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: Twynsta		**EudraCT No.:** 2009-017336-40	
Name of active ingredient: Telmisartan and amlodipine		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 18-JUN-2014	**Trial No. / U No.:** 1235.33 / U11-2618-03	**Date of trial:** 26 MAY 2010 – 07 JULY 2011	**Date of revision :** 08 FEB 2012

Title of trial:	Prospective, open label TElmisartan/AMlodipine single pill STudy to Assess the efficacy in patients with essential hypertension who are not controlled on RAASi mono-therapy being switched TEAMSTA switch
Principal/Coordinating Investigator:	[redacted]
Trial sites:	International, multicentre study, 44 active sites in 5 countries.
Publication (reference):	Data of this study have not been published
Clinical phase:	IIIb
Objectives:	The primary objective of this study was to evaluate the blood pressure control rate after 12 weeks of treatment with telmisartan/amlodipine FDC in patients who were previously not controlled on RAAS blocking mono-therapy (ARBs, ACEi, DRI).
Methodology:	Prospective, single-arm, open-label, uncontrolled, international, multi-centre, trial.
No. of subjects:	
planned:	entered:500
actual:	enrolled: 542 entered: 502 treated: 501 analysed (for primary endpoint)
Diagnosis and main criteria for inclusion:	Male or female patients ≥18 years of age with Stage 1or 2 hypertension (defined as SBP≥140 mmHg or ≥130 mmHg in DM and renal impaired patients and/or DBP ≥90 mmHg or ≥80 mmHg in DM and renal impaired patients) at the randomisation visit
Test product:	Telmisartan plus amlodipine (FDC) tablet
dose:	T80/A5 mg
mode of admin.:	p.o.

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batch no.:	B101001204
Test product:	Telmisartan plus amlodipine (FDC) tablet
dose:	T80/A10 mg
mode of admin.:	p.o.
batch no.:	B101001219
Duration of treatment:	12 weeks
Criteria for evaluation:	See below

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Efficacy / clinical pharmacology:	Primary endpoint: The primary endpoint for this trial is the percentage of patients achieving blood pressure control (defined as SBP<140 mmHg and DBP<90 mmHg) after 12 weeks of treatment, determined by in-clinic BP seated trough cuff measurements. Key secondary endpoint: Percentage of patients achieving BP control (SBP<140 mmHg and DPB<90 mmHg) using in-clinic BP seated trough cuff measurements at weeks 4 and 8. Other secondary endpoints: Percentage of patients achieving BP control using HBPM (SBP<135 mmHg and DPB<85 mmHg) at week 12. Change from baseline in the in-clinic measured mean pulse pressure and mean blood pressure after 4, 8 and 12 weeks. Response variables after 4, 8, and 12 weeks of treatment for in-clinic measurements in patients with diabetes or renal impairment (DBP and SBP control rate, DBP and SBP response) Renal impairment is defined as a creatinine >133µmol/l (1.5mg/dl) in male patients and a creatinine >124µmol/l (1.3mg/dl) in female patients or a creatinine clearance between 30-60 ml/min. Percentage of patient in BP categories after 4, 8 and 12 weeks. (optimal, normal, high normal and high) Response variables after 4, 8, and 12 weeks of treatment for home BP seated trough cuff measurments (HBPM) (DBP and SBP control rate, DBP and SBP response) Proportion of patients requiring up titration to T80/A10 to achieve BP control.
Safety:	Adverse events (AE), changes from baseline in pulse rate, incidence of peripheral oedema.

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Statistical methods:	Descriptive statistics, including number of patients, mean, standard deviation (SD), minimum, and maximum for continuous variables were calculated for all primary and secondary endpoints. Categorical variables were summarized using frequencies and percentages.

SUMMARY – CONCLUSIONS:

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Efficacy / clinical pharmacology results:

This 12-week trial was designed to evaluate the effects on blood pressure of the fix dose combination of T/A in patients not controlled on monotherapy with RAAS inhibition. Out of the 494 patients (FAS), 262 patients (53.0%) received T80/A5 while 232 patients (47.0%) were titrated to T80/A10 after 4 or 8 weeks. The titrated patients presented with modestly higher baseline blood pressure (SBP 153.4 mmHg vs 149.6 mmHg and DBP 92.2 mmHg vs 91.5 mmHg) and longer duration of hypertension (8.1 years vs 5.6 years) at baseline. Otherwise these two populations (titrated and non-titrated patients) as well as the five predefined sub-groups based on previous RASi treatment presented with comparable demographics and baseline characteristics.

The primary endpoint was the percentage of patients achieving blood pressure control (defined as SBP<140 mmHg and DBP<90 mmHg) after 12 weeks of treatment, determined by in-clinic seated trough cuff measurements. BP control rate at 12 weeks was 67.6% (95% CI 63.3−71.7). BP control rate at 12 weeks was 80.9% in patients remaining on T80/A5 (212 out of 262 patients) and 52.6% in patients titrated to T80/A10 (122 out of 232 patients).

The percentage of patients with BP control at 4 weeks was 53.0% (95% CI 48.5−57.5) and at 8 weeks 66.8% (95% CI 62.5−70.9), and remained stable at week 12. In the 262 patients who were not uptitrated BP control at 4 and 8 weeks were 80.2% and 87.0%, respectively. In the 232 patients who were uptitrated to T80/A10 FDC, the BP control was at 4 and 8 weeks 22.4% and 44.0% respectively.

The percentage of patients being controlled at 12 weeks with home blood pressure measurements (HBPM) using the guidelines, cut-off values of SBP< 135 mmHg and DBP < 85 mmHg were 47.6%, 43.8% (95% CI 38.9−48.7) and 42.1% (95% CI 37.2−47.0) (day, morning and evening), respectively. Using the standard in-clinic cut-off values of SBP<140 mmHg and DBP< 90 mmHg the 12 week control rate s were 68.2%, 62.8% and 60.4%. Response rates for total BP, SBP and DBP for both in-clinic BP and HBPM were higher then the control rates and in line with earlier studies.

Of 214 patients with BP measurements uptitrating resulted in SBP/DBP decrease from -7.4/-4.1 mmHg on T80/A5 to -15.6/-9.4 mmHg on T80/A10.

At baseline, 69% of patients had grade 1 HTN and 26.5% grade 2 or 3 HTN. After 12 weeks, 27.1% of patients had grade 1 HTN and 4.3% had grade 2 or 3 HTN. All treatments were effective compared to baseline therapy.

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Safety results:

Overall, T80/A5 FDC and T80/A10 FDC for 12 weeks was well tolerated. The safety and tolerability data obtained were consistent with the known safety and tolerability profiles of telmisartan and amlodipine.

During the treatment period, similar percentages of patients in T80/A5 FDC and T80/A10 FDC groups reported AEs (24.6% in the T80/A5 FDC group and 31.5% in the T80/A10 FDC group). Most AEs were of mild intensity. The most frequently reported AE was peripheral edema for both dosages. (5.2% in T80/A5 FDC group and 17.2% in T80/A10 FDC group). Two other more frequently reported AEs were dizziness and headache, with an overall incidence of 2.6% and 2.8%, respectively.

During the treatment period AEs that are typically associated with a decrease in blood pressure occurred infrequently. The frequency of dizziness was higher in the T80/A5 FDC group than in the T80/A10 FDC group (2.2% v. 0.9%, respectively). Hypotension and orthostatic hypotension were reported each as an AE by two subjects in total (0.4%), one patient receiving T80/A5 FDC and one patient receiving T80/A10 FDC with clinically meaningful orthostatic hypotension in the latter.

No deaths occurred during the treatment period. Three SAE were reported in this study, two during the treatment period (on-treatment SAE) and 1 in the post-treatment period (post-treatment SAE).: The on-treatment SAEs were duodenal ulcer reported in the T80/A5 FDC group and trauma with multiple fractures reported in the T80/A10 FDC group. Both were reported as SAEs due to hospitalization.. The post-treatment SAE was occurred in a patient who experienced pneumonia with sepsis requiring hospitalization. All SAEs were considered by the investigator not to be related to the study medication.

During the treatment period, AEs leading to discontinuation of study medication were infrequent and occurred in 18 patients (3.6%) in the overall trial. Main reasons for discontinuation were the occurrence of AEs, non-compliance to the protocol, or refusing to take the study medication.

Drug-related adverse events were experienced by 79 patients (15.8%): 42 patients (8.4%) during treatment with T80/A5 and 40 patients (17.2%) during treatment with T80/A10.

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Conclusions: Twelve weeks of treatment with the fixed-dose combination of telmisartan plus amlodipine provided blood pressure control in approximately 2/3 of patients previously not controlled on RAASi monotherapy. The effect was consistent regardless of previous treatment. Patients needing uptitration from T80/A5 to T80/A10 were patients with a longer duration of hypertension and modestly higher baseline blood pressure. T/A FDC was safe and well tolerated and consistent with previous observations.

Trial Synopsis - Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement disposition results and results for the 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: 2
Change from baseline in in−clinic measured mean BP over time	Table 15.2.2.2: 1
DBP control rates using in−clinic BP measurements over time	Table 15.2.2.3: 1
SBP control rates using in−clinic BP measurements over time	Table 15.2.2.3: 3
DBP response rates using in−clinic BP measurements over time	Table 15.2.2.4: 1
SBP response rates using in−clinic BP measurements over time	Table 15.2.2.4: 2
Patients in BP categories over time	Table 15.2.2.5: 1
DBP control rates for home BP measurements over time	Table 15.2.2.6: 1
SBP control rates for home BP measurements over time	Table 15.2.2.6: 2
DBP response rates for home BP measurements over time	Table 15.2.2.6: 3
SBP response rates for home BP measurements over time	Table 15.2.2.6: 4

Table 15.1.1: 2 Disposition of patients by previous antihypertensive therapy and overall - TS

	Previous RAASi therapy					
	Telmisartan N (%)	Valsartan N (%)	Olmesartan N (%)	ACE inhibitors N (%)	Other ARBs and/or DRIs N (%)	Overall N (%)
Entered and treated	82 (100.0)	98 (100.0)	39 (100.0)	147 (100.0)	135 (100.0)	501 (100.0)
Not prematurely discontinued	77 (93.9)	90 (91.8)	34 (87.2)	130 (88.4)	118 (87.4)	449 (89.6)
Prematurely discontinued	5 (6.1)	8 (8.2)	5 (12.8)	17 (11.6)	17 (12.6)	52 (10.4)
Adverse events	2 (2.4)	4 (4.1)	2 (5.1)	5 (3.4)	5 (3.7)	18 (3.6)
Worsening of disease under study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Worsening of other pre-existing disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	2 (2.4)	4 (4.1)	2 (5.1)	5 (3.4)	5 (3.7)	18 (3.6)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	2 (0.4)
Administrative	2 (2.4)	3 (3.1)	1 (2.6)	10 (6.8)	10 (7.4)	26 (5.2)
Non compliant with protocol	0 (0.0)	1 (1.0)	1 (2.6)	3 (2.0)	7 (5.2)	12 (2.4)
Lost to follow-up	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	3 (0.6)
Refused to continue taking trial medication	0 (0.0)	2 (2.0)	0 (0.0)	7 (4.8)	2 (1.5)	11 (2.2)
Other	1 (1.2)	1 (1.0)	2 (5.1)	1 (0.7)	1 (0.7)	6 (1.2)

Table 15.2.2.2: 1 Change from baseline in in-clinic measured mean blood pressure by visit - FAS

	Baseline	Week 4	Week 8	Week 12
Number of patients, N	494	485	487	487
Systolic blood pressure [mmHg]				
Mean (SD)	151.41 (10.22)	137.82 (12.10)	135.09 (11.70)	134.54 (11.64)
Min Max	123.0 188.7	100.7 181.0	89.3 179.0	89.3 173.3
Change from baseline [mmHg]				
Mean (SD)		-13.58 (11.95)	-16.37 (12.34)	-16.92 (12.24)
Diastolic blood pressure [mmHg]				
Mean (SD)	91.83 (8.76)	83.55 (9.09)	81.46 (8.57)	81.36 (8.65)
Min Max	55.0 116.0	47.7 111.7	57.3 112.3	51.7 112.7
Change from baseline [mmHg]				
Mean (SD)		-8.24 (8.77)	-10.33 (8.88)	-10.43 (8.83)

Table 15.2.2.3: 1 DBP control rates using in-clinic BP measurements by visit - FAS

	Total
Number of patients, N	494
DBP control rates	
Baseline, N (%)	117 (23.7)
95% - CI	20.0 - 27.7
Week 4, N(%)	313 (63.4)
95% - CI	58.9 - 67.6
Week 8, N(%)	368 (74.5)
95% - CI	70.4 - 78.3
Week 12, N(%)	373 (75.5)
95% - CI	71.5 - 79.2

DBP control: DBP <90 mmHg or <80 mmHg in patients with diabetes or renal impairment

Table 15.2.2.3: 3 SBP control rates using in-clinic BP measurements by visit - FAS

	Total
Number of patients, N	494
SBP control rates	
Baseline, N (%)	25 (5.1)
95% - CI	3.3 - 7.4
Week 4, N(%)	247 (50.0)
95% - CI	45.5 - 54.5
Week 8, N(%)	305 (61.7)
95% - CI	57.3 - 66.0
Week 12, N(%)	311 (63.0)
95% - CI	58.5 - 67.2

SBP control: SBP <140 mmHg or <130 mmHg in patients with diabetes or renal impairment

Table 15.2.2.4: 1 DBP response rates using in-clinic BP measurements by visit - FAS

	Total
Number of patients, N	494
DBP response rates	
Baseline, N (%)	117 (23.7)
95% - CI	20.0 - 27.7
Week 4, N(%)	329 (66.6)
95% - CI	62.2 - 70.7
Week 8, N(%)	393 (79.6)
95% - CI	75.7 - 83.0
Week 12, N(%)	399 (80.8)
95% - CI	77.0 - 84.2

DBP response: DBP <90 mmHg or <80 mmHg in patients with diabetes or renal impairment or a reduction from baseline >=10 mmHg

Table 15.2.2.4: 2 SBP response rates using in-clinic BP measurements by visit - FAS

	Total
Number of patients, N	494
SBP response rates	
Baseline, N (%)	25 (5.1)
95% - CI	3.3 - 7.4
Week 4, N(%)	337 (68.2)
95% - CI	63.9 - 72.3
Week 8, N(%)	388 (78.5)
95% - CI	74.7 - 82.1
Week 12, N(%)	393 (79.6)
95% - CI	75.7 - 83.0

SBP response: SBP <140 mmHg or <130 mmHg in patients with diabetes or renal impairment or a reduction from baseline >=15 mmHg

Table 15.2.2.5: 1 Frequency of patients in blood pressure categories by visit - FAS

	Baseline N (%)	Week 4 N (%)	Week 8 N (%)	Week 12 N (%)
Number of patients, N	494 (100.0)	482 (100.0)	487 (100.0)	487 (100.0)
BP optimal	0 (0.0)	20 (4.1)	27 (5.5)	22 (4.5)
BP normal	1 (0.2)	95 (19.7)	108 (22.2)	139 (28.5)
BP high normal	21 (4.3)	147 (30.5)	195 (40.0)	173 (35.5)
Grade 1 hypertension	341 (69.0)	188 (39.0)	135 (27.7)	132 (27.1)
Grade 2 hypertension	127 (25.7)	30 (6.2)	21 (4.3)	20 (4.1)
Grade 3 hypertension	4 (0.8)	2 (0.4)	1 (0.2)	1 (0.2)

BP optimal: SBP <120 mmHg and DBP <80 mmHg
BP normal: SBP <130 mmHg and DBP <85 mmHg but not optimal
BP high-normal: SBP <140 mmHg and DBP <90 mmHg but not normal
Grade 1 hypertension: SBP <160 mmHg and DBP <100 mmHg but not high-normal
Grade 2 hypertension: SBP <180 mmHg and DBP <110 mmHg but not grade 1
Grade 3 hypertension: SBP >= 180 mmHg or DBP >=110 mmHg

Table 15.2.2.6: 1 DBP control rates for HBPM measurements by visit - FAS

	Total
Number of patients, N	409
DBP control rates Morning	
Week 4, N(%)	256 (62.6)
95% - CI	57.7 - 67.3
Week 8, N(%)	242 (59.2)
95% - CI	54.2 - 64.0
Week 12, N(%)	252 (61.6)
95% - CI	56.7 - 66.4
DBP control rates Evening	
Week 4, N(%)	272 (66.5)
95% - CI	61.7 - 71.1
Week 8, N(%)	247 (60.4)
95% - CI	55.5 - 65.2
Week 12, N(%)	263 (64.3)
95% - CI	59.4 - 69.0

DBP control: DBP <85 mmHg

Table 15.2.2.6: 2 SBP control rates for HBPM measurements by visit - FAS

	Total
Number of patients, N	409
SBP control rates Morning	
Week 4, N(%)	204 (49.9)
95% - CI	44.9 - 54.8
Week 8, N(%)	198 (48.4)
95% - CI	43.5 - 53.4
Week 12, N(%)	206 (50.4)
95% - CI	45.4 - 55.3
SBP control rates Evening	
Week 4, N(%)	204 (49.9)
95% - CI	44.9 - 54.8
Week 8, N(%)	183 (44.7)
95% - CI	39.9 - 49.7
Week 12, N(%)	190 (46.5)
95% - CI	41.5 - 51.4

SBP control: SBP <135 mmHg

Table 15.2.2.6: 3 DBP response rates for HBPM measurements by visit - FAS

	Total
Number of patients, N	354
DBP response rates Morning	
Week 4, N(%)	256 (72.3)
95% - CI	67.3 - 76.9
Week 8, N(%)	242 (68.4)
95% - CI	63.2 - 73.2
Week 12, N(%)	252 (71.2)
95% - CI	66.2 - 75.9
DBP response rates Evening	
Week 4, N(%)	272 (76.8)
95% - CI	72.1 - 81.1
Week 8, N(%)	247 (69.8)
95% - CI	64.7 - 74.5
Week 12, N(%)	263 (74.3)
95% - CI	69.4 - 78.8

DBP response: DBP <85 mmHg or a reduction from baseline >=10 mmHg

Table 15.2.2.6: 4 SBP response rates for HBPM measurements by visit - FAS

	Total
Number of patients, N	299
SBP response rates Morning	
Week 4, N(%)	204 (68.2)
95% - CI	62.6 - 73.5
Week 8, N(%)	198 (66.2)
95% - CI	60.6 - 71.6
Week 12, N(%)	206 (68.9)
95% - CI	63.3 - 74.1
SBP response rates Evening	
Week 4, N(%)	204 (68.2)
95% - CI	62.6 - 73.5
Week 8, N(%)	183 (61.2)
95% - CI	55.4 - 66.8
Week 12, N(%)	190 (63.5)
95% - CI	57.8 - 69.0

SBP response: SBP <135 mmHg or a reduction from baseline >=15 mmHg