ICH E3 Synopsis of Clinical Study Report

SGLT2-inhibition with Empagliflozin reduces progression of diabetic retinopathy in patients with high risk of diabetic macular edema

Prospective, randomized, active controlled, double-blind, parallel group, monocenter phase IV study.

Investigational product: Empagliflozin
Indication: Patients with type 2 diabetes mellitus and with early to moderate stage diabetic retinopathy in one or both eyes

EudraCT number: 2016-000825-38:

Study initiation date (first patient enrolled): 12.06.2017
Last patient completed: 16.08.2018
Date of early study termination: 18.09.2018

Protocol code number: M16-04EMPA-EYE
Development phase of study: IV

Sponsor of the Clinical Trial:

Hannover Medical School
Carl-Neuberg-Straße 1
30625 Hannover

Principal investigator:

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This study was performed in compliance with Good Clinical Practices (GCP), including the archiving of essential documents

Version / Date: 1.2/ 10.04.2019

2 Synopsis

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Empagliflozin, 25 mg film-coated tablets (Jardiance®, modified) Glimepiride, 2 mg tablets (Glimepiride ratiopharm®, study specific labelled)	Volume:	
Name of Active Ingredient: Empagliflozin Glimepiride	Page:	

Title of study:

SGLT2-inhibition with Empagliflozin red**u**ces **p**rogr**e**ssion of diabetic **r**etinopathy in patients with high risk of diabetic macular edema (The **SUPER**-Trial)

EudraCT number: 2016-000825-38

Protocol code number: M16-04EMPA-EYE

Information about study protocol versions:

Protocol version1.13, Date: 27.09.2016

Subsequent substantial amendment:
Protocol version 1.14, Date: 30.08.2017

Principal Investigator:

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Publication (reference):

Poster: Pielen A, Danzmann L, Awe M, May M, Schindler C, Framme C. SGLT2 Inhibitoren senken die Mortalität – verringern sie auch die diabetische Retinopathie? SUPER-Trial. 31.03./01.04.2017 Makula update 2017

Talk: Pielen A, Danzmann L, Awe M, Junker B, May M, Schindler C, Framme C. SUPER Trial – SGLT2 Inhibitoren senken die Mortalität – verringern sie auch die diabetische Retinopathie? Jahrestagung der Retinologischen Gesellschaft 23./24.06.2017

ICH E3 Synopsis – SUPER-Trial – EudraCT No. 2016-000825-38

Article: Pielen A, Danzmann L, Awe M, Junker B, May M, Schindler C, Framme C, Investigator Initiated Clinical Trials am Beispiel des SUPER-Trial: SGLT2-Inhibitoren senken die Mortalität – verringern sie auch die diabetische Retinopathie? In: Spitzenforschung in der Ophthalmologie 2017, Sonderband der DOG (Deutsche Ophthalmologische Gesellschaft) zur Jahrestagung 2017 Article: May M, Pielen A, Framke T, Junker B, Framme C, Schindler C. Progression of microangiopathy assessed with microaneurysm formation rate in patients treated with SGLT2-inhibitors – trial design. Article in preparation.	
Studied period (years): 06/2017 – 09/2018 date of first enrolment: 12.06.2017 date of last completed: 16.08.2018 early termination: yes, 18.09.2018 temporary halt(s): n/a	**Phase of development:** IV

Objectives:

Primary objective is to investigate whether diabetic retinopathy (DR) progression rate is slowed down by SGLT2 inhibitor treatment and thus a lower microaneurysm formation rate in subjects treated with Empagliflozin (intervention) compared to subjects treated with Glimepiride (control), both on top of standard blood glucose lowering treatment, will be achieved after 12 months.

Methodology:

This was a prospective, randomized, active control, two-arm parallel, double-blind, monocenter phase IV clinical trial to compare empagliflozin to glimepiride in patients with type 2 diabetes mellitus in addition to standard of care treatment. The randomization was stratified for ETDRS at baseline (20 vs 35).

Patients were randomized 1:1 to the double-blind treatment period:

arm 1: 25 mg/d empagliflozin and matching glimepiride placebo + unblinded pretreatment antidiabetic medication

arm 2: 2 mg/d glimepiride and matching empagliflozin placebo + unblinded pretreatment antidiabetic medication.

Number of patients (planned and analysed):

Planned:

To be allocated to trial: n=80 (40 per treatment arm)

To be analysed: n=80 (ITT population, 40 per treatment arm)

Analysed (after study has been prematurely terminated):

Randomised: total n=6, empagliflozin group n=3 , glimepiride group n=3

In primary analysis population (ITT-population): n=6 (empagliflozin group n=3 , glimepiride group n=3)

Diagnosis and main criteria for inclusion:

Patients with type 2 diabetes mellitus and with early to moderate stage diabetic retinopathy in one or both eyes were included in this clinical trial.

Inclusion criteria:

1. women and men between 18 - 80 years of age
2. type 2 diabetes mellitus

3. early to moderate stage diabetic retinopathy (ETDRS: 20 (microaneurysms only) to 35 (microaneurysms/ hemorrhages and/or hard exsudates)) in one or both eyes
4. stable HbA1c (± 0.5%) for at least 12 weeks
5. antidiabetic treatment with either diet, metformin, DPP4, GLP1, pioglitazone, acarbose, or respective combinations
6. HbA1c ≥ 6.5 and ≤ 10.0 %
7. body mass index < 46 kg/m2
8. office blood pressure ≤ 150/95 mmHg (confirmed on a second day; 24h ambulatory blood pressure measurement (ABPM) is allowed to check accuracy of office values; inclusion with 24h mean blood pressure ≤ 145/90 mm Hg is possible); patients with hypertension should be treated according to current treatment guidelines
9. either women without childbearing potential defined by:
    - at least 6 weeks after surgical sterilization by bilateral tubal ligation or bilateral oophorectomy
    - hysterectomy
    - ≥ 50 years and in postmenopausal state > 1 year
    - < 50 years and in postmenopausal state > 1 year with serum FSH > 40 IU/l and serum estrogen < 30 ng/l or a negative estrogen test, both at screening

    or women of childbearing potential with a negative serum ß-hCG pregnancy test at screening who agree to meet one of the following criteria from the time of screening, during the study and for a period of 4 days following the last administration of study medication:
    - correct use of one of the following accepted contraception methods: hormonal contraceptives (combined oral contraceptives, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release), intrauterine device (IUD/IUS) or a double barrier method, e.g. condom and occlusive cap (diaphragm or cervical/vault caps) with spermicide (foam, gel, film, cream or suppository)
    - true abstinence (periodic abstinence and withdrawal are not acceptable methods of contraception)
    - sexual relationship only with female partners
    - sterile male partners
10. signed written informed consent and willingness to comply with treatment and follow-up procedures
11. capability of understanding the investigational nature, potential risks and benefits of the clinical trial

Exclusion criteria:

1. Type 1 diabetes
2. uncontrolled diabetes mellitus type 2 with fasting glucose > 13.3 mmol/l confirmed on a second day
3. known or suspected hypersensitivity to empagliflozin, glimepiride, or any excipients; and / or known or suspected hypersensitivity to sulfonylureas, sulfonamides or SGLT2 inhibitors in general
4. history of multiple severe hypoglycemic episodes within the last two years
5. use of Insulin, SGLT2-inhibitor, sulfonylurea derivate or a glinide within past 3 months
6. clinical significant macular edema in both eyes and indication for intravitreal anti-VEGF treatment for both eyes at screening or baseline visit. Eyes with a small amount of intraretinal or subretinal fluid (seen in OCT) but no need for intravitreal treatment as judged by the investigator (according to current practice patterns) may be included. Eyes with a history of intravitreal treatment of macular edema which do not need ongoing intravitreal treatment at the time of screening may be included.
7. eye diseases or pathologies that prevent clear ophthalmoscopy and evaluation of study parameters, thus not allowing study participation according to the investigator´s judgment, such

as (but not only) vitreous hemorrhage, mature cataract, macular pathologies other than diabetic maculopathy

8. history of ketoacidosis or metabolic acidosis
9. use of loop diuretics
10. history of > 1 urogenital infection/year
11. any history of stroke, TIA, instable angina pectoris or myocardial infarction within last 3 months prior to baseline visit
12. congestive heart failure NYHA III and IV
13. severe valvular or left ventricular outflow obstruction disease needing intervention;
14. atrial fibrillation/flutter with a mean ventricular response rate at rest >100 beats per minute
15. chronic lower urinary tract infections (but not simple asymptomatic bacteriuria)
16. eGFR < 60 ml/min/1,73 m2 (MDRD-formula, confirmed on a second day)
17. chronic diarrhea, any clinical signs of volume depletion or a hematocrit > 48 % (women) and > 53 % (men)
18. elevated risk for volume depletion, e.g. history of severe volume depletion that required medical therapy
19. chronic liver disease (including known active hepatitis) and/or screening alanine transaminase (ALT) or aspartate transaminase (AST) > 3 x ULN (confirmed on a second day)
20. Subjects with known seropositivity to human immunodeficiency virus.
21. acute illness at screening or randomization according to judgement by the investigator or patient
22. drug or alcohol abuse
23. psychosomatic or psychiatric diseases requiring hospitalization during the last 12 months
24. clinical evidence of current malignancy with exception of basal cell or squamous cell carcinoma of the skin, and cervical intraepithelial neoplasia (5 years prior to randomization)
25. any medical or surgical intervention planned for the next 13 months after randomization not allowing study participation according to the investigator´s judgment
26. current participation in any other clinical trial or participation in another clinical trial within 30 days before screening

Test product, dose and mode of administration, batch number:

Test product: Empagliflozin, 25 mg film-coated tablets (Jardiance®, modified)

Active substance: Empagliflozin

Dose: 25 mg once daily

Mode of administration: per os

Batch number(s):

1610000117; packed as blinded batch number 201611002

Duration of treatment:

Per patient: 12-month double-blind treatment period

Reference therapy, dose and mode of administration, batch number:

Reference product (active comparator): Glimepiride, 2 mg tablets (Glimepiride ratiopharm®, study specific labelled)

Active substance: Glimepiride

Dose: 2 mg once daily

Mode of administration: per os

Batch number(s):

22546G002; packed as blinded batch number 201611001

Reference product: Placebo to empagliflozin, film-coated tablets
Dose: One film-coated tablet once daily
Mode of administration: per os
Batch number(s):
1610000118; packed as blinded batch number 201611002

Reference product: Placebo to glimepiride, tablets
Dose: One tablet once daily
Mode of administration: per os
Batch number(s):
22054G003; packed as blinded batch number 201611001

Endpoints/Outcomes

Primary Endpoint: Microaneurysm (MA) formation rate over 12 months, i.e. number of newly developed microaneurysms within 12 months

Statistical methods:

Efficacy: The type I error is set to 2.5% (one-sided).

Primary Hypothesis and Primary Endpoint:

The assumption of the study was that empagliflozin slows down retinopathy progression rate compared to subjects treated with sulfonylurea treatment by substantially decreased cellular glucotoxicity. Progression rate and risk of clinical significant macular edema development is monitored in the short term using microaneurysm (MA) formation rate. Thus, the primary endpoint is the MA formation rate over 12 months, i.e. the number of newly developed microaneurysms from baseline until the end of the study.

The primary hypothesis is:

H0: MA formation rate(Empa) ≥ MA formation rate(Glimepiride)

H1: MA formation rate(Empa) < MA formation rate(Glimepiride)

Since MA formation rates (MAFR) are (overdispersed) count data and the distribution of MAFR is skewed, a negative binomial regression model – adjusted for ETDRS at baseline (20 vs 35) – was planned to be used for the primary analysis. The randomization process is stratified for ETDRS at baseline (20 vs 35) as well.

The result will be expressed as a two-sided 95% confidence interval for the rate ratio (MA formation rate(Empa) / MA formation rate(Glimepirid)). The primary null hypothesis was planned to be rejected at a one-sided significance level of 2.5%, if the upper bound of this confidence interval is below 1.

The primary analysis will be conducted on the ITT population. In case the MA formation rate cannot be determined after 12 months, the 6 month observation will be used and the negative binomial regression model will take into account the different observation periods. If both follow up observations (after 6 and 12 month) of the MA formation rate are missing, imputation with the overall sample median will be employed.

Only one eye per patient will be analysed in the analysis. If both eyes fulfil the inclusion criterion (i.e. ETDRS = 20 or 35), the eye to be analysed will be randomly selected prior to the randomised treatment group allocation in the respective stratum.

There is only one primary endpoint thus no adjustment for multiple testing is needed. Interpretation of secondary hypotheses will be descriptively only. Safety analyses will be performed for the full set of patients. There is no interim analysis planned.

Secondary Endpoints:

Explorative analysis of secondary endpoints will be in line with the primary analysis for skewed count data (e.g. change in microaneurysm count at 6 and 12 months). Dichotomous secondary variables will be reported with absolute and relative frequencies per treatment group along with the corresponding 95% confidence intervals. Differences between different groups will be compared using binomial tests. Continuous secondary variables will be analyzed descriptively using means, standard deviations. Differences between treatment groups will be assessed by two-sided t-tests and 95% confidence intervals. Secondary analyses will be adjusted for ETDRS at baseline (20 vs 35) if indicated.
As an additional exploratory analysis, the primary analysis will be modified to take into account both eyes for those patients whose eyes are both eligible (i.e. ETDRS = 20 or 35). A generalized linear mixed model (GLMM) will be employed to account for the dependency between the two eyes of the same patient. This will be achieved by including the factor Patient as a random effect into the statistical model.
Secondary analyses will be performed in the ITT population. Interpretation of results from secondary analyses will be descriptively only.

Safety:
Safety analysis will be conducted for the whole study population as well as for both treatment groups separately. AEs and SAEs will be reported with absolute and relative frequencies per treatment group along with the corresponding 95% confidence intervals. Differences between different groups will be compared using binomial tests. Continuous safety variables will be analyzed descriptively using means and standard deviations. Differences between treatment groups will be assessed by two-sided t-tests and 95% confidence intervals.

Changes to the trial and the analysis

One substantial amendment (SA No. 1.0) was made to the original study protocol (version 1.13 of 27.09.2016).
SA No. 1.0 (resulting in study protocol version 1.14 of 30.08.2017) covered the following major changes:
- Change of the representative of the sponsor
- Specification of inclusion/exclusion criteria
- Specification of secondary objectives and endpoints
- Changes and specification of study examinations
- Specification of permitted and prohibited concomitant medications.

The trial was discontinued early due to a low recruitment rate. Only 6 instead of 80 patients were randomised and available for analysis. For one patient in the control arm and two patients in the experimental arm results for the primary endpoint at month 12 are available. 6 month data are available for two additional patients. The aforementioned analyses are not conducted as planned in the study protocol because a stratified analysis is not possible. All results will be presented in addition as either raw data or descriptive statistics. The same applies for secondary endpoints and safety data where all data are displayed as listings and absolute/relative frequencies.

Primary analysis population characteristics

Seven patients were included in the trial and signed an informed consent form. Six of these patients were randomized and are considered as the ITT analysis set. One patient (007-5089) was a screening failure and was not randomized. This patient will not be included in any of the following analyses. All results are based on the ITT analysis set.
Table 1 is an overview of the contribution of each patient (duration, reason for discontinuation) to the study.

Table 1: Participation and discontinuation information on all patients (based on data sets Demog, Treatmt, Random, Sp_adm, Eos)

Pat. ID	Date informed consent	Is the subject a screening failure?	Reason for screening failure	Date of randomization	First intake of study medication	Last intake of study medication	Date of last visit / last contact	Reason study participation was discontinued	Study completed according to study protocol?	If other reason, please specify
Subject. 1	12JUN17	no		03JUL17	04JUL17	03APR18	27APR18	Consent withdrawal	no	
Subject. 2	14JUL17	no		07AUG17	08AUG17	08DEC17	20DEC17	Consent withdrawal	no	
Subject. 3	21JUL17	no		11AUG17	11AUG17	06JUL18	20JUL18	Other reasons	no	Studie abgebrochen
Subject. 4	31JUL17	no		23AUG17	24AUG17	11JUL18	25JUL18	Other reasons	no	study termination
Subject. 5	16AUG17	no		06SEP17	07SEP17	31JUL18	16AUG18	Other reasons	no	Termination of study
Subject. 6	20NOV17	no		18DEC17	19DEC17	02JUL18	23JUL18	Other reasons	no	Studie wurde abgebrochen
Subject. 7	05JAN18	yes	blood pressure to high (more than one time) --> evaluation will be done by family doctor	.	.	.	25JAN18	Other reasons	no	Screening failure

Six patients were randomized to the experimental treatment arm (Empagliflozin) or to the control treatment arm (Glimepiride). Since the primary analysis was planned to compare the formation rate per patient and some patients had both eyes eligible to be analysed, we randomly determined the left or right eye to be analysed. Table 2 provides the randomisation results per patient.

Table 2: Randomisation and allocation information (based on data sets FPhoto_arc_mod, Studyeye, Random)

Pat. ID	Treatment	Right eye: DR level - field 2 (ETDRS, Visit 1)	Left eye: DR level - field 2 (ETDRS, Visit 1)	Eye to be used for analysis	Right eye: Suitable as study eye? (Visit 1)	Left eye: Suitable as study eye? (Visit 1)
Subject. 1	Control Group (Glimepiride)	Level 35	Level 20	right	yes	no
Subject. 2	Experimental Group (Empagliflozin)	Level 20	Other than level 20 or 35	right	yes	no
Subject. 3	Control Group (Glimepiride)	Level 20	Level 20	left	yes	yes
Subject. 4	Experimental Group (Empagliflozin)	Level 20	Level 20	left	yes	yes
Subject. 5	Experimental Group (Empagliflozin)	Level 20	Other than level 20 or 35	right	yes	no
Subject. 6	Control Group (Glimepiride)	Level 20	Level 20	right	yes	yes

Demographic data of all randomized patients are presented in Table 3. Categorical variables are presented as absolute and relative frequencies, whereas continuous variables are shown as mean, standard deviation (STD), minimum, median and maximum.

Table 3: Descriptive Statistics for Demographic Data

	Treatment		
	Control N=3	**Experimental N=3**	**Total N=6**
Age (years)			
N	3	3	6
MISSING	0	0	0
MEAN	62.67	65.67	64.17
STD	6.43	10.50	7.96
MIN	58	55	55
MEDIAN	60	66	63
MAX	70	76	76
Sex			
male	2 (66.7%)	0 (0.0%)	2 (33.3%)
female	1 (33.3%)	3 (100.0%)	4 (66.7%)
Race			
caucasian	3	3	6
Difference between onset of diabetes and randomisation (years)			
N	3	3	6
MISSING	0	0	0
MEAN	7.67	10.33	9
STD	8.33	8.39	7.62
MIN	1	5	1
MEDIAN	5	6	5.50
MAX	17	20	20
eGFR (MDRD formula) at Baseline			
N	3	3	6
MISSING	0	0	0
MEAN	90.05	76.73	83.39
STD	9.38	11.41	11.85

MIN	80.09	66.40	66.40
MEDIAN	91.35	74.82	84.54
MAX	98.72	88.98	98.72

Efficacy results:

Data for the Primary Endpoint at 12 months is available only from 3 patients. The MA formation rate was measured from two further patients at month 6 which will be used in the analysis. One patient has only a baseline measurement and its value will be imputed from the overall sample median. Table 4 provides an overview of all values from right and left eyes that were observed during the trial.

Table 4: Information from both eyes per patient (data set FPhoto_arc_mod)

Pat. ID	Treatment	Right eye: DR level - field 2 (ETDRS, Visit 1)	Left eye: DR level - field 2 (ETDRS, Visit 1)	Right eye: Microaneurysm count (Visit 1)	Left eye: Microaneurysm count (Visit 1)	Right eye: Microaneurysm count (12 Months)	Left eye: Microaneurysm count (12 Months)	Right eye: Microaneurysm formation rate (12 Months)	Left eye: Microaneurysm formation rate (12 Months)
Subject. 1	Control Group (Glimepiride)	Level 35	Level 20	1	1	.	.	.	.
Subject. 2	Experimental Group (Empagliflozin)	Level 20	Other than level 20 or 35	1	0	.	.	.	.
Subject. 3	Control Group (Glimepiride)	Level 20	Level 20	1	1	D	D	D	D
Subject. 4	Experimental Group (Empagliflozin)	Level 20	Level 20	4	4	2	1	2	0
Subject. 5	Experimental Group (Empagliflozin)	Level 20	Other than level 20 or 35	1	0	1	0	0	0
Subject. 6	Control Group (Glimepiride)	Level 20	Level 20	5	4	4	3	0	0

Abbreviation: D=not done

Based on the information of Table 4, the data needed for analysis of the primary endpoint is given in Table 5. Note that according to the study protocol only one eye per patient will be used in the analysis. Furthermore, the approach to dealing with missing data was described in section 8.2 of the study protocol (first step: use 6 month values, if data is still missing use overall sample median). Asterisks [(*), (**)] indicate imputed data in Table 5 for the primary endpoint. Additional information on MA formation rate and microaneurysm count at 6 months can be found in the Appendix (Table 8).

Table 5: Information for primary analysis of MA formation rate (data sets FPhoto_arc_mod, Random)

Patient	Treatment Group	ETDRS at Baseline	Left/right eye used for analysis	MA formation rate
1	control	35	right	0(*)
2	experimental	20	right	0(**)

3	control	20	left	0(*)
4	experimental	20	left	0
5	experimental	20	right	0
6	control	20	right	0

(*) value imputed from 6 months

(**) value imputed from overall median

Table 5 reveals (a) that the number of patients in the strata of ETDRS is unbalanced and small (1 vs. 2 in the control arm and 0 vs. 3 in the treatment arm) and (b) that the mean and variance are zero in both treatment arms for the primary endpoint. In fact, no difference between treatment groups can be observed.

The primary analysis according to the study protocol is a negative binomial regression model that uses the formation rate as dependent variable and treatment group and ETDRS at Baseline as independent variables. The results are extremely wide confidence intervals and the p-value equals 1. The model failed to converge and the negative of Hessian matrix was not positive definite, and thus, leading to unreliable results which are omitted

In summary, the analysis results of the primary endpoint are severely limited by a very small sample size, unbalanced strata and only results that are not different from zero. However, no differences between the two treatment arms have been observed.

Secondary endpoints

Reporting of secondary endpoints focuses on OCT and BCVA measurements as well as laboratory data.

BCVA measurements (ETDRS Letter Score) were scheduled at Screening, Baseline, 6 months and 12 months. Figures 1 and 2 display all measurements as line plots. In addition, all individual measurements can be found in the appendix, Table 9.

Likewise, OCT measurements were also scheduled at Screening, Baseline, 6 months and 12 months. Figures 3 and 4 show the according line plot, while individual measurements are Appendix, Table 10. No clinically significant macular edema were observed in this trial.

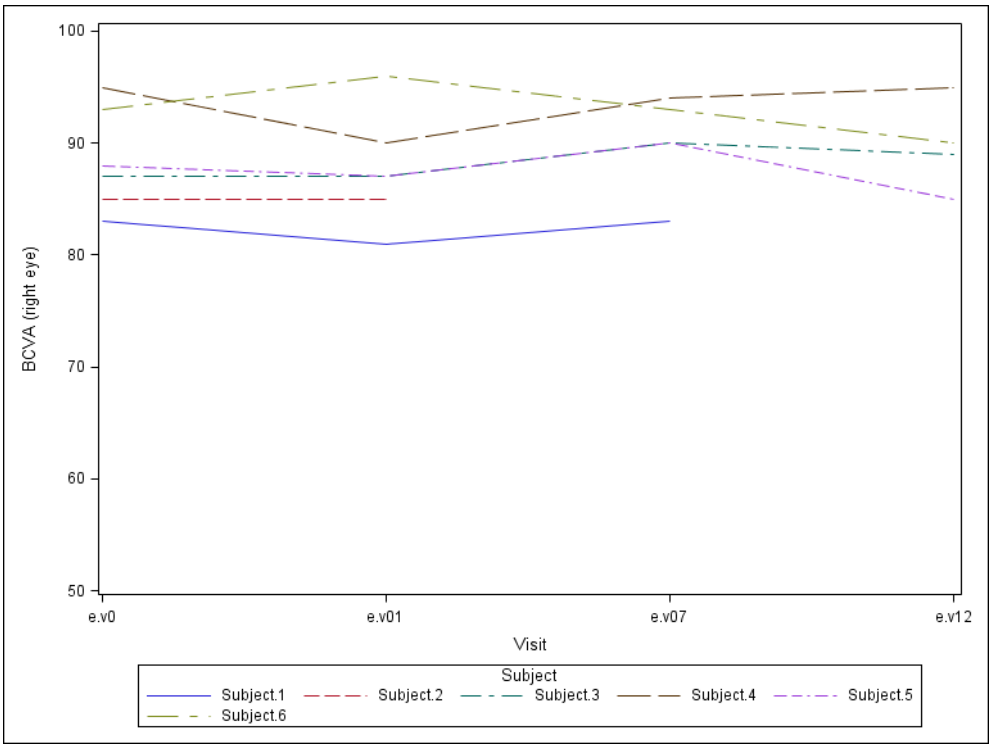

Figure 1: Line Plot of BCVA measurements (right eye) per subject over time

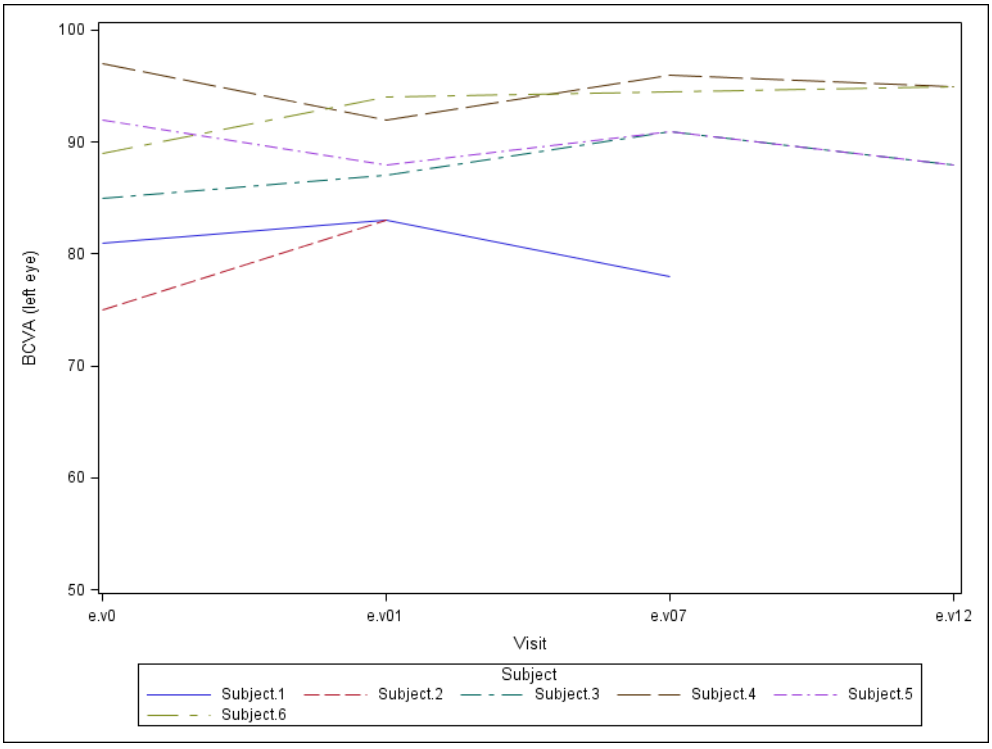

Figure 2: Line Plot of BCVA measurements (left eye) per subject over time

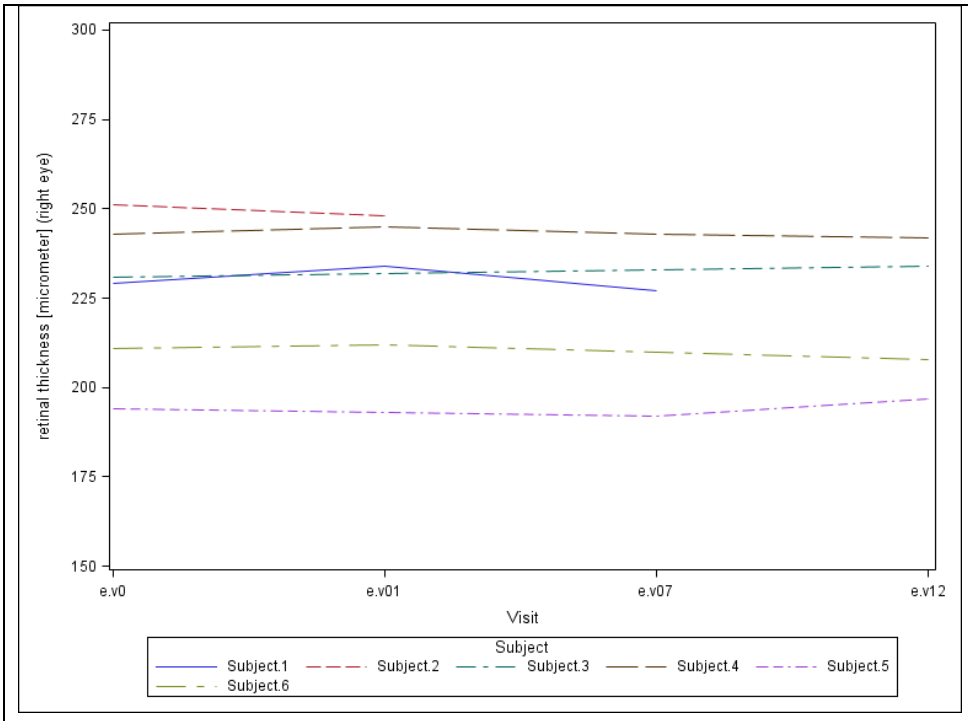

Figure 3: Retinal thickness per patient (right eye) at four different visits

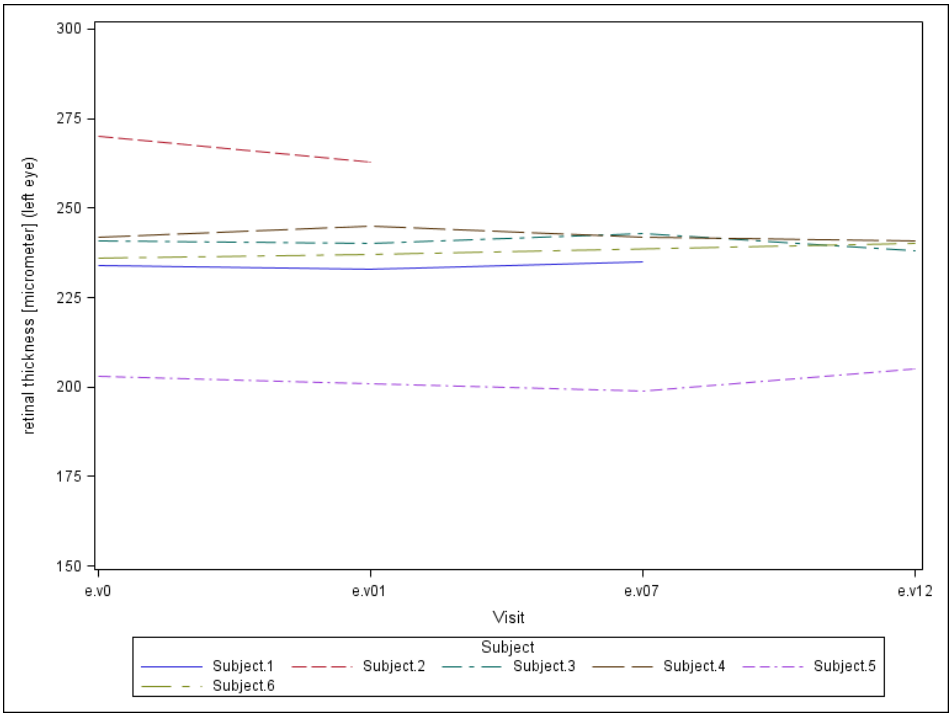

Figure 4: Retinal thickness per patient (right eye) at four different visits

In addition, all laboratory data will be displayed in the Appendix (Tables 11-14). Laboratory Data are presented descriptively as number of observations, mean, standard deviation, minimum and maximum. Five tables refer to different time points and they are displayed to characterize the course

of the trial at baseline, 6 months, 12 months and follow-up visit.

Of all 1253 measured laboratory values, 253 laboratory values were judged as "not clinically relevant", while 5 were classified as "clinically relevant". The latter ones are presented in Table 6.

Table 6: Laboratory values that were assessed as abnormal and "clinically relevant" (based on data set *Lab*)

Pat. ID	Treatment	Visit	Lab Test	Lower Limit	Measured value	Upper Limit	Unit	Assessment
Subject.5	Experimental Group (Empagliflozin)	e.v02	Thrombocytes	176	89	391	/nL	clinically relevant
	Experimental Group (Empagliflozin)	e.v04	Thrombocytes	176	105	391	/nL	clinically relevant
	Experimental Group (Empagliflozin)	e.v05	Thrombocytes	176	119	391	/nL	clinically relevant
Subject.6	Control Group (Glimepiride)	e.v02	Lipase	13	165.5	60	U/L	clinically relevant
	Control Group (Glimepiride)	e.v05	Lipase	13	271.3	60	U/L	clinically relevant

Abbreviations: e.v02 = Safety Visit 2 (Week 2), e.v04 = Safety Visit 4 (Week 12), e.v05 = Safety Visit 5 (Week 17)

Safety results:

Adverse Events are reported according to MedDRA 21.1 English at the System Organ Class (SOC) and Preferred Term (PT) level. All patients experienced at least one Adverse Event in the course of the trial. A total of 31 AEs from 6 patients were reported in this trial. Severity of the Adverse Events was graded according to the CTC grade (NCI CTCAE v 4.0) scale. No AEs higher than CTC grade 2 were reported. None of the AEs was classified as serious. Adverse events of special interest (AESI) were defined in the study protocol as hepatic injury, decreased renal function, metabolic acidosis, ketoacidosis, diabetic ketoacidosis and events involving lower limb amputation. No AESI were observed in this trial. No death was observed.

Table 7: Number of Adverse Events per patient, grouped by CTC grade

Patient	Treatment	Number of Adverse Events per patient and CTC Grade		Total
		Grade 1: mild	Grade 2: moderate	
Patient 1	Glimepiride	5	2	7
Patient 2	Empagliflozin	11	2	13
Patient 3	Glimepiride	0	2	2
Patient 4	Empagliflozin	1	0	1
Patient 5	Empagliflozin	3	2	5
Patient 6	Glimepiride	2	1	3

The use of concomitant medication is presented in Table 15 of the Appendix. A detailed listing with all

Adverse events is provided in Table 16 of the Appendix. The number of patients with at least one Adverse Event is reported in Table 17 of the Appendix. In addition, the frequencies of Adverse Events for SOC and PT classes are summarized in Table 18 of the Appendix. 12 Adverse Events were observed in the Glimepiride treatment arm, while 19 Adverse Events were reported in the Empagliflozin treatment arm.

Conclusion

This study compared subjects suffering from diabetic retinopathy treated with Empagliflozin (intervention) as compared to Glimepiride (control), both on top of standard blood glucose lowering treatment.
Primary objective was to investigate whether the diabetic retinopathy (DR) progression rate is slowed down by SGLT2 inhibitor treatment and thus a lower microaneurysm formation rate after 12 months (primary endpoint). One eye per patient was chosen at random as study eye. The trial was discontinued due to a low recruitment rate. Seven patients were screened and included into the trial and six of them were randomized to one of the two treatment arms. All analyses remain descriptive due to the early termination and the small number of patients. No new MA were observed in the course of the trial and the MA formation rate was 0 for all study eyes.
In consequence, among the very limited group of n = 6 patients observed we did not find relevant differences between the two treatment arms for the primary endpoint (MA formation rate). Differences for safety parameters were also not observed.

Date of report: 10.04.2019

Disclaimer: HCTC-KKS (Hannover Clinical Trial Center) has been responsible for data management and monitoring. Two validated data transfers were performed on 01.10.2018 and 21.01.2019. A careful assessment of plausibility has been conducted and findings were discussed and resolved.

3 Appendix

Table 8: Microaneurism count and formation rate for both eyes per patient at 6 months (data set FPhoto_arc_mod)

Pat. ID	Treatment	Right eye: Microaneurysm count (6 Months)	Left eye: Microaneurysm count (6 Months)	Right eye: Microaneurysm formation rate (6 Months)	Left eye: Microaneurysm formation rate (6 Months)
Subject.1	Control Group (Glimepiride)	1	1	0	0
Subject.2	Experimental Group (Empagliflozin)	.	.	.	.
Subject.3	Control Group (Glimepiride)	1	1	0	0
Subject.4	Experimental Group (Empagliflozin)	6	3	2	0
Subject.5	Experimental Group (Empagliflozin)	0	0	0	0
Subject.6	Control Group (Glimepiride)	.	.	.	.

Table 9: ETDRS Letter Score for left and right eye at different visits (Data Set Bcva_mod)

Pat. ID	Treatment	Visite	Right eye: Best-corrected visual acuity (ETDRS letter score)	Left eye: Best-corrected visual acuity (ETDRS letter score)
Subject.1	Control Group (Glimepiride)	Screening Visit	83	81
		Baseline Visit 1 (Day 0)	81	83
		Ophthalmological Assessment Visit 7 (Week 27)	83	78
Subject.2	Experimental Group (Empagliflozin)	Screening Visit	85	75
		Baseline Visit 1 (Day 0)	85	83
Subject.3	Control Group (Glimepiride)	Screening Visit	87	85
		Baseline Visit 1 (Day 0)	87	87
		Ophthalmological Assessment Visit 7 (Week 27)	90	91
		End of Treatment Visit 12 (Week 52)	89	88
Subject.4	Experimental Group (Empagliflozin)	Screening Visit	95	97
		Baseline Visit 1 (Day 0)	90	92
		Ophthalmological Assessment Visit 7 (Week 27)	94	96
		End of Treatment Visit 12 (Week 52)	95	95
Subject.5	Experimental Group (Empagliflozin)	Screening Visit	88	92
		Baseline Visit 1 (Day 0)	87	88
		Ophthalmological Assessment Visit 7 (Week 27)	90	91
		End of Treatment Visit 12 (Week 52)	85	88
Subject.6	Control Group (Glimepiride)	Screening Visit	93	89
		Baseline Visit 1 (Day 0)	96	94
		End of Treatment Visit 12 (Week 52)	90	95

Table 10: Individual OCT measurements for right and left eye at different visits (based on data set Oct)

Pat. ID	Treatment	Visite	Right eye: Central retinal thickness	Right eye: Clinically significant macular edema?	Right eye: Measurement of retinal perfusion (flow in OCT-A) performed?	Right eye: Need for (intravitreal) treatment?	Left eye: Central retinal thickness	Left eye: Clinically significant macular edema?	Left eye: Need for (intravitreal) treatment?	Left eye: Measurement of retinal perfusion (flow in OCT-A) performed?
Subject.1	Control Group (Glimepiride)	Screening Visit	229	no	yes	.	234	no	.	yes
	Control Group (Glimepiride)	Baseline Visit 1 (Day 0)	234	no	yes	.	233	no	.	yes
	Control Group (Glimepiride)	Ophthalmological Assessment Visit 7 (Week 27)	227	no	yes	.	235	no	.	yes
Subject.2	Experimental Group (Empagliflozin)	Screening Visit	251	no	yes	.	270	no	.	yes
	Experimental Group (Empagliflozin)	Baseline Visit 1 (Day 0)	248	no	no	.	263	no	.	no
Subject.3	Control Group (Glimepiride)	Screening Visit	231	no	yes	.	241	no	.	yes
	Control Group (Glimepiride)	Baseline Visit 1 (Day 0)	232	no	yes	.	240	no	.	yes
	Control Group (Glimepiride)	Ophthalmological Assessment Visit 7 (Week 27)	233	no	yes	.	243	no	.	yes
	Control Group (Glimepiride)	End of Treatment Visit 12 (Week 52)	234	no	yes	.	238	no	.	yes
Subject.4	Experimental Group (Empagliflozin)	Screening Visit	243	no	yes	.	242	no	.	yes
	Experimental Group (Empagliflozin)	Baseline Visit 1 (Day 0)	245	no	yes	.	245	no	.	yes
	Experimental Group (Empagliflozin)	Ophthalmological Assessment Visit 7 (Week 27)	243	no	yes	.	242	no	.	yes

Pat. ID	Treatment	Visite	Right eye: Central retinal thickness	Right eye: Clinically significant macular edema?	Right eye: Measurement of retinal perfusion (flow in OCT-A) performed?	Right eye: Need for (intravitreal) treatment?	Left eye: Central retinal thickness	Left eye: Clinically significant macular edema?	Left eye: Need for (intravitreal) treatment?	Left eye: Measurement of retinal perfusion (flow in OCT-A) performed?
	Experimental Group (Empagliflozin)	End of Treatment Visit 12 (Week 52)	242	no	yes	.	241	no	.	yes
Subject.5	Experimental Group (Empagliflozin)	Screening Visit	194	no	yes	.	203	no	.	yes
	Experimental Group (Empagliflozin)	Baseline Visit 1 (Day 0)	193	no	yes	.	201	no	.	yes
	Experimental Group (Empagliflozin)	Ophthalmological Assessment Visit 7 (Week 27)	192	no	yes	.	199	no	.	yes
	Experimental Group (Empagliflozin)	End of Treatment Visit 12 (Week 52)	197	no	yes	.	205	no	.	yes
Subject.6	Control Group (Glimepiride)	Screening Visit	211	no	yes	.	236	no	.	yes
	Control Group (Glimepiride)	Baseline Visit 1 (Day 0)	212	no	yes	.	237	no	.	yes
	Control Group (Glimepiride)	End of Treatment Visit 12 (Week 52)	208	no	yes	.	240	no	.	yes

Table 11: Descriptive Statistics for Laboratory measurements (Baseline Visit)

Analysevariable : LB_VALUE lb_value

Treatment	*lb_labtest*	*Anzahl Beob.*	*N*	*Anzahl fehl. Werte*	*Mittelwert*	*Std.abweichung*	*Minimum*	*Maximum*
Control Group (Glimepiride)	ALT	3	3	0	31.0	1.3	29.5	32.1
	AST	3	3	0	24.6	4.1	20.8	29.0
	Conjugated bilirubin	3	3	0	0.1	0.0	0.1	0.2
	Creatinine	3	3	0	0.8	0.2	0.7	1.0
	Gamma-GT	3	3	0	29.8	11.9	16.8	40.0
	Glucose (fasting)	3	3	0	159.7	7.6	153.0	168.0
	HDL	3	3	0	39.5	0.8	38.6	40.1
	HbA1c	3	2	1	7.8	0.8	7.2	8.4
	Hematocrit	3	3	0	45.2	3.2	43.3	48.9
	Hemoglobin	3	3	0	15.1	1.3	14.1	16.5
	INR	2	2	0	1.0	0.1	0.9	1.0
	LDL	3	2	1	103.0	56.6	63.0	143.0
	Lipase	3	3	0	23.6	12.9	15.9	38.5
	Potassium	3	3	0	4.8	0.2	4.5	5.0
	Red blood cell count (RBC)	3	3	0	5.2	0.6	4.7	5.8
	Sodium	3	3	0	141.0	2.6	138.0	143.0
	Thrombocytes	3	3	0	257.7	69.8	202.0	336.0
	Total bilirubin	3	3	0	0.3	0.1	0.2	0.5
	Total cholesterol	3	3	0	203.0	54.4	141.0	243.0
	Triglycerides	3	3	0	220.6	37.0	189.3	261.5
	Unconjugated bilirubin	3	3	0	0.2	0.1	0.1	0.3
	Urea	3	3	0	30.9	8.6	25.3	40.8
	White blood cell count (WBC)	3	3	0	8.2	2.1	6.4	10.5
	aPTT	2	2	0	28.4	2.3	26.7	30.0
Experimental Group (Empagliflozin)	ALT	3	3	0	27.0	8.3	17.7	33.6
	AST	3	3	0	25.4	1.7	23.5	26.8
	Conjugated bilirubin	3	3	0	0.2	0.0	0.1	0.2
	Creatinine	3	3	0	0.8	0.1	0.7	0.9
	Gamma-GT	3	3	0	28.9	14.6	12.8	41.4
	Glucose (fasting)	3	3	0	174.0	31.6	151.0	210.0
	HDL	3	3	0	92.0	25.5	68.3	119.0

Analysevariable : LB_VALUE lb_value

Treatment	*lb_labtest*	*Anzahl Beob.*	*N*	*Anzahl fehl. Werte*	*Mittelwert*	*Std.abweichung*	*Minimum*	*Maximum*
	HbA1c	3	3	0	7.3	0.1	7.2	7.4
	Hematocrit	3	3	0	36.5	5.0	31.9	41.9
	Hemoglobin	3	3	0	12.2	1.7	10.6	13.9
	INR	3	3	0	0.9	0.0	0.9	0.9
	LDL	3	3	0	143.0	50.6	91.0	192.0
	Lipase	3	3	0	44.2	5.6	38.7	49.8
	Potassium	3	3	0	4.9	0.3	4.5	5.2
	Red blood cell count (RBC)	3	3	0	4.1	0.6	3.6	4.8
	Sodium	3	3	0	141.7	1.5	140.0	143.0
	Thrombocytes	3	3	0	210.0	63.8	140.0	265.0
	Total bilirubin	3	3	0	0.3	0.1	0.2	0.5
	Total cholesterol	3	3	0	238.3	60.1	174.0	293.0
	Triglycerides	3	3	0	123.8	49.9	68.1	164.5
	Unconjugated bilirubin	3	3	0	0.2	0.1	0.1	0.3
	Urea	3	3	0	32.5	5.1	27.8	38.0
	White blood cell count (WBC)	3	3	0	5.3	2.4	3.3	8.0
	aPTT	3	3	0	28.1	1.5	26.8	29.7

Table 12: Descriptive Statistics for Laboratory measurements (Week 27)

Analysevariable : LB_VALUE lb_value

Treatment	*lb_labtest*	*Anzahl Beob.*	*N*	*Anzahl fehl. Werte*	*Mittelwert*	*Std.abweichung*	*Minimum*	*Maximum*
Control Group (Glimepiride)	ALT	2	2	0	36.9	19.2	23.3	50.4
	AST	2	2	0	27.5	6.2	23.1	31.8
	Conjugated bilirubin	2	2	0	0.1	0.0	0.1	0.2
	Creatinine	2	1	1	0.9	.	0.9	0.9
	Gamma-GT	2	2	0	29.1	16.1	17.7	40.4
	Glucose (fasting)	2	2	0	122.0	28.3	102.0	142.0
	HDL	2	2	0	41.7	5.2	38.0	45.4
	HbA1c	2	2	0	6.8	0.3	6.6	7.0
	Hematocrit	2	2	0	44.6	5.4	40.8	48.4
	Hemoglobin	2	2	0	14.5	1.3	13.6	15.4
	INR	2	2	0	0.9	0.1	0.9	1.0
	LDL	2	2	0	110.0	49.5	75.0	145.0
	Lipase	2	2	0	19.7	1.8	18.4	20.9
	Potassium	2	2	0	5.3	0.3	5.1	5.5
	Red blood cell count (RBC)	2	2	0	4.9	0.0	4.9	4.9
	Sodium	2	2	0	140.5	2.1	139.0	142.0
	Thrombocytes	2	2	0	288.0	63.6	243.0	333.0
	Total bilirubin	2	2	0	0.3	0.1	0.3	0.4
	Total cholesterol	2	2	0	193.5	57.3	153.0	234.0
	Triglycerides	2	2	0	210.0	12.5	201.1	218.8
	Unconjugated bilirubin	2	1	1	0.2	.	0.2	0.2
	Urea	2	2	0	35.7	11.5	27.6	43.8
	White blood cell count (WBC)	2	2	0	7.7	0.9	7.1	8.3
	aPTT	2	2	0	30.2	2.9	28.1	32.2
Experimental Group (Empagliflozin)	ALT	2	2	0	23.1	4.2	20.1	26.0
	AST	2	2	0	23.5	12.8	14.4	32.5
	Conjugated bilirubin	2	2	0	0.2	0.0	0.2	0.2
	Creatinine	2	2	0	0.7	0.0	0.7	0.8
	Gamma-GT	2	2	0	19.2	5.0	15.6	22.7
	Glucose (fasting)	2	2	0	127.5	4.9	124.0	131.0
	HDL	2	2	0	73.6	23.2	57.2	90.0

Analysevariable : LB_VALUE lb_value

Treatment	*lb_labtest*	*Anzahl Beob.*	*N*	*Anzahl fehl. Werte*	*Mittelwert*	*Std.abweichung*	*Minimum*	*Maximum*
	HbA1c	2	2	0	7.5	0.4	7.2	7.8
	Hematocrit	2	2	0	40.1	7.3	34.9	45.2
	Hemoglobin	2	2	0	13.3	2.1	11.8	14.7
	INR	2	1	1	1.0	.	1.0	1.0
	LDL	2	2	0	153.5	46.0	121.0	186.0
	Lipase	2	2	0	49.5	4.7	46.1	52.8
	Potassium	2	2	0	5.0	0.9	4.4	5.6
	Red blood cell count (RBC)	2	2	0	4.4	1.2	3.5	5.2
	Sodium	2	2	0	141.5	2.1	140.0	143.0
	Thrombocytes	2	2	0	211.0	80.6	154.0	268.0
	Total bilirubin	2	2	0	0.4	0.0	0.4	0.4
	Total cholesterol	2	2	0	253.0	42.4	223.0	283.0
	Triglycerides	2	2	0	129.6	97.7	60.5	198.6
	Unconjugated bilirubin	2	2	0	0.2	0.0	0.2	0.3
	Urea	2	2	0	35.2	8.6	29.1	41.2
	White blood cell count (WBC)	2	2	0	6.2	3.7	3.6	8.9
	aPTT	2	1	1	27.8	.	27.8	27.8

Table 13: Descriptive Statistics for Laboratory measurements (Week 52)

Analysevariable : LB_VALUE lb_value

Treatment	*lb_labtest*	*Anzahl Beob.*	*N*	*Anzahl fehl. Werte*	*Mittelwert*	*Std.abweichung*	*Minimum*	*Maximum*
Control Group (Glimepiride)	ALT	2	2	0	32.7	0.6	32.2	33.1
	AST	2	2	0	23.9	0.9	23.2	24.5
	Conjugated bilirubin	2	2	0	0.2	0.0	0.2	0.2
	Creatinine	2	2	0	0.9	0.1	0.9	1.0
	Gamma-GT	2	2	0	38.7	5.4	34.8	42.5
	Glucose (fasting)	2	2	0	145.5	0.7	145.0	146.0
	HDL	2	2	0	39.2	4.0	36.3	42.0
	HbA1c	2	2	0	7.0	0.2	6.9	7.2
	Hematocrit	2	2	0	45.8	3.8	43.1	48.5
	Hemoglobin	2	2	0	15.2	0.9	14.5	15.8
	INR	1	1	0	0.9	.	0.9	0.9
	LDL	2	2	0	126.5	94.0	60.0	193.0
	Lipase	2	2	0	28.0	15.6	17.0	39.0
	Potassium	2	2	0	4.5	0.3	4.3	4.8
	Red blood cell count (RBC)	2	2	0	5.2	0.8	4.6	5.7
	Sodium	2	2	0	142.0	0.0	142.0	142.0
	Thrombocytes	2	2	0	211.5	40.3	183.0	240.0
	Total bilirubin	2	2	0	0.4	0.1	0.3	0.4
	Total cholesterol	2	2	0	207.5	98.3	138.0	277.0
	Triglycerides	2	2	0	210.3	0.8	209.7	210.9
	Unconjugated bilirubin	2	2	0	0.2	0.1	0.2	0.3
	Urea	2	2	0	29.3	10.4	21.9	36.6
	White blood cell count (WBC)	2	2	0	7.4	0.2	7.2	7.5
	aPTT	1	1	0	27.7	.	27.7	27.7
Experimental Group (Empagliflozin)	ALT	2	2	0	20.1	6.4	15.6	24.6
	AST	2	2	0	29.8	18.2	16.9	42.6
	Conjugated bilirubin	2	2	0	0.2	0.1	0.2	0.3
	Creatinine	2	2	0	0.7	0.0	0.7	0.8
	Gamma-GT	2	2	0	15.3	8.3	9.4	21.2
	Glucose (fasting)	2	2	0	138.5	9.2	132.0	145.0
	HDL	2	2	0	142.5	58.7	101.0	184.0

Analysevariable : LB_VALUE lb_value

Treatment	*lb_labtest*	*Anzahl Beob.*	*N*	*Anzahl fehl. Werte*	*Mittelwert*	*Std.abweichung*	*Minimum*	*Maximum*
	HbA1c	2	2	0	7.0	0.1	6.9	7.1
	Hematocrit	2	2	0	39.2	7.5	33.9	44.5
	Hemoglobin	2	2	0	13.0	2.0	11.6	14.4
	INR	2	2	0	1.0	0.0	1.0	1.0
	LDL	2	2	0	138.5	24.7	121.0	156.0
	Lipase	2	2	0	46.0	2.0	44.6	47.4
	Potassium	2	2	0	5.0	0.5	4.6	5.3
	Red blood cell count (RBC)	2	2	0	4.2	1.1	3.5	5.0
	Sodium	2	2	0	140.5	0.7	140.0	141.0
	Thrombocytes	2	2	0	202.5	92.6	137.0	268.0
	Total bilirubin	2	2	0	0.6	0.3	0.3	0.8
	Total cholesterol	2	2	0	239.5	9.2	233.0	246.0
	Triglycerides	2	2	0	97.9	60.0	55.5	140.3
	Unconjugated bilirubin	2	2	0	0.3	0.2	0.2	0.5
	Urea	2	2	0	40.8	6.6	36.1	45.4
	White blood cell count (WBC)	2	2	0	5.0	2.2	3.5	6.5
	aPTT	2	2	0	30.2	0.2	30.0	30.3

Table 14: Descriptive Statistics for Laboratory Measurements (Follow up visit 2-3 weeks after EoT)

Analysevariable : LB_VALUE lb_value

Treatment	*lb_labtest*	*Anzahl Beob.*	*N*	*Anzahl fehl. Werte*	*Mittelwert*	*Std.abweichung*	*Minimum*	*Maximum*
Control Group (Glimepiride)	ALT	2	2	0	29.6	4.5	26.4	32.7
	AST	2	2	0	21.1	1.8	19.8	22.4
	Conjugated bilirubin	2	2	0	0.2	0.0	0.2	0.2
	Creatinine	2	2	0	1.0	0.0	1.0	1.0
	Gamma-GT	2	2	0	37.1	8.0	31.4	42.7
	Glucose (fasting)	2	2	0	165.0	42.4	135.0	195.0
	HbA1c	2	2	0	7.3	0.1	7.3	7.4
	Hematocrit	2	2	0	45.7	3.6	43.1	48.2
	Hemoglobin	2	2	0	15.4	1.4	14.4	16.4
	Lipase	2	2	0	29.0	10.2	21.8	36.2
	Potassium	2	2	0	4.3	0.4	4.1	4.6
	Red blood cell count (RBC)	2	2	0	5.3	0.9	4.6	5.9
	Sodium	2	2	0	141.0	0.0	141.0	141.0
	Thrombocytes	2	2	0	219.5	46.0	187.0	252.0
	Total bilirubin	2	2	0	0.4	0.0	0.3	0.4
	Unconjugated bilirubin	2	2	0	0.2	0.0	0.2	0.2
	Urea	2	2	0	32.2	0.9	31.5	32.8
	White blood cell count (WBC)	2	2	0	7.7	0.2	7.6	7.9
Experimental Group (Empagliflozin)	ALT	2	2	0	20.5	0.3	20.3	20.7
	AST	2	2	0	23.2	6.0	18.9	27.4
	Conjugated bilirubin	2	2	0	0.2	0.0	0.1	0.2
	Creatinine	2	2	0	0.7	0.1	0.6	0.7
	Gamma-GT	2	2	0	17.0	8.2	11.2	22.8
	Glucose (fasting)	2	1	1	157.0	.	157.0	157.0
	HbA1c	2	2	0	7.1	0.4	6.8	7.4
	Hematocrit	2	2	0	39.1	5.6	35.1	43.0
	Hemoglobin	2	2	0	13.1	1.6	11.9	14.2
	Lipase	2	2	0	46.2	3.7	43.6	48.8
	Potassium	2	2	0	4.6	0.5	4.2	4.9
	Red blood cell count (RBC)	2	2	0	4.2	1.0	3.5	4.9

Analysevariable : LB_VALUE lb_value

Treatment	*lb_labtest*	*Anzahl Beob.*	*N*	*Anzahl fehl. Werte*	*Mittelwert*	*Std.abweichung*	*Minimum*	*Maximum*
	Sodium	2	2	0	141.5	2.1	140.0	143.0
	Thrombocytes	2	2	0	204.5	77.1	150.0	259.0
	Total bilirubin	2	2	0	0.3	0.1	0.2	0.4
	Unconjugated bilirubin	2	2	0	0.1	0.0	0.1	0.2
	Urea	2	2	0	34.0	4.1	31.1	36.9
	White blood cell count (WBC)	2	2	0	5.6	2.7	3.6	7.5

Table 15: Listing of Concomitant Medication (based on dataset conmed)

Pat. ID	Treatment	Generic Name	Dose per day (incl. unit)	Route of administration	Start date (day)	Start date (month)	Start date (year)	End date (day)	End date (month)	End date (year)	Ongoing at study end?	Route of administration	Indication
Subject.1	Control Group (Glimepiride)	Symbicort	2	inhaled	.	.	2003	.	.	.	ongoing	medical history	Asthma
		Salbutamol	unknown	inhaled	.	.	2003	.	.	.	ongoing	medical history	Asthma
		Amlodipin	5mg	oral	.	.	2003	.	.	.	ongoing	medical history	Hypertonie
		Ramipril	10mg	oral	.	.	2003	.	.	.	ongoing	medical history	Hypertonie
		Xelevia	100mg	oral	.	.	2012	.	.	.	ongoing	medical history	Diabetes mellitus
		Circulo-Injel	1	oral	.	4	2017	.	.	.	ongoing	medical history	circulation disorder
		Dobensana	1,2mg / 0,6 mg	oral	6	12	2017	11	12	2017	.	adverse event	Common cold
		Azithromycin	500 mg	oral	9	12	2017	11	12	2017	.	adverse event	Common Cold
		Azithromycin	500 mg	oral	13	12	2017	15	12	2017	.	adverse event	Common Cold
Subject.2	Experimental Group (Empagliflozin)	Salbutamol	2 hub	inhaled	.	.	2011	.	.	.	ongoing	medical history	Asthma bronchiale
		Spiriva	2 hub	inhaled	.	.	2011	.	.	.	ongoing	medical history	Asthma bronchiale
		Yanumet	2 (1050mg)	oral	.	.	1997	.	.	.	ongoing	medical history	diabetes mellitus type 2
		Valsacor comp	1 (160/25 mg)	oral	.	.	1995	.	.	.	ongoing	medical history	arterial hypertension
		omeprazol	1 (40 mg)	oral	.	3	2017	.	.	.	ongoing	prophylaxis	Proton pump inhibitor

Pat. ID	Treatment	Generic Name	Dose per day (incl. unit)	Route of administration	Start date (day)	Start date (month)	Start date (year)	End date (day)	End date (month)	End date (year)	Ongoing at study end?	Route of administration	Indication
Subject.3	Control Group (Glimepiride)	Metformin	850 mg	oral	.	.	2002	.	.	.	ongoing	medical history	Diabetes mellitus
		Simvahexal	30 mg	oral	.	.	2002	.	.	.	ongoing	medical history	Cholesterin senker
		Amlodipin	10 mg	oral	.	.	2015	.	.	.	ongoing	medical history	Hypertonie
		Furosemid	40 mg (as needed)	oral	.	.	2011	14	7	2017	.	prophylaxis	Entwässerung
		ASS	100 mg	oral	.	.	2015	.	.	.	ongoing	medical history	Hypertonie
		Tamsublock	0,4 mg	oral	.	.	2015	.	.	.	ongoing	medical history	Prostatahyperplasie
		Hydrochlorothiazid	12,5 mg	oral	.	.	2007	.	.	.	ongoing	medical history	CVI
		Berlosin	500 mg	oral	23	10	2017	.	.	.	ongoing	other	lumbago
		Doxycyclin	100 mg, QD	oral	20	2	2018	11	3	2018	.	adverse event	Boil on the right thigh
		Candesartan	16 mg	oral	6	6	2018	.	.	.	ongoing	medical history	Hypertonie
Subject.4	Experimental Group (Empagliflozin)	METFORMIN	2 (1700 mg)	oral	31	7	2017	.	.	.	ongoing	medical history	DIABETES MELLITUS TYPE II
		Ibuprofen	400 mg	oral	28	2	2018	7	3	2018	.	adverse event	Common cold
Subject.5	Experimental Group (Empagliflozin)	METFORMIN	1000 mg (TID)	oral	.	3	2011	.	.	.	ongoing	medical history	DIABETES MELLITUS TYPE II
		IBUPROFEN	400 mg (in demand)	oral	.	10	2010	.	.	.	ongoing	medical history	LOW BACK PAIN
		cefpodoxim	200 mg (BID)	oral	12	2	2018	17	2	2018	.	adverse event	Bronchitis

Pat. ID	Treatment	Generic Name	Dose per day (incl. unit)	Route of administration	Start date (day)	Start date (month)	Start date (year)	End date (day)	End date (month)	End date (year)	Ongoing at study end?	Route of administration	Indication
		TOLPERISON Hydrochlorid	50 mg (TID)	oral	27	4	2018	3	5	2018	.	adverse event	Back pain
Subject.6	Control Group (Glimepiride)	Metformin	1000 mg	oral	.	.	2016	.	.	.	ongoing	medical history	Diabetes mellitus, Typ II

Table 16: Listing of all Adverse Events (based on data set Ae_meddra)

Pat. ID	Treatment	AE Term	Is AE serious?	Is the adverse event of special interest (AESI, see protocol chapter 7.1 for definitions)?	Start date (day)	Start date (month)	Start date (year)	End date (day)	End date (month)	End date (year)	CTC grade (NCI CTCAE v 4.0)	Causality to the study drug?	Causality to the study procedures?	Measures taken with regard to study medication	Concomitant medication	Therapeutic or diagnostic measures (except medication)	Other	Unexplained tachycardia	PT	SOC
Subject. 1	Control Group (Glimepiride)	dizziness	no	no	4	7	2017	5	7	2017	mild (grade 1)	yes	no	None	no	no	no	completely recovered/back to baseline conditions	Dizziness	Nervous system disorders
		pain with micturating	no	no	16	8	2017	18	8	2017	moderate (grade 2)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Dysuria	Renal and urinary disorders
		hypoglycemia	no	no	18	10	2017	18	10	2017	moderate (grade 2)	yes	no	None	no	no	no	completely recovered/back to baseline conditions	Hypoglycaemia	Metabolism and nutrition disorders
		Common cold	no	no	5	12	2017	14	1	2018	mild (grade 1)	no	no	None	yes	no	no	completely recovered/back to baseline conditions	Nasopharyngitis	Infections and infestations
		Swelling right foot	no	no	16	3	2018	.	.	.	mild (grade 1)	yes	no	None	no	no	no	not recovered (persistently not changing)	Peripheral swelling	General disorders and administration site conditions
		Dizziness	no	no	4	7	2017	20	11	2017	mild (grade 1)	yes	no	None	no	no	no	completely recovered/back to baseline conditions	Dizziness	Nervous system disorders

Pat. ID	Treatment	AE Term	Is AE serious?	Is the adverse event of special interest (AESI, see protocol chapter 7.1 for definitions)?	Start date (day)	Start date (month)	Start date (year)	End date (day)	End date (month)	End date (year)	CTC grade (NCI CTCAE v 4.0)	Causality to the study drug?	Causality to the study procedures?	Measures taken with regard to study medication	Concomitant medication	Therapeutic or diagnostic measures (except medication)	Other	Unexplained tachycardia	PT	SOC
		elevated blood sugar	no	no	3	4	2018	.	.	.	mild (grade 1)	yes	no	Study drug discontinued	no	no	no	not recovered (persistently not changing)	Blood glucose increased	Investigations
Subject. 2	Experimental Group (Empagliflozin)	Headache	no	no	8	8	2017	13	8	2017	mild (grade 1)	yes	no	None	no	no	no	completely recovered/back to baseline conditions	Headache	Nervous system disorders
		Nausea	no	no	8	8	2017	13	8	2017	mild (grade 1)	yes	no	None	no	no	no	completely recovered/back to baseline conditions	Nausea	Gastrointestinal disorders
		Dizziness	no	no	8	8	2017	13	8	2017	mild (grade 1)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Dizziness	Nervous system disorders
		overthrow	no	no	15	8	2017	15	8	2017	moderate (grade 2)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Vomiting	Gastrointestinal disorders
		abrasion both knees	no	no	15	8	2017	27	10	2017	mild (grade 1)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Skin abrasion	Injury, poisoning and procedural complications
		Urinary tract infection	no	no	8	10	2017	15	10	2017	mild (grade 1)	yes	no	None	no	no	no	completely recovered/back to baseline conditions	Urinary tract infection	Infections and infestations

Pat. ID	Treatment	AE Term	Is AE serious?	Is the adverse event of special interest (AESI, see protocol chapter 7.1 for definitions)?	Start date (day)	Start date (month)	Start date (year)	End date (day)	End date (month)	End date (year)	CTC grade (NCI CTCAE v 4.0)	Causality to the study drug?	Causality to the study procedures?	Measures taken with regard to study medication	Concomitant medication	Therapeutic or diagnostic measures (except medication)	Other	Unexplained tachycardia	PT	SOC
		Nausea	no	no	10	10	2017	.	.	.	mild (grade 1)	no	no	None	no	no	no	unknown	Nausea	Gastrointestinal disorders
		Dizziness	no	no	10	10	2017	.	.	.	mild (grade 1)	no	no	None	no	no	no	unknown	Dizziness	Nervous system disorders
		Decreased GFR	no	no	21	8	2017	25	9	2017	mild (grade 1)	yes	no	None	no	no	no	completely recovered/back to baseline conditions	Glomerular filtration rate decreased	Investigations
		circulatory disturbance	no	no	25	9	2017	25	9	2017	mild (grade 1)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Cardiovascular disorder	Cardiac disorders
		Feeling of poorer vision	no	no	9	10	2017	11	10	2017	mild (grade 1)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Visual impairment	Eye disorders
		Dizziness	no	no	16	11	2017	16	11	2017	moderate (grade 2)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Dizziness	Nervous system disorders
		norovirus	no	no	8	12	2017	20	12	2017	mild (grade 1)	no	no	Study drug discontinued	no	no	no	completely recovered/back to baseline conditions	Gastroenteritis norovirus	Infections and infestations
Subject. 3	Control Group (Glimepiride)	Worsening of low back pain	no	no	2	9	2017	20	7	2018	moderate (grade 2)	no	no	None	no	no	no	not recovered (persistently not changing)	Back pain	Musculoskeletal and connective tissue disorders

Pat. ID	Treatment	AE Term	Is AE serious?	Is the adverse event of special interest (AESI, see protocol chapter 7.1 for definitions)?	Start date (day)	Start date (month)	Start date (year)	End date (day)	End date (month)	End date (year)	CTC grade (NCI CTCAE v 4.0)	Causality to the study drug?	Causality to the study procedures?	Measures taken with regard to study medication	Concomitant medication	Therapeutic or diagnostic measures (except medication)	Other	Unexplained tachycardia	PT	SOC
		Boil on the right thigh	no	no	12	2	2018	11	3	2018	moderate (grade 2)	no	no	None	yes	no	no	completely recovered/back to baseline conditions	Furuncle	Infections and infestations
Subject. 4	Experimental Group (Empagliflozin)	Common cold	no	no	28	2	2018	14	3	2018	mild (grade 1)	no	no	None	yes	no	no	completely recovered/back to baseline conditions	Nasopharyngitis	Infections and infestations
Subject. 5	Experimental Group (Empagliflozin)	Shoulder / neck pain	no	no	14	10	2017	25	10	2017	moderate (grade 2)	no	no	None	yes	no	no	completely recovered/back to baseline conditions	Musculoskeletal pain	Musculoskeletal and connective tissue disorders
		Cold	no	no	27	11	2017	30	11	2017	moderate (grade 2)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Nasopharyngitis	Infections and infestations
		thrombocytopenia	no	no	18	9	2017	7	2	2018	mild (grade 1)	yes	no	None	no	no	no	completely recovered/back to baseline conditions	Thrombocytopenia	Blood and lymphatic system disorders
		Bronchitis	no	no	12	2	2018	17	2	2018	mild (grade 1)	no	no	None	yes	no	no	completely recovered/back to baseline conditions	Bronchitis	Infections and infestations
		Back pain	no	no	27	4	2018	3	5	2018	mild (grade 1)	no	no	None	yes	no	no	completely recovered/back to baseline conditions	Back pain	Musculoskeletal and connective tissue disorders

ICH E3 Synopsis – SUPER-Trial – EudraCT No. 2016-000825-38

Pat. ID	Treatment	AE Term	Is AE serious?	Is the adverse event of special interest (AESI, see protocol chapter 7.1 for definitions)?	Start date (day)	Start date (month)	Start date (year)	End date (day)	End date (month)	End date (year)	CTC grade (NCI CTCAE v 4.0)	Causality to the study drug?	Causality to the study procedures?	Measures taken with regard to study medication	Concomitant medication	Therapeutic or diagnostic measures (except medication)	Other	Unexplained tachycardia	PT	SOC
Subject. 6	Control Group (Glimepiride)	Elevation of lipase due to excessive alcohol intake	no	no	3	1	2018	6	2	2018	mild (grade 1)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Lipase increased	Investigations
		diarrhoae	no	no	20	1	2018	21	1	2018	mild (grade 1)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Diarrhoea	Gastrointestinal disorders
		Elevation of lipase	no	no	13	4	2018	28	5	2018	moderate (grade 2)	no	no	None	no	no	no	completely recovered/back to baseline conditions	Lipase increased	Investigations

Table 17: Number of patients with at least one AE broken down by SOC and PT

		treatment	
Type of AE Specification	**Glimepiride N=3**	**Empagliflozin N=3**	**Total N=6**
Number of patients with at least one AE	3 (100.0%)	3 (100.0%)	6 (100.0%)
Blood and lymphatic system disorders	-	1 (33.3%)	1 (16.7%)
Thrombocytopenia	-	1 (33.3%)	1 (16.7%)
Cardiac disorders	-	1 (33.3%)	1 (16.7%)
Cardiovascular disorder	-	1 (33.3%)	1 (16.7%)
Eye disorders	-	1 (33.3%)	1 (16.7%)
Visual impairment	-	1 (33.3%)	1 (16.7%)
Gastrointestinal disorders	1 (33.3%)	1 (33.3%)	2 (33.3%)
Diarrhoea	1 (33.3%)	-	1 (16.7%)
Nausea	-	1 (33.3%)	1 (16.7%)
Vomiting	-	1 (33.3%)	1 (16.7%)
General disorders and administration site conditions	1 (33.3%)	-	1 (16.7%)
Peripheral swelling	1 (33.3%)	-	1 (16.7%)
Infections and infestations	2 (66.7%)	3 (100.0%)	5 (83.3%)
Bronchitis	-	1 (33.3%)	1 (16.7%)
Furuncle	1 (33.3%)	-	1 (16.7%)
Gastroenteritis norovirus	-	1 (33.3%)	1 (16.7%)
Nasopharyngitis	1 (33.3%)	2 (66.7%)	3 (50.0%)
Urinary tract infection	-	1 (33.3%)	1 (16.7%)
Injury, poisoning and procedural complications	-	1 (33.3%)	1 (16.7%)
Skin abrasion	-	1 (33.3%)	1 (16.7%)
Investigations	2 (66.7%)	1 (33.3%)	3 (50.0%)
Blood glucose increased	1 (33.3%)	-	1 (16.7%)
Glomerular filtration rate decreased	-	1 (33.3%)	1 (16.7%)
Lipase increased	1 (33.3%)	-	1 (16.7%)
Metabolism and nutrition disorders	1 (33.3%)	-	1 (16.7%)
Hypoglycaemia	1 (33.3%)	-	1 (16.7%)
Musculoskeletal and connective tissue disorders	1 (33.3%)	1 (33.3%)	2 (33.3%)
Back pain	1 (33.3%)	1 (33.3%)	2 (33.3%)
Musculoskeletal pain	-	1 (33.3%)	1 (16.7%)
Nervous system disorders	1 (33.3%)	1 (33.3%)	2 (33.3%)
Dizziness	1 (33.3%)	1 (33.3%)	2 (33.3%)
Headache	-	1 (33.3%)	1 (16.7%)

		treatment	
Type of AE Specification	**Glimepiride N=3**	**Empagliflozin N=3**	**Total N=6**
Renal and urinary disorders	1 (33.3%)	-	1 (16.7%)
Dysuria	1 (33.3%)	-	1 (16.7%)

Table includes each adverse event term only once per patient. Percentages are calculated using the total number of patients per treatment group as the denominator.

Table 18: Number of AEs broken down by SOC and PT

Type of AE Specification	Treatment Glimepiride N=3	Empagliflozin N=3	Total N=6
Total number of AE	12	19	31
Blood and lymphatic system disorders	-	1 (5.3%)	1 (3.2%)
Thrombocytopenia	-	1 (5.3%)	1 (3.2%)
Cardiac disorders	-	1 (5.3%)	1 (3.2%)
Cardiovascular disorder	-	1 (5.3%)	1 (3.2%)
Eye disorders	-	1 (5.3%)	1 (3.2%)
Visual impairment	-	1 (5.3%)	1 (3.2%)
Gastrointestinal disorders	1 (8.3%)	3 (15.8%)	4 (12.9%)
Diarrhoea	1 (8.3%)	-	1 (3.2%)
Nausea	-	2 (10.5%)	2 (6.5%)
Vomiting	-	1 (5.3%)	1 (3.2%)
General disorders and administration site conditions	1 (8.3%)	-	1 (3.2%)
Peripheral swelling	1 (8.3%)	-	1 (3.2%)
Infections and infestations	2 (16.7%)	5 (26.3%)	7 (22.6%)
Bronchitis	-	1 (5.3%)	1 (3.2%)
Furuncle	1 (8.3%)	-	1 (3.2%)
Gastroenteritis norovirus	-	1 (5.3%)	1 (3.2%)
Nasopharyngitis	1 (8.3%)	2 (10.5%)	3 (9.7%)
Urinary tract infection	-	1 (5.3%)	1 (3.2%)
Injury, poisoning and procedural complications	-	1 (5.3%)	1 (3.2%)
Skin abrasion	-	1 (5.3%)	1 (3.2%)
Investigations	3 (25.0%)	1 (5.3%)	4 (12.9%)
Blood glucose increased	1 (8.3%)	-	1 (3.2%)
Glomerular filtration rate decreased	-	1 (5.3%)	1 (3.2%)
Lipase increased	2 (16.7%)	-	2 (6.5%)
Metabolism and nutrition disorders	1 (8.3%)	-	1 (3.2%)
Hypoglycaemia	1 (8.3%)	-	1 (3.2%)
Musculoskeletal and connective tissue disorders	1 (8.3%)	2 (10.5%)	3 (9.7%)
Back pain	1 (8.3%)	1 (5.3%)	2 (6.5%)
Musculoskeletal pain	-	1 (5.3%)	1 (3.2%)
Nervous system disorders	2 (16.7%)	4 (21.1%)	6 (19.4%)
Dizziness	2 (16.7%)	3 (15.8%)	5 (16.1%)
Headache	-	1 (5.3%)	1 (3.2%)

	Treatment		
Type of AE Specification	**Glimepiride N=3**	**Empagliflozin N=3**	**Total N=6**
Renal and urinary disorders	1 (8.3%)	-	1 (3.2%)
Dysuria	1 (8.3%)	-	1 (3.2%)

Table includes all adverse events. Percentages are calculated using the total number of events per treatment group as the denominator.