Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2007-002422-29	
Name of active ingredient: Telmisartan and amlodipine		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 03 December 2009	**Trial No. / U No.:** 1235.8 / U09-2135-01	**Dates of trial:** 10 MAR 2008 – 19 JUN 2009	**Date of revision:** Not applicable

Title of trial:	An open-label follow-up trial of the efficacy and safety of chronic administration of the combination of telmisartan 40 mg + amlodipine 10 mg or the combination of telmisartan 80 mg + amlodipine 10 mg tablets alone or in combination with other antihypertensive medications in patients with hypertension
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study conducted at 88 sites in 12 countries
Publication (reference):	Data of this study have not been published
Clinical phase:	III
Objectives:	The primary objective was to assess the efficacy and safety of the fixed-dose combination (FDC) of telmisartan 40 mg + amlodipine 10 mg (T40/A10) and the FDC of telmisartan 80 mg + amlodipine 10 mg (T80/A10) alone or in addition to other antihypertensive therapies during open-label treatment for at least 6 months.
Methodology:	This was a randomised, open-label, follow-up study with a planned duration of 34 weeks in patients who had completed the preceding study 1235.6. After 4 weeks run-in treatment with the FDC T40/A10, patients were randomised to the FDC T80/A10 or the FDC T40/A10 in a 3:2 ratio. After a further 4 weeks, if diastolic blood pressure (DBP) control in patients in the T40/A10 group was inadequate (i.e. DBP ≥90 mmHg), the dose was up-titrated to T80/A10. If DBP control was inadequate, additional antihypertensive therapy could be added after the 4-week visit (if randomised to T80/A10), or after the 8-week visit (if randomised to T40/A10) at regular visits or interim visits. Trough seated blood pressure (BP) was measured 20 to 30 h post-dose at each visit. The planned exposure was 34 weeks for T40/A10 in patients who were randomised to T40/A10 and stayed on this dose, and 26 to 30 weeks for T80/A10 in patients either randomised or up-titrated to this higher dose.
No. of subjects:	
planned:	Entered: 900

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actual:	Enrolled: 838 Treated: 838 Analysed for the primary endpoint: 835 Analysed for safety: 838 (exposure to T40/A10) 611 (exposure to T80/A10)
Diagnosis and main criteria for inclusion:	Male or female patients with previously uncontrolled hypertension who had completed the preceding trial 1235.6 in the previous 14 days. Trial 1235.6 was a randomised, double-blind comparison of T40/A10, T80/A10 and amlodipine 10 mg (A10) for 8 weeks. All patients who entered 1235.6 had previously failed to respond to A10 (defined as seated DBP ≥90 mmHg after 6 weeks treatment with open-label A10).
Test product:	Telmisartan 40 mg / amlodipine 10 mg FDC
dose:	1 tablet (40 mg / 10 mg) once daily
mode of admin.:	oral
batch no.:	B081002987, B071002704, B071002460, B071002444
Test product:	Telmisartan 80 mg / amlodipine 10 mg FDC
dose:	1 tablet (80 mg / 10 mg) once daily
mode of admin.:	oral
batch no.:	B081002988, B071002701, B071002459, B071002445
Reference therapy:	Not applicable
dose:	Not applicable
mode of admin.:	Not applicable
batch no.:	Not applicable
Duration of treatment:	34 weeks: 4 weeks T40/A10 run-in; additional 30 weeks on T40/A10 for patients randomised to and remaining on this dose, or additional 30 weeks on T80/A10 for patients randomised to and remaining on this dose, or additional 4 weeks on T40/A10 and 26 weeks on T80/A10 for patients up-titrated at week 8.

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Criteria for evaluation:

Efficacy: The primary endpoint was the proportion of patients achieving DBP control (trough seated DBP <90 mmHg). Secondary endpoints were the change in trough seated DBP / systolic blood pressure (SBP), proportions of patients achieving trough DBP <80 mmHg, SBP control, DBP / SBP response, BP categories (optimal/normal/high-normal BP, stage 1/stage 2 hypertension), the proportion of patients requiring additional antihypertensive therapy to achieve DBP control, BP reduction by use of additional antihypertensive treatment, time to additional antihypertensive treatment, and the proportion of patients requiring up-titration to achieve DBP control.

Safety: Reported adverse events (AEs) , laboratory assessments, vital signs

Statistical methods: Descriptive statistics only were performed.

SUMMARY – CONCLUSIONS:

Efficacy results: Overall 95.7% of patients completed the trial; the main reason for premature discontinuation was the occurrence of AEs (1.9%). The patient population consisted of white patients (99.4%), with the majority being male (56.2%). Mean age was 56.4 years. Mean trough seated BP at baseline of study 1235.6 was 147.6/95.6 mmHg for all patients; mean trough seated BP at the end of the preceding trial (end of trial [EOT] 1235.6) was 138.2/87.7 mmHg for all patients. The dose groups in this trial were generally well matched for demographic and baseline parameters. A total of 14.7% of patients took at least 1 additional antihypertensive medication at some time during the study.

Patients were grouped by dose received when their BP was evaluated at the EOT visit in this trial; in the treated set: n=219 for T40/A10 (i.e. randomised to T40/A10 and dose prior to EOT visit T40/A10); n=436 for Rand T80/A10 (i.e. randomised to T80/A10 and dose prior to EOT visit T80/A10); n=91 for Titrate T80/A10 (i.e. randomised to T40/A10 and up-titrated at the 8-week visit to T80/A10); n=92 for T/A10+ (i.e. additional antihypertensive medication prior to EOT visit). When grouped by double-blind treatment in the preceding trial, 276 patients (33.1%) had been treated with pre-A10, 277 patients (33.2%) with pre-T40/A10, and 282 patients (33.8%) with pre-T80/A10. No dose reductions were reported.

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Efficacy results (continued)

At baseline of the preceding study 1235.6, 4 patients (0.5%) in the full analysis set (FAS) had trough DBP control (trough DBP <90 mmHg); at the end of the preceding trial, 59.5% of patients in the FAS had achieved DBP control. The proportion of patients with DBP control increased continuously during this open-label trial; 89.2% of patients achieved DBP control by the end of this trial.

The analyses of the secondary efficacy endpoints supported the results of the primary endpoint analysis. They consistently showed mean reductions in trough SBP/DBP with corresponding increases in the percentage of patients with trough SBP and DBP control and increases in response rates. Also the proportion of patients with optimal, normal, or high-normal BP (i.e. BP <140/90 mmHg) increased substantially from the end of the preceding trial to the end of this open-label trial.

For an overview of the efficacy endpoints overall and by dose received prior to EOT visit refer to the table below.

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Efficacy results (continued)

Table: Results for primary and selected secondary efficacy endpoints, based on the FAS

	T40/A10		Rand T80/A10		Titrate T80/A10		T/A10+*		Total	
Patients, n (%)	216	(100.0)	436	(100.0)	91	(100.0)	92	(100.0)	835	(100.0)
Primary endpoint: Trough DBP control <90 mmHg, n (%)										
BL 1235.6	1	(0.5)	2	(0.5)	0	(0.0)	1	(1.1)	4	(0.5)
EOT 1235.6	148	(68.5)	273	(62.6)	44	(48.4)	32	(34.8)	497	(59.5)
EOT 1235.8	201	(93.1)	402	(92.2)	72	(79.1)	70	(76.1)	745	(89.2)
Selected secondary endpoints:										
Mean change in trough SBP/DBP at EOT visit* (mmHg)										
From BL of trial 1235.6	-14.8 /-13.4		-15.9/-13.4		-14.9/-11.5		-12.4/-10.6		-15.1/-12.9	
From EOT 1235.6	-4.7/-4.4		-6.0/-5.0		-6.6/-5.5		-5.6/-5.4		-5.7/-4.9	
Trough DBP response, n (%)										
EOT 1235.6	153	(70.8)	278	(63.8)	44	(48.4)	37	(40.2)	512	(61.3)
EOT 1235.8	201	(93.1)	405	(92.9)	71	(78.0)	73	(79.3)	750	(89.8)
Trough SBP response, n (%)										
EOT 1235.6	156	(72.2)	295	(67.7)	54	(59.3)	44	(47.8)	549	(65.7)
EOT 1235.8	190	(88.0)	401	(92.0)	75	(82.4)	69	(75.0)	735	(88.0)

* The T/A10+ group comprised all patients who received additional antihypertensive medications; BL: baseline

For the 121 (14.5%) patients in the FAS who received additional anti-hypertensive medications at any time during the study, the mean time to the first intake of additional antihypertensive medication was 91.9 days. The mean reduction in trough SBP/DBP from the visit before the intake of additional antihypertensive medication to the last trough value was −7.8/−6.8 mmHg. For 582 patients with a dose increase (randomisation or up-titration) from T40/A10 to T80/A10 and with trough values available at the visits before and after increase, the mean reduction in trough SBP/DBP from the visit before to the visit after dose increase was −3.6/−2.9 mmHg.

No impact of the randomised, double-blind treatment in the preceding trial 1235.6 on primary and secondary endpoints at the end of this open label trial was observed.

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Safety results:

Consistent with the study design, the median exposure to T40/A10 was 32 days and the median exposure to T80/A10 was 210 days. A total of 215 patients had exposure to T40/A10 of at least 6 months; 549 patients had exposure to T80/A10 of at least 6 months.

For the 838 patients included in this report, AEs were reported in 12.2% of patients while receiving T40/A10 and 25.7% while receiving T80/A10. When adjusted for exposure, the proportion of patients with AEs was comparable between both treatments (T40/A10: 50.19 patients per 100 patient-years; T80/A10: 46.25 patients per 100 patient-years). When adjusted for exposure, only minor numerical differences between treatments were noted on the SOC and PT level. On the PT level, the most frequently reported AE was peripheral oedema (T40/A10: 2.1%, 8.86 patients/100 patient-years; T80/A10: 4.4%, 7.95 patients/100 patient-years).

The majority of AEs were of mild or moderate intensity; AEs of severe intensity were reported in 0.6% of patients (2.46 patients/100 patient-years) while receiving T40/A10 and in 1.0% of patients (1.77 patients/100 patient-years) while receiving T80/A10. Based on these low numbers, no relevant differences on the PT level between both treatments could be detected. Study drug-related AEs were reported in 3.3% of patients (13.78 patients/100 patient-years) while receiving T40/A10 and in 6.2% (11.19 patients/100 patient-years) while receiving T80/A10. The most frequently reported drug-related AE was peripheral oedema (T40/A10: 1.9%, 7.87 patients/100 patient-years; T80/A10: 3.9%, 7.07 patients/100 patient-years). Other significant AEs according to ICH E3 were reported in 0.6% of patients (2.46 patients/100 patient-years) while receiving T40/A10 and in 1.0% (1.77 patients/100 patient-years) while receiving T80/A10; peripheral oedema was reported as a significant AE according to ICH E3 in 3 patients (1 with T40/A10 and 2 with T80/A10); no other PT was reported as an other significant AE in more than 1 patient. AEs leading to discontinuation were reported in 0.7% of patients while receiving T40/A10 and in 1.5% while receiving T80/A10; peripheral oedema was reported as an AE leading to discontinuation in 3 patients (1 with T40/A10 and 2 with T80/A10); no other PT was reported as an AE leading to discontinuation in more than 1 patient.

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Safety results (continued)	Serious adverse events were reported in 0.5% of patients (1.97 patients/100 patient-years) while receiving T40/A10 and in 2.1% (3.83 patients/100 patient-years) while receiving T80/A10. One SAE (aortic dissection, T80/A10) was fatal. On the PT level, atrial fibrillation and pulmonary embolism were each reported by 2 patients (1 in each group) and hypertensive crisis was reported as an SAE by 2 patients receiving T80/A10; no other SAE was reported in more than 1 patient. None of the SAEs were considered study drug-related by the investigators. Other than the fatal event, 3 further patients were reported as having not recovered from their SAEs at the end of the trial (1 patient with an immediately life-threatening pulmonary embolism on T40/A10; 1 patient with an ankle fracture and 1 patient with ureteric calculus, both on T80/A10). When analysed by treatment in the preceding study 1235.6, no clinically relevant differences between the pre-treatment groups were found for the AEs reported in the first 4 weeks of treatment in this open-label trial. Overall, there were no safety concerns for the clinical laboratory parameters. There were no laboratory abnormalities reported as SAEs; 1 patient (T40/A10 treatment group) had increased blood creatinine reported as an other significant AE according to ICH E3 (patient discontinued). No relevant changes were noted for mean pulse rate and weight during the trial.
Conclusions:	The analysis of the complete patient population confirmed the conclusions of the interim analysis (U09-1517-01). Long-term (at least 6 months), open-label treatment with the FDCs T40/A10 and T80/A10 was effective; most patients (89.2%) achieved trough DBP <90 mmHg. The proportion of patients on a T/A FDC who received additional antihypertensive medication was low (14.5%). Clinically relevant mean reductions in SBP/DBP were achieved in all dose groups. Patients responded to T40/A10 or T80/A10 in a similar manner irrespective of their randomised therapy in the preceding double-blind study. The treatment with T40/A10 and T80/A10 was well tolerated, and the safety profiles of both FDCs were consistent with the established safety profiles of telmisartan and amlodipine.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement results for the primary and secondary endpoints of the trial.

Results for	**presented in**
Patients achieving DBP control at 34 weeks (Primary endpoint)	Table 15.2.1: 2
Patients achieving SBP control at 34 weeks (Secondary endpoint)	Table 15.2.2: 1
Patients in each BP category at 34 weeks (Secondary endpoint)	Table 15.2.6: 1
Patients requiring additional anti-hypertensive therapy to achieve DBP control (Secondary endpoint)	Table 15.2.7: 3
Trough DBP control before and after dose increase	Table 15.2.8: 1

Table 15.2.1: 2 Last dose level subgroup comparison of trough DBP control (<90mmHg) at the end of study - full analysis set

Trough DBP control 1	T40/A10	Rand T80/A10	Titrate T80/A10	T/A10+
Number of patients	216	436	91	92
Trough DBP control 1 [N (%)]				
N	216 (100.0)	436 (100.0)	91 (100.0)	92 (100.0)
No (DBP >= 90 mmHg)	15 (6.9)	34 (7.8)	19 (20.9)	22 (23.9)
Yes (DBP < 90 mmHg)	201 (93.1)	402 (92.2)	72 (79.1)	70 (76.1)
Comparison to T40/A10				
Odds ratio		0.88	0.28	0.24
95% CI		(0.47 , 1.66)	(0.14 , 0.59)	(0.12 , 0.48)
Comparison to Rand T80/A10				
Odds ratio			0.32	0.27
95% CI			(0.17 , 0.59)	(0.15 , 0.49)
Comparison to Titrate T80/A10				
Odds ratio				0.84
95% CI				(0.42 , 1.68)

Table 15.2.2: 1 Trough SBP control by visit and last dose level subgroup - full analysis set

Trough SBP control	T40/A10	Rand T80/A10	Titrate T80/A10	T/A10+	Total
Number of patients	216(100.0)	436(100.0)	91(100.0)	92(100.0)	835(100.0)
Baseline (1235.6)					
No [N(%)]	167(77.3)	364(83.5)	74(81.3)	80(87.0)	685(82.0)
Yes [N(%)]	47(21.8)	70(16.1)	13(14.3)	11(12.0)	141(16.9)
End of preceding study (1235.6)					
No [N(%)]	72(33.3)	184(42.2)	46(50.5)	63(68.5)	365(43.7)
Yes [N(%)]	141(65.3)	246(56.4)	45(49.5)	29(31.5)	461(55.2)
Week 4					
No [N(%)]	47(21.8)	155(35.6)	41(45.1)	64(69.6)	307(36.8)
Yes [N(%)]	165(76.4)	275(63.1)	46(50.5)	26(28.3)	512(61.3)
Week 8					
No [N(%)]	28(13.0)	105(24.1)	54(59.3)	66(71.7)	253(30.3)
Yes [N(%)]	186(86.1)	326(74.8)	36(39.6)	23(25.0)	571(68.4)
Week 14					
No [N(%)]	34(15.7)	77(17.7)	27(29.7)	60(65.2)	198(23.7)
Yes [N(%)]	180(83.3)	358(82.1)	63(69.2)	31(33.7)	632(75.7)
Week 22					
No [N(%)]	35(16.2)	81(18.6)	15(16.5)	43(46.7)	174(20.8)
Yes [N(%)]	176(81.5)	348(79.8)	72(79.1)	48(52.2)	644(77.1)
End of study					
No [N(%)]	37(17.1)	70(16.1)	21(23.1)	41(44.6)	169(20.2)
Yes [N(%)]	179(82.9)	366(83.9)	70(76.9)	51(55.4)	666(79.8)

Control = SBP <140 mmHg

Table 15.2.6: 1 Trough BP normality classes by visit and last dose level subgroup - full analysis set

Trough BP normal	T40/A10	Rand T80/A10	Titrate T80/A10	T/A10+	Total
Stage 1 hypertension [N(%)]	33(15.3)	82(18.8)	31(34.1)	57(62.0)	203(24.3)
Stage 2 hypertension [N(%)]	4(1.9)	8(1.8)	3(3.3)	10(10.9)	25(3.0)
Week 22					
Optimal [N(%)]	14(6.5)	14(3.2)	2(2.2)	2(2.2)	32(3.8)
Normal [N(%)]	59(27.3)	148(33.9)	17(18.7)	6(6.5)	230(27.5)
High normal [N(%)]	102(47.2)	174(39.9)	48(52.7)	29(31.5)	353(42.3)
Stage 1 hypertension [N(%)]	29(13.4)	89(20.4)	19(20.9)	45(48.9)	182(21.8)
Stage 2 hypertension [N(%)]	7(3.2)	4(0.9)	1(1.1)	9(9.8)	21(2.5)
End of study					
Optimal [N(%)]	12(5.6)	20(4.6)	5(5.5)	3(3.3)	40(4.8)
Normal [N(%)]	70(32.4)	146(33.5)	14(15.4)	13(14.1)	243(29.1)
High normal [N(%)]	94(43.5)	189(43.3)	46(50.5)	29(31.5)	358(42.9)
Stage 1 hypertension [N(%)]	32(14.8)	76(17.4)	23(25.3)	43(46.7)	174(20.8)
Stage 2 hypertension [N(%)]	8(3.7)	5(1.1)	3(3.3)	4(4.3)	20(2.4)

Optimal defined as SBP<120mmHg and DBP<80mmHg, Normal defined as SBP<130mmHg and DBP<85mmHg
High-Normal defined as SBP<140mmHg and DBP<90mmHg, Stage 1 hypertension defined as SBP<160mmHg
and DBP<100mmHg and Stage 2 hypertension is defined as SBP>=160mmHg or DBP>=100mmHg

Source data: Appendix 16.2, Listing 6.2 bpcat.sas 30JUL2009

Table 15.2.7: 3 Trough DBP control pre- and post- additional antihypertensives - full analysis set

	Pre-antihypertensive		
Post-antihypertensive	No (DBP >=90 mmHg)	Yes (DBP <90 mmHg)	Total
No (DBP >=90 mmHg)	23 (19.0)	4 (3.3)	27 (22.3)
Yes (DBP <90 mmHg)	67 (55.4)	27 (22.3)	94 (77.7)
Total	90 (74.4)	31 (25.6)	121 (100.0)

Note: Only patients taking additional antihypertensives with pre and post values summarised
3 patients received antihypertensive treatment that was not considered add-on
Pre-antihyper.: trough BPs taken prior to starting CT, end of study 1235.6 used if necessary
Post-antihyper.: trough BPs taken from the last visit during 1235.8

Table 15.2.8: 1 Trough DBP control before and after dose increase - full analysis set

	Before dose increase		
After dose increase	No (DBP >=90 mmHg)	Yes (DBP <90 mmHg)	Total
No (DBP >=90 mmHg)	90 (15.5)	18 (3.1)	108 (18.6)
Yes (DBP <90 mmHg)	168 (28.9)	306 (52.6)	474 (81.4)
Total	258 (44.3)	324 (55.7)	582 (100.0)

Note: All patients who increased dose to T80/A10 with before and after trough BP values are summarised
Before dose increase: trough BPs taken prior to increasing dose to T80/A10
After dose increase : trough BPs taken from first visit after increasing dose to T80/A10