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.

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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..

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.:** 2010-022718-17	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 1 of 30	**Synopsis No.:**
Module:		**Volume:**	
Disclosure Synopsis date*: 03 JUN 2014	**Trial No. / Doc No.:** 1245.31 / c02645257	**Dates of trial:** 22 FEB 2011 – 23 MAY 2013	**Date of revision:** Not applicable

Title of trial:	A phase III double-blind, extension, placebo-controlled parallel group safety and efficacy trial of BI 10773 (10 and 25 mg once daily) and sitagliptin (100 mg once daily) given for minimum 76 weeks (including 24 weeks of preceding trial) as monotherapy or with different background therapies in patients with type 2 diabetes mellitus previously completing trial 1245.19, 1245.20 or 1245.23
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre trial: 243 trial sites in 20 countries (China, India, Japan, Korea, Philippines, Taiwan, Thailand, Belgium, France, Germany, Greece, Ireland, Slovakia, Slovenia, Switzerland, Turkey, Ukraine, Mexico, Canada, United States)
Publication (reference):	Ferrannini E, Berk A, Hantel S, Pinnetti S, Hach T, Woerle HJ, Broedl UC. Long-term safety and efficacy of empagliflozin, sitagliptin, and metformin: an active-controlled, parallel-group, randomized, 78-week open-label extension study in patients with type 2 diabetes. Published Ahead of Print online: November 1, 2013. doi: 10.2337/dc13-0663. Diabetes Care 2013. 36:4015-4021 [P13-14349]
Clinical phase:	III
Objectives:	The main objective of this extension study was to investigate the long-term safety and tolerability and the long-term efficacy of BI 10773 (empagliflozin; 10 or 25 mg once daily) compared with • sitagliptin (100 mg once daily) or placebo as monotherapy (preceding trial 1245.20) • placebo on a background of pioglitazone (preceding trial 1245.19) • placebo on a background of metformin alone (preceding trial 1245.23 Met) • placebo on a background of metformin with sulfonylurea (preceding trial 1245.23 Met+SU) in patients with type 2 diabetes mellitus.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

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Methodology:	This extension study consists of 3 studies under one study number. The studies varied with regard to background therapy (drug-naive patients and patients on 3 different background therapies, i.e. pioglitazone, metformin only, or metformin plus sulfonylurea). Each study was designed as a randomised, double-blind, active or placebo-controlled, parallel group comparison. Patients continued on the treatment to which they had been randomised in the preceding trial in double-blind fashion; no re-randomisation was performed in the extension trial. All analyses were performed separately for each of the 4 studies. All data of the respective preceding trial were combined with the data of the extension trial, and the final analysis was performed after the last patient had completed 52 weeks of treatment in the extension trial. Patients from the preceding trials were included in the analyses irrespective of participation in the extension; no separate analyses were done for the extension period alone. An interim analysis of the trial data has been performed based on interim database lock on 29 May 2012. The respective results are presented in a separate report. Database lock for the final analysis (28 June 2013) occurred after the last patient had been treated for 52 weeks in the extension.
No. of subjects	
planned:	Screening, randomisation and start of treatment occurred in the preceding trials (1245.19, 1245.20, 1245. 23). It was expected to have a total of 1920 patients rolling over from the preceding trials into the extension trial 1245.31. In each treatment group (empagliflozin 10 mg, empagliflozin 25 mg, or placebo), 150 patients from the preceding trial 1245.20, 112 patients from the preceding trial 1245.19, and 164 patients from the preceding trial 1245.23 were expected to roll over. Also, 150 patients receiving sitagliptin were expected to roll over from the preceding trial 1245.20.
actual:	Numbers of patients who entered the preceding trials, who were treated, who entered the extension trial, and who completed 76 weeks of treatment are displayed in Table 1. Note that screening, randomisation, and start of treatment occurred in the preceding trial.

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actual (continued):

Also, note that a total of 1870 patients were included in the extension trial (i.e., having sign an inform consent). However, 13 patients from site [redacted] were excluded from Randomised Set and Treated Set because of fraud, leaving a total of 1857 patients being included in the Treated Set.

All patients who entered the preceding trials and received at least one dose of the study medications were included in the full analysis set (FAS) (for secondary endpoints), with the exception of 1 patient on pioglitazone, 1 patient on metformin, and 3 patients in metformin + sulfonylurea background.

The patients in the FAS who completed the required minimum treatment duration of 526 days (approximately 76 weeks) and did not prematurely discontinue the trial were included in the FAS-completers.

Table 1 Patients entering the preceding trials, treated, who entered the extension trial, and who completed 76 weeks of treatment

		Placebo	Empa 10 mg	Empa 25 mg	Sita 100 mg	Total
Drug-naive (1245.20)	preceding trial	228	224	224	223	899
	treated	229	224	223	223	899
	extension	136	165	159	155	615
	FAS-completers	114	148	142	136	540
Pioglitazone (1245.19)	preceding trial	166	165	168	n.a.	499
	treated	165	165	168	n.a.	498
	extension	93	106	106	n.a.	305
	FAS-completers	76	93	96	n.a.	265
Metformin (1245.23)	preceding trial	207	217	214	n.a.	638
	treated	206	217	214	n.a.	637
	extension	138	173	152	n.a.	463
	FAS-completers	120	161	136	n.a.	417
Metformin/SU (1245.23)	preceding trial	225	226	218	n.a.	669
	treated	225	224	217	n.a.	666
	extension	145	164	165	n.a.	474
	FAS-completers	127	153	152	n.a.	432

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Diagnosis and main criteria for inclusion:	Patients with type 2 diabetes mellitus who have successfully completed the preceding blinded studies 1245.19, 1245.20, or 1245.23 (Met and Met+SU groups).
Test product:	Empagliflozin tablets 10 mg; empagliflozin tablets 25 mg
dose:	10 or 25 mg once daily
mode of admin.:	Oral
batch no.:	Empagliflozin 10 mg: 003437A, 004897, 007105 Empagliflozin 25 mg: 003533, 007768, 007769
Reference therapy:	Placebo tablets matching empagliflozin 10 mg Placebo tablets matching empagliflozin 25 mg Placebo tablets matching sitagliptin 100 mg
dose:	Not applicable
mode of admin.:	Oral
batch no.:	Matching empagliflozin 10 mg: 88624 (corresponding to 88367), 88494, 93416 Matching empagliflozin 25 mg: 88430 (corresponding to 88627), 88655, 93485 Matching sitagliptin 100 mg: B101003629, B101003628, B111002030
Reference therapy:	Sitagliptin tablets 100 mg
dose:	100 mg once daily
mode of admin.:	Oral
batch no.:	V6588 (B091004442), W2221 (B101003629), Y0310
Duration of treatment:	In addition to the 24 weeks of treatment in the preceding trial, patients were to be treated for at least 52 weeks. Patients were to remain in the trial until the last patient had been treated for a total of 76 weeks. After treatment discontinuation or completion, patients were to be followed-up for safety reason during a 4-week follow-up period. The maximum treatment duration in the extension (dependent on recruitment time) was estimated to be 130 weeks.
Criteria for evaluation (final report):	

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Efficacy:

No primary efficacy endpoint was defined in the trial protocol (the primary efficacy endpoint was analysed at week 24 of the preceding trials). Secondary endpoints of efficacy were the change from baseline in HbA_{1c}, body weight, waist circumference, fasting plasma glucose (FPG), and systolic and diastolic blood pressure (SBP and DBP) after a total treatment duration of 52 and 76 weeks (preceding trial + extension). For baseline, the baseline values from the preceding trial were used, i.e. the last evaluation prior to the first intake of any study medication in the preceding trial.

Strictly for the purpose of disclosure of the trial results on clinicaltrials.gov, a primary endpoint had to be formally selected after final database lock. The change from baseline in HbA_{1c} at Week 52 and 76 was selected as primary endpoint for disclosure, since this was the primary endpoint analysed at Week 24 of the preceding trials. However, in the remainder of this report, change in HbA_{1c} is described as a secondary endpoint as originally planned and no changes to the pre-specified analyses were made.

Further efficacy endpoints included (assessed as incidences at Week 52 and 76, except for the change over time):

- Change over time for secondary endpoint parameters
- HbA_{1c} <7.0% (absolute response)
- Use of rescue medication

Change from baseline at Week 52 and 76 and at last on-treatment value were considered in the following parameters for patients rolling over from trials 1245.20 and 1245.23 (Met and Met+SU groups): C-peptide, fasting plasma insulin, proinsulin/insulin ratio, insulin/C-peptide ratio, insulin/glucose ratio, homeostasis model assessment for insulin resistance (HOMA-IR) index, homeostasis model assessment for insulin secretion (HOMA-IS) index, disposition index.

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Safety:	Safety was the main objective of this extension trial. Adverse events (AEs), Clinical Event Committee-adjudicated events, and adverse events of special interest (AESIs) including protocol-specified significant AEs (decreased renal function and hepatic injury), hypoglycaemic events, urinary tract infection, genital infection, and volume depletion; change from baseline in clinical laboratory assessments, eGFR, albumin/creatinine ratio, and vital signs. Safety was assessed on safety data collected up to the maximum treatment duration of 130 weeks.
Statistical methods	No confirmatory statistical analysis was performed, as this study was considered an extension of the preceding trials 1245.19, 1245.20, and 1245.23 (Met and Met+SU groups); therefore no primary efficacy endpoint in a statistical sense was defined for this trial. All statistical analyses were performed separately for each of the 4 studies (i.e. drug-naive patients and the 3 antidiabetic background therapies); no pooled analysis across studies was carried out in this clinical trial report. For the final analysis presented here, the data of the respective preceding trial were combined with those obtained in the extension trial, and the final analysis was performed after the last patient had completed 52 weeks of treatment in the extension trial (database lock on 28 June 2013). All patients participating in the preceding trial were included in this analysis and no separate analysis of the extension trial was performed. For secondary efficacy endpoints, the change from baseline at Week 76 was assessed using an analysis of covariance model (ANCOVA); patients were assigned to treatment groups as randomised. The main efficacy analyses were based on the full analysis set (FAS), which contained all randomised patients who received at least 1 dose of study drug and had a baseline HbA_{1c} assessment, irrespective of participation in the extension trial. Missing values due to a treatment duration below 76 weeks and values after intake of rescue medication were replaced by the last observed measurement on treatment (last observation carried forward, LOCF). A sensitivity analysis was performed for patients who completed 76 weeks of treatment (FAS-completers-76).

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Statistical methods (continued):

The secondary endpoints were further analysed using a restricted maximum likelihood-based mixed model repeated measures (MMRM) applied to the FAS based on observed cases (OC; data that were observed while patients were on treatment, i.e., excluding the missing data). For categorical endpoints and use of rescue therapy, treatments were compared using a logistic regression model. Time to first rescue therapy was analysed by Kaplan-Meier estimates and treatment groups were compared using a log-rank test. Endpoints based on biomarkers were evaluated using descriptive statistics and ANCOVA modelling.

Safety analyses were performed on the treated set with treatment assignment based on the first treatment received in the preceding trial. Analyses were performed using descriptive statistics. Time-to-event analyses were performed for adjudicated events, hypoglycaemic events, and for certain AESIs.

SUMMARY - CONCLUSIONS:

Efficacy results - drug naive:

Drug-naive patients (preceding trial 1245.20)

The efficacy and safety analyses were based on all treated patients from the preceding trial, and based on the combined data of the preceding trial and the extension trial (up to final database lock). The extension trial was not separately analysed.

Disposition, demographics, baseline characteristics, and compliance

Of the 899 treated patients, most were treated in Asia (61.4%), followed by North America (23.7%) and Europe (14.9%). A total of 615 patients rolled over into the extension trial.

Over the entire period of the trial, discontinuation from treatment was more common for placebo (50.9%) than for empagliflozin 10 mg (36.2%), empagliflozin 25 mg (39.3%), and sitagliptin (42.2%); it occurred most frequently due to patients not entering the extension trial (20.9%).

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Efficacy results - drug-naive (continued):

The majority of patients were male (61.3%). Most were Asian (64.1%) or White (33.6%), with a mean age of 55.0 years (SD 11.0 years). Mean baseline HbA_{1c} was 7.88% (SD 0.82%) and the mean weight was 78.42 kg (SD 19.22 kg). A total of 38.0% of the patients were blood pressure controlled at baseline (<130/80 mmHg), and hypertension (50.7%) was most common with regard to medical history. There were no clinically meaningful differences in baseline characteristics between patients who continued in the extension and patients who did not continue in the extension.

Treatment compliance was high and balanced across treatments, with 95.2% of the patients within the 80 to 120% range.

Secondary endpoints and further endpoints

Both empagliflozin groups showed a significant decrease relative to placebo in mean HbA_{1c}, FPG, body weight, waist circumference, and SBP at Week 76, based on exploratory treatment comparisons using an ANCOVA model applied to the FAS (LOCF). Both empagliflozin groups also showed a significant decrease in mean values for all secondary endpoint parameters relative to sitagliptin, except for HbA_{1c} which decreased significantly relative to sitagliptin in the 25 mg group and numerically in the 10 mg group. For an overview; see Table 2 below.

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Efficacy results - drug-naive (continued):

Table 2 Treatment comparisons for the adjusted mean change at Week 76 - FAS (LOCF)

		Difference to placebo		Difference to sitagliptin	
Parameter	Empa dose	Adjusted mean change (SE)	95% CI	Adjusted mean change (SE)	95% CI
HbA_{1c} [%]	10 mg	−0.78 (0.08)	(−0.94,−0.63)	−0.12 (0.08)	(−0.28, 0.04)
	25 mg	−0.89 (0.08)	(−1.04,−0.73)	−0.22 (0.08)	(−0.38,−0.07)
Body weight [kg]	10 mg	−1.81 (0.28)	(−2.35,−1.26)	−2.34 (0.28)	(−2.89,−1.80)
	25 mg	−2.02 (0.28)	(−2.56,−1.48)	−2.56 (0.28)	(−3.10,−2.01)
Waist circumf. [cm]	10 mg	−1.6 (0.5)	(−2.7,−0.6)	−2.0 (0.6)	(−3.1,−0.9)
	25 mg	−1.7 (0.5)	(−2.8,−0.6)	−2.1 (0.6)	(−3.2,−1.0)
FPG [mg/dL]	10 mg	−31.7 (2.9)	(−37.4,−25.9)	−15.4 (3.0)	(−21.2, −9.6)
	25 mg	−34.9 (2.9)	(−40.7,−29.1)	−18.7 (3.0)	(−24.5,−12.8)
SBP [mmHg]	10 mg	−3.4 (1.1)	(−5.5,−1.2)	−3.7 (1.1)	(−5.9,−1.6)
	25 mg	−3.4 (1.1)	(−5.6,−1.2)	−3.8 (1.1)	(−6.0,−1.6)
DBP [mmHg]	10 mg	−1.0 (0.7)	(−2.3, 0.4)	−1.5 (0.7)	(−2.8,−0.2)
	25 mg	−1.0 (0.7)	(−2.4, 0.3)	−1.6 (0.7)	(−2.9,−0.2)

Adjusted values are based on ANCOVA with last observation carried forward; data after the initiation of rescue medication were excluded.

At Week 52, the adjusted mean change in HbA_{1c} relative to placebo was -0.79% (95% CI: -0.94, -0.64) for the empagliflozin 10 mg group and -0.91% (95% CI: -1.06, -0.76) for the empagliflozin 25 mg group. The difference versus sitagliptin was -0.12% (95% CI: -0.27, 0.03) for empagliflozin 10 mg and -0.24% (95% CI: -0.39, -0.09) for empagliflozin 25 mg.

A total of 39.4% of the patients discontinued the trial, which resulted in a large number of missing data. Therefore the analyses of the FAS based on the LOCF approach must be interpreted in the context of the totality of data including sensitivity analyses. The results on the FAS-completers (LOCF or OC approach) were similar to those on the FAS (LOCF); some deviations from the FAS results were observed, but no general trend emerged with regard to the treatment effect of the empagliflozin doses.

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Efficacy results - drug-naive (continued):	The analysis of secondary endpoint parameters over time showed a reduction of the adjusted mean values for up to 24 weeks after baseline that was generally sustained until Week 76, as based on an MMRM model applied to the FAS (OC). Mean SBP values fluctuated after Week 24 for empagliflozin 10 mg but were consistently reduced compared with placebo. ANCOVA data of mean changes over time based on the FAS (LOCF) or FAS-completers (LOCF or OC approach) were consistent with the MMRM data for all secondary endpoint parameters. Percentage of treatment responders for both empagliflozin groups was numerically higher than placebo and sitagliptin with regard to patients achieving HbA_{1c} less than 7.0%. Use of rescue medication was less frequent in the empagliflozin groups than in the placebo and sitagliptin groups.
Efficacy results - pioglitazone:	*Pioglitazone background medication (preceding trial 1245.19)* The efficacy and safety analyses were based on all treated patients from the preceding trial, and based on the combined data of the preceding trial and the extension trial (up to final database lock). The extension trial was not separately analysed. <u>Disposition, demographics, baseline characteristics, and compliance</u> Of the 498 treated patients, most were treated in Asia (54.4%), followed by North America (28.3%) and Europe (17.3%). Over the entire period of the trial, discontinuation from treatment was more common for placebo (54.5%) than for empagliflozin 10 mg (44.8%) and empagliflozin 25 mg (45.2%); it occurred most frequently due to patients not entering the extension trial (30.5%). A total of 305 patients rolled over into the extension trial. There were similar numbers of male (48.4%) and female (51.6%) patients. Most patients were Asian (57.8%) or White (39.6%), with a mean age of 54.5 years (SD 9.8 years). The mean HbA_{1c} value at baseline was 8.09% (SD 0.88%) and the mean weight was 78.34 kg (SD 19.70 kg). A total of 44.4% of the patients were blood pressure controlled at baseline (<130/80 mmHg), and hypertension (58.2%) was most common with regard to medical history.

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Efficacy results - pioglitazone (continued):

There were no clinically meaningful differences in baseline characteristics between patients who continued in the extension and patients who did not continue in the extension.Treatment compliance was high and balanced across treatments, with 95.2% of the patients within the 80 to 120% range.

Secondary endpoints and further endpoints

Both empagliflozin groups showed a significant decrease relative to placebo in mean HbA_{1c}, body weight, and FPG, at Week 76, based on exploratory treatment comparisons using an ANCOVA model applied to the FAS (LOCF). For waist circumference, the empagliflozin 10 mg showed significant decrease relative to placebo and empagliflozin 25 mg showed numerical decrease, while for SBP and DBP, the empagliflozin 25 mg showed significant decrease relative to placebo and the empagliflozin 10 mg showed numerical decrease; see Table 3 below.

Table 3 Treatment comparisons for the adjusted mean change at Week 76 - FAS (LOCF)

		Difference to placebo	
Parameter	Empa dose	Adjusted mean change (SE)	95% CI
HbA_{1c} [%]	10 mg	−0.59 (0.10)	(−0.79,−0.40)
	25 mg	−0.69 (0.10)	(−0.88,−0.50)
Body weight [kg]	10 mg	−1.97 (0.37)	(−2.69,−1.24)
	25 mg	−1.71 (0.37)	(−2.43,−0.99)
Waist circumf. [cm]	10 mg	−1.4 (0.6)	(−2.5,−0.3)
	25 mg	−0.9 (0.6)	(−1.9, 0.2)
FPG [mg/dL]	10 mg	−23.3 (4.1)	(−31.4,−15.3)
	25 mg	−27.4 (4.1)	(−35.4,−19.4)
SBP [mmHg]	10 mg	−2.0 (1.2)	(−4.5, 0.4)
	25 mg	−3.7 (1.2)	(−6.1,−1.3)
DBP [mmHg]	10 mg	−1.5 (0.8)	(−3.0, 0.0)
	25 mg	−2.2 (0.8)	(−3.7,−0.7)

Adjusted values are based on ANCOVA with last observation carried forward; data after the initiation of rescue medication were excluded.

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Efficacy results - pioglitazone (continued):

At Week 52, the adjusted mean change in HbA_{1c} relative to placebo was -0.60% (95% CI: -0.79, -0.41) for the empagliflozin 10 mg group and -0.68% (95% CI: -0.87, -0.49) for the empagliflozin 25 mg group.

A total of 46.8% of the patients discontinued the trial, which resulted in a large number of missing data. Therefore the analyses of the FAS based on the LOCF approach must be interpreted in the context of the totality of data including sensitivity analyses. The results on the FAS-completers (LOCF or OC approach) were similar to those on the FAS (LOCF); some deviations from the FAS results were observed, but no general trend emerged with regard to the treatment effect of the empagliflozin doses.

The analysis of secondary endpoint parameters over time showed a reduction of the adjusted mean values for up to 24 weeks after baseline that was generally sustained until Week 76, as based on an MMRM model applied to the FAS (OC).In the empagliflozin 10 mg group, the reduction in mean SBP was not sustained after Week 24; mean DBP in this group fluctuated after Week 24 but was consistently reduced compared with placebo. ANCOVA data of mean changes over time based on the FAS (LOCF) or FAS-completers (LOCF or OC approach) were consistent with the MMRM data for all secondary endpoint parameters.

Percentage of treatment responders for both empagliflozin groups was numerically higher than placebo with regard to patients achieving HbA_{1c} less than 7.0%. Use of rescue medication was less frequent in the empagliflozin groups than in the placebo group.

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Efficacy results - metformin:

Metformin background medication (preceding trial 1245.23)

The efficacy and safety analyses were based on all treated patients from the preceding trial, and based on the combined data of the preceding trial and the extension trial (up to final database lock). The extension trial was not separately analysed.

Disposition, demographics, baseline characteristics, and compliance

Of the 637 treated patients, the largest proportion was treated in Asia (42.5%), followed by Europe (30.3%), North America (22.8%), and Latin America (4.4%).

Over the entire period of the trial, discontinuation from treatment was more common for placebo (44.4%) than for empagliflozin 10 mg (28.6%) and empagliflozin 25 mg (36.6%); it occurred most frequently due to patients not entering the extension trial (20.1%). A total of 463 patients rolled over into the extension trial.

There were slightly more male (56.7%) than female (43.3%) patients. Most were White (53.1%) or Asian (45.4%), with a mean age of 55.7 years (SD 9.9 years). The mean baseline HbA_{1c} value was 7.90% (SD 0.85%) and the mean weight was 81.19 kg (SD 18.79 kg). A total of 34.7% of the patients were blood pressure controlled at baseline (<130/80 mmHg), and hypertension (55.7%) was most common with regard to medical history.

There were no clinically meaningful differences in baseline characteristics between patients who continued in the extension and patients who did not continue in the extension.Treatment compliance was high and balanced across treatments, with 95.1% of the patients within the 80 to 120% range.

Secondary endpoints and further endpoints

Both empagliflozin groups showed a significant decrease relative to placebo in mean HbA_{1c}, body weight, waist circumference, FPG, and SBP at Week 76, and empagliflozin 25 mg showed a numerical decrease in mean DBP at Week 76, based on exploratory treatment comparisons using an ANCOVA model applied to the FAS (LOCF). For an overview; see Table 4 below.

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Efficacy results - metformin (continued):

Table 4 Treatment comparisons for the adjusted mean change at Week 76- FAS (LOCF)

		Difference to placebo	
Parameter	Empa dose	Adjusted mean change (SE)	95% CI
HbA_{1c} [%]	10 mg	−0.61 (0.07)	(−0.75, −0.46)
	25 mg	−0.73 (0.07)	(−0.88, −0.58)
Body weight [kg]	10 mg	−1.93 (0.30)	(−2.52, −1.34)
	25 mg	−2.19 (0.30)	(−2.79, −1.60)
Waist circumf. [cm]	10 mg	−1.6 (0.4)	(−2.4, −0.8)
	25 mg	−1.1 (0.4)	(−1.9, −0.3)
FPG [mg/dL]	10 mg	−25.1 (2.8)	(−30.5, −19.6)
	25 mg	−31.4 (2.8)	(−36.9, −25.9)
SBP [mmHg]	10 mg	−4.4 (1.1)	(−6.6, −2.3)
	25 mg	−3.7 (1.1)	(−5.9, −1.5)
DBP [mmHg]	10 mg	−2.0 (0.7)	(−3.4, −0.5)
	25 mg	−1.4 (0.7)	(−2.8, 0.1)

Adjusted values are based on ANCOVA with last observation carried forward; data after the initiation of rescue medication were excluded.

At Week 52, the adjusted mean change in HbA_{1c} relative to placebo was -0.62% (95% CI: -0.75, -0.48) for the empagliflozin 10 mg group and -0.69% (95% CI: -0.83, -0.55) for the empagliflozin 25 mg group.

A total of 33.8% of the patients discontinued the trial, which resulted in a large number of missing data. Therefore the analyses of the FAS based on the LOCF approach must be interpreted in the context of the totality of data including sensitivity analyses. The results on the FAS-completers (LOCF or OC approach) were similar to those on the FAS (LOCF); some deviations from the FAS results were observed, but no general trend emerged with regard to the treatment effect of the empagliflozin doses.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Efficacy results - metformin (continued):	The analysis of secondary endpoint parameters over time showed a reduction of the adjusted mean values for up to 24 weeks after baseline that was generally sustained until Week 76, as based on an MMRM model applied to the FAS (OC); mean SBP and mean DBP values fluctuated after Week 24 in both empagliflozin groups but were consistently reduced compared with placebo. ANCOVA data of mean changes over time based on the FAS (LOCF) or FAS-completers (LOCF or OC approach) were consistent with the MMRM data for all secondary endpoint parameters. Percentage of treatment responders for both empagliflozin groups was numerically higher than placebo with regard to patients achieving HbA_{1c} less than 7.0%. Use of rescue medication was less frequent in the empagliflozin groups than in the placebo group.
Efficacy results - metformin+SU	*Metformin and sulfonylurea background medication (preceding trial 1245.23)* The efficacy and safety analyses were based on all treated patients from the preceding trial, and based on the combined data of the preceding trial and the extension trial (up to final database lock). The extension trial was not separately analysed. <u>Disposition, demographics, baseline characteristics, and compliance</u> Of the 666 treated patients, most were treated in Asia (55.4%), followed by Europe (20.6%), North America (17.6%), and Latin America (6.5%). Over the entire period of the trial, discontinuation from treatment was more common for placebo (46.2%) than for empagliflozin 10 mg (34.7%) and empagliflozin 25 mg (33.3%); it occurred most frequently due to patients not entering the extension trial (20.3%). A total of 474 patients rolled over into the extension trial. There were similar numbers of male (50.9%) and female (49.1%) patients. Most patients were Asian (57.2%) or White (39.3%), and the mean age was 57.1 years (SD 9.2 years). Mean baseline HbA_{1c} was 8.10% (SD 0.83%) and the mean weight was 76.93 kg (SD 18.00 kg).

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Efficacy results - metformin+SU (continued):

A total of 36.6% of the patients were blood pressure controlled at baseline (<130/80 mmHg), and hypertension (59.6%) was most common with regard to medical history. There were no clinically meaningful differences in baseline characteristics between patients who continued in the extension and patients who did not continue in the extension.

Treatment compliance was high and balanced across treatments, with 94.1% of the patients within the 80 to 120% range.

Secondary endpoints and further endpoints

Both empagliflozin groups showed a significant decrease relative to placebo in mean HbA_{1c}, body weight, waist circumference, FPG, and SBP, and a numerical decrease relative to placebo in mean DBP at Week 76, based on exploratory treatment comparisons. For an overview; see Table 5 below.

Table 5 Treatment comparisons for the adjusted mean change at Week 76-FAS (LOCF)

		Difference to placebo	
Parameter	Empa dose	Adjusted mean change (SE)	95% CI
HbA_{1c} [%]	10 mg	-0.72 (0.08)	(-0.87, -0.56)
	25 mg	-0.69 (0.08)	(-0.85, -0.53)
Body weight [kg]	10 mg	-1.81 (0.27)	(-2.34, -1.27)
	25 mg	-1.64 (0.27)	(-2.18, -1.11)
Waist circumf. [cm]	10 mg	-1.2 (0.4)	(-2.1, -0.4)
	25 mg	-1.0 (0.4)	(-1.9, -0.2)
FPG [mg/dL]	10 mg	-31.0 (3.1)	(-37.0, -24.9)
	25 mg	-31.8 (3.1)	(-37.9, -25.7)
SBP [mmHg]	10 mg	-2.2 (1.0)	(-4.1, -0.3)
	25 mg	-2.1 (1.0)	(-4.1, -0.2)
DBP [mmHg]	10 mg	-1.1 (0.7)	(-2.4, 0.1)
	25 mg	-0.9 (0.7)	(-2.2, 0.4)

Adjusted values are based on ANCOVA with last observation carried forward; data after the initiation of rescue medication were excluded.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Efficacy results - metformin+SU (continued):

At Week 52, the adjusted mean change in HbA_{1c} relative to placebo was -0.74% (95% CI: -0.89, -0.59) for the empagliflozin 10 mg group and -0.70% (95% CI: -0.85, -0.55) for the empagliflozin 25 mg group.

A total of 35.9% of the patients discontinued the trial, which resulted in a large number of missing data. Therefore the analyses of the FAS based on the LOCF approach must be interpreted in the context of the totality of data including sensitivity analyses. The results on the FAS-completers (LOCF or OC approach) were similar to those on the FAS (LOCF); some deviations from the FAS results were observed, but no general trend emerged with regard to the treatment effect of the empagliflozin doses.

The analysis of secondary endpoint parameters over time showed a reduction of the adjusted mean values for up to 24 weeks after baseline that was generally sustained until Week 76, as based on an MMRM model applied to the FAS (OC); mean SBP and mean DBP values fluctuated after Week 24 in both empagliflozin groups. ANCOVA data of mean changes over time based on the FAS (LOCF) or FAS-completers (LOCF or OC approach) were consistent with the MMRM data for all secondary endpoint parameters.

Percentage of treatment responders for both empagliflozin groups was numerically higher than placebo with regard to patients achieving HbA_{1c} less than 7.0%. Use of rescue medication was less frequent in the empagliflozin groups than in the placebo group.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-022718-17	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 18 of 30	**Synopsis No.:**
Module:		**Volume:**	
Disclosure Synopsis date*: 03 JUN 2014	**Trial No. / Doc No.:** 1245.31 / c02645257	**Dates of trial:** 22 FEB 2011 – 23 MAY 2013	**Date of revision:** Not applicable

Safety results - drug-naive:

Drug-naive patients (preceding trial 1245.20)

The safety analyses were based on the combined data of the preceding trial and the extension trial (up to final database lock). The extension trial was not analysed separately.

All entered patients were treated with study medication and included in the safety analyses (899 patients). Mean, median, and total exposure in the placebo group were lower than in the other treatment groups. The mean exposure time was 433.0 days (SD 283.3 days) in the placebo group (median of 526.0 days), 516.2 days (SD 258.0 days) in the empagliflozin 10 mg group (median of 616.0 days), 507.5 days (SD 263.8 days) in the empagliflozin 25 mg group (median of 616.0 days), and 493.4 days (SD 259.3 days) in the sitagliptin group (median of 550.0 days). Overall, 48.0% to 62.8% of the patients were treated for more than 76 weeks.

The percentage of patients with at least one reported treatment-emergent adverse event was similar across treatment groups (placebo: 76.4%, empagliflozin 10 mg: 76.8%, empagliflozin 25 mg: 78.0%, sitagliptin: 72.2%). The highest percentage of patients with adverse events was reported for the Medical dictionary for drug regulatory activities (MedDRA) system organ class (SOC) 'infections and infestations' in each treatment group: 37.1% for placebo, 42.0% for empagliflozin 10 mg, 40.8% for empagliflozin 25 mg, and 37.2% for sitagliptin. The majority of adverse events were of mild or moderate intensity. Severe adverse events were reported with similar frequencies between groups (placebo: 6.1%, empagliflozin 10 mg: 7.6%, empagliflozin 25 mg: 6.7%, and sitagliptin: 7.6%). The frequency of drug-related adverse events, as assessed by the investigator, was higher with empagliflozin (empagliflozin 10 mg: 21.9%, empagliflozin 25 mg: 23.3%) than with placebo (15.7%) or sitagliptin (13.9%).

Few patients experienced adverse events leading to premature discontinuation of trial medication ((placebo: 6.6%, empagliflozin 10 mg: 4.9%, empagliflozin 25 mg: 4.0%, sitagliptin: 4.9%). The percentage of patients with SAEs was slightly higher with placebo (10.0%) and empagliflozin 10 mg (11.2%) than with empagliflozin 25 mg (7.2%) and sitagliptin (8.1%). One patient in the placebo group (myocardial infarction) and 1 patient in the sitagliptin group (sudden death) died during the study.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Safety results - drug-naive (continued):	Confirmed hypoglycaemic events were reported for 2 patients (0.9%) in the placebo group, 2 patients (0.9%) in the empagliflozin 10 mg group, 2 patients (0.9%) in the empagliflozin 25 mg group, and 2 patients (0.9%) in the sitagliptin group. All episodes were of mild intensity; none of the patients required assistance (except for 1 patient on empagliflozin 10 mg) or discontinued trial medication because of the hypoglycaemic event. No event led to hospitalisation of the patient. Decreased renal function (based on an SMQ) was not reported in patients on placebo but was reported for 4 patients on empagliflozin 10 mg, 3 patients on empagliflozin 25 mg, and 3 patients on sitagliptin. Mean changes in serum creatinine and eGFR from baseline after 76 weeks were small and similar across treatment groups. There were 2 patients in the empagliflozin 10 mg group showing a ≥2-fold increase from baseline in creatinine values and creatinine greater than upper limit of normal (no patient in the placebo group, empagliflozin 25 mg group, or sitagliptin group). Overall, 27 patients had hepatic adverse events (based on SMQs): 6 patients in the placebo group, 7 patients in the empagliflozin 10 mg group, 7 patients in the empagliflozin 25 mg group, and 7 patients in the sitagliptin group. Three patients in the empagliflozin 25 mg group had laboratory values consistent with a potential Hy's law case: 1 patient with infectious hepatitis (hepatitis A diagnosed on clinical basis), 1 patient with bile duct cancer, and 1 patient with drug-induced hepatitis following anti-tuberculosis treatment. Due to the alternative explanations for the enzyme elevation, these cases were not confirmed as Hy's law cases. The proportion of patients with urinary tract infections (based on a customised MedDRA search) was similar across treatment groups was 10.9% with placebo, 9.4% with empagliflozin 10 mg, and 9.0% each with empagliflozin 25 mg and sitagliptin. The percentage of patients with genital infections (based on a customised MedDRA search) was greater in the empagliflozin groups than in the placebo or sitagliptin group: 1.7% in the placebo group, 5.8% in the empagliflozin 10 mg group, 6.3% in the empagliflozin 25 mg group, and 0.9% in the sitagliptin group.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Safety results - drug-naive (continued):	Overall, there were 12 patients who had adverse events in the BICMQ 'volume depletion' 1 patient in the placebo group, 6 patients in the empagliflozin 10 mg group, 2 patients in the empagliflozin 25 mg group, and 3 patients in the sitagliptin group. Mean changes from baseline in differentials (automatic and absolute), electrolytes, enzymes, substrates, and plasma proteins were negligible. Mean haematocrit values slightly decreased from baseline to last value on treatment with placebo, did not change with sitagliptin, and increased with empagliflozin 10 mg and empagliflozin 25 mg. A decrease in uric acid was noted in the empagliflozin groups compared with placebo or sitagliptin. The analysis mean change from baseline in lipid parameters showed an increase relative to placebo at Week 76 in total cholesterol with empagliflozin 25 mg, in HDL cholesterol with both empagliflozin groups, and in LDL cholesterol with empagliflozin 25 mg. Neither dose showed a relevant difference to placebo in mean change from baseline for the LDL/HDL cholesterol ratio, non-HDL cholesterol, and triglycerides. Generally, parameters that showed decrease or increase from baseline to last value on treatment showed a return towards baseline at the 4-week follow-up visit. Overall, pulse rate changes over time were small and similar in all treatment groups.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-022718-17	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 21 of 30	**Synopsis No.:**
Module:		**Volume:**	
Disclosure Synopsis date*: 03 JUN 2014	**Trial No. / Doc No.:** 1245.31 / c02645257	**Dates of trial:** 22 FEB 2011 – 23 MAY 2013	**Date of revision:** Not applicable

Safety results - pioglitazone:

Pioglitazone background medication (preceding trial 1245.19)

The safety analyses were based on the combined data of the preceding trial and the extension trial (up to final database lock). The extension trial was not separately analysed.

All but 1 entered patient were treated with study medication and included in the safety analyses (498 patients). The mean exposure time was 403.5 days (SD 245.9) in the placebo group (median of 391.0 days), 449.4 days (SD 249.3 days) in the empagliflozin 10 mg group (median of 539.0 days), and 456.7 days (SD 252.9) in the empagliflozin 25 mg group (median of 536 days). Overall, 41.8% (placebo) to 54.5% (empagliflozin 10 mg) of patients were treated for more than 76 weeks.

The overall frequency of adverse events was similar across treatment groups (placebo: 82.4%, empagliflozin 10 mg: 76.4%, empagliflozin 25 mg: 82.1%). The highest frequency of patients with adverse events was reported for the SOC 'infections and infestations'; percentages were similar across treatment groups: 44.2% for placebo, 40.0% for empagliflozin 10 mg, and 46.4% for empagliflozin 25 mg. Most patients had adverse events of mild or moderate intensity. Severe adverse events were reported for fewer patients in the 2 empagliflozin groups (3.6% and 4.8% for empagliflozin 10 mg and 25 mg, respectively) than in the placebo group (8.5%). The frequency of patients with drug-related adverse events, as assessed by the investigator, was largely similar across treatment groups (placebo: 24.8%, empagliflozin 10 mg: 20.0%, empagliflozin 25 mg: 23.2%).

Few patients experienced adverse events leading to premature discontinuation of trial medication (4.2% on placebo, 3.0% on empagliflozin 10 mg, and 4.8% on empagliflozin 25 mg). The percentage of patients with SAEs was slightly higher with empagliflozin than with placebo: 6.7% on placebo, 7.9% on empagliflozin 10 mg, and 8.9% on empagliflozin 25 mg.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Safety results - pioglitazone (continued):	Five patients died during the study (1 patient in the placebo group with skin ulcer, myocardial ischaemia, and decreased haemoglobin, 1 patient on empagliflozin 10 mg with sudden death, 1 patient on empagliflozin 25 mg because of cerebrovascular accident, 1 patient on empagliflozin 25 mg with cardiorespiratory arrest occurring post-treatment, and 1 patient on empagliflozin 25 mg with oesophageal rupture). Confirmed hypoglycaemic events were reported at similar frequencies in all 3 treatment groups: 7 patients (4.2%) in the placebo group, 3 patients (1.8%) in the empagliflozin 10 mg group, and 5 patients (3.0%) in the empagliflozin 25 mg group. All episodes were of mild intensity except in 1 patient on placebo and 1 patient on empagliflozin 25 mg for which the episode was moderate. One patient in the placebo group and 1 patient in the empagliflozin 25 mg group required assistance because of the hypoglycaemic event. No patients discontinued trial medication because of the hypoglycaemic event. No hypoglycaemic event led to hospitalisation of the patient. Decreased renal function (based on an SMQ) was reported for 1 patient in the placebo group, 3 patients in the empagliflozin 10 mg, and 2 patients in the empagliflozin 25 mg groups. Mean changes in serum creatinine and eGFR from baseline after 76 weeks were very small and similar across treatment groups. One patient in the placebo group showed a ≥2-fold increase from baseline in creatinine values and creatinine greater than upper limit of normal. Overall, 11 patients had hepatic adverse events (based on SMQs): 3 patients in the placebo group, 1 patient in the empagliflozin 10 mg group, and 7 patients in the empagliflozin 25 mg group. One patient on empagliflozin 25 mg had laboratory values consistent with a potential Hy's law case (this patient was diagnosed with hepatitis E). Due to the alternative explanation for the enzyme elevation, this case was not confirmed as a Hy's law case.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Safety results - pioglitazone (continued):	The proportion of patients with urinary tract infections (based on a customised MedDRA search) was greater in the placebo group than in the empagliflozin groups: 26.7% with placebo, 22.4% with empagliflozin 10 mg, and 22.0% with empagliflozin 25 mg. The percentage of patients with genital infections (based on a customised MedDRA search) was greater in the empagliflozin 10 mg and empagliflozin 25 mg group than in the placebo group: 3.0% in the placebo group, 10.3% in the empagliflozin 10 mg group, and 4.2% in the empagliflozin 25 mg group. Only 2 patients (both in the empagliflozin 25 mg group) had an adverse event in the BICMQ 'volume depletion'. Mean changes from baseline in differentials (automatic and absolute), electrolytes, enzymes, substrates, and plasma proteins were negligible. No change in haematocrit values was observed with placebo, whereas a slight increase was observed in the empagliflozin groups. On average, uric acid levels decreased more in patients on empagliflozin 10 or 25 mg than in patients on placebo. The analysis of mean change from baseline in lipid parameters showed an increase relative to placebo at Week 76 in HDL cholesterol with empagliflozin 10 mg. Neither empagliflozin dose showed a relevant difference relative to placebo in mean change from baseline in total cholesterol, LDL cholesterol, LDL/HDL cholesterol ratio, non-HDL cholesterol, and triglycerides. Generally, parameters that showed decrease or increase from baseline to last value on treatment showed a return towards baseline at the 4-week follow-up visit. Pulse rate changes over time were small and similar in all treatment groups.

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Safety results - metformin:

Metformin background medication (preceding trial 1245.23)

The safety analyses were based on the combined data of the preceding trial and the extension trial (up to final database lock). The extension trial was not analysed separately.

All but 1 entered patient were treated with study medication and included in the safety analyses (637 patients). The mean exposure time was 487.5 days (SD 276.4 days) in the placebo group (median of 621.0 days), 573.9 days (SD 236.4 days) in the empagliflozin 10 mg group (median of 698.0 days), and 524.5 days (SD 267.0 days) in the empagliflozin 25 mg group (median of 623.5 days). Overall, 58.3% (placebo) to 74.2% (empagliflozin 10 mg) of patients were treated for more than 76 weeks.

The percentage of patients with at least one reported treatment-emergent adverse event was lower with empagliflozin 25 mg than with placebo or empagliflozin 10 mg (placebo: 77.7%, empagliflozin 10 mg: 80.2%, empagliflozin 25 mg: 72.0%). The highest frequency of patients with adverse events was reported for the SOC 'infections and infestations' with a slightly lower frequency in the empagliflozin groups compared with placebo: 46.1% for placebo, 42.4% for empagliflozin 10 mg, and 40.7% for empagliflozin 25 mg. Most patients had adverse events of mild or moderate intensity. Severe adverse events were reported with similar frequencies between treatment groups: 8.3% for placebo, 6.9% for empagliflozin 10 mg, and 7.9% for empagliflozin 25 mg.

There were more adverse events assessed by the investigator as drug-related in the empagliflozin 10 mg group (30.4%) than in the placebo (22.2%) and empagliflozin 25 mg (20.1%) groups. Few patients experienced adverse events leading to premature discontinuation of trial medication (4.9% on placebo, 3.2% on empagliflozin 10 mg, and 5.6% on empagliflozin 25 mg). The percentage of patients who had SAEs was slightly greater in the placebo group than in the empagliflozin groups: 11.7% on placebo, 8.8% on empagliflozin 10 mg, and 7.9% on empagliflozin 25 mg. No patient died during the study.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Safety results - metformin (continued):	Confirmed hypoglycaemic events were reported for 7 patients (3.4%) in the placebo group, 9 patients (4.1%) in the empagliflozin 10 mg group, and 9 patients (4.2%) in the empagliflozin 25 mg group. One patient in the placebo group experienced a hypoglycaemic event of severe intensity. In 3 patients (1 patient on placebo and 2 patients on empagliflozin 10 mg) the intensity of the event was moderate. One patient on empagliflozin 10 mg required assistance because of an hypoglycaemic event and none of the patients discontinued treatment or were hospitalised. Decreased renal function (based on SMQs) was reported for 4 patients in the empagliflozin 25 mg group. Mean changes in serum creatinine and eGFR from baseline up to 76 weeks were small and similar across treatment groups. There was no patient showing a ≥2-fold increase from baseline in creatinine values and creatinine greater than upper limit of normal. Overall, 16 patients had hepatic adverse events (based on an SMQ): 9 patients in the placebo group, 4 patients in the empagliflozin 10 mg group, and 3 patients in the empagliflozin 25 mg group. No potential Hy's law cases were reported. The proportion of patients with urinary tract infections (based on a customised MedDRA search) was similar across treatment groups: 13.6% with placebo, 14.3% with empagliflozin 10 mg, and 10.3% with empagliflozin 25 mg. The percentage of patients with genital infections (based on a customised MedDRA search) was greater in the empagliflozin groups than in the placebo group: 0.5% in the placebo group, 8.3% in the empagliflozin 10 mg group, and 9.3% in the empagliflozin 25 mg group. Overall, there were 3 patients who had adverse events in the BICMQ 'volume depletion' (2 patients in the empagliflozin 10 mg group, and 1 patient in the empagliflozin 25 mg group).

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Safety results - metformin (continued):

Mean changes from baseline in differentials (automatic and absolute), electrolytes, enzymes, substrates, and plasma proteins were negligible. A slight decrease in mean haematocrit from baseline to last value on treatment was noted in the placebo group whereas a slight increase was seen in the empagliflozin groups. A decrease in uric acid was noted in the empagliflozin groups compared with placebo.

The analysis of mean change from baseline in lipid parameters showed an increase relative to placebo at Week 76 in total cholesterol with empagliflozin 10 mg and in HDL cholesterol with empagliflozin doses. Neither empagliflozin doses showed relevant changes relative to placebo in LDL cholesterol, LDL/HDL cholesterol ratio, non-HDL cholesterol, and triglycerides.

Generally, parameters that showed decrease or increase from baseline to last value on treatment showed a return towards baseline at the 4-week follow-up visit.

Pulse rate changes over time were small and similar in all treatment groups.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-022718-17	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 27 of 30	**Synopsis No.:**
Module:		**Volume:**	
Disclosure Synopsis date*: 03 JUN 2014	**Trial No. / Doc No.:** 1245.31 / c02645257	**Dates of trial:** 22 FEB 2011 – 23 MAY 2013	**Date of revision:** Not applicable

Safety results - metformin+SU:

Metformin and sulfonylurea background medication (preceding trial 1245.23)

The safety analyses were based on the combined data of the preceding trial and the extension trial (up to final database lock). The extension trial was not analysed separately.

All but 3 of the entered patients were treated with study medication and included in the safety analyses (666 patients). The mean exposure time was 487.9 days (SD 285.8 days) in the placebo group (median of 619.0 days), 556.2 days (SD 276.1 days) in the empagliflozin 10 mg group (median of 700.0 days), and 564.2 days (SD 274.6 days) in the empagliflozin 25 mg group (median of 700.0 days). Overall, 56.4% (placebo) to 70.0% (empagliflozin 25 mg) of patients were treated for more than 76 weeks.

The percentage of patients with at least one reported treatment-emergent adverse event was similar across treatment groups (placebo: 81.3%, empagliflozin 10 mg: 81.7%, and empagliflozin 25 mg: 82.0%). The highest frequency of adverse events was reported for the MedDRA SOC 'infections and infestations' with similar frequencies in all treatment groups: 48.4% for placebo, 46.4% for empagliflozin 10 mg, and 49.3% for empagliflozin 25 mg. Most patients had adverse events of mild or moderate intensity. Severe adverse events were reported for slightly fewer patients in the 2 empagliflozin groups (6.3% and 8.8% for empagliflozin 10 mg and 25 mg, respectively) than in the placebo group (12.9%). A higher percentage of patients on empagliflozin 10 mg or 25 mg experienced drug-related adverse events compared with placebo (placebo: 26.2%, empagliflozin 10 mg: 35.7%, and empagliflozin 25 mg: 31.8%).

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Safety results - metformin+SU (continued):

Few patients experienced adverse events leading to premature discontinuation of trial medication (7.1% on placebo, 4.5% on empagliflozin 10 mg, and 6.9% on empagliflozin 25 mg). The percentage of patients who had SAEs was similar in the 3 treatment groups: 13.8% on placebo, 12.9% on empagliflozin 10 mg, and 11.1% on empagliflozin 25 mg. Three deaths were reported. One patient on empagliflozin 10 mg died of acute myocardial infarction. One patient on empagliflozin 25 mg died post-treatment (neutropenic fever, pancytopenia, and sepsis). One patient on placebo died post-study (acute left ventricular failure/acute failure left heart).

More patients were reported with confirmed hypoglycaemic events in the empagliflozin treatment groups than in the placebo group: 15.6% in the placebo group, 23.7% in the empagliflozin 10 mg group, and 19.4%in the empagliflozin 25 mg group. There was no patient with a severe episode. One patient on placebo and 1 patient on empagliflozin 10 mg required assistance because of a hypoglycaemic event. A total of 13 patients received therapy (unspecified) and no patients discontinued study drug due to the hypoglycaemic event. None of the hypoglycaemic events led to hospitalisation of a patient.

Decreased renal function (based on an SMQ) was reported for 2 patients on placebo and 5 patients on empagliflozin 10 mg. Mean changes in serum creatinine and eGFR from baseline up to 76 weeks were small and similar across treatment groups. There were 2 patients in the empagliflozin 10 mg treatment group showing a ≥2-fold increase from baseline in creatinine values and creatinine greater than upper limit of normal.

Overall, 21 patients had hepatic adverse events (based on SMQs): 10 patients in the placebo group, 3 patients in the empagliflozin 10 mg group, and 8 patients in the empagliflozin 25 mg group. No potential Hy's law cases were reported.

*The content of this Synopsis is identical with the original CTR 1245.31 (Doc. No.: c02155992-02, Doc. Date: 23 MAY 2014), only the Disclosure Synopsis date was added.

Safety results - metformin+SU (continued):

The proportion of patients with urinary tract infections (based on a customised MedDRA search) was similar across treatment groups: 16.0% with placebo, 17.0% with empagliflozin 10 mg, and 16.1% with empagliflozin 25 mg. Three patients in the placebo group developed a urinary tract infection of severe intensity (1 patient with haemorrhagic cystitis; 1 patient with urinary tract infection; and 1 patient with urinary tract infection and urosepsis); all 3 patients were hospitalised because of the event. The percentage of patients with genital infections (based on a customised MedDRA search) was greater in the empagliflozin groups than in the placebo group: 0.9% in the placebo group, 4.5% in the empagliflozin 10 mg group, and 6.0% in the empagliflozin 25 mg group. None of the patients had a genital infection of severe intensity.

Overall, there were 4 patients who had adverse events in the BICMQ 'volume depletion' (1 patient in the placebo group, 2 patients in the empagliflozin 10 mg group, and 1 patient in the empagliflozin 25 mg group).

Mean changes from baseline in differentials (automatic and absolute), electrolytes, enzymes, substrates, and plasma proteins were negligible. Mean haematocrit values slightly decreased from baseline to last value on-treatment with placebo but slightly increased with empagliflozin 10 mg and empagliflozin 25 mg. Mean uric acid levels showed a small decrease with placebo and a larger decrease with empagliflozin.

The analysis of the mean change from baseline in lipid parameters showed an increase relative to placebo in HDL cholesterol with both empagliflozin doses. Neither dose showed relevant differences relative to placebo in mean change from baseline in total cholesterol, LDL cholesterol, LDL/HDL cholesterol ratio, non-HDL cholesterol, and triglycerides.

Generally, parameters that showed decrease or increase from baseline to last value on treatment showed a return towards baseline at the 4-week follow-up visit.

Pulse rate changes over time were small and similar in all treatment groups.

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-022718-17	
Name of active ingredient: Empagliflozin (BI 10773)		**Page:** 30 of 30	**Synopsis No.:**
Module:		**Volume:**	
Disclosure Synopsis date*: 03 JUN 2014	**Trial No. / Doc No.:** 1245.31 / c02645257	**Dates of trial:** 22 FEB 2011 – 23 MAY 2013	**Date of revision:** Not applicable

Conclusions:

Over 1510 patients with type 2 diabetes were evaluated for over 76 weeks using either 10 mg or 25 mg empagliflozin compared with placebo or sitagliptin on background of no antidiabetic treatment, or compared with placebo only on background of pioglitazone, metformin only, or metformin and sulfonylurea. Treatment with empagliflozin 10 mg or 25 mg resulted in a clinically meaningful and sustained improvement of glucose control, weight, and blood pressure for over 76 weeks of treatment. Both doses were safe and well tolerated compared with placebo and sitagliptin in drug-naive patients and compared with placebo in patients receiving background therapies. The percentages of patients with confirmed hypoglycaemic events were overall low and generally similar across treatment groups. In patients with metformin and sulfonylurea background therapy, the incidence of confirmed hypoglycaemia was greater in the empagliflozin groups than in the placebo group. Overall, the occurrence of urinary tract infection was similar in each treatment groups. Genital infections were more often observed in patients treated with empagliflozin than in those treated with placebo or sitagliptin but were not severe, mostly not recurrent, and responded to standard therapy.

In this extension trial, both doses of empagliflozin were safe and associated with clinically meaningful and sustained efficacy for over 76 weeks when compared with placebo or sitagliptin.

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