Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-002421-68	
Name of active ingredients: Telmisartan and amlodipine		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Report date: 25 March 2009	**Trial No. / U No.:** 1235.6 / U09-1261-01	**Dates of trial:** 22 NOV 2007 – 17 OCT 2008	**Date of revision :** Not applicable

Title of trial:	An eight-week randomised, 3-arm, double-blind study to compare the safety and efficacy of the combination of telmisartan 40 mg + amlodipine 10 mg versus telmisartan 80 mg + amlodipine 10 mg versus amlodipine 10 mg monotherapy in patients with hypertension who fail to respond adequately to treatment with amlodipine 10 mg monotherapy **Te**lmisartan plus **Am**lodipine **St**udy in **A**mlodipine **10** mg Non-Responders in Hypertension: **TEAMSTA-10**
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre study conducted at 97 sites in 14 countries
Publication (reference):	Data from this study have not been published
Clinical phase:	III
Objectives:	The primary objective of this trial was to demonstrate that the fixed-dose combination (FDC) telmisartan 40 mg and amlodipine 10 mg (T40/A10) or the FDC telmisartan 80 mg and amlodipine 10 mg (T80/A10) was superior to A10 in reducing blood pressure (BP) at 8 weeks in patients who failed to respond to 6 weeks treatment with A10.
Methodology:	This was a randomised, controlled, double-blind, non-responder design study. Patients who failed to respond adequately (response: diastolic BP <90 mmHg) to an open-label treatment of 6 weeks with A10 (preceded by 2 weeks with A5) were randomised in a 1:1:1 ratio to an 8-week double-dummy treatment with either T40/A10 or T80/A10 or A10. Seated trough BP was measured 20 to 30 h post-dose at each visit.
No. of subjects: **planned:**	entered: 756 patients

actual:	enrolled: 1531 entered: 949 A10: entered: 315 treated: 315 analysed (for primary endpoint): 305 T40/A10: entered: 315 treated: 315 analysed (for primary endpoint): 306 T80/A10: entered: 319 treated: 317 analysed (for primary endpoint): 310
Diagnosis and main criteria for inclusion:	Adult male or female patients with essential hypertension and uncontrolled BP (defined as seated diastolic blood pressure [DBP] ≥95 mmHg in antihypertensive-treated patients and seated DBP ≥100 mmHg in patients not antihypertensive-treated) at date of informed consent were enrolled and eligible for run-in monotherapy. Patients who did not respond adequately (defined as DBP ≥90 mmHg) to A10 run-in monotherapy were randomised.
Test product:	Telmisartan 40 mg and amlodipine 10 mg FDC
dose:	1 tablet (40 mg / 10 mg) once daily
mode of admin.:	oral
batch no.:	B071002444, B071002460 (verum T40/A10), B071000942 (placebo matching T40/A10)
Test product:	Telmisartan 80 mg and amlodipine 10 mg FDC
dose:	1 tablet (80 mg / 10 mg) once daily
mode of admin.:	oral
batch no.:	B071002445, B071002459 (verum T80/A10), B71000940 (placebo matching T80/A10)
Reference therapy:	Amlodipine 10 mg
dose:	2 capsules (5 mg) once daily
mode of admin.:	oral
batch no.:	B061003098 (verum A5), B071000872 (placebo matching A5)

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Duration of treatment:	A run-in treatment phase of 2 weeks with A5 and 6 weeks with A10 was followed by an 8-week randomised treatment phase.
Criteria for evaluation:	
Efficacy:	The primary endpoint was the change from baseline in trough seated DBP. Secondary endpoints were the change from baseline trough seated systolic blood pressure (SBP), proportions of patients achieving trough DBP / SBP control, trough DBP / SBP response, proportions of patients with optimal, normal, high-normal BP, stage 1, and stage 2 hypertension, and incidence of oedema.
Safety:	Reported adverse events (AEs), reported cases of oedema, laboratory assessments, physical examination
Statistical methods:	Changes from baseline for BP were assessed by analysis of covariance (ANCOVA) with treatment and country as main effects and baseline as a covariate. Mantel-Haenszel tests controlling for country were used to analyse the trough BP control and response endpoints, and a stratified (for country) Wilcoxon-Mann-Whitney signed rank test was used to compare the categorisation of trough BP values.
SUMMARY – CONCLUSIONS:	
Efficacy results:	Of the patients treated with run-in medication, 30.0% were not randomised. Of the 407 patients not randomised, the majority had achieved trough seated DBP <90 mmHg (232 patients at the end of the run-in phase); 100 patients were not randomised due to AEs. There were 947 randomised and treated patients, of which 4.4% discontinued prematurely, with comparable frequencies in all 3 treatment groups (A10: 4.4%; T40/A10: 5.7%; T80/A10: 3.2%). Almost all of the randomised patients were white (99.4%), the proportion of male patients was 55.8%, the mean age was 56.5 years, and mean trough seated BP at the end of the run-in treatment, i.e. at baseline, was 147.5/95.6 mmHg. The treatment groups were generally well matched for demographic and baseline parameters.

Efficacy results: (continued)

Tests for the primary endpoint analyses followed a pre-specified hierarchical closed testing sequence. Firstly, superiority of T80/A10 over A10 and then the superiority of T40/A10 over A10 for the change from baseline to the last visit in trough seated DBP was demonstrated. In the T80/A10 and T40/A10 groups a greater reduction in the adjusted (for baseline and country) mean DBP (T80/A10: −9.3 mmHg; T40/A10: −9.2 mmHg) was observed than in the A10 group (−6.5 mmHg). The difference between the adjusted means of T80/A10 and A10 was −2.8 mmHg (95% CI: −3.8, −1.8) and was statistically significant ($p<0.0001$). The difference between the adjusted means of T40/A10 and A10 was −2.8 mmHg (95% CI: −3.8, −1.8) and was also statistically significant ($p<0.0001$).

The analysis of the secondary endpoints showed greater BP decreases in the T40/A10 and T80/A10 groups than in the A10 group. For peripheral oedema, no relevant differences were observed between the pooled combination groups and the A10 group.

Efficacy results: (continued)

The results for the primary and secondary endpoints are summarised in the following table:

	A10 n=305	T40/A10 n=306	T80/A10 n=310
Primary endpoint			
Adj. mean (SE) DBP change[1]	−6.5 (0.45)	−9.2 (0.45)	−9.3 (0.45)
Comp. to A10, p-value		<0.0001	<0.0001
Secondary endpoints			
Adjusted mean (SE) SBP change[1]	−7.4 (0.66)	−11.1 (0.66)	−11.3 (0.66)
Comp. to A10, p-value		<0.0001	<0.0001
Pts. with DBP contr. <90 mmHg, n (%)	156 (51.1)	195 (63.7)	206 (66.5)
Comp. to A10, p-value		0.002	<0.001
Pts. with DBP contr. <80 mmHg, n (%)	18 (5.9)	39 (12.7)	39 (12.6)
Comp. to A10, p-value		0.004	0.004
Pts. with DBP response, n (%)	163 (53.4)	202 (66.0)	213 (68.7)
Comp. to A10, p-value		0.002	<0.001
Pts. with SBP control, n (%)	153 (50.2)	180 (58.8)	187 (60.3)
Comp. to A10, p-value		0.027	0.008
Pts. with SBP response, n (%)	165 (54.1)	198 (64.7)	204 (65.8)
Comp. to A10, p-value		0.006	0.002
Trough seated BP categories, n (%)			
Optimal	0 (0.0)	12 (3.9)	6 (1.9)
Normal	36 (11.8)	43 (14.1)	50 (16.1)
High normal	77 (25.2)	91 (29.7)	106 (34.2)
Stage 1 hypertension	157 (51.5)	139 (45.4)	133 (42.9)
Stage 2 hypertension	35 (11.5)	21 (6.9)	15 (4.8)
Comp. to A10, p-value		0.006	<0.001
Peripheral oedema[2], n (%)	22 (7.0)	48 (7.6)	
Comparison to A10, p-value		0.7138	

[1] Adjusted for baseline and country

[2] No oedema-related events other than peripheral oedema were reported

Safety results:

Mean exposure to run-in treatment was about 16 days for the A5 run-in treatment and about 43 days for the A10 run-in treatment. Mean exposure to randomised treatment was about 57 days in all 3 treatment groups.

During the run-in phase, 9.7% of patients reported AEs while receiving A5 and 22.9% while receiving A10. The most frequently reported AEs (incidence ≥1%)

Safety results: (continued)

were peripheral oedema (A5: 3.1%; A10: 16.6%) and headache (A5: 2.0%; A10: 0.8%). Severe AEs were reported in 0.3% of patients while receiving A5 and in 1.2% while receiving A10. Drug-related AEs were reported in 4.5% of patients during A5 treatment and in 18.1% during A10 treatment. Adverse events leading to premature discontinuation were reported in 1.8% of patients while on A5 and in 7.4% of patients while on A10. Serious adverse events, none of which were considered drug-related, were reported in 4 patients while they took A10 (0.3%). Other significant AEs (i.e. non-serious AEs that led to discontinuation or dose reduction) affected 2.0% of patients (A5) and 7.4% of patients (A10), respectively.

The incidence of randomised and treated patients with AEs was comparable between the treatment groups (A10: 20.0%; T40/A10: 17.5%; T80/A10: 21.5%). The most frequently reported AE was peripheral oedema (A10: 7.0%; T40/A10: 6.7%; T80/A10: 8.5%). Other preferred terms reported in ≥ 1% but less than 2.5% of patients in any treatment group were hypercholesterolaemia, arthralgia, diabetes mellitus, and hypertriglyceridaemia. Both on the system organ class and preferred term level, the incidences of AEs were generally comparable between all 3 treatment groups. Adverse events of severe intensity (A10: 1.6%; T40/A10: 1.3%; T80/A10: 0.9%) and drug-related AEs (A10: 8.6%; T40/A10: 7.9%; T80/A10: 9.8%) were also reported at comparable frequencies. During the randomised phase, 4 SAEs were reported (A10: 1 patient; T40/A10: 3 patients), none of which were considered drug-related. One patient (T40/A10) had a fatal rupture of a cerebral aneurysm. Other significant AEs according to ICH E3 were reported at similar frequencies in all treatment groups (A10: 1.9%; T40/A10: 2.5%; T80/A10: 1.6%).

Safety results: (continued)

A summary of the incidence of peripheral oedema and AEs during the double-blind phase is given in the table below:

	A10		T40/A10		T80/A10	
	n	(%)	n	(%)	n	(%)
Number of patients	315	(100.0)	315	(100.0)	317	(100.0)
Pts. with any AEs	**63**	**(20.0)**	**55**	**(17.5)**	**68**	**(21.5)**
Oedema peripheral	22	(7.0)	21	(6.7)	27	(8.5)
Pts. with severe AEs	**5**	**(1.6)**	**4**	**(1.3)**	**3**	**(0.9)**
Oedema peripheral	2	(0.6)	1	(0.3)	0	(0.0)
Pts. with drug-related AEs	**27**	**(8.6)**	**25**	**(7.9)**	**31**	**(9.8)**
Oedema peripheral	20	(6.3)	17	(5.4)	22	(6.9)
Pts. with AEs leading to disc.	**7**	**(2.2)**	**9**	**(2.9)**	**4**	**(1.3)**
Oedema peripheral	6	(1.9)	3	(1.0)	2	(0.6)
Pts with SAEs	**1**	**(0.3)**	**3**	**(1.0)**	**0**	**(0.0)**

No patient discontinued the double-blind phase due to treatment-emergent laboratory abnormality reported as an AE. There were no clinically relevant between-group differences for clinical laboratory parameters.

Conclusions:

In patients with hypertension completing the run-in phase and not adequately controlled after a 6-week run-in phase with open-label A10 (preceded by 2 weeks with A5), treatment with the fixed-dose combinations T40/A10 or T80/A10 led to additional, clinically relevant BP reductions after 8 weeks. Both T/A groups were statistically superior to continued A10 treatment in reducing trough seated DBP. All analyses of continuous and categorical secondary BP efficacy endpoints showed better results for the 2 T/A groups than for the A10 group. The mean SBP and DBP change from baseline was numerically greater in the T80/A10 group than in the T40/A10 group. During the run-in phase, 7.4% of patients discontinued A10 due to AEs (mainly peripheral oedema). During the double-blind phase, the safety profiles of both T/A groups were comparable with A10 monotherapy and in agreement with the established safety profiles of telmisartan and amlodipine. The rate of peripheral oedema was generally comparable between all 3 treatment groups in patients able to tolerate A10 monotherapy; however, fewer patients discontinued double-blind study treatment due to oedema in the T/A groups than during continued A10 treatment.