Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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Title of trial:	A phase III, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg and 25 mg administered once daily) as add on to pre-existing antidiabetic therapy over 52 weeks in patients with type 2 diabetes mellitus and renal impairment and insufficient glycaemic control.
Coordinating Investigators:	[redacted]
Trial sites:	Multi-centre trial: 127 trial sites in 15 countries (Canada, France, Hong Kong, India, Malaysia, Netherlands, Philippines, Poland, Portugal, Russia, Slovakia, South Africa, Spain, United States, United Kingdom)
Publication (reference):	Data from this trial have not been published.
Clinical phase:	III
Objectives:	The objective of the current study is to investigate the efficacy, safety and tolerability of empagliflozin treatment (10 mg and 25 mg, once daily) compared to placebo treatment as add-on to pre-existing antidiabetic therapy in patients with type 2 diabetes mellitus with insufficient glycaemic control and different degrees of renal impairment based on the estimated glomerular filtration rate (eGFR) at screening (mild: eGFR ≥60 to <90 ml/min/1.73m², moderate: eGFR ≥30 to <60 ml/min/1.73m², severe: eGFR ≥15 to <30 ml/min/1.73m²) over 52 weeks.
Methodology:	This was a randomised, double-blind, placebo-controlled, parallel-group comparison study. Randomisation was stratified by HbA_{1c}, renal function, and background medication at screening. A 2-week open-label placebo run-in period preceded randomisation. Patients were to be followed up for 3-weeks after last intake of study drug or after the premature discontinuation visit.

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No. of subjects:

planned: Entered: 682

actual:

Overall population

Enrolled (total): 1317
Entered (total): 741
- Placebo: entered: 321 treated: 319
- Empagliflozin 10 mg: entered: 98 treated: 98
- Empagliflozin 25 mg: entered: 322 treated: 321

Patients with mild renal impairment (eGFR ≥60 and <90 ml/min/1.73m²)

Entered (total): 292
- Placebo: entered: 97 treated: 95 analysed (for primary endpoint): 95
- Empagliflozin 10 mg: entered: 98 treated: 98 analysed (for primary endpoint): 98
- Empagliflozin 25 mg: entered: 97 treated: 97 analysed (for primary endpoint): 97

Patients with moderate renal impairment (eGFR ≥30 and <60 ml/min/1.73m²)

Entered (total): 375
- Placebo: entered: 187 treated: 187 analysed (for primary endpoint): 187
- Empagliflozin 25 mg: entered: 188 treated: 187 analysed (for primary endpoint): 187

Patients with severe renal impairment (eGFR ≥15 and <30 ml/min/1.73m²)

Entered (total): 74
- Placebo: entered: 37 treated: 37 analysed: 37
- Empagliflozin 25 mg: entered: 37 treated: 37 analysed: 37

Diagnosis and main criteria for inclusion: Patients with type 2 diabetes mellitus and insufficient glycaemic control (HbA_{1c} ≥7.0 and ≤10.0%) despite antidiabetic therapy and renal impairment with eGFR between 15 and <90 mL/min/1.73m²; age ≥18; body mass index (BMI) ≤45 kg/m^2

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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: 909474A, 909475A, 3436, 003437A Empagliflozin 25 mg: 909473A, 001747A, 3532, 3530
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, 88494, 88493 Placebo matching empagliflozin 25 mg: 85114, 85092, 86606, 88655, 88651
Duration of treatment:	Two-week placebo run-in; 52-week treatment period; 3-week follow-up period.
Criteria for evaluation:	
Efficacy:	The primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of treatment for a combined set of patients with mild or moderate renal impairment, for patients with mild, and for patients with moderate renal impairment. The following other exploratory efficacy endpoints were defined: change from baseline in HbA_{1c} after 52 weeks of treatment; occurrence of a treat to target efficacy response (HbA_{1c} of <7.0% and <6.5%) and of a relative efficacy response (HbA_{1c} lowering by a least 0.5%) after 24 and 52 weeks of treatment; change from baseline in HbA_{1c}, fasting plasma glucose (FPG), weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and waist circumference by visit over time; change from baseline in FPG, body weight, waist circumference, systolic and diastolic blood pressure after 24 and 52 weeks of treatment; occurrence of weight reduction of >5%, occurrence of blood pressure response with blood pressure lower than 130/80 mmHg after 24 and 52 weeks of treatment; composite endpoint of the following conditions at weeks 24 and 52: HbA_{1c} reduction from baseline of ≥0.5%, reduction in SBP from baseline >3 mmHg, body weight reduction from baseline of >2%.; use of rescue therapy. Trough plasma concentrations of empagliflozin were analysed as pharmacokinetic parameters.

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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 adverse events related to volume depletion and bone fractures. Change from baseline in clinical laboratory assessments, vital signs, and 12-lead ECG.
Statistical methods:	The primary endpoint was analysed for groups of patients based on their level of renal impairment at screening (mild and moderate combined, mild, moderate,). An analysis of covariance (ANCOVA) model was applied on the full analysis set with treatment and background therapy as fixed classification effects and HbA_{1c} at baseline as linear covariate. For analyses of the combined group of patients with mild or moderate renal impairment, renal impairment was included in the model as a fixed classification effect. A hierarchical testing sequence was applied with an overall type I error maintained at 5%. Missing data was imputed using the last observation carried forward (LOCF) approach. Sensitivity analyses of the primary endpoint were performed using ANCOVA models similar to the primary analysis, and a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach applied on different patient populations. Other exploratory efficacy endpoints were analysed for groups of patients based on their renal impairment category at screening. Continuous exploratory endpoints were analysed using a similar model as used for the primary analysis. Categorical exploratory endpoints were tabulated. Binary exploratory endpoints were analysed using logistic regression; odds ratios, the respective 95% confidence intervals and p-values were obtained. Patients with severe renal impairment at screening were included in the descriptive statistics but not the statistical modelling. Pharmacokinetic analysis consisted of individual concentration-time data and descriptive statistics for trough concentrations. Safety analysis was performed using descriptive statistics on the overall population for the entire 52-week study duration; additional analyses were performed on selected safety parameters by renal impairment category and for the first 24 weeks of treatment. ANCOVA and MMRM analyses were performed for lipid parameters.

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SUMMARY – CONCLUSIONS:

Efficacy results:

In this study, 1317 patients were enrolled by 127 centres in 15 countries in Asia, Europe, and North America. A total of 741 patients were randomised based on their renal function at screening; 738 patients were treated with study medication. Overall, 292 patients with mild renal impairment were randomised in a 1:1:1 ratio to either placebo (97 patients), empagliflozin 10 mg (98 patients), or empagliflozin 25 mg (97 patients); all patients except 2 patients in the placebo group were treated. In total, 375 patients with moderate renal impairment were randomised in a 1:1 ratio to either placebo (187 patients) or empagliflozin 25 mg (188 patients); all patients except 1 patient in the empagliflozin 25 mg group were treated. In addition, a combined set of patients with mild or moderate renal impairment was defined for analysis, which comprised 282 patients treated with placebo and 284 patients treated with empagliflozin 25 mg. In total, 74 patients with severe renal impairment were randomised in a 1:1 ratio to either placebo (37 patients) or empagliflozin 25 mg (37 patients) treatment; all of these patients were treated.

Of the treated patients, 91.0% with mild renal impairment, 88.5% with moderate renal impairment, 89.6% with mild or moderate renal impairment, and 68.9% with severe renal impairment completed the 52-week treatment period. The most frequent reason for premature treatment discontinuation was adverse events; reported for 4.5% of patients with mild renal impairment, 4.3% of patients with moderate renal impairment, and 18.9% of patients with severe renal impairment.

The demographic and most baseline characteristics were well balanced across the treatment groups for the overall patient population. More than half (58.3%) of the patients were male; 60.3% of patients were White and 36.0% were Asian. In the overall population, the mean (SD) age was 63.9 (8.8) years. Mean (SD) baseline HbA_{1c} was 8.04 (0.82)%, FPG was 145.4 (41.9) mg/dL, weight was 85.0 (20.0) kg, BMI was 30.74 (5.49) kg/m^2, waist circumference was 104.4 (14.8) cm, systolic blood pressure (SBP) was 136.9 (18.1) mmHg, and diastolic blood pressure (DBP) was 75.9 (9.6) mmHg. Most patients (61.5%) had been diagnosed with diabetes for more than 10 years.

Efficacy results: (continued)

The proportion of White patients was higher in the group of patients with mild renal impairment (68.3%) than in patients with moderate (56.1%) or severe (50.0%) renal impairment.

Patients with mild and moderate renal impairment at screening had similar mean

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Efficacy results: (continued)

(SD) baseline HbA_{1c} (mild: 8.03 [0.79]%, moderate: 8.04 [0.79]%, severe: 8.11 [1.01]%), FPG (mild: 146.4 [35.2] mg/dL, moderate: 143.3 [43.5] mg/dL, severe: 152.2 [55.8] mg/dL), and SBP (mild: 135.3 [16.6] mmHg, moderate: 136.5 [18.2] mmHg, severe: 145.6 [21.2] mmHg). Mean (SD) baseline weight was slightly higher in patients with mild renal impairment than in other renal impairment groups (mild: 88.7 [21.1] kg, moderate: 82.9 [18.8] kg, severe: 81.0 [19.0] kg).

Overall compliance was between 80% and 120% for 95.9% of patients in the treatment groups; 96.6% of patients with mild, 97.1% of patients with moderate, and 87.8% of patients with severe renal impairment had compliance within this range.

Primary endpoint

The main efficacy endpoint analysis was performed on the full analysis set (FAS) of patients using an LOCF approach to impute missing data; it was analysed for the combined set of patients with mild or moderate renal impairment and also for the separate groups of patients with mild renal impairment and moderate renal impairment. Superiority of empagliflozin 25 mg over placebo was demonstrated for the change of HbA_{1c} after 24 weeks of treatment for patients with mild renal impairment, moderate renal impairment, and for the combined set of patients with mild or moderate renal impairment. The change in HbA_{1c} after 24 weeks of treatment with empagliflozin 10 mg was tested for patients with mild renal impairment; the analysis demonstrated superiority of empagliflozin 10 mg over placebo. A summary of the treatment differences in HbA_{1c} adjusted mean changes from baseline for the analysed groups of renal impairment is included in Table 2: 1 below. Sensitivity analyses of the primary endpoint confirmed superiority of empagliflozin over placebo in all analysed groups.

The change in HbA_{1c} at Week 24 was also tested in patients with chronic kidney disease stage 3A (moderate renal impairment A: eGFR ≥45 and <60 ml/min/1.73m²) and 3B (moderate renal impairment B: eGFR ≥30 and <45 ml/min/1.73m²); the adjusted mean treatment differences for empagliflozin 25 mg compared with placebo were -0.46% (95% CI: -0.66, -0.27) for patients with moderate A renal impairment and -0.39% (95% CI: -0.58, -0.19) for patients with moderate B renal impairment.

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Efficacy results: (continued)

Table 2: 1 Change from baseline versus placebo for the primary endpoint at Week 24 (FAS), LOCF

Renal impairment category/ Comparison vs. placebo at Week 24	Empagliflozin 10 mg	Empagliflozin 25 mg
Mild or moderate renal impairment		
Adjusted[1] mean HbA_{1c} (SE)	-	-0.51 (0.06)
95% confidence interval	-	(-0.62, -0.39)
p-value	-	<0.0001
Mild renal impairment		
Adjusted[2] mean HbA_{1c} (SE)	-0.52 (0.10)	-0.68 (0.10)
95% confidence interval	(-0.72, -0.32)	(-0.88, -0.49)
p-value	<0.0001	<0.0001
Moderate renal impairment		
Adjusted[1] mean HbA_{1c} (SE)	-	-0.42 (0.07)
95% confidence interval	-	(-0.56, -0.28)
p-value	-	<0.0001

[1] ANCOVA model includes treatment, renal function, background medication , and baseline HbA_{1c}
[2] ANCOVA model includes treatment, background medication , and baseline HbA_{1c}
SE = Standard error

Other exploratory efficacy endpoints

In patients with mild or moderate renal impairment, analysis of HbA_{1c} changes at Week 52 and over time showed that reductions achieved at Week 24 in the empagliflozin treatment groups were maintained until the end of the study. Results were supported by the analysis of absolute (HbA_{1c} levels of <7.0% or <6.5%) and relative efficacy responses (≥0.5% reduction in HbA_{1c}) relative to baseline after 24 and 52 weeks of treatment; higher proportions of patients in the mild and moderate renal impairment groups treated with empagliflozin achieved these targets compared with patients receiving placebo.

Consistent reductions in FPG were noted at Week 24 in the empagliflozin treatment groups for patients with mild or moderate renal impairment which were maintained until the end of the study at Week 52. For patients with severe renal impairment, the descriptive analyses of changes in HbA_{1c} and FPG showed no reduction for the empagliflozin treatment group when compared with placebo.

For patients with mild, moderate, or severe renal impairment, higher reductions in body weight, SBP, and DBP were observed at Week 24 in the empagliflozin

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	treatment groups than in the placebo group; changes were maintained until Week 52. In all renal impairment categories, more patients in the empagliflozin treatment groups than in the placebo group showed a reduction in body weight of more than 5% from baseline at Week 24 and Week 52; among patients not already at the blood pressure goal (SBP <130 mmHg and DBP <80 mmHg) at baseline, more patients in the randomised empagliflozin treatment groups than in the placebo group reached this target after 24 weeks of treatment. In each renal impairment group, lower proportions of patients in the empagliflozin treatment groups than in the placebo group required the use of rescue medication during the first 24 weeks of the study. The PK analysis showed that steady-state concentrations of empagliflozin were maintained during the course of the study. The increase in empagliflozin exposure with dose was roughly proportional with an increase in dose from 10 mg to 25 mg. Empagliflozin exposure increased with a decrease in renal function, was generally similar in males and females at both dose levels, and no relevant change was observed with an increase in age. With an increase in body weight, empagliflozin exposure decreased; exposure was also slightly higher in Asians compared with Whites.
Safety results:	All 738 patients (290 patients with mild renal impairment, 374 patients with moderate renal impairment, 74 patients with severe renal impairment) who took at least one dose of study medication during the randomised treatment period, were included in the analysis of overall safety. Safety by renal impairment category is presented below. <u>Overall safety</u> The mean (SD) exposure time was 338.4 (79.6) days for the placebo group, 345.7 (74.1) days for the empagliflozin 10 mg group, and 335.6 (85.7) days for the empagliflozin 25 mg group. The total duration of exposure was 92.7 patient years to empagliflozin 10 mg, and 294.9 patient years to empagliflozin 25 mg.
Safety results: (continued)	Overall, 84.6% of patients in the placebo group, 87.8% of patients in the empagliflozin 10 mg group, and 83.5% of patients in the empagliflozin 25 mg group reported at least 1 adverse event during the 52 week treatment period. Additional analysis of safety in the first 24 weeks showed a similar overall safety profile. Adverse events leading to premature discontinuation of trial medication were reported for 17 patients (5.3%) in the placebo group, 4 patients (4.1%) in the empagliflozin 10 mg group, and 21 patients (6.5%) in the empagliflozin 25 mg

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	group. Most adverse events were of mild or moderate intensity; adverse events of severe intensity were reported for 11.0% of patients in the placebo group, 6.1% of patients in the empagliflozin 10 mg group, and 10.6% of patients in the empagliflozin 25 mg group. Adverse events considered to be drug-related by the investigator were reported for 27.3% of patients in the placebo group, 37.0% of patients in the empagliflozin 10 mg group, and 31.5% of patients in the empagliflozin 25 mg group. Serious adverse events were reported for 13.8% of patients in the placebo group, 6.1% of patients in the empagliflozin 10 mg group, and 12.5% patients in the empagliflozin 25 mg group. Eight patients died during the study; 4 deaths occurred on treatment (3 in the placebo group, 1 in the empagliflozin 25 mg group), 1 death occurred in the post-treatment phase (empagliflozin 25 mg group), and 3 deaths occurred post-study (2 in the placebo group, 1 screening failure). In the first 24 weeks, confirmed hypoglycaemic events were reported for 22.9% of patients in the placebo group, 23.5% of patients in the empagliflozin 10 mg group, and 22.1% of patients in the empagliflozin 25 mg group. During the initial 24 week treatment period, severe episodes (requiring assistance) were reported for 5 patients (1.6%) in the placebo group, 1 patient (1.0%) in the empagliflozin 10 mg group, and 5 patients (1.6%) in the empagliflozin 25 mg group. Adverse events related to bone fractures were more frequently reported in the placebo group than in the empagliflozin treatment group; adverse events related to volume depletion were reported in a higher frequency for patients in the empagliflozin 25 mg group than in the placebo group and overall lower frequencies for patients in the empagliflozin 10 mg group.
Safety results: (continued)	Small changes in markers of renal function (creatinine and eGFR) during the treatment phase were noted for all treatment groups, but were generally reversible after the end of treatment in the empagliflozin groups. Improvements in albuminuria and urine albumin/creatinine ratios were observed for the empagliflozin treatment groups. No lab constellation recorded in this study 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 (placebo: 14.7%, empagliflozin 10 mg: 14.3%, empagliflozin 25 mg: 14.6%). The overall frequency of genital infections was low; higher proportions of patients in the empagliflozin treatment groups than in the placebo group reported genital infections (placebo: 2.5%, empagliflozin 10 mg

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Safety results: (continued)

group: 7.1%, empagliflozin 25 mg: 3.4%); no case lead to treatment discontinuation.

Mean changes from baseline in differentials (automatic and absolute), electrolytes, enzymes, and plasma proteins were minimal after 52 weeks of randomised treatment. No changes in electrolytes were observed for any treatment group. Haematocrit and haemoglobin values increased in the empagliflozin treatment groups and decreased in the placebo group; however, changes were reversible in the empagliflozin treatment groups. A small decrease in uric acid values was noted for the empagliflozin treatment groups.

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

Patients with mild renal impairment

For patients with mild renal impairment, 87.4% of patients in the placebo group, 87.8% in the empagliflozin 10 mg group, 80.4% of patients in the empagliflozin 25 mg group reported at least 1 adverse event during the entire 52 week treatment period. Similar safety profiles were noted for the analysis after 24 weeks of treatment. Serious adverse events were reported for 11.6% of patients in the placebo group, 6.1% of patients in the empagliflozin 10 mg group, and 7.2% of patients in the empagliflozin 25 mg group. No deaths were reported in this group.

After 24 weeks of treatment, confirmed hypoglycaemic events were reported for 20.0% of patients in the placebo group, 23.5% of patients in the empagliflozin 10 mg group, and 18.6% of patients in the empagliflozin 25 mg group.

During the entire study period, urinary tract infections were reported for 15.8% of patients in the placebo group, 14.3% of patients in the empagliflozin 10 mg group, and 9.3% of patients in the empagliflozin 25 mg group. Genital infections were reported for 6.3% of patients in the placebo group, 7.1% of patients in the empagliflozin 10 mg group, and 5.2% of patients in the empagliflozin 25 mg group.

Lipid parameters were analysed at Week 24 by ANCOVA modelling. There were no notable differences to placebo in mean changes from baseline for total cholesterol, LDL cholesterol, LDL/HDL cholesterol ratio, triglycerides, and non-HDL cholesterol in the empagliflozin treatment groups; numerical increase was noted only for HDL cholesterol in the empagliflozin 25 mg group.

Patients with moderate renal impairment

For patients with moderate renal impairment, 83.4% of patients in the placebo group and 83.4% of patients in the empagliflozin 25 mg group reported at least 1 adverse

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Safety results: (continued)	event during the entire 52 week treatment period. Similar safety profiles were noted for the Week 24 analysis. Serious adverse events were reported for 12.3% of patients in the placebo group and 11.8% of patients in the empagliflozin 25 mg group. Four deaths were reported in this group; 2 patients on treatment (1 patient in the placebo group, 1 patient in the empagliflozin 25 mg group), 1 patient post-treatment (empagliflozin 25 mg), and 1 patient post-study (placebo). During the initial 24 weeks of treatment, confirmed hypoglycaemic events were reported for 23.0% of patients in the placebo group and 20.9% of patients in the empagliflozin 25 mg group. For the entire treatment period, urinary tract infections were reported for 15.5% of patients in the placebo group and 16.6% of patients in the empagliflozin 25 mg group; genital infections for 1.1% of patients in the placebo group and 2.7% of patients in the empagliflozin 25 mg group. Lipid parameters were analysed at Week 24 by ANCOVA modelling; there were no notable differences to placebo in mean changes from baseline in total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL cholesterol ratio, triglycerides, and non-HDL cholesterol in the empagliflozin treatment group. <u>Patients with severe renal impairment</u> For patients with severe renal impairment, 83.8% of patients in the placebo group and 91.9% of patients in the empagliflozin 25 mg group reported at least 1 adverse event during treatment at Week 52. Similar safety profiles were noted for the Week 24 analysis. Serious adverse events were reported for 27.0% of patients in the placebo group and 29.7% of patients in the empagliflozin 25 mg group. Three deaths were reported in this group (placebo arm; 2 on treatment and 1 post-study). For the initial treatment period of 24 weeks, confirmed hypoglycaemic events were reported for 29.7% of patients in the placebo group and 37.8% of patients in the empagliflozin 25 mg group. During the entire study, urinary tract infections were reported for 8.1% of patients in the placebo group and 18.9% of patients in the empagliflozin 25 mg group. Genital infections were reported for only 1 patient (2.7%) in the empagliflozin 25 mg group.
Conclusions:	Treatment with empagliflozin 10 mg and 25 mg in patients with mild renal impairment and empagliflozin 25 mg in patients with moderate renal impairment led to statistically significant and clinically meaningful reductions in HbA_{1c} in comparison with placebo after 24 weeks of treatment; reductions were maintained

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until the end of the study at Week 52. Consistent reductions in FPG and clinically meaningful changes in body weight and blood pressure were noted for empagliflozin treatment. Overall, empagliflozin treatment was generally well tolerated and showed similar safety profiles compared with placebo treatment in patients with mild or moderate renal impairment; frequencies of urinary tract infections were balanced across treatment groups and higher proportions of patients treated with empagliflozin than with placebo reported genital infections. Changes in renal function after 52 weeks empagliflozin treatment were small and were reversible within a 3 week follow up period. In summary, this study showed that empagliflozin is efficacious in reducing HbA_{1c} and is generally well tolerated in patients with mild or moderate renal impairment. Thus, empagliflozin has a favourable benefit/risk ratio in patients with renal impairment with an eGFR $\geq$30 ml/min/1.73m^2.

Trial Synopsis – Appendix

The result table on the following page supplements the trial results presented in the Trial Synopsis. The appended table provides results for patient disposition as summarized below.

Results for	presented in
Patient Disposition at 52 weeks	Table 15.1.1.1: 2

Table 15.1.1.1: 2 Disposition of patients at week 52 - screened patients set

	Placebo N (%)	Empa 10mg N (%)	Empa 25mg N (%)	Total N (%)
Screened				1317
Started placebo run-in				826
Not entered				576
Entered	321	98	322	741
Not treated	2	0	1	3
Treated	319 (100.0)	98 (100.0)	321 (100.0)	738 (100.0)
Not prematurely discontinued from trial medication	278 (87.1)	88 (89.8)	280 (87.2)	646 (87.5)
Prematurely discontinued from trial medication	41 (12.9)	10 (10.2)	41 (12.8)	92 (12.5)
Adverse event	18 (5.6)	4 (4.1)	21 (6.5)	43 (5.8)
Worsening of disease under study	2 (0.6)	0	3 (0.9)	5 (0.7)
Worsening of other pre-existing disease	4 (1.3)	0	5 (1.6)	9 (1.2)
Other adverse event	12 (3.8)	4 (4.1)	13 (4.0)	29 (3.9)
Lack of efficacy	0	0	1 (0.3)	1 (0.1)
Non compliant with protocol	1 (0.3)	1 (1.0)	4 (1.2)	6 (0.8)
Lost to follow-up	3 (0.9)	0	3 (0.9)	6 (0.8)
Patient refusal to continue, not due to AE	10 (3.1)	4 (4.1)	8 (2.5)	22 (3.0)
Other	9 (2.8)	1 (1.0)	4 (1.2)	14 (1.9)
Not prematurely discontinued from trial	284 (89.0)	91 (92.9)	284 (88.5)	659 (89.3)
No termination visit	2 (0.6)	1 (1.0)	0	3 (0.4)
Prematurely discontinued from trial	35 (11.0)	7 (7.1)	37 (11.5)	79 (10.7)
Lost to follow-up	3 (0.9)	1 (1.0)	5 (1.6)	9 (1.2)
Consent withdrawn	29 (9.1)	6 (6.1)	30 (9.3)	65 (8.8)
Death	3 (0.9)	0	2 (0.6)	5 (0.7)
Other	0	0	0	0

'Entered' means randomised
Source data: Appendix 16.2.1, Listing 1