Clinical trial results:
A phase III randomised, double-blind, active-controlled parallel group efficacy and safety study of BI 10773 compared to glimepiride administered orally during 104 weeks with a 104 week extension period in patients with type 2 diabetes mellitus and insufficient glycaemic control despite metformin treatment

Summary

EudraCT number	2009-016244-39
Trial protocol	NL NO FI SE IT ES GB PT CZ AT
Global end of trial date	28 August 2015

Results information

Result version number	v1 (current)
This version publication date	02 September 2016
First version publication date	02 September 2016

Trial information

Trial identification

Sponsor protocol code	1245.28

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01167881
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 August 2013
Global end of trial reached?	Yes
Global end of trial date	28 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to investigate the efficacy, safety, and tolerability of empagliflozin (25 mg once daily) compared with glimepiride (1 to 4 mg once daily) as add-on therapy to immediate release metformin given for 104 weeks, with a 104-week extension period in patients with type 2 diabetes mellitus with insufficient glycaemic control. The 4-year analysis was planned to assess the long-term (208-week) efficacy and safety of empagliflozin vs. glimepiride. All analyses of data at 208 weeks were exploratory. The analysis done at 4 years included analysis of primary or secondary endpoints (1-2 years) which were exploratory, therefore we are not disclosing any of the endpoints from this report (4 years). The primary and secondary endpoints at 1 and 2 years is being disclosed in this final disclosure with updated disposition information, baseline characteristics and AEs.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required. Separate informed consent forms were required for participation in the 104-week extension.

Background therapy:

Patients were asked to continue their background therapy of immediate release metformin in an unchanged dose and dosing regimen throughout the trial.

Evidence for comparator:

The active comparator in this trial was glimepiride capsule 1-4 mg administered orally once daily.

Actual start date of recruitment	26 August 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 178
Country: Number of subjects enrolled	Austria: 53
Country: Number of subjects enrolled	Canada: 221
Country: Number of subjects enrolled	Colombia: 57
Country: Number of subjects enrolled	Czech Republic: 105
Country: Number of subjects enrolled	Finland: 164
Country: Number of subjects enrolled	Hong Kong: 38
Country: Number of subjects enrolled	India: 241
Country: Number of subjects enrolled	Italy: 69

Country: Number of subjects enrolled	Malaysia: 116
Country: Number of subjects enrolled	Mexico: 217
Country: Number of subjects enrolled	Netherlands: 56
Country: Number of subjects enrolled	Norway: 63
Country: Number of subjects enrolled	Philippines: 152
Country: Number of subjects enrolled	Portugal: 25
Country: Number of subjects enrolled	South Africa: 181
Country: Number of subjects enrolled	Spain: 114
Country: Number of subjects enrolled	Sweden: 121
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Taiwan: 55
Country: Number of subjects enrolled	Thailand: 74
Country: Number of subjects enrolled	United Kingdom: 128
Country: Number of subjects enrolled	United States: 202
Worldwide total number of subjects	2637
EEA total number of subjects	898

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	2023
From 65 to 84 years	614
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

An optional 2-year extension was implemented in this trial through a protocol amendment, which brought the total length of treatment to 4 years. However, some sites did not participate in the 2-year extension, and so considered patients to have completed treatment after 2 years.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The placebo run-in period of this trial was performed open-label, i.e. both the investigator and the patient knew that the patient received placebo during the run-in period. The randomised period of this trial was performed double-blind. Two unblinded analyses (at 1 and 2 years) were done prior to the end of the 4-year treatment period.

Arms

Are arms mutually exclusive?	Yes
Arm title	Empaglifozin 25 mg

Arm description:

Patients received one empagliflozin 25 mg tablet and one placebo glimepiride capsule orally once daily. Empagliflozin: 25 mg once daily. Placebo: Placebo matching glimepiride 1-4 mg. Out of 769, four patients randomised to the empagliflozin 25 mg arm were not treated. Consequently, number of subject that started is 769 but only 765 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

Arm type	Experimental
Investigational medicinal product name	Empaglifozin 25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin tablets 25 mg once daily was administered orally.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matching glimepiride 1-4 mg capsule was administered once daily orally.

Arm title	Glimepiride 1-4 mg

Arm description:

Patients received one glimepiride capsule and one placebo empagliflozin tablet orally once daily. Glimepiride: 1-4 mg once daily. Placebo: Placebo matching empagliflozin.

Arm type	Active comparator
Investigational medicinal product name	Glimepiride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Glimepiride capsule 1-4 mg was administered orally once daily.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo matching empagliflozin tablet was administered orally once daily.

Number of subjects in period 1[1]	Empaglifozin 25 mg	Glimepiride 1-4 mg
Started	765	780
Completed after 2 years treatment	95 [2]	127 [3]
Completed after 4 years treatment	515 [4]	462 [5]
Completed	610	589
Not completed	155	191
Adverse event, serious fatal	8	7
Other reason not defined	31	55
Non compliant with protocol	9	18
Patient refusal to cont., not due to AE	45	40
Adverse event, non-fatal	39	44
Lost to follow-up	19	20
Lack of efficacy	4	7

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: An optional 2-year extension was implemented in this trial through a protocol amendment, which brought the total length of treatment to 4 years. However, some sites did not participate in the 2-year extension, and so considered patients to have completed treatment after 2 years.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: An optional 2-year extension was implemented in this trial through a protocol amendment, which brought the total length of treatment to 4 years. However, some sites did not participate in the 2-year extension, and so considered patients to have completed treatment after 2 years.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: An optional 2-year extension was implemented in this trial through a protocol amendment, which brought the total length of treatment to 4 years. However, some sites did not participate in the 2-year extension, and so considered patients to have completed treatment after 2 years.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: An optional 2-year extension was implemented in this trial through a protocol amendment, which brought the total length of treatment to 4 years. However, some sites did not participate in the 2-year extension, and so considered patients to have completed treatment after 2 years.

Baseline characteristics

Reporting groups	
Reporting group title	Empaglifozin 25 mg
Reporting group description:	
Patients received one empagliflozin 25 mg tablet and one placebo glimepiride capsule orally once daily. Empagliflozin: 25 mg once daily. Placebo: Placebo matching glimepiride 1-4 mg. Out of 769, four patients randomised to the empagliflozin 25 mg arm were not treated. Consequently, number of subject that started is 769 but only 765 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.	
Reporting group title	Glimepiride 1-4 mg
Reporting group description:	
Patients received one glimepiride capsule and one placebo empagliflozin tablet orally once daily. Glimepiride: 1-4 mg once daily. Placebo: Placebo matching empagliflozin.	

Reporting group values	Empaglifozin 25 mg	Glimepiride 1-4 mg	Total
Number of subjects	765	780	1545
Age categorical Units: Subjects			

Age Continuous			
Full Analysis Set (FAS), All patients randomised, treated with at least one dose of study drug, and with a baseline HbA1c value.			
Units: years			
arithmetic mean	56.2	55.7	
standard deviation	± 10.3	± 10.4	-
Gender, Male/Female Units: participants			
Female	333	359	692
Male	432	421	853

End points

End points reporting groups

Reporting group title	Empaglifozin 25 mg

Reporting group description:

Patients received one empagliflozin 25 mg tablet and one placebo glimepiride capsule orally once daily. Empagliflozin: 25 mg once daily. Placebo: Placebo matching glimepiride 1-4 mg. Out of 769, four patients randomised to the empagliflozin 25 mg arm were not treated. Consequently, number of subject that started is 769 but only 765 reported to ensure consistent reporting with baseline characteristics that includes only treated patients.

Reporting group title	Glimepiride 1-4 mg

Reporting group description:

Patients received one glimepiride capsule and one placebo empagliflozin tablet orally once daily. Glimepiride: 1-4 mg once daily. Placebo: Placebo matching empagliflozin.

Primary: The change from baseline in glycosylated haemoglobin (HbA1c) after 104 weeks of treatment.

End point title	The change from baseline in glycosylated haemoglobin (HbA1c) after 104 weeks of treatment.

End point description:

FAS (LOCF) – Full Analysis Set (FAS) with Last Observation Carried Forward (LOCF); Values after start of antidiabetic rescue therapy were set to missing and last observation carried forward (LOCF) was used for imputation of missing values.

End point type	Primary

End point timeframe:

Baseline and 104 weeks.

End point values	Empaglifozin 25 mg	Glimepiride 1-4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765[1]	780[2]		
Units: Percentage				
arithmetic mean (standard error)	-0.66 (± 0.03)	-0.55 (± 0.03)		

Notes:

[1] - FAS (LOCF)

[2] - FAS (LOCF)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing Hierarchy for main analysis (104 weeks): 1. Non-inferiority in HbA1c change from baseline at 104 weeks. 2. Superiority in body weight change from baseline at 104 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 104 weeks. 4. Superiority in HbA1c change from baseline at 104 weeks. 5. Superiority in systolic blood pressure change from baseline at 104 weeks. 6. Superiority in diastolic blood pressure change from baseline at 104 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg

Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.11
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.2
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

[3] - Non-inferiority was tested through a two-sided 97.5% confidence interval for the treatment effect of empagliflozin minus the effect of glimepiride in change from baseline in HbA1c. The null-hypothesis of material inferiority of empagliflozin was rejected if the confidence interval was entirely below the non-inferiority margin 0.3%. ANCOVA with treatment, geographical region, renal function at baseline as fixed effects and baseline HbA1c as linear covariate.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Testing Hierarchy for main analysis (104 weeks): 1. Non-inferiority in HbA1c change from baseline at 104 weeks. 2. Superiority in body weight change from baseline at 104 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 104 weeks. 4. Superiority in HbA1c change from baseline at 104 weeks. 5. Superiority in systolic blood pressure change from baseline at 104 weeks. 6. Superiority in diastolic blood pressure change from baseline at 104 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0153 [5]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.11
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.2
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

[4] - ANCOVA with treatment, geographical region, renal function at baseline as fixed effects and baseline HbA1c as linear covariate.
[5] - The superiority tests performed at 104 weeks and the superiority tests performed at 52 weeks both used a nominal significance level of 2.5% to maintain the overall significance level of 5%.

Secondary: The change in body weight from baseline after 104 weeks of treatment.

End point title	The change in body weight from baseline after 104 weeks of treatment.

End point description:

End point type	Secondary

End point timeframe:

Baseline and 104 weeks.

End point values	Empaglifozin 25 mg	Glimepiride 1-4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765[6]	780[7]		
Units: kilograms				
arithmetic mean (standard error)	-3.11 (± 0.13)	1.33 (± 0.13)		

Notes:

[6] - FAS (LOCF)

[7] - FAS (LOCF)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing Hierarchy for main analysis (104 weeks): 1. Non-inferiority in HbA1c change from baseline at 104 weeks. 2. Superiority in body weight change from baseline at 104 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 104 weeks. 4. Superiority in HbA1c change from baseline at 104 weeks. 5. Superiority in systolic blood pressure change from baseline at 104 weeks. 6. Superiority in diastolic blood pressure change from baseline at 104 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4.46
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-4.87
upper limit	-4.05
Variability estimate	Standard error of the mean
Dispersion value	0.18

Notes:

[8] - The superiority tests performed at 104 weeks and the superiority tests performed at 52 weeks both used a nominal significance level of 2.5% to maintain the overall significance level of 5%. ANCOVA with treatment, geographical region, renal function at baseline as fixed effects and baseline weight, baseline HbA1c as linear covariates.

Secondary: The occurrence of confirmed hypoglycaemic events during 104 weeks of treatment.

End point title	The occurrence of confirmed hypoglycaemic events during 104 weeks of treatment.

End point description:

Treated Set (TS), all patients treated with at least one dose of randomised study drug.

End point type	Secondary

End point timeframe:

Baseline and 104 weeks.

End point values	Empaglifozin 25 mg	Glimepiride 1-4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765[9]	780[10]		
Units: participants				
number (not applicable)	19	189		

Notes:

[9] - TS

[10] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing Hierarchy for main analysis (104 weeks): 1. Non-inferiority in HbA1c change from baseline at 104 weeks. 2. Superiority in body weight change from baseline at 104 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 104 weeks. 4. Superiority in HbA1c change from baseline at 104 weeks. 5. Superiority in systolic blood pressure change from baseline at 104 weeks. 6. Superiority in diastolic blood pressure change from baseline at 104 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	< 0.0001 [12]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.102
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.06
upper limit	0.173

Notes:

[11] - Cochran-Mantel-Haenszel test adjusting for baseline HbA1c (<8.5 / >=8.5).

[12] - The superiority tests performed at 104 weeks and the superiority tests performed at 52 weeks both used a nominal significance level of 2.5% to maintain the overall significance level of 5%.

Secondary: The change in Systolic Blood Pressure (SBP) from baseline after 104 weeks of treatment.

End point title	The change in Systolic Blood Pressure (SBP) from baseline after 104 weeks of treatment.

End point description:

FAS (LOCF-H) – Full Analysis Set (FAS) with Last Observation Carried Forward (LOCF); Values after start of anti-diabetic rescue therapy or change of anti-hypertensive therapy were set to missing and last observation carried forward (LOCF) was used for imputation of missing values.

End point type	Secondary

End point timeframe:

Baseline and 104 weeks.

End point values	Empaglifozin 25 mg	Glimepiride 1-4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765[13]	780[14]		
Units: mmHg				
arithmetic mean (standard error)	-3.1 (± 0.5)	2.5 (± 0.5)		

Notes:

[13] - FAS (LOCF-H)

[14] - FAS (LOCF-H)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing Hierarchy for main analysis (104 weeks): 1. Non-inferiority in HbA1c change from baseline at 104 weeks. 2. Superiority in body weight change from baseline at 104 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 104 weeks. 4. Superiority in HbA1c change from baseline at 104 weeks. 5. Superiority in systolic blood pressure change from baseline at 104 weeks. 6. Superiority in diastolic blood pressure change from baseline at 104 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	< 0.0001 [16]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-7
upper limit	-4.2
Variability estimate	Standard error of the mean
Dispersion value	0.6

Notes:

[15] - ANCOVA with treatment, geographical region, renal function at baseline as fixed effects and baseline SBP, baseline HbA1c as linear covariates.

[16] - The superiority tests performed at 104 weeks and the superiority tests performed at 52 weeks both used a nominal significance level of 2.5% to maintain the overall significance level of 5%.

Secondary: The change in Diastolic Blood Pressure (DBP) from baseline after 104 weeks of treatment.

End point title	The change in Diastolic Blood Pressure (DBP) from baseline after 104 weeks of treatment.

End point description:

End point type	Secondary

End point timeframe:

Baseline and 104 weeks.

End point values	Empaglifozin 25 mg	Glimepiride 1-4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765[17]	780[18]		
Units: mmHg				
arithmetic mean (standard error)	-1.8 (± 0.3)	0.9 (± 0.3)		

Notes:

[17] - FAS (LOCF-H)

[18] - FAS (LOCF-H)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing Hierarchy for main analysis (104 weeks): 1. Non-inferiority in HbA1c change from baseline at 104 weeks. 2. Superiority in body weight change from baseline at 104 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 104 weeks. 4. Superiority in HbA1c change from baseline at 104 weeks. 5. Superiority in systolic blood pressure change from baseline at 104 weeks. 6. Superiority in diastolic blood pressure change from baseline at 104 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	< 0.0001 [20]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.7
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-3.5
upper limit	-1.8
Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

[19] - ANCOVA with treatment, geographical region, renal function at baseline as fixed effects and baseline DBP, baseline HbA1c as linear covariates.

[20] - The superiority tests performed at 104 weeks and the superiority tests performed at 52 weeks both used a nominal significance level of 2.5% to maintain the overall significance level of 5%.

Secondary: The change from baseline in HbA1c after 52 weeks of treatment.

End point title	The change from baseline in HbA1c after 52 weeks of treatment.

End point description:

End point type	Secondary

End point timeframe:

Baseline and 52 weeks.

End point values	Empaglifozin 25 mg	Glimepiride 1-4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765[21]	780[22]		
Units: percentage of HbA1c				
arithmetic mean (standard error)	-0.73 (± 0.03)	-0.66 (± 0.03)		

Notes:

[21] - FAS (LOCF)

[22] - FAS (LOCF)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing Hierarchy for first interim analysis (52 weeks): 1. Non-inferiority in HbA1c change from baseline at 52 weeks. 2. Superiority in body weight change from baseline at 52 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 52 weeks. 4. Superiority in systolic blood pressure change from baseline at 52 weeks. 5. Superiority in diastolic blood pressure change from baseline at 52 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	equivalence[23]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.07
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-0.16
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.04

Notes:

[23] - Non-inferiority was tested through a two-sided 97.5% confidence interval for the treatment effect of empagliflozin minus the effect of glimepiride in change from baseline in HbA1c. The null-hypothesis of material inferiority of empagliflozin was rejected if the confidence interval is entirely below the non-inferiority margin 0.3%. ANCOVA with treatment, geographical region, renal function at baseline as fixed effects and baseline HbA1c as linear covariate.

Secondary: The change in body weight from baseline after 52 weeks of treatment.

End point title	The change in body weight from baseline after 52 weeks of treatment.

End point description:

End point type	Secondary

End point timeframe:

Baseline and 52 weeks.

End point values	Empaglifozin 25 mg	Glimepiride 1-4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765[24]	780[25]		
Units: kilograms				
arithmetic mean (standard error)	-3.21 (± 0.12)	1.59 (± 0.11)		

Notes:

[24] - FAS (LOCF)

[25] - FAS (LOCF)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing Hierarchy for first interim analysis (52 weeks): 1. Non-inferiority in HbA1c change from baseline at 52 weeks. 2. Superiority in body weight change from baseline at 52 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 52 weeks. 4. Superiority in systolic blood pressure change from baseline at 52 weeks. 5. Superiority in diastolic blood pressure change from baseline at 52 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	superiority[26]
P-value	< 0.0001 [27]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4.81
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-5.16
upper limit	-4.46
Variability estimate	Standard error of the mean
Dispersion value	0.16

Notes:

[26] - ANCOVA with treatment, geographical region, renal function at baseline as fixed effects and baseline weight, baseline HbA1c as linear covariates.

[27] - The superiority tests performed at 104 weeks and the superiority tests performed at 52 weeks both used a nominal significance level of 2.5% to maintain the overall significance level of 5%.

Secondary: The occurrence of confirmed hypoglycaemic events during 52 weeks of treatment.

End point title	The occurrence of confirmed hypoglycaemic events during 52 weeks of treatment.

End point description:

End point type	Secondary

End point timeframe:

Baseline and 52 weeks.

End point values	Empaglifozin 25 mg	Glimepiride 1-4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765[28]	780[29]		
Units: participants				
number (not applicable)	12	159		

Notes:

[28] - TS

[29] - TS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing Hierarchy for first interim analysis (52 weeks): 1. Non-inferiority in HbA1c change from baseline at 52 weeks. 2. Superiority in body weight change from baseline at 52 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 52 weeks. 4. Superiority in systolic blood pressure change from baseline at 52 weeks. 5. Superiority in diastolic blood pressure change from baseline at 52 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	superiority[30]
P-value	< 0.0001 [31]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	0.077
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.04
upper limit	0.148

Notes:

[30] - Cochran-Mantel-Haenszel test adjusting for baseline HbA1c (<8.5 / >=8.5).

[31] - The superiority tests performed at 104 weeks and the superiority tests performed at 52 weeks both used a nominal significance level of 2.5% to maintain the overall significance level of 5%.

Secondary: The change in Systolic Blood Pressure (SBP) from baseline after 52 weeks of treatment.

End point title	The change in Systolic Blood Pressure (SBP) from baseline after 52 weeks of treatment.

End point description:

End point type	Secondary

End point timeframe:

Baseline and 52 weeks.

End point values	Empaglifozin 25 mg	Glimepiride 1-4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765[32]	780[33]		
Units: mmHg				
arithmetic mean (standard error)	-3.6 (± 0.5)	2.2 (± 0.5)		

Notes:

[32] - FAS (LOCF-H)

[33] - FAS (LOCF-H)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing Hierarchy for first interim analysis (52 weeks): 1. Non-inferiority in HbA1c change from baseline at 52 weeks. 2. Superiority in body weight change from baseline at 52 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 52 weeks. 4. Superiority in systolic blood pressure change from baseline at 52 weeks. 5. Superiority in diastolic blood pressure change from baseline at 52 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	< 0.0001 [35]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-7.3
upper limit	-4.4
Variability estimate	Standard error of the mean
Dispersion value	0.6

Notes:

[34] - ANCOVA with treatment, geographical region, renal function at baseline as fixed effects and baseline SBP, baseline HbA1c as linear covariates.

[35] - The superiority tests performed at 104 weeks and the superiority tests performed at 52 weeks both used a nominal significance level of 2.5% to maintain the overall significance level of 5%.

Secondary: The change in Diastolic Blood Pressure (DBP) from baseline after 52 weeks of treatment.

End point title	The change in Diastolic Blood Pressure (DBP) from baseline after 52 weeks of treatment.

End point description:

End point type	Secondary

End point timeframe:

Baseline and 52 weeks.

End point values	Empaglifozin 25 mg	Glimepiride 1-4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	765[36]	780[37]		
Units: mmHg				
arithmetic mean (standard error)	-1.9 (± 0.3)	1 (± 0.3)		

Notes:

[36] - FAS (LOCF-H)

[37] - FAS (LOCF-H)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Testing Hierarchy for first interim analysis (52 weeks): 1. Non-inferiority in HbA1c change from baseline at 52 weeks. 2. Superiority in body weight change from baseline at 52 weeks. 3. Superiority in occurrence of confirmed hypoglycaemic adverse events at 52 weeks. 4. Superiority in systolic blood pressure change from baseline at 52 weeks. 5. Superiority in diastolic blood pressure change from baseline at 52 weeks.

Comparison groups	Empaglifozin 25 mg v Glimepiride 1-4 mg
Number of subjects included in analysis	1545
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	< 0.0001 [39]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.8
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	-3.7
upper limit	-2
Variability estimate	Standard error of the mean
Dispersion value	0.4

Notes:

[38] - ANCOVA with treatment, geographical region, renal function at baseline as fixed effects and baseline DBP, baseline HbA1c as linear covariates.

[39] - The superiority tests performed at 104 weeks and the superiority tests performed at 52 weeks both used a nominal significance level of 2.5% to maintain the overall significance level of 5%.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 4 years.

Adverse event reporting additional description:

There were 16 on-treatment deaths due to (any) serious AEs, but zero on-treatment deaths due to related serious AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Empaglifozin 25 mg

Reporting group description:

Patients received one empagliflozin 25 mg tablet and one placebo glimepiride capsule orally once daily. Empagliflozin: 25 mg once daily Placebo: Placebo matching glimepiride 1-4 mg.

Reporting group title	Glimepiride

Reporting group description:

Patients received one glimepiride capsule and one placebo empagliflozin tablet orally once daily. Glimepiride: 1-4 mg once daily Placebo: Placebo matching empagliflozin.

Serious adverse events	Empaglifozin 25 mg	Glimepiride	
Total subjects affected by serious adverse events			
subjects affected / exposed	161 / 765 (21.05%)	153 / 780 (19.62%)	
number of deaths (all causes)	8	8	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	2 / 765 (0.26%)	4 / 780 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	2 / 765 (0.26%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			

subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage IV			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant peritoneal neoplasm			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Melanoma recurrent			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic ocular melanoma			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal neoplasm benign			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic carcinoma			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 765 (0.26%)	6 / 780 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranasal sinus benign neoplasm			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			

subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia prophylaxis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oophorectomy bilateral			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Omentectomy			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 765 (0.13%)	5 / 780 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 765 (0.13%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			

Drug hypersensitivity			
subjects affected / exposed	0 / 765 (0.00%)	3 / 780 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	4 / 765 (0.52%)	3 / 780 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Menorrhagia			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatism			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Uterine prolapse			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 765 (0.26%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 765 (0.26%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung consolidation			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal obstruction			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Paranasal cyst			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Adjustment disorder			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Delusional disorder, unspecified type			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	3 / 765 (0.39%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns third degree			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Comminuted fracture			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	8 / 765 (1.05%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 765 (0.26%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			

subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 765 (0.13%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural constipation			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural headache			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			

subjects affected / exposed	2 / 765 (0.26%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 765 (0.13%)	7 / 780 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	4 / 765 (0.52%)	4 / 780 (0.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 765 (0.13%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	4 / 765 (0.52%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 765 (0.26%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	3 / 765 (0.39%)	8 / 780 (1.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 765 (0.00%)	3 / 780 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 765 (0.13%)	3 / 780 (0.38%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			

subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricle rupture			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 765 (0.13%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	8 / 765 (1.05%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic coma			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 765 (0.26%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radicular pain			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamic infarction			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 765 (0.26%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 765 (0.13%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Otosclerosis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tinnitus			

subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine ophthalmopathy			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open angle glaucoma			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 765 (0.13%)	3 / 780 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal neovascularisation			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 765 (0.26%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal varices			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal varices haemorrhage			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 765 (0.39%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			

subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	4 / 765 (0.52%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis haemorrhagic			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	2 / 765 (0.26%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 765 (0.13%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	4 / 765 (0.52%)	5 / 780 (0.64%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disorder			

subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-alcoholic steatohepatitis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertension			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder prolapse			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			

subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 765 (0.13%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 765 (0.13%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary-dependent Cushing's syndrome			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthralgia			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical spinal stenosis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 765 (0.26%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	2 / 765 (0.26%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle twitching			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	4 / 765 (0.52%)	4 / 780 (0.51%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	2 / 765 (0.26%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovitis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 765 (0.39%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis escherichia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 765 (0.13%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	3 / 765 (0.39%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	4 / 765 (0.52%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			

subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious mononucleosis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 765 (0.26%)	6 / 780 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 765 (0.13%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonellosis			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 765 (0.13%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis gastrointestinal			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	3 / 765 (0.39%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			

subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 765 (0.00%)	1 / 780 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 765 (0.13%)	0 / 780 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 765 (0.00%)	2 / 780 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Empaglifozin 25 mg	Glimepiride	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	580 / 765 (75.82%)	637 / 780 (81.67%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	55 / 765 (7.19%)	105 / 780 (13.46%)	
occurrences (all)	65	115	
Nervous system disorders			

Dizziness			
subjects affected / exposed	62 / 765 (8.10%)	67 / 780 (8.59%)	
occurrences (all)	81	106	
Headache			
subjects affected / exposed	59 / 765 (7.71%)	68 / 780 (8.72%)	
occurrences (all)	85	83	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	62 / 765 (8.10%)	67 / 780 (8.59%)	
occurrences (all)	79	93	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	53 / 765 (6.93%)	62 / 780 (7.95%)	
occurrences (all)	63	79	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	70 / 765 (9.15%)	86 / 780 (11.03%)	
occurrences (all)	84	116	
Back pain			
subjects affected / exposed	93 / 765 (12.16%)	90 / 780 (11.54%)	
occurrences (all)	116	109	
Musculoskeletal pain			
subjects affected / exposed	43 / 765 (5.62%)	43 / 780 (5.51%)	
occurrences (all)	45	46	
Osteoarthritis			
subjects affected / exposed	23 / 765 (3.01%)	41 / 780 (5.26%)	
occurrences (all)	41	47	
Pain in extremity			
subjects affected / exposed	51 / 765 (6.67%)	50 / 780 (6.41%)	
occurrences (all)	56	57	
Infections and infestations			
Bronchitis			
subjects affected / exposed	34 / 765 (4.44%)	64 / 780 (8.21%)	
occurrences (all)	46	88	
Gastroenteritis			

subjects affected / exposed	38 / 765 (4.97%)	47 / 780 (6.03%)	
occurrences (all)	46	56	
Influenza			
subjects affected / exposed	71 / 765 (9.28%)	73 / 780 (9.36%)	
occurrences (all)	94	86	
Nasopharyngitis			
subjects affected / exposed	90 / 765 (11.76%)	106 / 780 (13.59%)	
occurrences (all)	158	190	
Pharyngitis			
subjects affected / exposed	42 / 765 (5.49%)	44 / 780 (5.64%)	
occurrences (all)	48	67	
Upper respiratory tract infection			
subjects affected / exposed	103 / 765 (13.46%)	97 / 780 (12.44%)	
occurrences (all)	180	165	
Urinary tract infection			
subjects affected / exposed	137 / 765 (17.91%)	121 / 780 (15.51%)	
occurrences (all)	213	213	
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	51 / 765 (6.67%)	48 / 780 (6.15%)	
occurrences (all)	55	50	
Hyperglycaemia			
subjects affected / exposed	152 / 765 (19.87%)	227 / 780 (29.10%)	
occurrences (all)	242	374	
Hypoglycaemia			
subjects affected / exposed	41 / 765 (5.36%)	228 / 780 (29.23%)	
occurrences (all)	80	1267	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 October 2010	The following changes to the trial design and procedures were made: 1. The body composition sub-study was introduced to investigate the changes in visceral body fat content and distribution as well as to measure any changes in BMD after 52 and 104 weeks of trial medication. 2. The occurrence of all confirmed hypoglycaemias, whether they were asymptomatic or symptomatic, were to be recorded. 3. Change in weight of >2% was to be documented since this was to be included in a composite endpoint. 4. Patients with acute coronary syndrome were excluded rather than those with a myocardial infarction since this umbrella term was used to cover any group of clinical symptoms compatible with acute myocardial ischemia. 5. Percentage of patients with SBP/DBP <130/80 mmHg after 52 weeks and 104 weeks was added as a key secondary endpoint. 6. Exempting cardiovascular outcome events from expedited and unblinded reporting to avoid jeopardising the integrity of this double-blind trial and inclusion of a definition of cardiovascular outcome events that were to be reported on the CRF pages instead of on an SAE form (however, this change was not implemented). Cardiovascular outcome events that occurred during the screening/run in phase were to be considered as SAEs and not as outcome events. 7. Hepatic injury was added as a significant AE to fulfill the requirements of FDA as recommended in their Guidance for Industry: Drug induced liver disease. 8. Clinically relevant abnormalities found on physical examination at Visit 2 or ECG at Visit 3 were considered to have already existed prior to signing of the informed consent and therefore were considered as baseline conditions instead of AEs unless there was a good reason to assume they first appeared after signing of consent. 9. For triglycerides, a reflex test for direct LDL cholesterol was to be triggered if triglycerides were >400 mg/dL/4.52 mmol/L. 10. Measurement of urinary alpha-1 microglobulin was deleted.
26 May 2011	The Protocol amendment was implemented approximately 9 months after the first patient entered the study. This amendment introduced changes to clarify wording and study procedures to be performed/data to be collected, to introduce some administrative changes, and to correct minor typographical errors and inconsistencies between the synopsis, study flow charts, the CRF, and the text of the protocol, or to align procedures in this protocol with the other phase III empagliflozin studies. In addition, the following changes to the trial design were made: 1. To fulfill a request by the FDA and ensure the follow-up period was of sufficient duration to allow collection of safety related information, such as potential changes in physiology, the follow-up period was extended from 1 week to 4 weeks. This was to be performed for all patients, including those who discontinued prematurely. The study flow chart, synopsis, protocol text, and CRF were updated to account for this change. The following changes to the trial procedures were made: 2. Lipid profile, waist circumference, and bone markers were also to be assessed at the end of the follow-up period; endpoints were updated to reflect these changes. 3. Because the change to the protocol regarding the reporting of cardiovascular events as outcome events was not implemented, cardiovascular outcome events were not to be exempted from expedited reporting and were to be as originally classified and handled as SAEs.

01 February 2012	The Protocol amendment was implemented approximately 17 months after the first patient entered the study. This amendment introduced changes to clarify wording and study procedures to be performed/data to be collected, to comply with the sponsor's SOPs, and to correct minor typographical errors and inconsistencies between the synopsis, study flow charts, the CRF, and the text of the protocol, or to align procedures in this protocol with the other phase III empagliflozin studies. The following changes to the trial design were made: 1. The 104-week, double-blind, double-dummy treatment period of the trial was extended to 208 weeks by adding a further 104 weeks of double-blind treatment (referred to as the 104-week extension treatment period). This was to be implemented for all patients who signed an additional informed consent, including those who discontinued prematurely. The study flow chart, synopsis, text, and CRF were updated to account for this change. This change in design was required because both US and EU regulatory agencies (FDA and EMA) asked the sponsor to provide data on long-term safety and long-term efficacy (durability of efficacy) for empagliflozin. In addition, the following changes to the trial procedures were made: 2. The definition of drug-induced liver injury as a significant AE was extended to fulfill the requirements of FDA as recommended in their Guidance for Industry: Drug induced liver disease. 3. A clarification was added that LADA was assessed at baseline only.
13 August 2012	The protocol amendment was implemented before database lock for the interim analysis at 52 weeks. To assess fully the difference of the 2 trial medications, a superiority hypothesis for HbA1c was added to the 104-week time point. Thus, the main objective of the trial was amended to describe that the study was designed to show non-inferiority of empagliflozin to glimepiride with the option to show superiority if non-inferiority was met.
12 May 2014	This amendment introduced changes to clarify wording and study procedures to be performed/data to be collected, to introduce some administrative changes (including a change in TCM and a change in workplace for the coordinating investigator), and to correct minor inconsistencies between the synopsis, study flow charts, the CRF, and the text of the protocol, or to align procedures/analyses in this protocol with the other phase III empagliflozin studies or BI’s SOPs. Of note, the following changes to the trial procedures were made: 1. Protocol-specified significant AEs (hepatic injury and decreased renal function) were renamed as AESIs at all appropriate points throughout the protocol to comply with BI’s internal SOPs. 2. Reporting procedures of AEs and SAEs were updated to comply with BI’s SOPs, including the reporting of nonserious AESIs in an expedited manner similar to the reporting of SAEs. 3. The adjudication of hepatic AEs and cases of cancer was described. 4. To describe the unblinding of the TCM that took place after the second database lock (at 104 weeks).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

It should be noted that not all patients were followed up for 4 years with regard to the frequencies of adverse events presented up to 4 years.
The actual long term follow-up duration was 24.27 months.

Notes: