Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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erName of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
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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 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite treatment with metformin alone or metformin in combination with a sulphonylurea
Coordinating Investigators:	[redacted]
Trial sites:	Multi centre trial: 148 trial sites enrolled patients in 12 countries (Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, United States)
Publication (reference):	Data from this trial have not been published.
Clinical phase:	III
Objectives:	The objective of this trial was to investigate the efficacy, safety, and tolerability of empagliflozin (10 mg and 25 mg once daily) compared with placebo given for 24 weeks as add-on therapy to metformin or metformin plus sulphonylurea in patients with type 2 diabetes mellitus with insufficient glycaemic control. A further objective was to investigate efficacy and safety of 25 mg empagliflozin in patients with very poor glycaemic control (HbA_{1c} >10%) in an open-label arm.
Methodology:	This was a randomised, placebo-controlled, double-blind, parallel-group comparison study. Randomisation was stratified by HbA_{1c} at screening, renal function at screening, and geographical region. A 2-week open-label placebo run-in period preceded randomisation. Patients allocated to the open-label arm started treatment with 25 mg empagliflozin without a run-in period. Patients who completed the planned 24-week treatment period in this trial were eligible to continue their randomised treatment by enrolling in the extension trial BI 1245.31. Patients who did not enter the extension trial were to be followed-up for 1 week.

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Methodology: (continued)	The 2 parts of the study were defined by the background medication the patients received at baseline and were regarded as independent substudies; the background medication was either metformin alone (substudy A) or metformin plus sulphonylurea (substudy B). Background medication was to be taken during the entire trial duration (including placebo run-in period) with dose unchanged.
Number of subjects:	
planned:	Entered: 1230 patients (615 patients on metformin alone, 615 patients on metformin plus sulphonylurea) plus 160 patients in the open-label arm
actual:	Enrolled (total): 2256 Randomised (total): 1307 Assigned to open-label treatment (total): 172 *SUBSTUDY A: METFORMIN ONLY BACKGROUND MEDICATION* Empagliflozin 10 mg: Entered: 217 treated: 217 analysed (for primary endpoint): 217 Empagliflozin 25 mg: Entered: 214 treated: 213 analysed (for primary endpoint): 213 Placebo: Entered: 207 treated: 207 analysed (for primary endpoint): 207 Open-label empagliflozin 25 mg: Entered: 69 treated: 69 analysed (for primary endpoint): 69 *SUBSTUDY B: METFORMIN PLUS SULPHONYLUREA BACKGROUND MEDICATION* Empagliflozin 10 mg: Entered: 226 treated: 225 analysed (for primary endpoint): 225 Empagliflozin 25 mg: Entered: 218 treated: 216 analysed (for primary endpoint): 216 Placebo: Entered: 225 treated: 225 analysed (for primary endpoint): 225 Open-label empagliflozin 25 mg: Entered: 103 treated: 101 analysed (for primary endpoint): 101

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Diagnosis and main criteria for inclusion:	Patients with type 2 diabetes mellitus and insufficient glycaemic control (HbA_{1c} ≥7.0 and ≤10.0%) despite therapy with metformin alone or metformin plus sulphonylurea; age ≥18 years; Body mass index ≤45 kg/m^2. Patients with an HbA_{1c} >10% and fulfilling all remaining inclusion criteria were eligible for inclusion in the 25 mg empagliflozin open-label arm.
Test product:	Empagliflozin tablets 10 mg; empagliflozin tablets 25 mg
dose:	10 mg or 25 mg once daily
mode of admin.:	Oral
batch no.:	Empagliflozin 10 mg: 003435, 909474A Empagliflozin 25 mg: 909473A, 909472A, 001747A, 003530
Reference therapy:	Placebo tablets matching empagliflozin 10 mg and 25 mg tablets
dose:	Not applicable
mode of admin.:	Oral
batch no.:	Placebo matching empagliflozin 10 mg: 84835, 84870, 88440, 88493 Placebo matching empagliflozin 25 mg: 85114, 88651, 85092, 88644
Duration of treatment:	Two-week placebo run-in (except for patients allocated to the open-label treatment arm); 24-week treatment period; 1-week follow-up period or enrolment in extension trial BI 1245.31.
Criteria for evaluation:	
Efficacy:	The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment. The key secondary endpoints were the change from baseline in body weight and mean daily plasma glucose (MDG) after 24 weeks of treatment. Further secondary endpoints were defined as the occurrence of a treat-to-target response (HbA_{1c} under treatment of <7.0% and <6.5%), occurrence of relative efficacy response (HbA_{1c} lowering by at least 0.5%), change in fasting plasma glucose (FPG), waist circumference, and systolic and diastolic blood pressure from baseline, occurrence of blood pressure response with blood pressure lower than 130/80 mmHg, percentage of patients with history of hypertension and not

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Efficacy: (continued)	at blood pressure goal of <130/80 mmHg at baseline achieving blood pressure response, weight reduction by >5%, and a composite endpoint (HbA_{1c} reduction of ≥0.5%, reduction of systolic blood pressure by >3 mmHg, and decrease in body weight >2%); all of which were assessed after 24 weeks of treatment. In addition, change in HbA_{1c}, FPG, and blood pressure by visit over time were evaluated. Use of rescue medication was assessed. Endpoints based on biomarkers were defined as change from baseline after 24 weeks of treatment for C-peptide, fasting plasma insulin, ratios of proinsulin/insulin, insulin/C-peptide, and insulin/glucose, homeostasis model assessment for insulin resistance and secretion, and disposition index. Endpoints for a meal tolerance test were defined as change from baseline of post-prandial glucose after 24 weeks of treatment, incremental area under the curve (iAUC) for glucose, C-peptide, and insulin, and derived ratios. Trough plasma concentrations of empagliflozin during the treatment period were analysed as pharmacokinetic parameters.
Safety:	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 infections, genital infections, and volume depletion; change from baseline in clinical laboratory assessments, vital signs, and 12-lead ECG
Statistical methods:	Statistical analyses were performed separately for substudy A and substudy B. The primary endpoint was analysed by testing of the superiority hypothesis of empagliflozin treatment versus placebo using an analysis of covariance (ANCOVA) with randomised treatment, geographical region, and renal function as fixed effects and baseline HbA_{1c} as linear covariate. Sensitivity analysis of the primary endpoint was performed by ANCOVA modelling, using a restricted maximum likelihood (REML)-based mixed model repeated measures approach, and a multiple imputation approach. The key secondary endpoints were analysed using ANCOVA modelling similar to the primary endpoint analysis in a hierarchical testing approach. Key categories used for subgroup analyses of primary and key secondary endpoints were age, race, baseline HbA_{1c}, gender, and time since diagnosis of diabetes.

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Statistical methods: (continued)

For further endpoints FPG and blood pressure ANCOVA modelling was used and descriptive statistics were calculated for all further endpoints. Endpoints based on biomarkers and MTT were evaluated using descriptive statistics and ANCOVA for the change from baseline after 24 weeks of treatment. Use of rescue medication was analysed using logistic regression with treatment as a factor and continuous HbA_{1c} as covariate. In addition, time to first use of rescue medication was analysed by Kaplan-Meier survival probability estimates and compared using a log-rank test.

The data of the open-label part were analysed using descriptive statistics.

Safety analysis was performed using descriptive statistics. ANCOVA analyses were performed for lipid parameters.

SUMMARY – CONCLUSIONS:

Efficacy results:

SUBSTUDY A: METFORMIN ONLY BACKGROUND MEDICATION

This substudy included 970 enrolled patients from 136 centres in 12 countries in Asia, Europe, North America, and Latin America. A total of 638 patients were randomised in a 1:1:1 ratio to receive treatment with empagliflozin 10 mg (217 patients), empagliflozin 25 mg (214 patients) or placebo (207 patients) in addition to their metformin background therapy. A total of 637 patients were treated with randomised study medication. Of those, 46 patients (7.2%) prematurely discontinued study medication (empagliflozin 10 mg: 3.7%, empagliflozin 25 mg: 8.0%, placebo: 10.1%) with the main reason for discontinuation being the occurrence of adverse events (empagliflozin 10 mg: 0.9%, empagliflozin 25 mg: 2.3%, placebo: 3.4%).

Overall, 69 patients were entered into the open-label treatment group. In total, 58 patients (84.1%) completed the 24-week treatment period.

The demographic and baseline characteristics were comparable between the randomised treatment groups. Overall, 56.7% of patients were male; 53.1% were White and 45.4% were of Asian race. The mean (SD) age was 55.7 (9.9) years. At baseline, 44.3% of patients had normal renal function (eGFR ≥90 ml/min/1.73m²), 50.2% had mild renal impairment (eGFR ≥60 to <90 mL/min/1.73m²), and 5.5% had moderate renal impairment (eGFR ≥30 to <60 mL/min/1.73m²). Mean (SD) baseline HbA_{1c} was similar across the randomised treatment groups (empagliflozin 10 mg: 7.94 [0.79]%, empagliflozin 25 mg:

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Efficacy results: (continued)

7.86 [0.87]%, placebo: 7.90 [0.85]%). Mean (SD) weight (empagliflozin 10 mg: 81.59 [18.51] kg, empagliflozin 25 mg: 82.21 [19.29] kg, placebo: 79.73 [18.57] kg) and MDG (empagliflozin 10 mg: 168.03 [32.14] mg/dL, empagliflozin 25 mg: 167.87 [34.14] mg/dL, placebo: 169.53 [37.77] mg/dL) were also similar in the treatment groups. Overall mean (SD) baseline FPG was 153.3 (33.0) mg/dL, waist circumference was 99.5 (13.7) cm, systolic blood pressure (SBP) was 129.4 (14.6), diastolic blood pressure (DBP) was 78.7 (8.1) mmHg, and BMI was 29.18 (5.49) kg/m^2. Most patients had been diagnosed with diabetes for >1 to 5 years (36.1%) or >5 to 10 years (32.5%).

In the open-label group, 59.4% of the patients were male, 71.0% of patients were White and 20.3% were of Asian race. The mean (SD) age was 49.8 (11.5) years. The majority of patients had normal renal function (62.3%) or mild renal impairment (36.2%); 1.4% had moderate renal impairment at baseline. Overall mean (SD) baseline HbA_{1c} was 11.07 (1.29)%, weight was 85.07 (21.96) kg, BMI was 30.37 (5.51) kg/m^2, MDG was 226.32 (54.14) mg/dL, FPG was 203.6 (64.0) mg/dL, SBP was 126.2 (11.4), DBP was 79.3 (7.9) mmHg, and waist circumference was 99.8 (13.3) cm; 40.6% of patients had been diagnosed with diabetes for >1 to 5 years.

Overall compliance was between 80% and 120% for 95.9% of patients in the randomised treatment groups. In the open-label group, 92.8% of patients had overall compliance within this range.

Primary endpoint

The main efficacy endpoint analysis was performed on the full analysis set (FAS) of patients (empagliflozin 10 mg: 217 patients, empagliflozin 25 mg: 213 patients, placebo: 207 patients) using the last observation carried forward (LOCF) approach to impute missing data. Superiority of empagliflozin 10 mg and 25 mg over placebo was demonstrated for the change of HbA_{1c} after 24 weeks of treatment. A summary of the treatment difference in HbA_{1c} adjusted mean change from baseline is included in Table 2: 1 below. Sensitivity analyses confirmed the superiority of both doses of empagliflozin over placebo.

For open-label treatment with 25 mg empagliflozin the mean change (SD) from baseline at Week 24 in HbA_{1c} was -2.78 (1.73)% for LOCF imputation and -3.23 (1.49)% for OC (observed case) imputation.

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Efficacy results: (continued)

Key secondary endpoints

Superiority of empagliflozin 10 mg and 25 mg over placebo in change of body weight and mean daily glucose (MDG) from baseline was demonstrated after 24 weeks of treatment. Sensitivity analyses confirmed the superiority of empagliflozin over placebo treatment. A higher mean reduction from baseline in MDG was observed for both empagliflozin treatment groups compared with placebo when OC imputation was used. The results for the analyses of both key secondary endpoints are included in Table 2: 1 below.

For the open-label group, a mean change (SD) from baseline at Week 24 in weight of -1.33 (3.53) kg using LOCF and -1.91 (4.11) kg using OC imputation, and a mean change (SD) from baseline in MDG of -35.47 (48.12) mg/dL using LOCF and -76.25 (42.96) mg/dL using OC imputation was observed.

Table 2: 1 Change from baseline versus placebo for the primary and key secondary endpoints at Week 24 (FAS), LOCF - (metformin only)

Comparison vs. placebo at 24 weeks	Empagliflozin 10 mg	Empagliflozin 25 mg
HbA_{1c} [%]		
Adjusted mean (standard error)	-0.57 (0.07)	-0.64 (0.07)
97.5% confidence interval	(-0.72, -0.42)	(-0.79, -0.48)
p-value	<0.0001	<0.0001
Body weight [kg]		
Adjusted mean (standard error)	-1.63 (0.24)	-2.01 (0.24)
97.5% confidence interval	(-2.17, -1.08)	(-2.56, -1.46)
p-value	<0.0001	<0.0001
MDG [mg/dL]		
Adjusted mean (standard error)	-7.65 (2.74)	-12.37 (2.75)
97.5% confidence interval	(-13.81, -1.48)	(-18.55, -6.19)
p-value	0.0055	<0.0001

Other endpoints

In line with the reduction in HbA_{1c}, consistent reductions in FPG from baseline were noted in comparison to placebo treatment for both doses of empagliflozin. In addition, clinically meaningful reductions in blood pressure were noted for both doses of empagliflozin. Reductions in waist circumference in the empagliflozin treatment groups were consistent with reduction in body weight

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Efficacy results: (continued)

after 24 weeks of treatment. A higher proportion of patients treated with empagliflozin 10 mg or 25 mg compared with placebo reached target HbA_{1c} levels of <7.0% or <6.5%, had a HbA_{1c} reduction of at least 0.5%, and achieved the composite endpoint after 24 weeks of randomised treatment. Among patients not already at the blood pressure goal of SBP <130 mmHg and DBP <80 mmHg at baseline, more patients in the randomised empagliflozin treatment groups than in the placebo group reached the blood pressure goal after 24 weeks of treatment. The proportions of patients who required the use of rescue medication during randomised treatment was lower in the empagliflozin groups than in the placebo group.

For the open-label group, reductions in FPG were in line with the reduction in HbA_{1c}. In addition, reductions in waist circumference, SBP, and DBP were noted from baseline at Week 24; the results were supported by the proportions of patients achieving the criteria for the composite endpoint.

Empagliflozin trough concentrations were maintained during the course of the study for both dose groups. The increase in empagliflozin exposure was roughly proportional with an increase in dose from 10 mg to 25 mg. Similar exposure was observed in males and females, up to an age of 65 years, in all weight, race, geographical region, and ethnicity group categories. Exposure increased with a decrease in renal function.

SUBSTUDY B: METFORMIN PLUS SULPHONYLUREA BACKGROUND MEDICATION

This substudy included 1010 enrolled patients from 129 centres in 12 countries in Asia, Europe, North America, and Latin America. A total of 669 patients were randomised in a 1:1:1 ratio to receive treatment with either empagliflozin 10 mg (226 patients), empagliflozin 25 mg (218 patients) or placebo (225 patients) in addition to their metformin plus sulphonylurea background therapy. A total of 666 patients were treated with randomised study medication. Of those, 58 patients (8.7%) prematurely discontinued study medication (empagliflozin 10 mg: 7.6%, empagliflozin 25 mg: 7.9%, placebo: 10.7%) with the main reason for discontinuation being the occurrence of adverse events (empagliflozin 10 mg: 2.7%, empagliflozin 25 mg: 3.2%, placebo: 3.6%).

Overall, 101 patients were treated with empagliflozin 25 mg on an open-label basis. In total, 85 patients (84.2%) completed the 24-week treatment period.

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Efficacy results: (continued)

The demographic and baseline characteristics were comparable between the randomised treatment groups. Overall, 50.9% of patients were male; 57.2% were of Asian race and 39.3% were White. The mean (SD) age was 57.1 (9.2) years. At baseline, 42.0% of patients had normal renal function, 49.2% had mild renal impairment, and 8.7% had moderate renal impairment. Mean (SD) baseline HbA_{1c} was similar across the randomised treatment groups (empagliflozin 10 mg: 8.07 [0.81]%, empagliflozin 25 mg: 8.10 [0.83]%, placebo: 8.15 [0.83]%). Mean (SD) weight (empagliflozin 10 mg: 77.08 [18.34] kg, empagliflozin 25 mg: 77.50 [18.81] kg, placebo: 76.23 [16.88] kg) and MDG (empagliflozin 10 mg: 170.28 (29.06) mg/dL, empagliflozin 25 mg: 172.72 (37.79) mg/dL, placebo: 170.45 (30.38) mg/dL) were also similar in the treatment groups. Overall mean (SD) baseline FPG was 153.0 (34.2) mg/dL, waist circumference was 96.4 (13.4) cm, SBP was 128.9 (14.1), DBP was 78.6 (8.8) mmHg, and BMI was 28.18 (5.27) kg/m^2. Most patients had been diagnosed with diabetes for >5 to 10 years (37.1%) or for more than 10 years (40.4%).

In the open-label group, 53.5% of the patients were male, 49.5% of patients were White and 47.5% were of Asian race. The mean (SD) age was 53.4 (10.5) years. The majority of patients had normal renal function (53.5%) or mild renal impairment (41.6%); 5.0% had moderate renal impairment at baseline. Overall mean (SD) baseline HbA_{1c} was 11.18 (1.25)%, weight was 76.43 (18.21) kg, BMI was 28.70 (5.49) kg/m^2, MDG was 233.07 (63.34) mg/dL, FPG was 200.4 (60.8) mg/dL, SBP was 126.4 (12.4), DBP was 78.3 (8.8) mmHg, and waist circumference was 97.6 (13.9) cm; 37.6 % of patients had been diagnosed with diabetes for more than 10 years, 32.7% for >5 to 10 years.

Overall compliance was between 80% and 120% for 95.2% of patients in the randomised treatment groups. In the open-label group, 93.1% of patients had overall compliance within this range.

Primary endpoint

The main efficacy endpoint analysis was performed on the full analysis set (FAS) of patients (empagliflozin 10 mg: 225 patients, empagliflozin 25 mg: 216 patients, placebo: 225 patients) using the LOCF approach to impute missing data. Superiority of empagliflozin 10 mg and 25 mg over placebo was demonstrated for the change of HbA_{1c} after 24 weeks of treatment. A summary of the treatment difference in HbA_{1c} adjusted mean change from baseline is

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Efficacy results: (continued)

included in Table 2: 2 below. Sensitivity analyses confirmed the superiority of both doses of empagliflozin over placebo.

For open-label treatment with 25 mg empagliflozin the mean change (SD) from baseline at Week 24 in HbA_{1c} was -2.53 (1.52)% for LOCF imputation and -2.89 (1.37)% for OC imputation.

Key secondary endpoints

Superiority of empagliflozin 10 mg and 25 mg over placebo in terms of body weight and mean daily glucose (MDG) change from baseline was demonstrated after 24 weeks of treatment. Sensitivity analyses confirmed the superiority of empagliflozin over placebo treatment. A higher mean reduction from baseline in MDG was observed for both empagliflozin treatment groups compared with placebo when OC imputation was used. The results for the analyses of both key secondary endpoints are included in Table 2: 2 below.

For the open-label group, a mean change (SD) from baseline in weight of -1.29 (2.99) kg using LOCF and -1.76 (3.42) kg using OC imputation, and in MDG of -29.34 (47.44) mg/dL using LOCF and -61.04 (52.60) mg/dL using OC imputation was observed.

Table 2: 2 Change from baseline versus placebo for the primary and key secondary endpoints at Week 24 (FAS), LOCF - (metformin plus sulphonylurea)

Comparison vs. placebo at 24 weeks	Empagliflozin 10 mg	Empagliflozin 25 mg
HbA_{1c} [%]		
Adjusted mean (standard error)	-0.64 (0.07)	-0.59 (0.07)
97.5% confidence interval	(-0.79, -0.49)	(-0.74, -0.44)
p-value	<0.0001	<0.0001
Body weight [kg]		
Adjusted mean (standard error)	-1.76 (0.22)	-1.99 (0.22)
97.5% confidence interval	(-2.25, -1.28)	(-2.48, -1.50)
p-value	<0.0001	<0.0001
MDG [mg/dL]		
Adjusted mean (standard error)	-10.02 (2.53)	-13.06 (2.70)
97.5% confidence interval	(-15.72, -4.32)	(-19.15, -6.98)
p-value	<0.0001	<0.0001

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Efficacy results: (continued)

Other endpoints

In line with the reduction in HbA_{1c}, consistent reductions in FPG from baseline were noted in comparison to placebo treatment for both doses of empagliflozin. In addition, clinically meaningful reductions in systolic blood pressure were noted for both doses of empagliflozin. Reductions in waist circumference in the empagliflozin treatment groups were consistent with reduction in body weight after 24 weeks of treatment. A higher proportion of patients treated with empagliflozin 10 mg or 25 mg compared with placebo reached target HbA_{1c} levels of <7.0% or <6.5%, had a HbA_{1c} reduction of at least 0.5%, and achieved the composite endpoint after 24 weeks of randomised treatment. Among patients not already at the blood pressure goal of SBP <130 mmHg and DBP <80 mmHg at baseline, more patients in the randomised empagliflozin treatment groups than in the placebo group reached the blood pressure goal after 24 weeks of treatment. The proportions of patients who required the use of rescue medication during randomised treatment was lower in the empagliflozin groups than in the placebo group.

For the open-label group, reductions in FPG were in line with the reduction in HbA_{1c}. In addition, reductions in waist circumference, SBP, and DBP were noted from baseline at Week 24; the results were supported by the proportions of patients achieving the criteria for the composite endpoint.

Empagliflozin trough concentrations were maintained during the course of the study for both dose groups. The increase in empagliflozin exposure was roughly proportional with an increase in dose from 10 mg to 25 mg. Similar exposure was observed in males and females, up to an age of 65 years, in all weight, race, geographical region, and ethnicity group categories. Exposure increased with a decrease in renal function.

Safety results:

SUBSTUDY A: METFORMIN ONLY BACKGROUND MEDICATION

All 706 patients who were treated with study medication in this substudy, were included in the safety analysis. The mean (SD) exposure time was 170.0 (12.2) days for the empagliflozin 10 mg group, 164.0 (28.2) days for the empagliflozin 25 mg group and 161.4 (35.4) days for the placebo group. The total duration of exposure was 101 patient years to empagliflozin 10 mg and 96.1 patient years to empagliflozin 25 mg.

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Safety results: (continued)

In the open-label arm, the mean (SD) exposure time was 160.8 (35.2) days with a total exposure time to empagliflozin 25 mg of 30.4 patient years.

The frequency of patients with at least one reported AE on treatment was 57.1% in the empagliflozin 10 mg group, 49.5% in the empagliflozin 25 mg group, and 58.7% in the placebo group. The highest frequency of adverse events was reported for the MedDRA system organ class 'infections and infestations' with similar frequencies in all randomised treatment groups (empagliflozin 10 mg: 21.2%, empagliflozin 25 mg: 23.4%, placebo: 23.3%). The AE reported with the highest incidence at the preferred term level was nasopharyngytis (empagliflozin 10 mg: 5.5%, empagliflozin 25 mg: 7.0%, placebo: 7.8%).

AEs were mostly of mild or moderate intensity; severe adverse events were reported for 2.3% of patients in the empagliflozin 10 mg group, 2.8% of patients in the empagliflozin 25 mg group, and 3.4% of patients in the placebo group. Few AEs leading to premature discontinuation of trial medication were reported (empagliflozin 10 mg: 0.9%, empagliflozin 25 mg: 2.3%, placebo: 3.4%). Adverse events considered to be drug-related by the investigator were reported for 16.1% of patients in the empagliflozin 10 mg group, 12.6% of patients in the empagliflozin 25 mg group, and 12.1% of patients in the placebo group.

SAEs were reported for 7 patients (3.2%) in the empagliflozin 10 mg group, 5 patients (2.3%) in the empagliflozin 25 mg group, and 7 patients (3.4%) in the placebo group. No patient died in this substudy.

Confirmed hypoglycaemic events were reported for 4 patients (1.8%) in the empagliflozin 10 mg group, 3 patients (1.4%) in the empagliflozin 25 mg group, and 1 patient (0.5%) in the placebo group. No severe hypoglycaemic events were reported.

Changes in markers of renal function (creatinine and eGFR) during the treatment phase were generally small and similar in the randomised treatment groups. No lab constellation recorded in this substudy was consistent with potential Hy´s law for any patient.

The overall frequency of adverse events related to urinary tract infections was similar across treatment groups (empagliflozin 10 mg: 11 patients [5.1%], empagliflozin 25 mg: 12 patients [5.6%], placebo: 10 patients [4.9%]); the proportion of female patients reporting urinary tract infections in the

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Safety results: (continued)

empagliflozin treatment groups was higher than in the placebo group. The incidence of genital infections reported during the trial was low, with 8 patients (3.7%) in the empagliflozin 10 mg group, 10 patients (4.7%) in the empagliflozin 25 mg group, but no patients in the placebo group; the proportion of female patients was higher than the proportion of male patients reporting genital infections.

In the open-label group, 55.1% of patients reported at least 1 AE. AEs of severe intensity were reported by 1 patient (1.4%). Investigator-defined drug-related adverse events were reported for 11 patients (15.9%). Premature discontinuation of trial medication due to AEs and serious adverse events were each reported for 1 patient in the open-label group. Confirmed hypoglycaemic events were reported for 2 patients (2.9%); UTIs for 5 patients (7.2%), 4 of which were female. Genital infection was reported by 1 patient.

Mean changes from baseline in differentials (automatic and absolute), enzymes, and plasma proteins were negligible after 24 weeks of randomised treatment. No changes in electrolytes were observed for any treatment group. Numerically urine albumin/creatinine ratio decreased for empagliflozin 10 mg and 25 mg treatment when compared to placebo treatment; haematocrit values in the empagliflozin treatment groups increased in comparison to the placebo groups and uric acid decreased in both empagliflozin treatment groups compared to placebo. For the randomised empagliflozin treatment groups, numerical increase in mean values of HDL cholesterol and LDL cholesterol were noted after 24 weeks when compared to placebo; no major differences to placebo in mean changes from baseline were noted for both empagliflozin doses in total cholesterol, LDL/HDL cholesterol ratio, non-HDL cholesterol, and triglycerides.

Overall in this substudy, no increase in pulse rate was observed for empagliflozin treatment; changes over time were small and comparable in all treatment groups.

SUBSTUDY B: METFORMIN PLUS SULPHONYLUREA BACKGROUND MEDICATION

All 767 patients who were treated with study medication in this substudy, were included in the safety analysis. The mean (SD) exposure time was 164.8 (27.7) days for the empagliflozin 10 mg group, 161.1 (37.0) days for the empagliflozin

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Safety results: (continued)

25 mg group and 162.0 (33.3) days for the placebo group. The duration of exposure was 101 patient years to empagliflozin 10 mg and 95.7 patient years to empagliflozin 25 mg.

In the open-label arm, the mean (SD) exposure time was 159.0 (35.5) days with a total exposure time to empagliflozin 25 mg of 44 patient years.

The frequency of patients at least one reported AE on treatment was 67.9% in the empagliflozin 10 mg group, 64.1% in the empagliflozin 25 mg group, and 62.7% in the placebo group. The highest frequency of adverse events was reported for the MedDRA system organ class 'infections and infestations' with similar frequencies in all randomised treatment groups (empagliflozin 10 mg: 27.2%, empagliflozin 25 mg: 28.1%, placebo: 24.0%). The AE reported with the highest incidence at the preferred term level was hypoglycaemia (empagliflozin 10 mg: 15.6%, empagliflozin 25 mg: 12.9%, placebo: 9.8%).

AEs were mostly of mild or moderate intensity and severe adverse events were reported for 1.8% of patients in the empagliflozin 10 mg group, 1.4% of patients in the empagliflozin 25 mg group, and 4.4% of patients in the placebo group. AEs leading to premature discontinuation of trial medication were reported for 2.7% of patients in the empagliflozin 10 mg group, 3.2% of patients in the empagliflozin 25 mg group, and 3.6% of patients in the placebo group. Adverse events considered to be drug-related by the investigator were reported for 24.1% of patients in the empagliflozin 10 mg group, 19.8% of patients in the empagliflozin 25 mg group, and 15.1% of patients in the placebo group.

Serious adverse events were reported for 11 patients (4.9%) in the empagliflozin 10 mg group, 1 patient (0.5%) in the empagliflozin 25 mg group, and 14 patients (6.2%) in the placebo group. Two patients died during the study: 1 patient due to acute myocardial infarction in the empagliflozin 10 mg group, and 1 patient due to acute left ventricular failure in the post-study period in the placebo group.

Confirmed hypoglycaemic events were reported for 36 patients (16.1%) in the empagliflozin 10 mg group, 25 patients (11.5%) in the empagliflozin 25 mg group, and 19 patients (8.4%) in the placebo group. No severe hypoglycaemic events were reported.

During the randomised treatment phase, 1 patient in the empagliflozin 10 mg group was reported with a protocol-specified significant adverse event of 2-fold

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increase in creatinine from baseline. Changes in markers of renal function (creatinine and eGFR) during the treatment phase were generally small and similar in the randomised treatment groups. No lab constellation recorded in this substudy was consistent with potential Hy´s law for any patient.

The overall frequency of adverse events related to urinary tract infections was similar across treatment groups (empagliflozin 10 mg: 23 patients [10.3%], empagliflozin 25 mg: 18 patients [8.3%], placebo: 18 patients [8.0%]); the proportion of female patients reporting urinary tract infections in the empagliflozin treatment groups was higher than in the placebo group. The incidence of genital infections reported during the trial was low, with 6 patients (2.7%) in the empagliflozin 10 mg group, 5 patients (2.3%) in the empagliflozin 25 mg group, and 2 patients (0.9%) in the placebo group. The proportion of female patients reporting genital infections in the empagliflozin treatment groups was higher than in the placebo group.

In the open-label group, 67.3% of patients reported at least 1 AE. Premature discontinuation of trial medication due to AEs, as well as serious adverse events were reported for 5 patients (5.0%) each. Investigator-defined drug-related adverse events were reported for 19 patients (18.8%); 3 patients (3.0%) reported AEs with severe intensity. Confirmed hypoglycaemic events were reported for 7 patients (6.9%), UTIs were reported for 3 patients (6.4%), genital infections for 2 patients (2.0%).

Mean changes from baseline in differentials (automatic and absolute), enzymes, and plasma proteins were negligible after 24 weeks of treatment. No changes in electrolytes were observed for any treatment group. Numerically urine albumin/creatinine ratio decreased for empagliflozin 10 mg and 25 mg treatment when compared to placebo treatment; haematocrit values in the empagliflozin treatment groups increased in comparison to the placebo groups and uric acid decreased in both empagliflozin treatment groups compared to placebo. For the randomised empagliflozin treatment groups, numerical increase in mean HDL cholesterol for both empagliflozin doses and in total cholesterol for empagliflozin 25 mg was observed when compared with placebo. No major differences to placebo were noted for mean changes of LDL cholesterol, LDL/HDL cholesterol ratio, non-HDL cholesterol, and triglycerides for both empagliflozin doses and for total cholesterol for empagliflozin 10 mg.

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Safety results: (continued)	Overall in this substudy, no increase in pulse rate was observed for empagliflozin treatment; changes over time were small and comparable in all treatment groups.
Conclusions:	Treatment with empagliflozin 10 mg and 25 mg resulted in statistically significant and clinically meaningful reduction in HbA_{1c}, body weight, and mean daily glucose in comparison to placebo as add-on therapy to existing background medication of metformin only or metformin plus sulphonylurea in patients with type 2 diabetes and insufficient glycaemic control. Consistent results were observed in exploratory endpoints FPG and 2h PPG. There was an increased rate of hypoglycaemia when empagliflozin was administered in addition to metformin and sulphonylurea. Although the overall incidences of urinary tract infections were low and similar across treatment groups, in female patients a higher incidence of UTIs during treatment with empagliflozin than with placebo was noted. The overall incidence of genital infections was low. However, a higher proportion of patients in the empagliflozin treatment groups compared with the placebo group reported genital infections, most of these were female. Overall, empagliflozin treatment was generally well tolerated and showed similar safety profiles compared to placebo treatment in patients with metformin only and metformin plus sulphonylurea background medication.