Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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: Twynsta®		**EudraCT No.:** 2007-002409-36	
Name of active ingredients: Telmisartan and amlodipine		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Disclosure Synopsis Date: 26 MAY 2014	**Trial No. / U No.:** 1235.5 / U09-1201-03	**Dates of trial:** 01 NOV 2007 – 06 SEP 2008	**Date of revision:** 09 DEC 2010

Title of trial:	An eight-week randomised, 4-arm, double-blind study to compare the efficacy and safety of combinations of telmisartan 40 mg + amlodipine 5 mg versus telmisartan 80 mg + amlodipine 5 mg versus amlodipine 5 mg monotherapy versus amlodipine 10 mg monotherapy in patients with hypertension who fail to respond adequately to treatment with amlodipine 5 mg monotherapy **Te**lmisartan plus **Am**lodipine **St**udy in **A**mlodipine **5** mg Non-Responders in Hypertension: TEAMSTA-5
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre study conducted at 129 sites in 12 countries on 4 continents (Europe, Asia, North America, and Africa)
Publication (reference):	Data of 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 5 mg (T40/A5) or the FDC telmisartan 80 mg and amlodipine 5 mg (T80/A5) is superior to amlodipine 5 mg (A5) and not inferior vs. amlodipine 10 mg (A10) in reducing blood pressure (BP) at 8 weeks and to demonstrate that the incidence of oedema is lower for the pooled treatment groups T40/A5 and T80/A5 than for the A10 treatment group. This was tested in patients who failed to respond adequately (diastolic BP [DBP] ≥90 mmHg) to a 6-week treatment with A5.
Methodology:	This was a randomised, controlled, double-blind, non-responder study. Patients who failed to respond adequately (diastolic BP ≥90 mmHg) to a 6-week open-label treatment with A5 were randomised in a 1:1:1:1 ratio to an 8-week triple-dummy treatment with either T40/A5 or T80/A5 or A5 or A10. Trough seated BP was measured approximately 24 hours post-dose at each visit.

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No. of subjects:	
planned:	entered: 1012
actual:	enrolled: 1487 entered: 1098 A5: entered: 267 treated: 267 analysed (for primary endpoint): 255 A10: entered: 276 treated: 276 analysed (for primary endpoint): 261 (for BP), 276 (for oedema) T40/A5: entered: 278 treated: 277 analysed (for primary endpoint): 270 (for BP), 277 (for oedema) T80/A5: entered: 277 treated: 277 analysed (for primary endpoint): 271 (for BP), 277 (for oedema)
Diagnosis and main criteria for inclusion:	Adult patients with essential hypertension and uncontrolled BP at start of run-in (defined as seated DBP ≥95 mmHg in patients treated with antihypertensives and DBP ≥100 mmHg in patients not treated with antihypertensives) were enrolled. Patients who did not respond adequately (defined as DBP ≥90 mmHg) after 6 weeks of treatment with open-label A5 monotherapy were randomised.
Test product:	Telmisartan 40 mg / amlodipine 5 mg FDC
dose:	1 tablet (40 mg / 5 mg) once daily
mode of admin.:	Oral
batch no.:	B071002461 (T40/A5), B071000938 (placebo matching T40/A5)
Test product:	Telmisartan 80 mg / amlodipine 5 mg FDC
dose:	1 tablet (80 mg / 5 mg) once daily
mode of admin.:	Oral

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batch no.:	B071002456 (T80/A5), B071000941 (placebo matching T80/A5)
Reference therapy:	Amlodipine 5 mg
dose:	1 capsule (5 mg) once daily
mode of admin.:	Oral
batch no.:	B061003098 (A5), B071000872 (placebo matching A5)
Reference therapy:	Amlodipine 10 mg
dose:	2 capsules (5 mg) once daily
mode of admin.:	Oral
batch no.:	B061003098 (A5), B071000872 (placebo matching A5)
Duration of treatment:	A 6-week run-in treatment with A5 was followed by an 8-week randomised treatment phase.
Criteria for evaluation:	
Efficacy:	There were 2 co-primary endpoints, the change from baseline in trough seated DBP and the incidence of oedema during the double-blind phase. Secondary endpoints were trough seated systolic blood pressure (SBP); proportions of patients achieving DBP and SBP control, DBP and SBP response; proportions of patients with optimal, normal, high-normal BP, stage-I, and stage-II hypertension.
Safety:	Reported adverse events including reported cases of oedema, laboratory assessments, physical examination (only at Screening), 12-lead electrocardiogram (ECG).
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. The incidences of oedema were compared employing a logistic regression model. Mantel-Haenszel tests controlling for country were used to analyse the BP control and response endpoints, and a stratified (for country) Wilcoxon-Mann-Whitney signed rank test was used to compare the categorised BP values.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Of the 1097 randomised and treated patients, 4.6% discontinued prematurely, with the highest proportion noted for the A10 group (8.7%) and the lowest for the T40/A5 group (1.4%). Overall, 77.4% of the treated patients were white, the proportion of male patients was 62.2%, the mean age was 54.2 years, and mean trough seated BP at the end of the run-in treatment, i.e. at baseline, was 149.6/96.6 mmHg. The treatment groups were generally well matched for demographic and baseline parameters.

Tests for the primary endpoint analyses followed a pre-specified hierarchical closed testing procedure. Firstly, superiority of both T80/A5 and T40/A5 over A5 for the change from baseline in trough seated DBP was demonstrated. The difference between the adjusted means (95% CI) of T80/A5 and A5 was −4.9 mmHg (−6.2,−3.7) with p<0.0001. The corresponding difference between T40/A5 and A5 was −3.6 mmHg (−4.9,−2.4) with p<0.0001. In the subsequent steps, it was shown that both T80/A5 and T40/A5 were non-inferior to A10 (non-inferiority margin +2 mmHg) and afterwards that both T80/A5 (p<0.0001) and T40/A5 (p=0.029) were superior to A10 in reducing trough seated DBP. The difference between the adjusted means of T80/A5 and A10 was −2.7 mmHg (−3.9,−1.4) and was −1.4 mmHg (−2.7,−0.1) for T40/A5 vs. A10.

The analysis of the incidence of 'general oedema' (MedDRA preferred terms of peripheral oedema, generalised oedema, and oedema) was part of the pre-specified, closed hierarchical testing procedure for the primary endpoint. The rate of general oedema in the pooled T/A groups (4.3%) was significantly lower than that in the A10 group (27.2%), a difference of large clinical relevance with an odds ratio (95% CI) of 0.12 (0.07, 0.19) and p<0.0001.

The analyses of the secondary endpoints showed greater BP decreases in the T80/A5 and T40/A5 groups than in the A5 group. In addition, the T80/A5 group exhibited greater BP lowering than the A10 group, while T40/A5 displayed at least numerically better BP effects than A10 for most of the secondary endpoints:

For trough seated SBP change from baseline, the adjusted mean difference was −8.8 mmHg (−10.7, −6.9) with a p-value of <0.0001 between T80/A5 and A5, −7.4 mmHg (−9.3, −5.5) with a p-value of <0.0001 between T40/A5 and A5,

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Efficacy results: (continued)

−3.9 mmHg (−5.7, −2.0) with a p-value of <0.0001 between T80/A5 and A10, and −2.4 mmHg (−4.3, −0.6) with a p-value of 0.010 between T40/A5 and A10.

Summary of efficacy results:

Trough seated BP [mmHg] and 'general oedema' AEs	A5 n=255	A10 n=261	T40/A5 n=270	T80/A5 n=271
Primary endpoint				
Adj.[1] mean (SE) DBP change	-5.7 (0.5)	-8.0 (0.5)	-9.4 (0.5)	-10.6 (0.5)
Pts. with 'gen. oedema', n (%)	23 (8.6)	75 (27.2)	14 (5.1)	10 (3.6)
Secondary endpoints				
Adj. mean (SE) SBP change	-6.2 (0.7)	-11.1 (0.7)	-13.6 (0.7)	-15.0 (0.7)
Pts with DBP control, n (%)	107 (42.0)	148 (56.7)	153 (56.7)	173 (63.8)
Pts with DBP response, n (%)	116 (45.5)	163 (62.5)	177 (65.6)	187 (69.0)
Pts with SBP control, n (%)	100 (39.2)	142 (54.4)	162 (60.0)	178 (65.7)
Pts with SBP response, n (%)	118 (46.3)	166 (63.6)	187 (69.3)	200 (73.8)
BP categories, n (%)				
Optimal	2 (0.8)	5 (1.9)	19 (7.0)	21 (7.7)
Normal	23 (9.0)	30 (11.5)	35 (13.0)	51 (18.8)
High normal	42 (16.5)	68 (26.1)	63 (23.3)	67 (24.7)
Stage I hypertension	118 (46.3)	126 (48.3)	127 (47.0)	110 (40.6)
Stage II hypertension	70 (27.5)	32 (12.3)	26 (9.6)	22 (8.1)

[1] Adjusted for baseline and country.

Safety results:

Mean exposure to run-in treatment (A5) was about 42 days. Mean exposure to randomised treatment was about 56 days in all 4 treatment groups.

While receiving run-in treatment, 27.4% of patients reported AEs. The most frequently affected system organ classes (incidence ≥5%) were general disorders and administration site conditions, infections and infestations, and nervous system disorders. On preferred term level, the most frequent AEs (incidence ≥1%) were peripheral oedema (6.1%), headache (3.0%), dizziness (1.4%), and bronchitis (1.2%). Twenty-one patients (1.5%) had severe AEs. Drug-related AEs were reported in 10.1% of the patients. AEs that led to premature discontinuation were reported in 3.5% of the patients. SAEs, none of which were considered drug-related, were reported in 14 patients (1.0%). One of these

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patients died from a cerebrovascular accident. Other significant AEs (i.e. non-serious AEs that led to discontinuation or dose reduction) affected 3.3% of patients.

Safety results: (continued)

The incidence of AEs during the double-blind phase of the trial was lower in the T/A groups and in the A5 group than in the A10 group. The most frequently affected system organ classes (overall incidence ≥5%) were general disorders and administration site conditions, infections and infestations, musculoskeletal and connective tissue disorders, and nervous system disorders. General disorders and administration site conditions occurred more often in the A10 group (29.0%) than in the A5 group (11.2%) and the T/A groups (T40/A5: 6.9%, T80/A5: 7.6%). On preferred term level, the most frequently reported AEs (incidence ≥2%) were peripheral oedema, headache, and dizziness. Peripheral oedema was reported more than 5 times more often in the A10 group than in the T/A combination treatment groups. Severe AEs were reported with higher incidences for the amlodipine monotherapy groups than for the T/A groups. Drug-related AEs were by far most frequent in the A10 group. This large difference was due to the high incidence of drug-related peripheral oedema in the A10 group. The frequency of discontinuations due to AEs was several times greater in the A10 group than in the other 3 groups, again mainly due to the occurrence of peripheral oedema. Six patients (0.5%) reported SAEs, none of which was fatal nor considered to be drug-related. Other significant AEs were most frequently reported in the A10 group (8.0% vs. 1.9% for A5, 1.1% for T40/A5, 1.4% for T80/A5), again due to the much higher occurrence of peripheral oedema (5.8% for A10 vs. 0.7% for A5, 0.4% for T40/A5, 0 for T80/A5).

Summary of AEs during the double-blind phase (with most frequent AE per category):

AE category MedDRA PT	A5 n (%)	A10 n (%)	T40/A5 n (%)	T80/A5 n (%)
Number of patients	267 (100.0)	276 (100.0)	277 (100.0)	277 (100.0)
Patients with any AEs	**99 (37.1)**	**132 (47.8)**	**98 (35.4)**	**93 (33.6)**
Oedema peripheral	22 (8.2)	74 (26.8)	14 (5.1)	10 (3.6)
Patients with severe AEs	**5 (1.9)**	**8 (2.9)**	**3 (1.1)**	**1 (0.4)**
Oedema peripheral	2 (0.7)	5 (1.8)	0	0
Patients with related AEs	**34 (12.7)**	**77 (27.9)**	**22 (7.9)**	**24 (8.7)**

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	Oedema peripheral	19 (7.1)	62 (22.5)	9 (3.2)	8 (2.9)
	Patients with disc. AEs	**5 (1.9)**	**21 (7.6)**	**3 (1.1)**	**4 (1.4)**
	Oedema peripheral	2 (0.7)	15 (5.4)	1 (0.4)	0
	Patients with SAEs	**2 (0.7)**	**1 (0.4)**	**2 (0.7)**	**1 (0.4)**

Safety results: (continued)

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

Conclusions:

In patients with hypertension not adequately controlled after a 6-week run-in phase with A5, treatment with the fixed-dose combinations T40/A5 or T80/A5 led to additional, clinically relevant BP reductions after another 8 weeks of randomised treatment. Both T40/A5 and T80/A5 were not only superior to continued treatment with A5 but also to treatment with the maximum registered amlodipine dose of A10 in reducing trough seated DBP. All analyses of secondary efficacy endpoints showed better results for the 2 T/A groups than for the A5 group. In addition, T80/A5 was consistently more efficacious than A10 for continuous and categorical BP endpoints. Mean BP reductions for T40/A5 were statistically significantly greater than for A10.

All treatments were well tolerated. For the pooled T/A group (T40/A5 and T80/A5), a substantially lower rate of oedema was noted than for A10; the treatment difference was statistically and clinically significant. The oedema rate was also numerically lower for combination treatment than for A5. Discontinuations due to oedema AEs were much less frequent in the T/A groups than for A10. The safety profiles for the T/A and amlodipine treatments observed during this study were entirely consistent with the known safety profiles of telmisartan and amlodipine. Both T40/A5 and T80/A5 were more effective than either continuing therapy with A5 or up-titrating to A10.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement the results for the patient disposition of the trial.

Results for	presented in
Patient Disposition	Table 15.1.1: 3

Table 15.1.1: 3 Disposition of patients (double-blind phase) - enrolled set

	A5 N (%)	A10 N (%)	T40/A5 N (%)	T80/A5 N (%)	Total N (%)
Enrolled					1487
Not entered/randomised					389
Entered/randomised	267	276	278	277	1098
Not treated	0	0	1	0	1
Treated	267 (100.0)	276 (100.0)	277 (100.0)	277 (100.0)	1097 (100.0)
Not prematurely discontinued trial medication	255 (95.5)	252 (91.3)	273 (98.6)	266 (96.0)	1046 (95.4)
Prematurely discontinued from trial medication	12 (4.5)	24 (8.7)	4 (1.4)	11 (4.0)	51 (4.6)
Adverse event	6 (2.2)	22 (8.0)	3 (1.1)	4 (1.4)	35 (3.2)
AE study disease worsening	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
AE other disease worsening	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.2)
AE other	5 (1.9)	20 (7.2)	3 (1.1)	4 (1.4)	32 (2.9)
Lack of efficacy	0 (0.0)	0 (0.0)	1 (0.4)	2 (0.7)	3 (0.3)
Non compliant with protocol	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.1)	4 (0.4)
Lost to follow-up	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Consent withdrawn	2 (0.7)	1 (0.4)	0 (0.0)	1 (0.4)	4 (0.4)
Other	3 (1.1)	0 (0.0)	0 (0.0)	1 (0.4)	4 (0.4)