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: Not applicable		**EudraCT No.:** 2011-000347-25	**Synopsis No.:**
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 1 of 8	
Module:		**Volume:**	
Report date: 02 Jan 2013	**Trial No. / U No.:** 1245.48 / U12-1526-01	**Date of trial:** 20 JUN 2011 – 13 JUL 2012	**Date of revision:** Not applicable

Title of trial:	A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg, 25 mg) administered orally, once daily over 12 weeks in hypertensive patients with type 2 diabetes mellitus
Coordinating Investigators:	[redacted]
Trial sites:	Multi-centre trial: 121 trial sites in 12 countries (Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Lebanon, The Netherlands, Norway, Sweden, USA)
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The objective of this trial was to investigate the efficacy and safety of empagliflozin 10 mg and 25 mg compared with placebo in patients with type 2 diabetes mellitus (T2DM) and hypertension, administered once daily for 12 weeks.
Methodology:	Randomised, double-blind, placebo-controlled, parallel-group comparison in patients with T2DM and hypertension. Randomisation was stratified by glycosylated haemoglobin (HbA_{1c}) at screening, renal function at baseline, background antihypertensive therapy, and geographical region. A 2-week open-label placebo run-in period preceded randomisation. Patients were treated for 12-weeks with empagliflozin (10 mg or 25 mg) or matching placebo tablets.

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No. of subjects:	
planned:	Entered: 816 patients, 272 in each treatment group
actual:	Enrolled: 1830 Placebo: Entered: 272 treated: 272 analysed (for primary endpoint): 271 Empagliflozin 10 mg: Entered: 276 treated: 276 analysed (for primary endpoint): 276 Empagliflozin 25 mg: Entered: 277 treated: 276 analysed (for primary endpoint): 276
Diagnosis and main criteria for inclusion:	Patients with T2DM, insufficient glycaemic control (HbA_{1c} ≥7.0 and ≤10.0%), age ≥18 years, body mass index ≤45 kg/m^2, and hypertension, with a systolic blood pressure (SBP) of 130 to 159 mmHg and a diastolic BP (DBP) of 80 to 99 mmHg.
Test product:	Empagliflozin film-coated tablet
dose:	10 or 25 mg once daily
mode of admin.:	Oral
batch no.:	003435, 003436, 004897 (10 mg); 003531B, 003532B (25 mg)

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Reference therapy:	Placebo matching empagliflozin 10 mg tablets Placebo matching empagliflozin 25 mg tablets
dose:	Not applicable
mode of admin.:	Oral, tablets
batch no.:	88367 (matching empagliflozin 10 mg) 88651, 88644 (matching empagliflozin 25 mg)
Duration of treatment:	Two-week placebo run-in; 12-week treatment period; 2-week follow-up period. Background antidiabetic and antihypertensive medication was to be taken during the entire trial duration (including placebo run-in period) at an unchanged dose.
Criteria for evaluation:	
Efficacy:	The primary endpoint was the change from baseline in HbA_{1c} after 12 weeks of treatment. The co-primary endpoint was the change from baseline in mean 24-h SBP after 12 weeks of treatment. The key secondary endpoint was the change from baseline in mean 24-h DBP after 12 weeks of treatment
Safety:	Adverse events (AEs), Clinical Event Committee-adjudicated events, and AEs of special interest (AESIs), including protocol-specified significant AEs (decreased renal function and hepatic injury), hypoglycaemic events, urinary tract infections, genital infections, and volume depletion; change from baseline in clinical laboratory assessments, vital signs, and 12-lead electrocardiogram (ECG).
Statistical methods:	Primary endpoint: Testing of superiority hypothesis versus placebo with an analysis of covariance (ANCOVA), with randomised treatment, geographical region, number of antihypertensive medications, and renal function as fixed effects, and baseline HbA_{1c} as linear covariate. Co-primary endpoint and key secondary endpoint: ANCOVA similar to primary endpoint; for the co-primary endpoint the baseline mean 24-h SBP and for the key secondary endpoint the baseline mean 24-h DBP were additionally included in the analysis. Safety: safety analysis was performed using descriptive statistics. Analyses of covariance were performed for lipid parameters.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Of the 1830 patients enrolled, 825 were entered and 824 were treated.

Overall, 95.5% of patients assigned to treatment (94.5% of patients in the placebo group, 96.0% of patients in the empagliflozin 10 mg group, and 96.0% of patients in the empagliflozin 25 mg group) completed the 12-week treatment period.

Thirty-seven patients (4.5%) prematurely discontinued trial medication (placebo: 5.5%, empagliflozin 10 mg: 4.0%, and empagliflozin 25 mg: 4.0%) with the main reason for discontinuation being the occurrence of AEs (placebo: 1.8%, empagliflozin 10 mg: 1.8%, empagliflozin 25 mg: 2.2%).

The demographic and baseline characteristics were comparable between the randomised treatment groups. Overall, 60.1% of patients were male and 93.7% were White. The mean (SD) age was 60.2 (9.0) years and the mean (SD) BMI was 32.60 (5.08) kg/m^2. Patients had most frequently been diagnosed with diabetes for >10 years (39.5%) or >5 to 10 years (32.2%).

Overall, the mean (SD) baseline HbA_{1c} was 7.90 (0.74)%, the mean (SD) baseline 24-h mean SBP (ambulatory blood pressure monitoring; ABPM) was 131.4 (12.3) mmHg, the mean (SD) baseline 24-h DBP (ABPM) was 75.0 (7.8) mmHg, the mean (SD) weight was 95.17 (18.22) kg, the mean (SD) baseline fasting plasma glucose (FPG) was 159.9 (37.1) mg/dL, the mean (SD) baseline trough sitting SBP was 142.1 (12.3) mmHg, the mean (SD) baseline trough sitting DBP was 83.9 (7.0) mmHg, 145 (17.6%) patients had a positive orthostatic BP test at baseline.

The results of the main analyses of the primary, co-primary, and key secondary endpoints are shown in Table 1 below. Both empagliflozin doses demonstrated superiority over placebo for changes in HbA_{1c}, mean 24-h SBP (ABPM), and mean 24-h DBP (ABPM). The primary analysis was performed on the full analysis set (FAS); values after the patient started rescue medication were excluded from analysis and imputed with a last observation carried forward (LOCF) procedure. The co-primary and key secondary analyses were performed on the FAS (LOCF-H), for which the values measured after a change in antihypertensive therapy or rescue therapy were set to missing before being imputed by the LOCF technique.

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Efficacy results: (continued)

Table 1 Change from baseline at Week 12 in the primary, co-primary, and key secondary endpoints – full analysis set, last observation carried forward

	Empagliflozin 10 mg	Empagliflozin 25 mg
HbA_{1c} [%]		
Adjusted mean difference to placebo (SE)	-0.62 (0.05)	-0.65 (0.05)
95% confidence interval	(-0.72, -0 52)	(-0.75, -0.55)
p-value	<0.0001	<0.0001
Mean 24-h SBP [mmHg]		
Adjusted mean difference to placebo (SE)	-3.44 (0.69)	-4.16 (0.68)
95% confidence interval	(-4.78, -2.09)	(-5.50, -2.83)
p-value	<0.0001	<0.0001
Mean 24-h DBP [mmHg]		
Adjusted mean difference to placebo (SE)	-1.36 (0.40)	-1.72 (0.40)
95% confidence interval	(-2.15, -0 56)	(-2.51, -0.93)
p-value	0.0008	<0.0001

Other endpoints: The following other efficacy endpoints supported the findings for the primary, co-primary, and key secondary endpoints regarding the positive effect of the empagliflozin treatment (both doses) compared with placebo: proportion of patients with HbA_{1c} <7% after 12 weeks of treatment, change from baseline in FPG after 12 weeks of treatment, change from baseline in daytime and night-time mean SBP and DBP after 12 weeks of treatment (ABPM), change from baseline in trough mean sitting SBP and DBP after 12 weeks of treatment, proportion of patients reaching trough mean sitting BP < 130/80 mmHg after 12 weeks of treatment, composite endpoint at Week 12 (all 3 fulfilled: reduction in HbA_{1c} by at least 0.5%, SBP (office measurement) by >3 mmHg, and body weight by >2% compared to baseline), change from baseline in awake time and sleep time mean SBP and DBP after 12 weeks of treatment (ABPM), and change from baseline in hourly mean SBP and DBP over the 24-h measurement period after 12 weeks of treatment (ABPM). The antihypertensive effect of empagliflozin was reversible according the analysis of change from baseline in trough mean sitting SBP and DBP at Week 14.

The endpoints change from baseline in body weight after 12 weeks of treatment, change from baseline in waist circumference after 12 weeks of treatment, and proportion of patients with a body weight reduction >5% after 12 weeks of treatment, yielded results in favour of the empagliflozin groups compared with the placebo group. The proportions of patients using rescue medication were low and comparable across all treatment groups.

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Safety results:

The mean (SD) exposure to randomised study medication was 84.4 (13.2) days in the placebo group, 85.4 (9.7) days in the empagliflozin 10 mg group, and 84.6 (9.9) days in the empagliflozin 25 mg group.

The frequency of patients reported with at least 1 AE on treatment was 52.6% in the placebo group, 48.9% in the empagliflozin 10 mg group, and 51.4% in the empagliflozin 25 mg group. The highest frequency of AEs was reported for the MedDRA system organ class 'infections and infestations' with similar frequencies across treatment groups (placebo: 20.6%, empagliflozin 10 mg: 20.3%, empagliflozin 25 mg: 22.8%).

Drug-related AEs (as assessed by the investigator) were reported for 7.7% of patients in the placebo group, 19.9% of patients in the empagliflozin 10 mg group, and 19.6% of patients in the empagliflozin 25 mg group. There was no specific imbalance for single preferred terms (PTs) across treatment groups.

Adverse events were mostly of mild or moderate intensity; severe AEs were reported for 1.8% of patients in the placebo group, 1.8% of patients in the empagliflozin 10 mg group, and 1.1% of patients in the empagliflozin 25 mg group.

The frequencies of patients with AEs leading to premature discontinuation of the trial medication were: 1.8% in the placebo group, 1.4% in the empagliflozin 10 mg group, and 2.2% in the empagliflozin 25 mg group

Serious AEs were reported for 7 patients (2.6%) in the placebo group, 3 patients (1.1%) in the empagliflozin 10 mg group, and 4 patients (1.4%) in the empagliflozin 25 mg group. One patient in the empagliflozin 10 mg group died in this study (sudden death).

Confirmed hypoglycaemic AEs were reported for 13 patients (4.8%) in the placebo group, 18 patients (6.5%) in the empagliflozin 10 mg group, and 17 patients (6.2%) in the empagliflozin 25 mg group. No severe hypoglycaemic events were reported.

Changes from baseline at Week 12 in creatinine and in mean estimated glomerular filtration rate (eGFR) were small and returned towards baseline levels at follow-up.

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No cases of investigator-reported decreased renal function or hepatic injury were reported. No lab constellation recorded in this study was consistent with potential Hy's law for any patient.

Urinary tract infections were reported for 10 patients (3.7%) in the placebo group, 11 patients (4.0%) in the empagliflozin 10 mg group, and 13 patients (4.7%) in the empagliflozin 25 mg group. Genital infections were reported for 1 patient (0.4%) in the placebo group, 14 patients (5.1%) in the empagliflozin 10 mg group, and 15 patients (5.4%) in the empagliflozin 25 mg group.

The proportions of patients with a positive orthostatic BP test after 12 weeks of treatment were higher in the empagliflozin groups than the placebo group; this difference was not accompanied by an increased risk for AEs related to hypotension.

Only 2 patients were reported with AEs consistent with volume depletion during the trial: 1 in the empagliflozin 10 mg group (syncope) and 1 in the placebo group (hypotension and orthostatic hypotension). No AEs for the PT 'hypotension' were reported in the empagliflozin groups.

Overall, there were no clinically meaningful changes from baseline in safety laboratory parameters (differential blood cell counts; blood or urine levels of electrolytes, enzymes, substrates, and proteins) after 12 weeks of treatment. Numerically, mean haematocrit values increased more from baseline with empagliflozin 10 mg (+ 3.6%) and empagliflozin 25 mg (+ 3.2%) compared with placebo (+ 0.4%). A greater decrease in uric acid was noted in the empagliflozin groups compared with placebo. Slight numerical increases in mean absolute change from baseline were observed for the empagliflozin 25 mg group in total cholesterol, LDL cholesterol, LDL/HDL cholesterol ratio. There were no changes in HDL cholesterol or triglycerides for either of the empagliflozin groups.

Pulse rate changes were small and comparable across groups and did not increase under empagliflozin treatment, despite the reduction in BP.

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Conclusions:	Taken together, the efficacy and safety evaluation suggests a favourable benefit-risk ratio for patients with T2DM, insufficient glycaemic control, and hypertension. The reductions in mean 24-h SBP and DBP in addition to the efficient reduction in HbA_{1c} levels and the low risk of hypoglycaemia and hypotension are potential additional benefits of empagliflozin versus currently available oral antidiabetic treatment options.

Trial Synopsis – Appendix

The appended tables on the following pages supplement the trial results presented in the Trial Synopsis. They complement 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**
Change from baseline in mean 24−hour DBP after 12 weeks of treatment	Table 15.2.3.1.1: 1
Proportion of patients with HbA_{1c} <7% after 12 weeks of treatment	Table 15.2.4.1: 1
Change from baseline in FPG after 12 weeks of treatment	Table 15.2.4.2: 2
Change from baseline in body weight after 12 weeks of treatment	Table 15.2.4.3: 1
Change from baseline in daytime mean SBP after 12 weeks of treatment	Table 15.2.4.5.1: 1
Change from baseline in daytime mean DBP after 12 weeks of treatment	Table 15.2.4.5.2: 1
Change from baseline in nighttime mean SBP after 12 weeks of treatment	Table 15.2.4.5.3: 1
Change from baseline in nighttime mean DBP after 12 weeks of treatment	Table 15.2.4.5.4: 1
Change from baseline in trough mean sitting SBP after 12 weeks of treatment	Table 15.2.4.5.7: 1
Change from baseline in trough mean sitting DBP after 12 weeks of treatment	Table 15.2.4.5.8: 1

Table 15.2.3.1.1: 1 Mean 24-hour DBP (ABPM) (mmHg) change from baseline ANCOVA results at week 12 - FAS (LOCF-H)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	271	276	276
Number of analysed patients	271	276	276
Baseline mean (SE)	75.16 (0.45)	75.13 (0.50)	74.64 (0.45)
Week 12			
Values at visit			
Mean (SE)	75.46 (0.45)	74.03 (0.48)	73.33 (0.46)
Adjusted* mean (SE)	75.30 (0.29)	73.94 (0.28)	73.58 (0.28)
Change from baseline			
Mean (SE)	0.30 (0.31)	-1.10 (0.30)	-1.32 (0.30)
Adjusted* mean (SE)	0.32 (0.29)	-1.04 (0.28)	-1.40 (0.28)
Comparison vs Placebo			
Adjusted* mean (SE)		-1.36 (0.40)	-1.72 (0.40)
95.0% confidence interval		(-2.15,-0.56)	(-2.51,-0.93)
p-value		0.0008	<0.0001

* Model for Week 12 includes baseline mean 24h DBP (p<0.0001), baseline HbA1c (p=0.3546) as linear covariate(s) and baseline eGFR (MDRD) (p=0.1179), geographical region (p=0.3975), baseline N of antihyperten. med. cat. (p=0.4422), treatment (p<0.0001) as fixed effect(s).

Table 15.2.4.1: 1 Logistic regression for HbA1c <7% at week 12- FAS (NCF) - patients with HbA1c >= 7% at baseline

	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	252	256	264
Number of analysed patients, N (%)	252 (100.0)	256 (100.0)	264 (100.0)
Number (%) satisfying HbA1c response <7.0% at week 12	18 (7.1)	79 (30.9)	79 (29.9)
95.0% Confidence interval [%]*	(4.3, 11.1)	(25.3, 36.9)	(24.5, 35.8)
Comparison vs Placebo			
Odds Ratio **		6.261	6.593
95.0% Confidence interval **		(3.506, 11.181)	(3.701, 11.747)
p-value **		<0.0001	<0.0001

* Exact 95% CI by Clopper and Pearson.
** Logistic regression includes treatment, baseline eGFR (MDRD), geographical region, baseline N of antihyperten. med. cat. and baseline HbA1c.

Table 15.2.4.2: 2 FPG (mg/dL) change from baseline ANCOVA results at week 12 - FAS (LOCF)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	271	276	276
Number of analysed patients	271	276	276
Baseline mean (SE)	160.07 (2.15)	156.96 (2.29)	162.79 (2.28)
Week 12			
Values at visit			
Mean (SE)	167.26 (2.71)	141.73 (1.86)	138.34 (1.83)
Adjusted* mean (SE)	167.09 (1.86)	143.34 (1.85)	136.89 (1.84)
Change from baseline			
Mean (SE)	7.19 (2.33)	-15.23 (2.01)	-24.45 (2.13)
Adjusted* mean (SE)	7.16 (1.86)	-16.60 (1.85)	-23.04 (1.84)
Comparison vs Placebo			
Adjusted* mean (SE)		-23.76 (2.63)	-30.20 (2.61)
95.0% confidence interval		(-28.91,-18.60)	(-35.32,-25.08)
p-value		<0.0001	<0.0001

* Model for Week 12 includes baseline fasting plasma glucose (p<0.0001), baseline HbA1c (p=0.0059) as linear covariate(s) and baseline eGFR (MDRD) (p=0.9554), geographical region (p=0.2801), baseline N of antihyperten. med. cat. (p=0.2471), treatment (p<0.0001) as fixed effect(s).

Table 15.2.4.3: 1 Body weight (kg) change from baseline ANCOVA results at week 12 - FAS (LOCF)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	271	276	276
Number of analysed patients	271	276	276
Baseline mean (SE)	95.22 (1.06)	94.71 (1.19)	95.59 (1.05)
Week 12			
Values at visit			
Mean (SE)	95.03 (1.07)	93.04 (1.17)	93.43 (1.02)
Adjusted* mean (SE)	94.99 (0.13)	93.50 (0.13)	93.01 (0.13)
Change from baseline			
Mean (SE)	-0.19 (0.09)	-1.67 (0.14)	-2.16 (0.14)
Adjusted* mean (SE)	-0.18 (0.13)	-1.68 (0.13)	-2.16 (0.13)
Comparison vs Placebo			
Adjusted* mean (SE)		-1.49 (0.18)	-1.98 (0.18)
95.0% confidence interval		(-1.85,-1.13)	(-2.33,-1.62)
p-value		<0.0001	<0.0001

* Model for Week 12 includes baseline weight (p<0.0001), baseline HbA1c (p=0.3658) as linear covariate(s) and baseline eGFR (MDRD) (p=0.4549), geographical region (p=0.7426), baseline N of antihyperten. med. cat. (p=0.7680), treatment (p<0.0001) as fixed effect(s).

Table 15.2.4.5.1: 1 Descriptive statistics for daytime mean SBP (ABPM) (mmHg) over time - FAS (LOCF-H, OC-H)

Imputation rule / Timepoint / Analysis / Statistic	Placebo	Empa 10mg	Empa 25mg
LOCF-excl.values after antihypert med.			
Week 12			
Change from baseline			
N* (%)	271 (100.0)	276 (100.0)	276 (100.0)
Mean	0.38	-3.40	-4.12
SD	8.74	9.55	9.55
Min	-36.0	-40.7	-47.5
Q1	-4.07	-9.11	-10.18
Median	0.00	-2.16	-3.36
Q3	5.34	0.93	0.00
Max	26.4	29.9	39.3
OC-excl. values after antihypert. med.			
Baseline			
Values at visit			
N* (%)	271 (100.0)	276 (100.0)	276 (100.0)
Mean	136.06	135.25	135.11
SD	11.99	13.03	12.24
Min	93.9	106.7	106.5
Q1	128.02	125.46	127.86
Median	134.90	133.69	134.15
Q3	142.68	143.34	142.66
Max	172.4	187.1	173.2

*% of patients in population. **Baseline observation carried forward.

Table 15.2.4.5.2: 1 Descriptive statistics for daytime mean DBP (ABPM) (mmHg) over time - FAS (LOCF-H, OC-H)

Imputation rule / Timepoint / Analysis / Statistic	Placebo	Empa 10mg	Empa 25mg
LOCF-excl.values after antihypert med.			
Week 12			
Change from baseline			
N* (%)	271 (100.0)	276 (100.0)	276 (100.0)
Mean	0.26	-1.28	-1.58
SD	5.36	5.41	5.35
Min	-21.9	-24.6	-19.7
Q1	-2.53	-3.77	-4.98
Median	0.00	-0.67	-0.63
Q3	3.20	1.67	1.48
Max	17.4	16.6	16.0
OC-excl. values after antihypert. med.			
Baseline			
Values at visit			
N* (%)	271 (100.0)	276 (100.0)	276 (100.0)
Mean	78.68	78.37	77.93
SD	7.73	8.40	7.93
Min	53.7	57.3	56.5
Q1	74.22	72.50	73.32
Median	78.33	78.33	77.82
Q3	83.21	84.33	83.34
Max	99.8	115.8	106.7

*% of patients in population. **Baseline observation carried forward.

Table 15.2.4.5.3: 1 Descriptive statistics for nighttime mean SBP (ABPM) (mmHg) over time - FAS (LOCF-H, OC-H)

Imputation rule / Timepoint / Analysis / Statistic	Placebo	Empa 10mg	Empa 25mg
LOCF-excl.values after antihypert med.			
Week 12			
Change from baseline			
N* (%)	271 (100.0)	276 (100.0)	276 (100.0)
Mean	0.51	-2.22	-2.47
SD	10.22	10.21	11.09
Min	-66.8	-74.0	-54.2
Q1	-3.79	-7.56	-7.47
Median	0.00	-0.67	-0.48
Q3	5.48	2.05	1.98
Max	28.7	32.8	45.4
OC-excl. values after antihypert. med.			
Baseline			
Values at visit			
N* (%)	271 (100.0)	276 (100.0)	276 (100.0)
Mean	123.09	123.52	123.30
SD	13.67	14.65	13.84
Min	79.5	89.5	87.7
Q1	113.83	113.58	113.39
Median	122.33	120.69	122.85
Q3	131.00	133.10	131.60
Max	185.0	185.9	168.9

*% of patients in population. **Baseline observation carried forward.

Table 15.2.4.5.4: 1 Descriptive statistics for nighttime mean DBP (ABPM) (mmHg) over time - FAS (LOCF-H, OC-H)

Imputation rule / Timepoint / Analysis / Statistic	Placebo	Empa 10mg	Empa 25mg
LOCF-excl.values after antihypert med.			
Week 12			
Change from baseline			
N* (%)	271 (100.0)	276 (100.0)	276 (100.0)
Mean	0.36	-0.80	-0.75
SD	6.80	6.21	6.32
Min	-41.2	-40.6	-21.4
Q1	-2.83	-4.58	-3.60
Median	0.00	0.00	-0.10
Q3	3.58	2.71	1.84
Max	25.2	16.0	22.4
OC-excl. values after antihypert. med.			
Baseline			
Values at visit			
N* (%)	271 (100.0)	276 (100.0)	276 (100.0)
Mean	68.17	68.66	68.04
SD	8.78	9.55	8.25
Min	45.2	47.4	46.3
Q1	62.35	62.08	62.24
Median	68.08	67.52	67.25
Q3	72.52	74.35	73.72
Max	113.9	102.0	92.5

*% of patients in population. **Baseline observation carried forward.

Table 15.2.4.5.7: 1 Trough mean sitting SBP [mmHg] change from baseline ANCOVA results at week 12 - FAS (LOCF-H)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	271	276	276
Number of analysed patients	271	276	276
Baseline mean (SE)	141.98 (0.75)	142.32 (0.73)	141.87 (0.76)
Week 12			
Values at visit			
Mean (SE)	141.41 (0.91)	137.59 (0.81)	136.42 (0.86)
Adjusted* mean (SE)	141.38 (0.70)	137.46 (0.69)	136.58 (0.69)
Change from baseline			
Mean (SE)	-0.57 (0.72)	-4.73 (0.76)	-5.45 (0.75)
Adjusted* mean (SE)	-0.67 (0.70)	-4.60 (0.69)	-5.47 (0.69)
Comparison vs Placebo			
Adjusted* mean (SE)		-3.92 (0.99)	-4.80 (0.98)
95.0% confidence interval		(-5.86,-1.98)	(-6.73,-2.87)
p-value		<0.0001	<0.0001

* Model for Week 12 includes baseline sys. blood pres. seat. (p<0.0001), baseline HbA1c (p=0.4533) as linear covariate(s) and baseline eGFR (MDRD) (p=0.1453), geographical region (p<0.0001), baseline N of antihyperten. med. cat. (p=0.6038), treatment (p<0.0001) as fixed effect(s).

Table 15.2.4.5.8: 1 Trough mean sitting DBP [mmHg] change from baseline ANCOVA results at week 12 - FAS (LOCF-H)

Visit Description Statistic	Placebo	Empa 10mg	Empa 25mg
Number of patients in analysis set	271	276	276
Number of analysed patients	271	276	276
Baseline mean (SE)	83.67 (0.43)	84.13 (0.44)	83.82 (0.41)
Week 12			
Values at visit			
Mean (SE)	82.65 (0.47)	80.96 (0.48)	80.80 (0.48)
Adjusted* mean (SE)	82.74 (0.39)	80.82 (0.39)	80.85 (0.39)
Change from baseline			
Mean (SE)	-1.02 (0.40)	-3.18 (0.43)	-3.01 (0.42)
Adjusted* mean (SE)	-1.13 (0.39)	-3.06 (0.39)	-3.02 (0.39)
Comparison vs Placebo			
Adjusted* mean (SE)		-1.93 (0.55)	-1.89 (0.55)
95.0% confidence interval		(-3.01,-0.84)	(-2.97,-0.82)
p-value		0.0005	0.0006

* Model for Week 12 includes baseline dia. blood pres. seat. (p<0.0001), baseline HbA1c (p=0.2923) as linear covariate(s) and baseline eGFR (MDRD) (p=0.5704), geographical region (p=0.0026), baseline N of antihyperten. med. cat. (p=0.3333), treatment (p=0.0004) as fixed effect(s).