3 (12.4)	-10.4 (10.8)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint – baseline	347	-2.0 (1.14)	-8.8 (2.03)	-6.0 (1.92)	-6.9 (1.91)	-7.5 (1.93)
Estimate of the mean				Treatment contrast to placebo		
Endpoint – baseline			-6.7 (2.3)	-4.2 (2.1)	-5.1 (2.2)	-5.7 (2.2)
P-value			0.016	0.180	0.084	0.042
95% CI			(-12.5, -0.93)	(-9.5, 1.2)	(-10.6, 0.45)	(-11.3, -0.16)

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		Placebo (N = 91)	150 mg Daglutril od (N = 90)	300 mg Daglutril od (N = 88)	150-300 mg Daglutril bid (N = 87)	600 mg Daglutril od (N = 86)
	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Mean Day-time MAP						
Baseline	431	113.6 (8.3)	115.4 (8.8)	113.5 (7.9)	113.2 (8.0)	113.7 (9.8)
Endpoint – baseline	360	-0.85 (8.3)	-5.2 (6.3)	-3.3 (7.3)	-6.8 (9.1)	-7.6 (7.9)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint – baseline	347	-1.7 (0.88)	-7.0 (1.57)	-3.7 (1.48)	-5.4 (1.48)	-6.1 (1.49)
Estimate of the mean				Treatment contrast to placebo		
Endpoint - baseline			-5.2 (1.8)	-2.1 (1.7)	-3.7 (1.7)	-4.4 (1.7)
P-value			0.017	0.559	0.110	0.042
95% CI			(-9.7, -0.71)	(-6.2, 2.0)	(-8.0, 0.54)	(-8.7, -0.12)

CI = confidence interval; DBP = diastolic blood pressure; df = degrees of freedom; ITT = Intent-to-treat; LSmean = least square mean; MAP = mean arterial pressure; N = Number of subjects in ITT sample in the daglutril and placebo groups; n = total number of subjects with data in these groups; SBP = systolic blood pressure; SD = Standard deviation; SE = standard error.

The following table presents a summary of the change from baseline to endpoint in mean night-time DBP, SBP and MAP (mmHg).

		Placebo (N = 91)	150 mg Daglutril od (N = 90)	300 mg Daglutril od (N = 88)	150-300 mg Daglutril bid (N = 87)	600 mg Daglutril od (N = 86)
	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Mean Night-time DBP						
Baseline	429	80.8 (9.6)	81.0 (9.1)	80.7 (9.5)	80.6 (8.6)	79.3 (9.0)
Endpoint - baseline	357	-0.19 (9.4)	-3.5 (7.3)	-3.3 (8.4)	-2.9 (8.2)	-5.0 (8.6)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint - baseline	344	-0.6 (0.91)	-8.1 (1.61)	-0.4 (1.53)	-2.4 (1.53)	-4.9 (1.53)
Estimate of the mean				Treatment contrast to placebo		
Endpoint - baseline			-7.5 (1.9)	0.10 (1.7)	-2.0 (1.8)	-4.4 (1.8)
P-value			<0.001	1.000	0.678	0.055
95% CI			(-12.2, -2.8)	(-4.2, 4.4)	(-6.4, 2.5)	(-8.8, 0.06)
Mean Night-time SBP						
Baseline	429	133.2 (14.4)	134.3 (14.1)	133.8 (15.3)	131.2 (13.7)	133.4 (14.4)
Endpoint - baseline	357	0.42 (12.4)	-5.4 (8.9)	-5.7 (11.8)	-5.2 (13.7)	-8.2 (12.8)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint - baseline	344	-0.3 (1.29)	-9.5 (2.27)	-3.4 (2.17)	-5.5 (2.16)	-7.6 (2.17)
Estimate of the mean				Treatment contrast to placebo		
Endpoint - baseline			-9.3 (2.7)	-3.2 (2.5)	-5.3 (2.6)	-7.4 (2.6)
P-value			0.002	0.557	0.131	0.015
95% CI			(-15.9, -2.6)	(-9.3, 3.0)	(-11.7, 1.0)	(-13.8, -1.1)

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		Placebo (N = 91)	150 mg Daglutril od (N = 90)	300 mg Daglutril od (N = 88)	150-300 mg Daglutril bid (N = 87)	600 mg Daglutril od (N = 86)
	n	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Mean Night-time MAP						
Baseline	429	99.0 (10.8)	99.4 (10.4)	99.1 (10.8)	98.2 (10.1)	98.3 (10.6)
Endpoint - baseline	357	0.35 (10.1)	-4.1 (7.7)	-4.2 (9.4)	-3.6 (9.8)	-6.3 (9.9)
	df	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)	LSmean (SE)
Endpoint - baseline	344	-0.0 (1.00)	-8.5 (1.76)	-1.1 (1.68)	-3.6 (1.67)	-6.1 (1.68)
Estimate of the mean				Treatment contrast to placebo		
Endpoint - baseline			-8.5 (2.1)	-1.1 (1.9)	-3.6 (2.0)	-6.2 (2.0)
P-value*			<0.001	0.952	0.223	0.008
95% CI			(-13.7, -3.3)	(-5.8, 3.6)	(-8.5, 1.3)	(-11.1, -1.3)

CI = confidence interval; DBP = diastolic blood pressure; df = degrees of freedom; ITT = Intent-to-treat; LSmean = least square mean; MAP = mean arterial pressure; N = Number of subjects in ITT sample in the daglutril and placebo groups; n = total number of subjects with data in these groups; SBP = systolic blood pressure; SD = Standard deviation; SE = standard error.

A similar pattern was observed for mean day-time and night-time DBP, SBP and MAP: statistically significant treatment differences in favor of daglutril were observed for 150 mg od daglutril on comparison with placebo in the mean decrease from baseline in day-time DBP at endpoint (p = 0.026); in day-time SBP at endpoint (p = 0.016) and at Week 4 (-7.4 [2.6], p = 0.016), Week 8 (-7.9 [2.7], p = 0.013) and Week 12 (-7.9 [3.2], p = 0.048); in day-time MAP at endpoint and at Week 4 (-5.5 [2.0], p = 0.020); in night-time DBP at endpoint and at Week 8 (-6.7 [2.0], p = 0.004) and Week 12 (-7.3 [2.6], p = 0.018); in night-time SBP at endpoint and at Week 8 (-9.2 [2.9], p = 0.008); and in night-time MAP at endpoint and at Week 8 (-7.9 [2.3], p = 0.002) and Week 12 (-7.7 [2.8], p = 0.024). Statistically significant treatment differences in favor of daglutril were also observed for 600 mg od daglutril on comparison with placebo in the mean decrease from baseline in: day-time SBP at endpoint and at Week 4 (-6.7 [2.6], p = 0.040); day-time MAP at endpoint; night-time DBP at Week 8 (-4.6 [1.9], p = 0.049); night-time SBP at endpoint and at Week 4 (-7.0 [2.7], p = 0.040); and night-time MAP at endpoint and at Week 4 (-5.9 [2.1], p = 0.021) and Week 8 (-6.0 [2.1], p = 0.017).

Heart Rate

There was no obvious difference on comparison of daglutril and placebo in the mean change from baseline in pulse or mean 24-hour heart rate or mean day-time and night-time heart rate and no apparent dose response relationship for daglutril was observed for these parameters.

Amlodipine

Amlodipine demonstrated antihypertensive efficacy on comparison with placebo: statistically significant treatment differences were observed in the mean change from baseline in office sitting DBP and SBP at all time points. At endpoint, the estimate (SE) of the treatment contrast to placebo was -8.1 (1.9) and -13.6 (3.0) for office sitting DBP and SBP, respectively;

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$p < 0.001$ for both parameters. Similar results were observed for 24-hour ABPM (mean 24-hour and day-time and night-time DBP, SBP and MAP).

Neurohormones

Mean increases from baseline in cGMP were observed for all groups at the time points measured. No statistically significant treatment differences in the mean changes from baseline in neurohormone concentrations were observed on comparison of daglutril with placebo or amlodipine with placebo, with the exception of aldosterone at Week 12 ($p = 0.048$): a greater mean increase from baseline was observed with amlodipine (27.95 pg/mL) compared with placebo (10.75 pg/mL).

Erectile Function

No notable changes from baseline were observed for any of the scores or functions of the erectile function questionnaire which was completed by a small number of subjects.

Plasma Concentrations

As was expected, a dose-dependent increase in geometric mean concentrations of the metabolite KC12615 was observed at 2 to 4 hours postdose at both the baseline visit and at Week 12. Trough plasma concentrations were low and highly variable.

The plasma concentrations of both daglutril and its metabolite were in the expected ranges.

Safety Results:

The following table presents a summary of the incidence of treatment-emergent AEs (TEAEs), treatment-emergent serious AEs (TESAEs), and withdrawals due to TEAEs.

No (%) of subjects:	150 mg Daglutril od (N = 95)	300 mg Daglutril od (N = 93)	150-300 mg Daglutril bid (N = 90)	600 mg Daglutril od (N = 88)	5-10 mg Amlodipine od (N = 89)	Placebo (N = 93)
with at least one TEAE	49 (51.6%)	47 (50.5%)	33 (36.7%)	31 (35.2%)	30 (33.7%)	36 (38.7%)
with at least one TESAE	0	2 (2.2%)	1 (1.1%)	0	0	2 (2.2%)
who withdrew due to a TEAE	1 (1.1%)	6 (6.5%)	4 (4.4%)	4 (4.5%)	5 (5.6%)	1 (1.1%)

N = Number of subjects in safety sample per treatment group; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

The incidence of subjects with at least one TEAE was higher in subjects who received 150 mg od or 300 mg od daglutril compared with subjects who received 150-300 mg bid daglutril, 600 mg od daglutril, 5-10 mg amlodipine od or placebo. The incidence of TESAEs was low and no TESAE was reported for more than one subject. The incidence of TEAEs leading to study termination was also low.

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The following table presents the incidence, by treatment group, of the most common TEAEs.

TEAE High level term	150 mg Daglutril od (N = 95)	300 mg Daglutril od (N = 93)	150-300 mg Daglutril bid (N = 90)	600 mg Daglutril od (N = 88)	5-10 mg Amlodipine od (N = 89)	Placebo (N = 93)
Oedema NEC	0	3 (3.2%)	2 (2.2%)	2 (2.3%)	11 (12.4%)	1 (1.1%)
Upper respiratory tract infections	5 (5.3%)	17 (18.3%)	7 (7.8%)	4 (4.5%)	1 (1.1%)	2 (2.2%)
Headaches NEC	4 (4.2%)	5 (5.4%)	6 (6.7%)	6 (6.8%)	4 (4.5%)	5 (5.4%)
Coughing and associated symptoms	5 (5.3%)	1 (1.1%)	2 (2.2%)	2 (2.3%)	1 (1.1%)	0

N = Number of subjects in safety sample per treatment group; NEC = not elsewhere classified;
TEAE = treatment-emergent adverse event.

The most commonly reported TEAE was upper respiratory tract infections which were reported for a greater proportion of daglutril-treated subjects compared to amlodipine- and placebo-treated subjects.
Treatment-emergent AEs considered to be related to study drug were more commonly reported for subjects in the 150 mg od daglutril group (27 subjects) compared with subjects in the 300 mg od, 150-300 mg bid and 600 mg od daglutril, 5-10 mg amlodipine od or placebo (12, 12, 10, 17 and 17 subjects, respectively). The most common related TEAEs were headache (13 subjects) and oedema peripheral (nine subjects). Events of headache considered to be related to study drug were more commonly reported with placebo than with the other treatments and all but one event of related oedema peripheral occurred with amlodipine.
The most common TEAEs related to laboratory parameters were blood creatine phosphokinase increased (nine subjects), GGT increased (four subjects), ALT increased (three subjects) and blood uric acid increased (three subjects each). There were no clinically relevant results associated with the clinical laboratory parameters, vital signs or ECG parameters.
Conclusion:

- The differences between the daglutril groups and placebo in the mean decrease from baseline in office sitting DBP at endpoint were not statistically significant so did not show the superiority of daglutril compared to placebo.
- This lack of superiority of daglutril, when compared to placebo, was supported by the secondary efficacy analysis: the treatment differences observed in the change from baseline in office sitting SBP and 24-hour ABPM were not consistent enough to warrant clinical significance.
- There was evidence for a linear relationship between dose and the decrease from baseline in office sitting DBP and SBP, as well as 24-hour DBP, SBP and MAP, at endpoint which indicated that blood pressure decreased with an increase in daglutril dose.
- The reason for the statistically significant treatment differences in 24-hour ABPM in favor of 150 mg od daglutril when compared with placebo is not well understood; it was expected that the office blood pressure and ABPM results would be consistent. There is

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currently no explanation for this treatment difference.

- Amlodipine demonstrated expected results on comparison with placebo with regard to its antihypertensive effect.
- There was no apparent effect of daglutril (or amlodipine) on the neurohormones big ET, cGMP, angiotensin II and aldosterone when compared to placebo.
- Trough plasma concentrations of KC12615 were low and highly variable.
- There were no unexpected safety results, except for the higher incidence of upper respiratory tract infections in the daglutril groups; the events of oedema observed with amlodipine are a common side effect associated with the treatment.