Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Micardis Plus®		**EudraCT No.:** 2008-007711-32	**Synopsis No.:**
Name of active ingredient: Telmisartan and Hydrochlorothiazide		**Page:** 1 of 8	
Module:		**Volume:**	
Report date: 18 MAR 2011	**Trial No. / U No.:** 502.550 / U11-1227-02	**Date of trial:** 26 Jun 2009 – 23 Apr 2010	**Date of revision :** 29 March 2011

Title of trial:	A randomised, double-blind, double dummy, active controlled, parallel group, forced titration study to compare the fixed-dose combination of Telmisartan 80mg plus Hydrochlorothiazide 25mg (T80/HCTZ25) versus Telmisartan 80mg (T80) monotherapy as first line therapy in patients with grade 2 or grade 3 hypertension (SBP ≥160 mmHg and DBP ≥100 mmHg)
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, see Appendix 16.1.4.
Publication (reference):	Data of this study have not been published.
Clinical phase:	IV
Objectives:	The primary objective was to demonstrate that the fixed-dose combination (FDC) of T80+H25 was superior as first-line therapy in reducing seated trough cuff systolic blood pressure (SBP) compared to the monotherapy of T80 in patients with grade 2 or grade 3 hypertension (SBP ≥160 mmHg and DBP ≥100 mmHg)
Methodology:	Randomised, double-blind, double-dummy, active-controlled, parallel-group, forced titration study with a screening period of up to 7 days, an open-label, placebo run-in period of 1 to 14 days, and a double-blind treatment period of 7 weeks with forced up-titration after 1 week. At the end of the run-in period, eligible patients were randomised in a ratio of 2:1 to daily treatment with T40+H12.5 followed by T80+H25 or with T40 followed by T80.
No. of subjects:	
planned:	entered: 840
actual:	enrolled: 1192 T40+H12.5 and T80+H25: entered: 599, treated: 594, analysed (for primary endpoint): 541 T40 and T80: entered: 295, treated: 294, analysed (for primary endpoint):263

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Name of finished product: Micardis Plus®		**EudraCT No.:** **2008-007711-32**	**Synopsis No.:**
Name of active ingredient: Telmisartan and Hydrochlorothiazide		**Page:** 2 of 8	
Module:		**Volume:**	
Report date: 18 MAR 2011	**Trial No. / U No.:** 502.550 / U11-1227-02	**Date of trial:** 26 Jun 2009 – 23 Apr 2010	**Date of revision :** 29 March 2011

Diagnosis and main criteria for inclusion:	Adult male and female patients with grade 2 or grade 3 hypertension (defined as mean seated cuff SBP ≥160 mmHg and DBP ≥100 mmHg) were randomised to double-blind study treatment.
Test product:	T40+H12.5: Telmisartan/Hydrochlorothiazide (40 mg/12.5 mg) FDC
dose:	1 tablet once daily for 1 week
mode of admin.:	oral
batch no.:	809487b
Test product:	T80+H25: Telmisartan/Hydrochlorothiazide (80 mg/25 mg) FDC
dose:	1 tablet once daily for 6 weeks
mode of admin.:	oral
batch no.:	809976 and 810126
Reference therapy:	T40: Telmisartan (40 mg) tablet
dose:	1 tablet once daily for 1 week
mode of admin.:	oral
batch no.:	807188
Reference therapy:	T80: Telmisartan (80 mg) tablet
dose:	1 tablet once daily for 6 weeks
mode of admin.:	oral
batch no.:	807193
Duration of treatment:	A 1 to 14-day run-in period with placebo (T40 and T40+H12.5 placebo) was followed by a 7-week double-blind period with T40+H12.5 (1 week) and T80+H25 (6 weeks) or with T40 (1 week) and T80 (6 weeks).

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Name of finished product: Micardis Plus®		**EudraCT No.:** **2008-007711-32**	
Name of active ingredient: Telmisartan and Hydrochlorothiazide		**Page:** 3 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 18 MAR 2011	**Trial No. / U No.:** 502.550 / U11-1227-02	**Date of trial:** 26 Jun 2009 – 23 Apr 2010	**Date of revision :** 29 March 2011

Criteria for evaluation:

Efficacy / clinical pharmacology:	Primary endpoint: change from baseline in mean seated trough cuff SBP to final visit (Week 7) Key secondary endpoints: Change from baseline in mean seated trough cuff SBP to Weeks 5 and 3 Secondary endpoints: change from baseline in mean seated trough cuff DBP to final visit; SBP and DBP control rates at final visit (Week 7), Weeks 5 and 3; BP control rate at final visit (Week 7); SBP and DBP response at final visit (Week 7); BP categories (optimal, normal, high normal; grade 1, 2, or 3 hypertension) at final visit (Week 7)
Safety:	Adverse events (AE), marked changes in laboratory parameters, changes from baseline in pulse rate, orthostatic changes in SBP and DBP, physical examination (screening), 12-lead electrocardiogram

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Name of finished product: Micardis Plus®		**EudraCT No.:** **2008-007711-32**	**Synopsis No.:**
Name of active ingredient: Telmisartan and Hydrochlorothiazide		**Page:** 4 of 8	
Module:		**Volume:**	
Report date: 18 MAR 2011	**Trial No. / U No.:** 502.550 / U11-1227-02	**Date of trial:** 26 Jun 2009 – 23 Apr 2010	**Date of revision :** 29 March 2011

Statistical methods:

A restricted maximum likelihood-based repeated measures approach was used for the evaluation of changes from baseline in mean seated trough cuff SBP/DBP including the fixed, categorical effects of treatment, week, treatment-by-week interaction, and country with the continuous covariates of baseline and baseline-by-week interaction.

The following closed hierarchical testing procedure was used to evaluate the primary and key secondary endpoints. Under this procedure, if and only if statistical significance was found for a particular test were any possible conclusions drawn from a subsequent test. Thus, all tests were performed using a two-sided α=0.05.

Primary endpoint:

1. Superiority of T80+H25 compared to T80 at the end of the 7-week treatment period in change from baseline in mean seated trough cuff SBP; if significant then,

Key secondary endpoints:

2. Superiority of T80+H25 compared to T80 following 5 weeks of treatment in change from baseline in mean seated trough cuff SBP; if significant then
3. Superiority of T80+H25 compared to T80 following 3 weeks of treatment in change from baseline in mean seated trough cuff SBP.

The endpoints of changes from baseline in mean seated trough cuff SBP/DBP were also evaluated based on an analysis of covariance (ANCOVA) model for each week with treatment and country as main effects and baseline as a covariate.

The categorical endpoints of SBP, DBP and BP control, as well as SBP and DBP response were evaluated by logistic regression including treatment and country as main effects and baseline as a covariate.

BP categories were analysed using the van Elteren test controlling for country.

Descriptive statistics were performed for all endpoints.

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Name of active ingredient: Telmisartan and Hydrochlorothiazide		**Page:** 5 of 8	
Module:		**Volume:**	
Report date: 18 MAR 2011	**Trial No. / U No.:** 502.550 / U11-1227-02	**Date of trial:** 26 Jun 2009 – 23 Apr 2010	**Date of revision :** 29 March 2011

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

The analysis of efficacy was based on BP measurements taken under trough conditions (i.e. 20–30 h after the last dose of trial medication). At baseline, mean (standard deviation [SD]) seated trough cuff SBP was 173.2 (9.4) mmHg in the T40/T80 group, and 172.2 (9.7) mmHg in the T40+H12.5/T80+H25 group. To Week 7, the adjusted mean change from baseline in SBP was –28.5 mmHg in the T40/T80 group and –37.0 mmHg in the T40+H12.5/T80+H25 group. This corresponded to an adjusted mean (95% confidence interval [CI]) difference between the two treatment groups of –8.5 (–10.6, –6.4) mmHg, in favour of a greater reduction in SBP in the T40+H12.5/T80+H25 group. This difference was statistically significant ($p<0.0001$).

At Weeks 3 and 5 the treatment effect of T40+H12.5/T80+H25 was greater than that of T40/T80, with an adjusted mean (95% CI) difference versus T40/T80 of –6.8 (–8.8, –4.7) mmHg at Week 3 and –7.3 (–9.3, –5.2) mmHg at Week 5. In both cases the difference was statistically significant ($p<0.0001$).

The primary objective of the trial of demonstrating that the FDC of T80+H25 was superior as first-line therapy in reducing seated trough cuff SBP compared to monotherapy with T80 in patients with grade 2 or 3 hypertension was thus met.

As expected, a greater benefit in terms of SBP reduction at Week 7 under treatment with T40+H12.5/T80+H25 was observed in patients with grade 3 hypertension at baseline compared to patients with grade 2 hypertension at baseline.

All results from the exploratory analyses of secondary and other endpoints supported the conclusions from the primary and key secondary efficacy endpoints.

A significantly greater reduction in mean DBP was observed for patients treated with combination therapy (–18.6 mmHg) compared with telmisartan monotherapy (–15.4 mmHg) at Week 7, after a consistent advantage was already observed at Weeks 3 and 5.

The SBP control rate and DBP control rate were higher in the T40+H12.5/T80+H25 group at all post-uptitration timepoints. In terms of the odds of achieving an SBP of <140 mmHg, patients treated with combination therapy were 136% more likely to achieve this clinical target at Week 7 compared with patients who received telmisartan monotherapy. The patients on

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Name of finished product: Micardis Plus®		**EudraCT No.:** **2008-007711-32**	**Synopsis No.:**
Name of active ingredient: Telmisartan and Hydrochlorothiazide		**Page:** 6 of 8	
Module:		**Volume:**	
Report date: 18 MAR 2011	**Trial No. / U No.:** 502.550 / U11-1227-02	**Date of trial:** 26 Jun 2009 – 23 Apr 2010	**Date of revision :** 29 March 2011

T40+H12.5/T80+H25 had an increase of 100% in the odds of achieving DBP control (DBP <90 mmHg) at Week 7.

The proportion of patients who met BP control (SBP of <140 mmHg; DBP <90 mmHg) at Weeks 3, 5 and 7 was consistently higher in patients treated with combination therapy.

A higher proportion of patients treated with combination therapy showed a reduction in SBP of >30 mmHg (67.9%) and >40 mmHg (40.5%) compared with patients treated with telmisartan monotherapy (46.7% and 23.9%, respectively) at Week 7; an advantage of T40+H12.5/T80+H25 was already observed at Weeks 3 and 5.

The SBP and DBP response rates were higher in the T40+H12.5/T80+H25 group at all post-uptitration timepoints.

Patients treated with T40+H12.5/T80+H25 were more likely to have a lower BP category (optimal [SBP <120 and DBP <80 mmHg], normal [SBP ≥120 to <130 and DBP ≥80 to <85 mmHg], high-normal [SBP ≥130 to <140 and DBP ≥85 to <90 mmHg]) at all post-uptitration timepoints. By Week 7, the proportion of patients in the T40+H12.5/T80+H25 group with optimal, normal, or high-normal BP was 7.7%, 23.7% and 24.1% respectively, compared to 2.1%, 12.6% and 20.0% in the T40/T80 group.

Diabetic patients were twice as likely to achieve their BP goal by Week 7 under treatment with T40+H12.5/T80+H25 than with T40/T80, and T40+H12.5/T80+H25 was advantageous over T40/T80 in the time to achievement of grade 1 hypertension.

This is a clinically meaningful achievement in a population of patients with grade 2 and 3 hypertension who are at risk for cardiovascular and renal complications of severely high BP.

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Name of active ingredient: Telmisartan and Hydrochlorothiazide		**Page:** 7 of 8	
Module:		**Volume:**	
Report date: 18 MAR 2011	**Trial No. / U No.:** 502.550 / U11-1227-02	**Date of trial:** 26 Jun 2009 – 23 Apr 2010	**Date of revision :** 29 March 2011

Safety results:

During the study period on high-dose treatment, overall frequencies of patients with AEs were comparable between the two treatment groups: 17.0% in the T80 group and 16.0% in the T80+H25 group. No SAEs or deaths were reported during the high-dose treatment phase. The frequencies of patients with AEs assessed by the investigator as related to study drug were slightly higher in the T80+H25 group than in the T80 group (4.6% vs 2.8%). The majority of the AEs reported after up-titration were mild or moderate in intensity. Severe AEs were only reported in 1 (0.3%) patient receiving T80 and 4 (0.7%) patients receiving T80+H25.

The frequency of patients with AEs leading to discontinuation was low overall, but slightly higher in the T80 group than in the T80+H25 group (2.8% vs 1.0%).

When assessed by MedDRA system organ class (SOC) and preferred term (PT), the frequencies of AEs reported after up-titration were generally similar in the two treatment groups; differences exceeding 1% were only seen for anxiety (T80: 1.7%, T80+H25: 0.2%), headache (2.1% vs 0.5%), and hypertension (1.4% vs 0.2%); all of these AEs were more common in patients receiving T80 monotherapy. The most frequently reported SOCs in both groups were infections and infestations (T80: 4.8% patients, T80+H25: 4.3% patients), nervous system disorders (2.8% vs 2.9%), and gastrointestinal disorders (2.8% vs 2.2%). The most frequently reported PTs in patients receiving T80 were headache (2.1%), anxiety (1.7%), hypertension (1.4%), upper respiratory tract infection (1.4%), and dizziness (1.0%). The most frequently reported PTs in patients receiving T80+H25 were dizziness (1.9%) and nasopharyngitis (1.4%).

Two SAEs were reported, one prior to forced up-titration and one during the post-treatment period. Both patients were hospitalised. Neither SAE was considered related to trial medication and both patients recovered from their SAEs.

Analysis of clinical laboratory parameters and vital signs did not give rise to any safety concerns.

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Name of active ingredient: Telmisartan and Hydrochlorothiazide		**Page:** 8 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 18 MAR 2011	**Trial No. / U No.:** 502.550 / U11-1227-02	**Date of trial:** 26 Jun 2009 – 23 Apr 2010	**Date of revision :** 29 March 2011

Conclusions:

Compared with treatment with T80 monotherapy, the FDC of T80+H25 provided statistically significant and clinically meaningful additional reductions in SBP (Week 7: adjusted mean difference of –8.5 mmHg). Statistically significant differences in seated trough cuff SBP were already observed at Week 3 (2 weeks after forced up-titration), with an adjusted mean difference of –6.8 mmHg, and at Week 5 (adjusted mean difference of –7.3 mmHg).

All results for the exploratory analyses of secondary and other endpoints supported the conclusions from the primary and key secondary efficacy endpoints. In summary, change from baseline in mean seated trough cuff DBP showed a greater treatment effect of T40+H12.5/T80+H25 over T40/T80 at all three post-uptitration timepoints (Weeks 3, 5, and 7), with an adjusted mean difference in DBP of –3.2 mmHg at Week 7. The SBP control rate, DBP control rate, and BP control rate were higher in the T40+H12.5/T80+H25 group at all post-uptitration timepoints. The SBP and DBP response rates were higher in the T40+H12.5/T80+H25 group at all post-uptitration timepoints. Patients treated with T40+H12.5/T80+H25 were more likely to have a lower BP category at all post-uptitration timepoints. Diabetic patients were twice as likely to achieve their BP goal by Week 7 under treatment with T40+H12.5/T80+H25 than with T40/T80. The frequency of patients with an SBP reduction of >30 or >40 mmHg was also higher under treatment with T40+H12.5/T80+H25 at all post-uptitration endpoints, and T40+H12.5/T80+H25 was advantageous over T40/T80 in the time to achievement of grade 1 hypertension.

The FDC of T80+H25 had a comparable safety profile to T80 monotherapy.

These results are considered to give a clear and robust demonstration of treatment benefit in terms of reduction of mean SBP and DBP, and demonstrate an enhanced benefit from treatment with T80+H25 over T80 in patients with grade 2 or 3 hypertension.

Trial Synopsis - Appendix

The appended tables on the following page supplements the trial results presented in the Trial Synopsis. They complement disposition results and results for secondary endpoints of the trial. Note that not all secondary endpoints defined in the trial protocol are presented in this synopsis because their number was too large to allow meaningful presentation in this format.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
Change from baseline in trough DBP at 7 weeks	Table 15.2.2.1: 2
Patients achieving SBP control at week 7	Table 15.2.2.2: 2
Patients achieving SBP control at week 5	Table 15.2.2.2: 3
Patients achieving SBP control at week 3	Table 15.2.2.2: 4
Patients achieving DBP control at week 7	Table 15.2.2.3: 2
Patients achieving DBP control at week 5	Table 15.2.2.3: 3
Patients achieving DBP control at week 3	Table 15.2.2.3: 4
Patients achieving BP control at week 7	Table 15.2.2.4: 2
Patients achieving SBP response at week 7	Table 15.2.2.5: 2
Patients achieving DBP response at week 7	Table 15.2.2.6: 2

Table 15.1.1: 1 Disposition of patients - enrolled patients

	T40/T80 N (%)	T40+H12.5/T80+H25 N (%)	Total N (%)
Enrolled			1192
Not entered/randomised			298
Entered/randomised	295 (100.0)	599 (100.0)	894 (100.0)
Non-compliance of site	1 (0.3)	5 (0.8)	6 (0.7)
Treated	294 (99.7)	594 (99.2)	888 (99.3)
Not prematurely discontinued from trial medication	269 (91.2)	558 (93.2)	827 (92.5)
Prematurely discontinued from trial medication	25 (8.5)	36 (6.0)	61 (6.8)
Adverse event	9 (3.1)	11 (1.8)	20 (2.2)
Worsening of disease under study	5 (1.7)	4 (0.7)	9 (1.0)
Worsening of other pre-existing disease	1 (0.3)	0 (0.0)	1 (0.1)
Other adverse event	3 (1.0)	7 (1.2)	10 (1.1)
Non compliant with protocol	8 (2.7)	12 (2.0)	20 (2.2)
Lost to follow-up	3 (1.0)	6 (1.0)	9 (1.0)
Patient refusal to continue taking trial medication	4 (1.4)	4 (0.7)	8 (0.9)
Other	1 (0.3)	3 (0.5)	4 (0.4)

It was asked only for primary reason.

Table 15.2.2.1: 2 Change from baseline in mean seated trough cuff diastolic blood pressure (DBP) [mmHg] by repeated measures ANCOVA - FAS (observed data)

	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Week 3	T40/T80	276	-14.4 (0.54)			
	T40+H12.5/T80+H25	567	-17.0 (0.38)	-2.7 (0.66)	(-4.0 , -1.4)	<.0001
Week 5	T40/T80	270	-15.3 (0.53)			
	T40+H12.5/T80+H25	550	-18.6 (0.37)	-3.2 (0.64)	(-4.5 , -2.0)	<.0001
Week 7	T40/T80	263	-15.4 (0.55)			
	T40+H12.5/T80+H25	541	-18.6 (0.38)	-3.2 (0.66)	(-4.5 , -1.9)	<.0001
Interaction treatment and week						
p-value						0.5129
Interaction baseline and week						
p-value						0.7862
Effect of country						
p-value						<.0001

* adjusted for baseline as a covariate. Significance tests are based on Least Squares (LS) means.
The statistical model includes the fixed, categorical effects of treatment, week, treatment-by-week interaction and country with the continuous covariate of baseline mean seated trough cuff DBP (at Visit 3) and baseline-by-week interaction.

Table 15.2.2.2: 2 SBP control (SBP < 140 mmHg) at week 7 - FAS

	T40/T80	T40+H12.5/T80+H25
Number of patients [N (%)]	285 (100.0)	573 (100.0)
Number (%) satisfying SBP control	122 (42.8)	363 (63.4)
95% Confidence interval [%]*	(37.0 , 48.8)	(59.3 , 67.3)
Comparison vs T40/T80		
Odds Ratio		2.36
95% Confidence interval**		(1.74 , 3.21)
p-value		<.0001

* exact 95% CI by Clopper and Pearson
** logistic regression with the fixed, categorical effects of treatment and country with the continuous covariate of baseline mean seated trough cuff SBP (at Visit 3), Wald confidence intervals used

Table 15.2.2.2: 3 SBP control (SBP < 140 mmHg) at week 5 - FAS

	T40/T80	T40+H12.5/T80+H25
Number of patients [N (%)]	284 (100.0)	572 (100.0)
Number (%) satisfying SBP control	119 (41.9)	355 (62.1)
95% Confidence interval [%]*	(36.1 , 47.9)	(57.9 , 66.1)
Comparison vs T40/T80		
Odds Ratio		2.30
95% Confidence interval**		(1.70 , 3.12)
p-value		<.0001

* exact 95% CI by Clopper and Pearson
** logistic regression with the fixed, categorical effects of treatment and country with the continuous covariate of baseline mean seated trough cuff SBP (at Visit 3), Wald confidence intervals used

Table 15.2.2.2: 4 SBP control (SBP < 140 mmHg) at week 3 - FAS

	T40/T80	T40+H12.5/T80+H25
Number of patients [N (%)]	276 (100.0)	567 (100.0)
Number (%) satisfying SBP control	97 (35.1)	306 (54.0)
95% Confidence interval [%]*	(29.5 , 41.1)	(49.8 , 58.1)
Comparison vs T40/T80		
Odds Ratio		2.19
95% Confidence interval**		(1.60 , 3.01)
p-value		<.0001

* exact 95% CI by Clopper and Pearson
** logistic regression with the fixed, categorical effects of treatment and country with the continuous covariate of baseline mean seated trough cuff SBP (at Visit 3), Wald confidence intervals used

Table 15.2.2.3: 2 DBP control (DBP < 90 mmHg) at week 7 - FAS

	T40/T80	T40+H12.5/T80+H25
Number of patients [N (%)]	285 (100.0)	573 (100.0)
Number (%) satisfying DBP control	150 (52.6)	389 (67.9)
95% Confidence interval [%]*	(46.7 , 58.5)	(63.9 , 71.7)
Comparison vs T40/T80		
Odds Ratio		2.00
95% Confidence interval**		(1.46 , 2.73)
p-value		<.0001

* exact 95% CI by Clopper and Pearson
** logistic regression with the fixed, categorical effects of treatment and country with the continuous covariate of baseline mean seated trough cuff DBP (at Visit 3), Wald confidence intervals used

Table 15.2.2.3: 3 DBP control (DBP < 90 mmHg) at week 5 - FAS

	T40/T80	T40+H12.5/T80+H25
Number of patients [N (%)]	284 (100.0)	572 (100.0)
Number (%) satisfying DBP control	150 (52.8)	391 (68.4)
95% Confidence interval [%]*	(46.8 , 58.7)	(64.4 , 72.2)
Comparison vs T40/T80		
Odds Ratio		2.02
95% Confidence interval**		(1.48 , 2.76)
p-value		<.0001

* exact 95% CI by Clopper and Pearson
** logistic regression with the fixed, categorical effects of treatment and country with the continuous covariate of baseline mean seated trough cuff DBP (at Visit 3), Wald confidence intervals used

Table 15.2.2.3: 4 DBP control (DBP < 90 mmHg) at week 3 - FAS

	T40/T80	T40+H12.5/T80+H25
Number of patients [N (%)]	276 (100.0)	567 (100.0)
Number (%) satisfying DBP control	131 (47.5)	343 (60.5)
95% Confidence interval [%]*	(41.4 , 53.5)	(56.3 , 64.5)
Comparison vs T40/T80		
Odds Ratio		1.74
95% Confidence interval**		(1.28 , 2.37)
p-value		0.0005

* exact 95% CI by Clopper and Pearson
** logistic regression with the fixed, categorical effects of treatment and country with the continuous covariate of baseline mean seated trough cuff DBP (at Visit 3), Wald confidence intervals used

Table 15.2.2.4: 2 BP control (SBP < 140 mmHg and DBP < 90 mmHg) at week 7 adjusted for baseline SBP - FAS

	T40/T80	T40+H12.5/T80+H25
Number of patients [N (%)]	285 (100.0)	573 (100.0)
Number (%) satisfying BP control	99 (34.7)	318 (55.5)
95% Confidence interval [%]*	(29.2 , 40.6)	(51.3 , 59.6)
Comparison vs T40/T80		
Odds Ratio		2.39
95% Confidence interval**		(1.76 , 3.26)
p-value		<.0001

* exact 95% CI by Clopper and Pearson
** logistic regression with the fixed, categorical effects of treatment and country with the continuous covariate of baseline mean seated trough cuff SBP (at Visit 3), Wald confidence intervals used

Table 15.2.2.5: 2 SBP response (SBP < 140 mmHg or a reduction of >= 15 mmHg) at week 7 - FAS

	T40/T80	T40+H12.5/T80+H25
Number of patients [N (%)]	285 (100.0)	573 (100.0)
Number (%) satisfying SBP response	233 (81.8)	527 (92.0)
95% Confidence interval [%]*	(76.8 , 86.1)	(89.4 , 94.1)
Comparison vs T40/T80		
Odds Ratio		2.62
95% Confidence interval**		(1.70 , 4.04)
p-value		<.0001

* exact 95% CI by Clopper and Pearson
** logistic regression with the fixed, categorical effects of treatment and country with the continuous covariate of baseline mean seated trough cuff SBP (at Visit 3), Wald confidence intervals used

Table 15.2.2.6: 2 DBP response (DBP < 90 mmHg or a reduction of >= 10 mmHg) at week 7 - FAS

	T40/T80	T40+H12.5/T80+H25
Number of patients [N (%)]	285 (100.0)	573 (100.0)
Number (%) satisfying DBP response	202 (70.9)	483 (84.3)
95% Confidence interval [%]*	(65.2 , 76.1)	(81.1 , 87.2)
Comparison vs T40/T80		
Odds Ratio		2.23
95% Confidence interval**		(1.57 , 3.16)
p-value		<.0001

* exact 95% CI by Clopper and Pearson
** logistic regression with the fixed, categorical effects of treatment and country with the continuous covariate of baseline mean seated trough cuff DBP (at Visit 3), Wald confidence intervals used