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 in patients with type 2 diabetes mellitus: Influences on left ventricular mass, function, and cardiac lipid content

EudraCT-No.: 2014-003313-28

Protocol Code No.: CRC-KliPha-001

Information about study protocol versions:

Protocol version 1.2, 02 JUN 2015

Subsequent substantial amendment:

Final protocol version 1.3, 30 SEP 2015

Investigators:

Prof. Dr. med. Jens Jordan (Principal Investigator)

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Prof. Dr. med. Christoph Schindler (Co-Investigator)

Study coordination:

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Study centre:

Hannover Medical School, Institute of Clinical Pharmacology, Carl-Neuberg-Str. 1, 30625 Hannover, Germany and Clinical Research Center Hannover, Feodor-Lynen-Str. 15, 30625 Hannover, Germany (monocenter study)

Study sponsor:

Hannover Medical School
Carl-Neuberg-Straße 1
30625 Hannover
Germany

Publication (reference):

none

Studied period (years):	**Phase of development:**
date of first enrolment: 13 MAY 2016 date of last completed: 27 SEP 2017 temporary halt: 30 JUN 2017 early termination: 29 JUN 2018	Phase IV

Objectives:

Primary Objective:

To demonstrate that left ventricular mass is reduced with Empagliflozin treatment compared to Glimepiride treatment on top of stable metformin background medication.

Secondary objectives:

- changes in cardiac dimensions, function, and metabolism
- changes in glucose homeostasis
- changes in body composition
- changes in ambulatory blood pressure
- changes in systemic and adipose tissue inflammatory markers and markers of insulin resistance

Methodology:

Randomized, active-controlled, mono-center, double-blinded, parallel-group, phase IV clinical trial

Number of patients (planned and analysed):

Planned:

To be allocated to trial: n=60 (n=30 each treatment group)

To be analysed: at least n=54 in total (n=27 per treatment group)

Analysed:

Randomised: total n=7 (Empagliflozin group n=3, Glimepiride group n=4)

The recruitment was stopped prematurely by the sponsor in accordance with the principal investigator because of the difficulties to recruit patients and to achieve the planned numbers of patients within a reasonable time frame. Neither safety nor IMP issues were involved in this decision.

Patient EM-01-006 was randomized to Glimepiride, but did not receive the allocated treatment due to discontinuation before the treatment period. This patient is excluded from all analyses (PP, ITT and safety population).

Patient EM-01-001 was randomized to Glimepiride and received the allocated treatment, but stopped study participation prematurely due to the adverse event of weight gain. Thus, the measurement for left ventricular mass at Visit 8 (the primary endpoint) is missing. This patient was excluded from analysis of the PP population, but included in analyses of the ITT and safety populations.

In primary analysis population (PP): n=5 (Empagliflozin group n=3, Glimepiride group n=2)

In safety population (equal to ITT): n=6 (Empagliflozin group n=3, Glimepiride group n=3)

Diagnosis and main criteria for inclusion and exclusion:

Inclusion:

1. women and men ≥40 and < 80 years of age
2. patients with type 2 diabetes mellitus on stable anti-diabetic treatment for the last 3 months; at screening the following treatment conditions are allowed:

· metformin + sulfonylurea with HbA1c ≥ 6.5% and ≤ 9.0%
· metformin monotherapy with HbA1c ≥ 7.5% and ≤ 9.0
· metformin + DPP-IV inhibitor with HbA1c≥ 6.5% and ≤ 9.0%

3. waist circumference ≥80 cm in women or ≥ 94 cm in men
4. office blood pressure ≤ 150/95 mm Hg with a stable dose of a maximum of 4 antihypertensive medications for the last 3 months (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)
5. 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
6. 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 reliable contraception methods. The following are acceptable: 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
7. signed written informed consent and willingness to comply with treatment and follow-up procedures
8. capability of understanding the investigational nature, potential risks and benefits of the clinical trial

Exclusion:

1. diabetes mellitus type 1
2. uncontrolled diabetes mellitus type 2 with fasting glucose > 13.3 mmol/l confirmed on a second day
3. previous treatment with insulin, GLP-1 analogues, or pioglitazone during the last year before screening
4. previous treatment with empagliflozin
5. acute illness at screening or randomization according to judgement by the investigator or patient
6. known or suspected hypersensitivity to empagliflozin, glimepiride or any excipients; known or suspected hypersensitivity to sulfonylureas or sulfonamides
7. history of multiple severe hypoglycemic episodes
8. any condition prohibiting MRI studies (e.g. metal implants, claustrophobia, body weight too high) including any suspected reaction after contrast agent application

9. patient actively attempted to lose weight or experienced unintentional clinically significant weight loss during the last 3 months
10. bariatric surgery or other gastrointestinal surgery procedures that induce chronic malabsorption
11. treatment with any weight loss drug in the preceding 6 months
12. planned significant changes of pre-study physical activity level during study participation
13. heart failure NYHA III – IV
14. patients with known severe cardiovascular disease (e.g. myocardial infarction, unstable angina, stable coronary artery disease, stroke or transient ischemic attack)
15. eGFR<60 ml/min/1,73 m^2
16. treatment with loop diuretics
17. chronic diarrhea, any clinical signs of volume depletion or a haematocrit > 48 % (women) and > 53 % (men)
18. history of severe volume depletion that required medical therapy
19. chronic lower urinary tract infections (but not simple asymptomatic bacteriuria)
20. known acute or chronic liver disease or screening ALT or AST> 3 x ULN
21. serum potassium < 3.6 or > 5.0 mmol/l
22. glucose-6-phosphate dehydrogenase deficiency
23. anemia of unknown origin
24. pregnancy or lactation period
25. treatment with systemic glucocorticoids during the last 3 months before screening
26. chronic treatment with NSAIDs
27. changes in thyroid hormone dosage (stable doses of thyroid hormones for the last 3 months are acceptable)
28. history of drug or alcohol abuse or current abuse
29. psychosomatic or psychiatric diseases requiring hospitalization during the last 12 months; ongoing treatment with one tricyclic or SSRI antidepressant drug at a stable dose since the last 3 months is acceptable except for fluoxetine
30. medical history of cancer except for strictly localized tumors
31. any medical or surgical intervention planned for the next 7 months after randomization not allowing study participation according to the investigator´s judgment
32. current participation in any other clinical trial or participation in another clinical trial within 30 days before screening

Study treatment intervention

Randomized IMP treatment was:

Arm 1: 25 mg/d Empagliflozin + Glimepiride placebo (two pills)

Arm 2: Empagliflozin placebo + Glimepiride (in pre-defined dose):

2a. 2 mg/d Glimepiride (one pill) + Glimepiride placebo (one pill)

2b. 4 mg/d Glimepiride (two 2 mg pills)

Glimepiride dose was specified by the investigator before randomization according to pre-study diabetes treatment and HbA1c at screening.

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

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

Active substance: Empagliflozin

Oral administration, 1 pill per day

Dosage per pill: 25 mg

Duration of treatment: 24 weeks

Batch number: 1508000049; packed as batch number CRC-KliPHa-001/001GE
1610000065; packed as batch number CRC-KliPHa-001/002GE

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

Glimepiride, 2 mg tablets (Glimepiride ratiopharm®, study specific labelled)

Active substance: Glimepiride

Oral administration, 1 or 2 pills per day

Dosage per pill: 2 mg

Duration of treatment: 24 weeks

Batch number: 15024G001; packed as batch number CRC-KliPHa-001/001GE

Placebo (Empagliflozin), film-coated tablets

Oral administration, 1 pill per day

Duration of treatment: 24 weeks

Batch number: 1508000048; packed as batch number CRC-KliPHa-001/001GE
1610000066; packed as batch number CRC-KliPHa-001/002GE

Placebo (Glimepiride), tablets

Oral administration, 1 or 2 pills per day

Duration of treatment: 24 weeks

Batch number: 16063G002; packed as batch number CRC-KliPHa-001/001GE

Changes to the conduct of the study

A substantial amendment (SA 1.0) was made to the study protocol version 1.2 of 02.06.2015 resulting in study protocol version 1.3 of 30.9.2015. The amendment covered the following major changes:

- Exclusion criteria clarified and supplemented
- Additions to the risk-benefit assessment with regard to:
  - Hypoglycaemia risk and provision of glucometers to the subjects
  - Cardiovascular risk of sulfonylureas and management
  - Addition of the use of a contrast agent in the magnetic resonance imaging
- Clarification of randomization procedure
- Specification of investigational medicinal product manufacturing chain
- Explanations on dose selection of Empagliflozin and Glimepiride
- Changes and specification of study examinations
- Specification of permitted and prohibited concomitant medications
- Definition of adverse events of special interest and management of them

The recruitment was stopped in June 2017. Due to the unforeseen long recruitment time and low recruitment rate the expiry date of the investigational medicinal products was reached.
In June 2018 this study was prematurely terminated by the sponsor in accordance with the principal investigator after only 7 patients have been included into the study because of the difficulties to recruit patients and to achieve the planned numbers of patients within a reasonable time frame. Neither safety nor IMP issues were involved in this decision.

To account for the low sample size, the pre-specified primary analysis model using several

covariates (ANCOVA model) was replaced by a simplified ANCOVA model using solely the treatment allocation and the baseline left ventricular mass as independent variables. Additionally, only the primary efficacy analysis with respective sensitivity analyses and analyses of AEs and SAEs were conducted. Nevertheless, all acquired data are given in the Appendix.

Endpoints/Outcomes

Primary endpoint

change in left ventricular mass determined by cMRI (24 weeks - baseline)

Secondary endpoints

- changes in left ventricular end-systolic and end-diastolic volume (24 weeks – baseline)
- change in left ventricular function (24 weeks – baseline)
- change in intramyocardial lipid content (24 weeks – baseline)
- change in diastolic function (echocardiography, 24 weeks – baseline)
- change in HbA1c (24 weeks – baseline)
- change in fasting glucose and insulin (24 weeks – baseline)
- changes in body weight, waist circumference, and body fat mass (24 weeks – baseline)
- change in ambulatory blood pressure and metabolic genes (24 weeks – baseline)

Exploratory endpoints

- change in plasma biomarkers of insulin resistance and inflammation (24 weeks –baseline)
- change in adipose tissue mRNA expression of inflammatory and metabolic genes (24 weeks – baseline)
- change in cardiac fibrosis (24 weeks – baseline)
- change in global long strain (24 weeks – baseline)

Safety variables

- blood electrolytes, blood count, hematocrit, liver function tests, blood urea and creatinine
- urine analysis (glucose will be measured but not reported to investigators)
- signs and symptoms of lower urinary tract infections or genital fungal infections
- all adverse events and serious adverse events

Statistical methods

Efficacy and primary endpoint

The type-I error is set to 5% (two-sided). The primary analysis was conducted in the per-protocol (PP) population. The PP population includes all patients who have evaluable measurements of left ventricular mass at baseline and at end of treatment. For the primary analysis, all randomized patients were analysed. The primary efficacy endpoint, change in left ventricular mass (defined as 24 weeks – baseline), was analysed by an analysis of covariance (ANCOVA) model with treatment group and baseline left ventricular mass as independent variable. Superiority of Empagliflozin compared to Glimepiride was assessed on the basis of the two-sided 95% confidence interval (CI) for

the mean difference (Empagliflozin - Glimepiride). A reduction of left ventricular mass would be concluded, if the upper bound of the two-sided 95% CI was below zero.

Safety

The safety analysis was conducted in the safety analysis set including all patients, who received at least one dose of the study drugs. Consequently, one patient was excluded from the safety analysis because study participation was stopped during the baseline visit prior to study drug administration. In this study, the ITT and the safety populations are identical.

AE and SAE are reported with absolute and relative frequencies per treatment group. Additionally, absolute and relative frequencies of the CTC grades of AE and SAE were compared between treatment groups.

Primary analysis population characteristics

In the PP population a total of 5 patients (Glimepiride group: n=2; Empagliflozin group: n=3) are analysed. 1/5=20% are male (Glimepiride group: 1/1 =50%; Empagliflozin group: 0/3=0%). Mean (± standard deviation) age is 63.0 (±7.5) years (Glimepiride group: 65.5 (±10.6); Empagliflozin group: 61.3 (±6.7)). Mean BMI is 27.7 (±2.6) kg/m^2 (Glimepiride group: 27.1 (±1.3); Empagliflozin group: 28.1 (±3.4)). At Baseline, the mean left ventricular mass in the PP population for all 6 patients was 97.6 (±14.2) g with a higher left ventricular mass in the Glimepiride group (103.9 (±23.5) g) compared to the Empagliflozin group (93.4 (±7.7) g). For a detailed descriptive analyses of the population characteristics see Table 1, Table 2, Table 4 and Table 8 in the appendix.

Efficacy results

The mean (±standard deviation) change in left ventricular mass from baseline to 24 weeks (24 weeks – baseline) in the Glimepiride group is -4.0 (±8.5) g and -5.4 (±7.1) g in the Empagliflozin group. The primary analysis model effect estimate for the difference in change in left ventricular mass (Empagliflozin – Glimepiride) is 2.3 with 95% confidence interval [-26.4, 31.0] and p-value 0.76. Thus, superiority of Empagliflozin over Glimepiride could not be demonstrated.

Detailed results of the primary analysis are given in Table 3 (descriptive statistics) and Table 5 (effect estimates) in the appendix.

A sensitivity analysis applying the primary analysis model in the ITT population, shows a treatment effect estimate of -1.4 with a 95% confidence interval [-19.3, 16.6] and p-value 0.83. In contrast to the primary analysis, here the point estimate for the treatment effect is in favour of Empagliflozin. However, the respective 95%-confidence intervals both include the null. Therefore, in both cases, the null-hypothesis of a difference between Empagliflozin and Glimepiride is rejected and thus, results are considered to be consistent (see Appendix).

Safety results

The safety analyses revealed no suspicious findings. Some AE could be attributed to the risks associated with the study medication and the study procedures as outlined in the study protocol and the informed consent form (e.g. weight gain, hypoglycaemia, vaginal fungal infection, hematoma after adipose tissue biopsy). Other AE are typical events reported in clinical studies (e.g. headache, back pain, abdominal pain). Due to occurrence of the AE “weight gain”, one patient stopped treatment and study participation. No AE of special interest (AESI) as laid down in protocol version 1.3 (hepatic injury, decreased renal function) was observed.

No SAE occurred during the conduct of this study. No study participant died during the study.

In total, 9 and 9 AEs occurred in the Glimepiride group (n=3) and in the Empagliflozin group (n=3), respectively. The highest AE grade observed was grade 3 in the Glimepiride group and grade 2 in the Empagliflozin group. All outcomes of the AEs were classified as “recovered”. A summary of the AE categorized by CTC grade analysed by treatment group, the number of patients with AEs and

number of events is given in the appendix. All AEs are also listed there in Table 27 and Table 28.

Conclusion

The mean change in left ventricular mass after 24 weeks treatment compared to baseline (24 weeks – baseline) in the Glimepiride group is -4.0 (±8.5) g and -5.4 (±7.1) g in the Empagliflozin group. The superiority of Empagliflozin compared to Glimepiride in reducing the left ventricular mass after 24 weeks treatment could not be demonstrated (primary analysis model effect estimate for the difference in change in left ventricular mass (Empagliflozin – Glimepiride) adjusted for baseline left ventricular mass is 2.3 with 95% confidence interval [-26.4, 31.0] and p-value 0.76). Based on the small number of analysed patients, no clinical relevant results were found.

The study did not reach the recruitment goal, the number of included patients was 7/60=12% of the planned sample size. The recruitment was stopped prematurely by the sponsor in accordance with the principal investigator because of the difficulties to recruit patients and to achieve the planned numbers of recruited patients within a reasonable time frame. Neither safety nor IMP issues were involved in this decision.

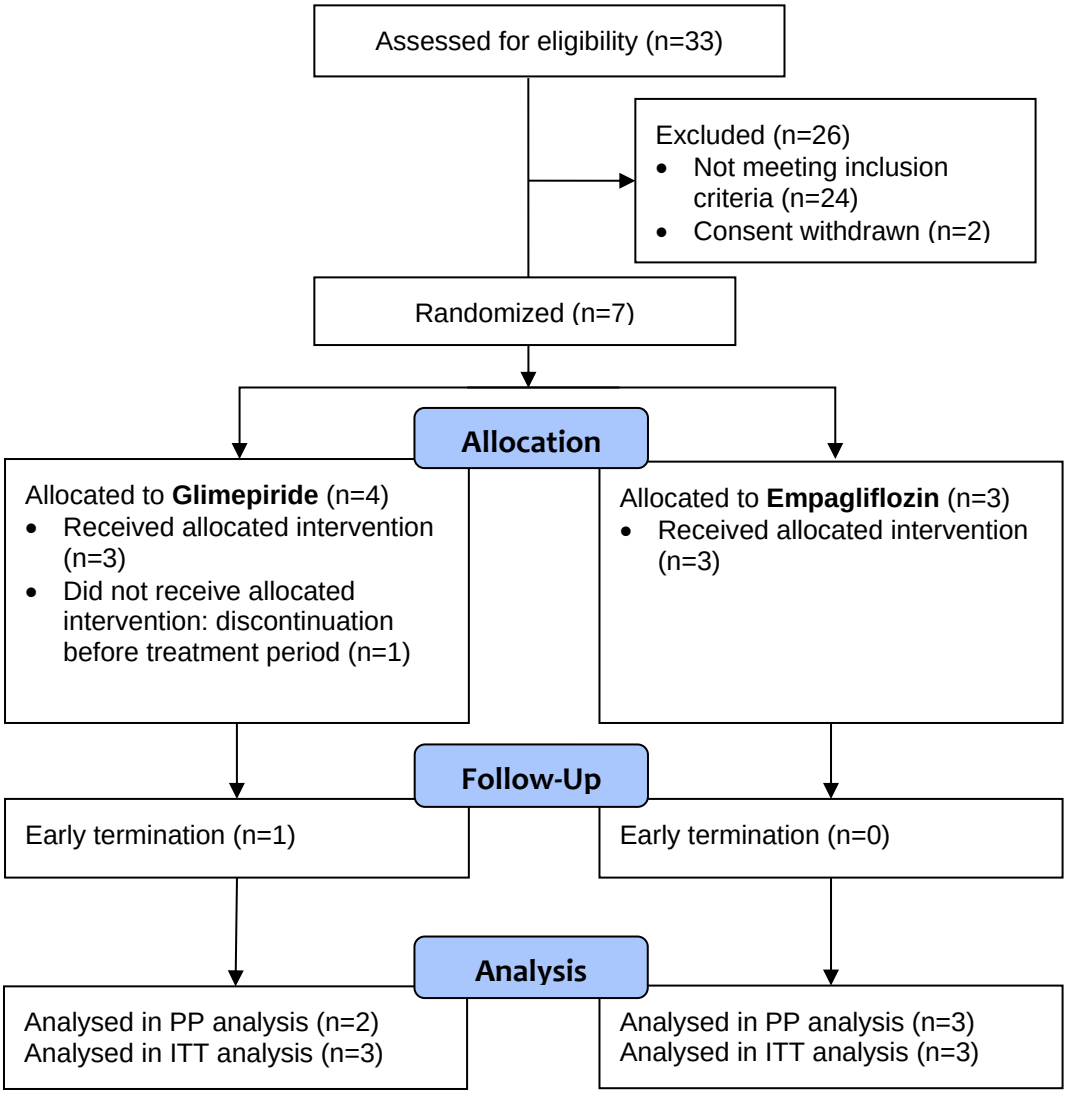
The overall safety profile was unremarkable with 18 AE in total, 2 grade 3 AE (headache, abdominal pain), no AESI, no SAE, and no death.

Date of report: 28 MAY 2019 rev 19 May 2020

1 Appendix

2 Study Flowchart

Figure 1: Study Flowchart



3 Overview in Tables

3.1 *Baseline Characteristics*

Table 1: Descriptive analysis of baseline characteristics – PP population

Baseline Analysis - PP-set

	Treatment		
	Glimepiride N=2	Empagliflozin N=3	Total N=5
height in m			
N	2	3	5
MEAN	1.73	1.68	1.70
STD	0.13	0.03	0.07
MIN	1.63	1.65	1.63
MEDIAN	1.73	1.68	1.68
MAX	1.82	1.70	1.82
MISSING	0	0	0
p-VALUE (T-TEST)			0.5565
sex			
female	1 (50.0%)	3 (100.0%)	4 (80.0%)
male	1 (50.0%)	0 (0.0%)	1 (20.0%)
p-VALUE (CHI^2)			0.1709
age in years			
N	2	3	5
MEAN	65.50	61.33	63
STD	10.61	6.66	7.45
MIN	58	54	54
MEDIAN	65.50	63	63
MAX	73	67	73
MISSING	0	0	0
p-VALUE (T-TEST)			0.6161
weight in kg			
N	2	3	5
MEAN	81.10	78.80	79.72
STD	16.55	7.22	9.80
MIN	69.40	71.30	69.40
MEDIAN	81.10	79.40	79.40
MAX	92.80	85.70	92.80
MISSING	0	0	0
p-VALUE (T-TEST)			0.8368
BMI in kg/m^2			
N	2	3	5
MEAN	27.07	28.09	27.68
STD	1.34	3.40	2.56

Baseline Analysis - PP-set

	Treatment		
	Glimepiride N=2	Empagliflozin N=3	Total N=5
MIN	26.12	24.67	24.67
MEDIAN	27.07	28.13	28.02
MAX	28.02	31.48	31.48
MISSING	0	0	0
p-VALUE (T-TEST)			0.7229
left ventricular mass in g			
N	2	3	5
MEAN	103.85	93.44	97.60
STD	23.50	7.74	14.16
MIN	87.23	88.89	87.23
MEDIAN	103.85	89.05	89.05
MAX	120.47	102.38	120.47
MISSING	0	0	0
p-VALUE (T-TEST)			0.5016

Table 2: Descriptive analysis of baseline characteristics – ITT population

Baseline Analysis - ITT-set

	Treatment		
	Glimepiride N=3	Empagliflozin N=3	Total N=6
height in m			
N	3	3	6
MEAN	1.67	1.68	1.67
STD	0.13	0.03	0.09
MIN	1.56	1.65	1.56
MEDIAN	1.63	1.68	1.67
MAX	1.82	1.70	1.82
MISSING	0	0	0
p-VALUE (T-TEST)			0.9368
sex			
female	2 (66.7%)	3 (100.0%)	5 (83.3%)
male	1 (33.3%)	0 (0.0%)	1 (16.7%)
p-VALUE (CHI^2)			0.2733
age in years			
N	3	3	6
MEAN	60.33	61.33	60.83
STD	11.68	6.66	8.52
MIN	50	54	50
MEDIAN	58	63	60.50
MAX	73	67	73
MISSING	0	0	0

Baseline Analysis - ITT-set

	Treatment		
	Glimepiride N=3	Empagliflozin N=3	Total N=6
p-VALUE (T-TEST)			0.9037
weight in kg			
N	3	3	6
MEAN	83.53	78.80	81.17
STD	12.44	7.22	9.46
MIN	69.40	71.30	69.40
MEDIAN	88.40	79.40	82.55
MAX	92.80	85.70	92.80
MISSING	0	0	0
p-VALUE (T-TEST)			0.5991
BMI in kg/m²			
N	3	3	6
MEAN	30.15	28.09	29.12
STD	5.43	3.40	4.21
MIN	26.12	24.67	24.67
MEDIAN	28.02	28.13	28.07
MAX	36.32	31.48	36.32
MISSING	0	0	0
p-VALUE (T-TEST)			0.6073
left ventricular mass in g			
N	3	3	6
MEAN	99.01	93.44	96.22
STD	18.62	7.74	13.11
MIN	87.23	88.89	87.23
MEDIAN	89.32	89.05	89.19
MAX	120.47	102.38	120.47
MISSING	0	0	0
p-VALUE (T-TEST)			0.6575

3.2 *Primary analysis*

Table 3: Descriptive analysis of primary endpoint – PP population

Change in left ventricular Mass in g (24 weeks - baseline) - PP set

Treatment group	N	Mean	Std. Dev.	Minimum	Median	Maximum
Glimepiride	2	-4.02	8.52	-10.04	-4.02	2.01
Empagliflozin	3	-5.39	7.09	-13.46	-2.54	-0.17

Table 4: Descriptive analysis of baseline left ventricular mass – PP population

Left ventricular Mass at Baseline in g - PP set						
Treatment group	**N**	**Mean**	**Std. Dev.**	**Minimum**	**Median**	**Maximum**
Glimepiride	2	103.85	23.50	87.23	103.85	120.47
Empagliflozin	3	93.44	7.74	88.89	89.05	102.38

Table 5: Results of the primary analysis model

Change in left ventricular mass (24 weeks - baseline) - PP set Results of primary ANCOVA model					
	Estimate	**Standard Error**	**p-Value**	**Lower CL**	**Upper CL**
Intercept	-40.69	27.16910365	0.2729	-157.6	76.21
Treatment: Empagliflozin	2.30	6.66200958	0.7627	-26.36	30.97
Left ventricular mass at baseline	0.35	0.25763417	0.3040	-0.76	1.46

Table 6: Treatment comparison based on the primary analysis model

Change in left ventricular mass in g (24 weeks - baseline) - PP set Treatment comparison adjusted for baseline left ventricular mass					
	Estimate	**Standard Error**	**p-Value**	**Lower CL**	**Upper CL**
Empagliflozin - Glimepiride	2.30	6.66200958	0.7627	-26.36	30.97

3.3 *Sensitivity Analyses*

Table 7: Descriptive analysis of primary endpoint – ITT population

Change in left ventricular Mass in g (24 weeks - baseline) - ITT set Missing values at 24 weeks are imputed with baseline values						
Treatment group	**N**	**Mean**	**Std. Dev.**	**Minimum**	**Median**	**Maximum**
Glimepiride	3	-2.68	6.46	-10.04	0.00	2.01
Empagliflozin	3	-5.39	7.09	-13.46	-2.54	-0.17

Table 8: Descriptive analysis of baseline left ventricular mass – ITT population

Left ventricular Mass in g at Baseline - ITT set						
Treatment group	**N**	**Mean**	**Std. Dev.**	**Minimum**	**Median**	**Maximum**
Glimepiride	3	99.01	18.62	87.23	89.32	120.47
Empagliflozin	3	93.44	7.74	88.89	89.05	102.38

Table 9: Sensitivity analysis - ANCOVA model applied in ITT population

Change in left ventricular mass (24 weeks - baseline) - ITT set
Results of primary ANCOVA model
Missing values at 24 weeks are imputed with baseline values

	Estimate	Standard Error	p-Value	Lower CL	Upper CL
Intercept	-26.85	23.64357098	0.3386	-102.1	48.39
Treatment: Empagliflozin	-1.35	5.63926588	0.8257	-19.30	16.59
Left ventricular mass at baseline	0.24	0.23557331	0.3762	-0.51	0.99

Table 10: Sensitivity analysis treatment comparison based on ANCOVA model applied in ITT population

Change in left ventricular mass (24 weeks - baseline) - ITT set
Treatment comparison adjusted for baseline left ventricular mass
Missing values at 24 weeks are imputed with baseline values

	Estimate	Standard Error	p-Value	Lower CL	Upper CL
Empagliflozin - Glimepiride	-1.35	5.63926588	0.8257	-19.30	16.59

Table 11: Sensitivity analysis of primary endpoint – two-sample t-test applied in the PP population

Change in left ventrikular Mass (24 weeks - baseline) - PP set
Unadjusted treatment comparison

	Estimate	Standard Error	p-Value	Lower CL	Upper CL
Empagliflozin - Glimepiride	-1.37	6.93415560	0.8555	-23.44	20.69

3.4 *Safety analysis*

Table 12: Analysis of AE by CTC grade – number of events (safety population)

Adverse events by CTC grade - safety population - Number of events

	Treatment	
	Glimepiride N=3	Empagliflozin N=3
Total number of AE	8*	9
Grade 1	4* (50.0%)*	2 (22.2%)
Grade 2	2 (28.6%)	7 (77.8%)
Grade 3	2 (28.6%)	-

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

***** Due to an accidental omission, one grade 1 AE in the glimepiride group was not recorded in the eCRF during the study conduct by the study physicians. This omission was not detected by external monitoring. Therefore, this AE is not contained in the electronic study database. However, this AE was recorded as termination reason for patient EM-01-001 and is therefore recorded in Table 26 which is based on the electronic database. For reasons of completeness, the study coordinator decided to add this AE in Tables 12, 13, 27 and 28 as well.

Table 13: Analysis of AEs by CTC grade – number of patients (safety population)

Adverse events by CTC grade - safety population - Number of patients

	Treatment	
	Glimepiride N=3	Empagliflozin N=3
Number of patients with at least one AE	2 (66.7%)*	3 (100.0%)
Grade 1	2 (66.7%)*	1 (33.3%)
Grade 2	2 (66.7%)	3 (100.0%)
Grade 3	1 (33.3%)	-

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.

* Due to an accidental omission, one grade 1 AE in the glimepiride group was not recorded in the eCRF during the study conduct by the study physicians. This omission was not detected by external monitoring. Therefore, this AE is not contained in the electronic study database. However, this AE was recorded as termination reason for patient EM-01-001 and is therefore recorded in Table 26 which is based on the electronic database. For reasons of completeness, the study coordinator decided to consider this AE in Tables 12, 13, 27 and 28 as well.

3.5 *Patient Data Listings*

3.5.1 *Anthropometry*

Table 14: Listing of Anthropometry Data - All Patients

Treatment	Patient	Highest population	Sex	Age (years)	Height (m)	Visit	Weight (kg)	Waist circumference (cm)	Fat mass (kg)	Fat mass (%)	Fat free Mass (kg)	Fat free Mass (%)
Empagliflozin	EM-01-002	PP	female	67	1.70	V0	71.30	97				
						V1	71.30	96	28.29	39.4	43.44	60.6
						V2	69.90	95				
						V3	69.80	95				
						V4	68.10	92				
						V5	66.60	93				
						V6	65.70	90.5				
						V7	64.60	92				
						V8	64.40	92.5	22.3	34.5	42.4	65.5
						V9	64.60	93				
	EM-01-005	PP	female	54	1.65	V0	85.70	105				
						V1	85.70	105	35.4	41.4	50.2	58.6
						V2	84.80	103				
						V3	84.50	103				
						V4	83.80	103				
						V5	83.70	104				
						V6	84.90	105				
						V7	85.60	106				
						V8	85.30	108	32.6	38.2	52.8	61.8
						V9	86.20	107				
	EM-01-007	PP	female	63	1.68	V0	79.40	102				

Treatment	Patient	Highest population	Sex	Age (years)	Height (m)	Visit	Weight (kg)	Waist circumference (cm)	Fat mass (kg)	Fat mass (%)	Fat free Mass (kg)	Fat free Mass (%)
						V1	79.40	97	40	50.4	39.5	49.6
						V2	79.70	95				
						V3	78.40	97				
						V4	78.60	98				
						V5	77.00	91				
						V8	77.20	91	38.7	49.5	39.5	50.5
						V9	78.20	95				
Glimepiride	EM-01-001	ITT	female	50	1.56	V0	88.40	105				
						V1	88.40	106	45.3	50.9	43.6	49.1
						V2	88.80	104				
						V3	88.40	101				
						V4	90.00	103				
						V5	90.00	106				
						V6	89.80	102				
						V9	88.80	101.5				
	EM-01-003	PP	male	73	1.82	V0	92.80	110				
						V1	92.80	114	30.4	32.7	62.6	67.3
						V2	94.90	109				
						V3	95.40	113				
						V4	94.30	111				
						V5	95.10	110				
						V6	95.60	110				
						V7	96.50	111				
						V8	97.40	115	31.8	67.4	65.6	67.4
						V9	95.20	110				
	EM-01-004	PP	female	58	1.63	V0	69.40	89				
						V1	69.40	83	27.6	39.8	41.8	60.2
						V2	69.00	88				

Treatment	Patient	Highest population	Sex	Age (years)	Height (m)	Visit	Weight (kg)	Waist circumference (cm)	Fat mass (kg)	Fat mass (%)	Fat free Mass (kg)	Fat free Mass (%)
						V3	69.70	90				
						V4	69.60	90.5				
						V5	69.40	88				
						V6	68.90	86				
						V7	69.50	89				
						V8	68.50	88	26.2	38.1	42.5	61.9
						V9	68.30	88				
	EM-01-006	Full-analysis set	female	75	1.70	V0	.	94				

3.5.2 *Drug Accountability*

Table 15: Listing of Drug Accountability Data (Label) - All Patients

Treatment	Patient	Highest population	Visit	Date of first drug intake	Date of dispension/return	Dispense: Treatment Label ID (Flask)	Dispense: Treatment Label ID (Blister 1)	Dispense: Treatment Label ID (Blister 2)	Return: Treatment Label ID (Flask)	Return: Treatment Label ID (Blister 1)	Return: Treatment Label ID (Blister 2)
Empagliflozin	EM-01-002	PP	V1	2016-06-30	2016-06-30	F.0002.1	B.1001.1	B.2004.1			
			V2		2016-07-14	F.002.1+ .7	B.1001.1+ .7	B.2004.1+ .7	F.002.1	B.1001.1	B.2004.1
			V3		2016-07-28	F.0002.2	B.1001.2	B.2004.2	F.0002.1	B.1001.1	B.2004.1
			V4		2016-08-25	F.0002.3	B.1001.3	B.2004.3	F.0002.2	B.1001.2	B.2004.2
			V5		2016-09-23	F.0002.4	B.1001.4	B.2004.4	F.0002.3	B.1001.3	B.2004.3
			V6		2016-10-20	F.0002.5	B.1001.5	B.2004.5	F.0002.4	B.1001.4	B.2004.4
			V7		2016-11-17	F.0002.6	B.1001.6	B.2004.6	F.0002.5	B.1001.5	B.2004.5
			V8		2016-12-15				F.0002.6 +.7	B.1001.6 +.7	B.2004.6 +.7
	EM-01-005	PP	V1	2017-02-14	2017-02-13	F.0004.1+.7	B.1003.1+.7	B.2008.7+.1			
			V2		2017-02-28	F.0004.1	B.1003.1	B.2008.1	F.0004.1	B.1003.1	B.2008.1
			V3		2017-03-14	F.0004.2	B.1003.2	B.2008.2	F.0004.1	B.1003.1	B.2008.1

Treatment	Patient	Highest population	Visit	Date of first drug intake	Date of dispension/return	Dispense: Treatment Label ID (Flask)	Dispense: Treatment Label ID (Blister 1)	Dispense: Treatment Label ID (Blister 2)	Return: Treatment Label ID (Flask)	Return: Treatment Label ID (Blister 1)	Return: Treatment Label ID (Blister 2)
			V4		2017-04-11	F.0004.3	B.1003.3	B.2008.3	F.0004.7	B.1003.2	B.2008.2
			V5		2017-05-08	F.0004.4	B.1003.4	B.2008.4	F.0004.3	B.1003.3	B.2008.3
			V6		2017-06-06	F.0004.5	B.1003.5	B.2008.5	F.0004.4	B.1003.4	B.2008.4
			V7		2017-07-07	F.0004.6	B.1003.6	B.2008.6	F.0004.5	B.1003.5	B.2008.5
			V8		2017-08-03				F.0004.6+4	B.1003.6	B.2008.6
	EM-01-007	PP	V1	2017-06-15	2017-06-14	F.0005.1/.7	B.1005.1/.7	B.2011.1/.7			
			V2		2017-06-27	F.0005.1	B.1005.1	B.2011.1	F.0005.1	B.1005.1	B.2011.1
			V3		2017-07-11	F.0005.2	B.1005.2	B.2011.2	F.0005.1	B.1005.1	B.2011.1
			V4		2017-08-08	F.0005.3	B.1005.3	B.2011.3	F.0005.2	B.1005.2	B.2011.2
			V5		2017-09-01	F.0005.4	B.1005.4	B.2011.4	F.0005.3	B.1005.3	B.2011.3
			V8		2017-09-27				F.0005.4+.7	B.1005.4+.7	B.2011.4+.7
Glimepiride	EM-01-001	ITT	V1	2016-06-29	2016-06-29	F.0001.1	B.1002.1	B.2001.1			
			V2		2016-07-13	F.0001.1 + .7	B.1002.1 + .7	B.2001.1 + .7	F.0001.1	B.1002.1	B.2001.1
			V3		2016-07-27	F.0001.2	B.1002.2	B.2001.2	F.0001.1	B.1002.1	B.2001.1
			V4		2016-08-24	F.0001.3	B.1002.3	B.2001.3	F.0001.2	B.1002.2	B.2001.2
			V5		2016-09-21	F.0001.4	B.1002.4	B.2001.4	F.0001.3	B.1002.3	B.2001.3
			V6		2016-10-19				F.0001.4+.7	B.1002.4+.7	B.2001.4+.7
	EM-01-003	PP	V1	2016-09-05	2016-09-05	F.0016.1+.7	B.1016.1+.7	B.2002.1+.7			
			V2		2016-09-19	F.0016.1	B.1016.1	B.2002.1	F.0016.1	B.1016.1	B.2002.1
			V3		2016-10-04	F.0016.2	B.1016.2	B.2002.2	F.0016.1	B.1016.1	B.2002.1
			V4		2016-11-01	F.0016.3	B.1016.3	B.2002.3	F.0016.2	B.1016.2	B.2002.2
			V5		2016-11-29	F.0016.4	B.1016.4	B.2002.4	F.0016.3	B.1016.3	B.2002.3
			V6		2016-12-22	F.0016.5	B.1016.5	B.2002.5	F.0016.4	B.1016.4	B.2002.4
			V7		2017-01-24	F.0016.6	B.1016.6	B.2002.6	F.0016.5	B.1016.5	B.2002.5
			V8		2017-02-20				F.0016.6+.7	B.1016.6+.7	B.2002.6+.7
	EM-01-004	PP	V1	2016-10-28	2016-10-27	F.0003.1 + .7	B.1004.1 + .7	B.2005.1 + .7			
			V2		2016-11-08	F.0003.1	B.1004.1	B.2005.1	F.0003.1	B.1004.1	B.2005.1
			V3		2016-11-25	F.0003.2	B.1004.2	B.2005.2	F.0003.1	B.1004.1	B.2005.1

Treatment	Patient	Highest population	Visit	Date of first drug intake	Date of dispension/return	Dispense: Treatment Label ID (Flask)	Dispense: Treatment Label ID (Blister 1)	Dispense: Treatment Label ID (Blister 2)	Return: Treatment Label ID (Flask)	Return: Treatment Label ID (Blister 1)	Return: Treatment Label ID (Blister 2)
			V4		2016-12-20	F.0003.3	B.1004.3	B.2005.3	F.0003.7	B.1004.7	B.2005.7
			V5		2017-01-19	F.0003.4	B.1004.4	B.2005.4	F.0003.3	B.1004.3	B.2005.3
			V6		2017-02-16	F.0003.5	B.1004.5	B.2005.5	F.0003.4	B.1004.4	B.2005.4
			V7		2017-03-16	F.0003.6	B.1004.6	B.2005.6	F.0003.5	B.1004.5	B.2005.5
			V8		2017-04-12				F.0003.6 +.2	B.1004.6 +.2	B.2005.6 +.2
	EM-01-006	Full-analysis set									

Table 16: Listing of Drug Accountability Data (Number) - All Patients

Treatment	Patient	Highest population	Visit	Date of first drug intake	Date of dispension/return	Amount dispensed in tablets (flask)	Amount dispensed in tablets (Blister 1)	Amount dispensed in tablets (Blister 2)	Amount returned in tablets (flask)	Amount returned in tablets (Blister 1)	Amount returned in tablets (Blister 2)
Empagliflozin	EM-01-002	PP	V1	2016-06-30	2016-06-30	30	28	28			
			V2		2016-07-14	46	42	42	16	14	14
			V3		2016-07-28	30	28	28	2	0	0
			V4		2016-08-25	30	28	28	2	0	0
			V5		2016-09-23	30	28	28	1	0	0
			V6		2016-10-20	30	28	28	3	1	1
			V7		2016-11-17	30	28	28	2	0	0
			V8		2016-12-15				31	26	26
	EM-01-005	PP	V1	2017-02-14	2017-02-13	60	56	56			
			V2		2017-02-28	0	0	0	0	0	0
			V3		2017-03-14	30	28	28	6	2	2
			V4		2017-04-11	30	28	28	1	1	0
			V5		2017-05-08	30	28	28	8	1	1
			V6		2017-06-06	30	28	28	9	2	2

Treatment	Patient	Highest population	Visit	Date of first drug intake	Date of dispension/return	Amount dispensed in tablets (flask)	Amount dispensed in tablets (Blister 1)	Amount dispensed in tablets (Blister 2)	Amount returned in tablets (flask)	Amount returned in tablets (Blister 1)	Amount returned in tablets (Blister 2)
			V7		2017-07-07	30	28	28	11	3	3
			V8		2017-08-03				31	3	3
	EM-01-007	PP	V1	2017-06-15	2017-06-14	60	56	56			
			V2		2017-06-27	18	15	15	18	15	15
			V3		2017-07-11	30	28	28	3	1	1
			V4		2017-08-08	30	28	28	2	0	0
			V5		2017-09-01	30	28	28	6	4	4
			V8		2017-09-27				34	30	30
Glimepiride	EM-01-001	ITT	V1	2016-06-29	2016-06-29	30	28	28			
			V2		2016-07-13	46	42	42	16	14	14
			V3		2016-07-27	30	28	28	2	0	0
			V4		2016-08-24	30	28	28	2	0	0
			V5		2016-09-21	30	28	28	3	1	1
			V6		2016-10-19	.	.	.	32	28	28
	EM-01-003	PP	V1	2016-09-05	2016-09-05	60	56	56			
			V2		2016-09-19	16	14	15	16	14	15
			V3		2016-10-04	30	28	28	1	0	0
			V4		2016-11-01	30	28	28	3	1	1
			V5		2016-11-29	30	28	28	2	0	0
			V6		2016-12-22	30	28	28	4	5	5
			V7		2017-01-24	30	28	28	0	0	0
			V8		2017-02-20				33	23	24
	EM-01-004	PP	V1	2016-10-28	2016-10-27	60	56	56			
			V2		2016-11-08	19	17	17	19	17	17
			V3		2016-11-25	30	28	28	2	0	0
			V4		2016-12-20	30	28	28	5	3	3
			V5		2017-01-19	30	28	28	0	0	0
			V6		2017-02-16	30	28	28	2	0	0

Treatment	Patient	Highest population	Visit	Date of first drug intake	Date of dispension/return	Amount dispensed in tablets (flask)	Amount dispensed in tablets (Blister 1)	Amount dispensed in tablets (Blister 2)	Amount returned in tablets (flask)	Amount returned in tablets (Blister 1)	Amount returned in tablets (Blister 2)
			V7		2017-03-16	30	28	28	2	0	0
			V8		2017-04-12				46	26	26
	EM-01-006	Full-analysis set									

3.5.3 Blood Pressure

Table 17: Listing of Blood Pressure Data (Part 1) - All Patients

Treatment	Patient	Highest population	Visit	1st BP diastolic (mm Hg)	2nd BP diastolic (mm Hg)	3rd BP diastolic (mm Hg)	1st BP systolic (mm Hg)	2nd BP systolic (mm Hg)	3rd BP systolic (mm Hg)
Empagliflozin	EM-01-002	PP	V0	83	83	85	145	132	155
			V1	77	84	78	141	139	139
			V2	77	77	77	133	123	132
			V3	71	66	68	116	116	119
			V4	75	76	74	119	128	120
			V5	78	74	73	128	119	118
			V6	76	81	76	127	130	132
			V7	73	72	72	120	127	119
			V8	72	75	76	125	124	123
			V9	75	77	76	139	129	127
	EM-01-005	PP	V0	84	78	81	122	117	115
			V1	69	73	63	120	121	122
			V2	67	71	68	112	108	109
			V3	71	77	75	119	119	113

Treatment	Patient	Highest population	Visit	1st BP diastolic (mm Hg)	2nd BP diastolic (mm Hg)	3rd BP diastolic (mm Hg)	1st BP systolic (mm Hg)	2nd BP systolic (mm Hg)	3rd BP systolic (mm Hg)
			V4	75	72	77	129	112	119
			V5	65	68	68	108	97	105
			V6	72	75	74	115	115	107
			V7	76	75	71	115	112	115
			V8	71	69	74	111	117	121
			V9	70	78	72	116	127	113
	EM-01-007	PP	V0	79	75	82	133	144	165
			V1	75	69	62	131	129	119
			V2	70	69	65	135	133	135
			V3	85	77	73	133	137	136
			V4	78	77	65	128	130	129
			V5	80	78	72	137	123	127
			V8	76	80	73	132	114	125
			V9	72	73	65	128	123	140
Glimepiride	EM-01-001	ITT	V0	90	93	81	148	143	140
			V1	83	89	83	130	129	123
			V2	82	76	77	124	127	129
			V3	67	78	84	131	121	119
			V4	90	73	90	126	125	137
			V5	80	85	84	132	123	125
			V6	85	84	91	135	124	120
			V9	89	81	72	123	135	127
	EM-01-003	PP	V0	79	82	72	142	152	131
			V1	77	76	64	124	126	110
			V2	71	69	72	115	122	119
			V3	72	74	70	127	128	120
			V4	67	67	67	129	123	130
			V5	79	69	72	147	127	126

Treatment	Patient	Highest population	Visit	1st BP diastolic (mm Hg)	2nd BP diastolic (mm Hg)	3rd BP diastolic (mm Hg)	1st BP systolic (mm Hg)	2nd BP systolic (mm Hg)	3rd BP systolic (mm Hg)
			V6	70	70	72	136	119	125
			V7	66	76	68	128	128	121
			V8	65	68	66	118	132	137
			V9	67	70	74	128	139	134
	EM-01-004	PP	V0	76	72	72	154	152	140
			V1	75	74	76	141	144	134
			V2	69	71	71	128	139	119
			V3	80	73	66	127	135	138
			V4	75	69	68	129	120	123
			V5	68	68	66	114	115	111
			V6	73	67	68	120	131	127
			V7	72	75	76	152	137	140
			V8	66	74	69	116	141	128
			V9	69	74	70	131	143	127
	EM-01-006	Full-analysis set	V0	65	72	74	141	154	151

Table 18: Listing of Blood Pressure Data (Part 2) - All Patients

Treatment	Patient	Highest population	Visit	1st heart rate (bpm)	2nd heart rate (bpm)	3rd heart rate (bpm)	24h BP diastolic (mmHg)	24h BP systolic (mmHg)	24h heart rate (bpm)
Empagliflozin	EM-01-002	PP	V0	62	63	66			
			V1	59	59	60	76	130	54
			V2	67	66	67			
			V3	61	61	61			
			V4	68	67	65			
			V5	62	62	61			
			V6	64	63	63			
			V7	65	64	65			
			V8	65	65	66	73	117	70
			V9	66	68	65			
	EM-01-005	PP	V0	75	72	79			
			V1	77	76	75	77	110	80
			V2	77	78	79			
			V3	64	72	69			
			V4	75	70	77			
			V5	80	74	77			
			V6	72	78	68			
			V7	79	80	79			
			V8	75	72	77	79	118	83
			V9	67	71	67			
	EM-01-007	PP	V0	63	64	64			
			V1	80	74	76	80	134	77
			V2	62	65	66			
			V3	75	75	73			
			V4	65	64	64			

Treatment	Patient	Highest population	Visit	1st heart rate (bpm)	2nd heart rate (bpm)	3rd heart rate (bpm)	24h BP diastolic (mmHg)	24h BP systolic (mmHg)	24h heart rate (bpm)
			V5	72	70	69			
			V8	74	74	74	79	136	85
			V9	67	64	65			
Glimepiride	EM-01-001	ITT	V0	68	68	59			
			V1	69	70	72	77	122	79
			V2	69	70	70			
			V3	73	72	74			
			V4	69	67	70			
			V5	66	68	67			
			V6	72	67	69			
			V9	71	68	72			
	EM-01-003	PP	V0	61	69	62			
			V1	66	69	70	75	130	74
			V2	67	62	68			
			V3	66	69	68			
			V4	65	62	62			
			V5	59	58	58			
			V6	71	72	70			
			V7	61	68	67			
			V8	65	62	60	80	143	73
			V9	63	63	65			
	EM-01-004	PP	V0	67	69	73			
			V1	69	69	75	71	121	84
			V2	73	73	72			
			V3	69	70	70			
			V4	73	75	74			
			V5	70	73	71			
			V6	68	69	67			

Treatment	Patient	Highest population	Visit	1st heart rate (bpm)	2nd heart rate (bpm)	3rd heart rate (bpm)	24h BP diastolic (mmHg)	24h BP systolic (mmHg)	24h heart rate (bpm)
			V7	71	74	76			
			V8	68	77	65	74	128	79
			V9	71	71	71			
	EM-01-006	Full-analysis set	V0	67	63	65			

3.5.4 *Echochardiography*

Table 19: Listing of Echocardiography - All Patients

Treatment	Patient	Highest population	Visit	A (cm/s)	DT (ms)	E (cm/s)	E/A	E/E	GLS (%)	LA-Vol (ml/m^2)	average E´ (cm/s)	E´ lateral (cm/s)	E´ septal (cm/s)
Empagliflozin	EM-01-002	PP	V1	94.7	259	75.4	0.8	17.8	20	24.1	4.3	5.8	2.7
			V8	118	236	79.1	0.7	20.3	20.1	35.3	3.9	3.8	4
	EM-01-005	PP	V1	87	289	83.7	1	13.6	21.2	22.7	6.2	7	5.3
			V8	90.5	222	89.5	.	12.8	20.7	29.7	7	8.2	5.8
	EM-01-007	PP	V1	78.3	240	81.7	1	11.9	19.5	57.1	6.9	5.6	8.2
			V8	66.7	220	58.5	0.9	8.1	21.1	44	7.2	9.7	4.7
Glimepiride	EM-01-001	ITT	V1	85.1	193	73.8	0.9	10.1	18	25.3	7.3	8.5	6.1
	EM-01-003	PP	V1	70.8	320	50.3	0.7	7.9	17.6	43.2	6.4	7.6	5.1
			V8	67.9	246	64.5	0.9	8.2	19.3	34	7.9	9.3	6.4
	EM-01-004	PP	V1	87.5	180	89.2	1	11.6	21	37.2	7.7	8.5	6.9
			V8	86.5	176	87.8	1	12.3	19.7	38.3	7.2	8.2	6.1
	EM-01-006	Full-analysis set											

3.5.5 *ECG Measurements*

Table 20: Listing of ECG Data - All Patients

Treatment	Patient	Highest population	Visit	Heart Rate (bpm)	PQ interval (ms)	QRS duration (ms)	QT time (ms)	QTc time (ms)	Sinus rhythm (yes/no)	If no sinus rythm, specification
Empagliflozin	EM-01-002	PP	V0	60	200	86	452	452	Yes	
			V1	57	188	90	452	439	Yes	
			V2	62	186	76	434	440	Yes	
			V3	56	188	82	454	438	Yes	
			V4	62	176	82	432	438	Yes	
			V5	54	194	86	438	415	Yes	
			V6	59	180	76	450	445	Yes	
			V7	60	184	78	446	446	Yes	
			V8	59	180	78	444	439	Yes	
			V9	64	170	82	444	458	Yes	
	EM-01-005	PP	V0	67	148	90	402	424	Yes	
			V1	60	140	86	394	394	Yes	
			V2	70	142	88	388	419	Yes	
			V3	57	138	90	416	404	Yes	
			V4	66	134	90	410	429	Yes	
			V5	66	134	86	398	417	Yes	
			V6	67	144	88	392	414	Yes	
			V7	72	146	90	406	444	Yes	
			V8	60	134	88	428	428	Yes	
			V9	62	136	92	412	418	Yes	
	EM-01-007	PP	V0	61	186	96	412	414	Yes	
			V1	66	180	94	390	408	Yes	

Treatment	Patient	Highest population	Visit	Heart Rate (bpm)	PQ interval (ms)	QRS duration (ms)	QT time (ms)	QTc time (ms)	Sinus rhythm (yes/no)	If no sinus rythm, specification
			V2	57	190	92	422	410	Yes	
			V3	66	180	94	398	417	Yes	
			V4	60	192	88	408	408	Yes	
			V5	63	198	86	410	419	Yes	
			V8	71	182	88	396	430	Yes	
			V9	57	192	96	408	397	Yes	
Glimepiride	EM-01-001	ITT	V0	55	142	88	434	415	Yes	
			V1	66	144	88	418	438	Yes	
			V2	64	142	90	420	433	Yes	
			V3	65	146	88	412	428	Yes	
			V4	65	124	90	412	428	Yes	
			V5	67	152	86	418	441	Yes	
			V6	63	140	84	414	423	Yes	
			V9	69	144	86	406	435	Yes	
	EM-01-003	PP	V0	55	172	114	436	417	Yes	
			V1	58	170	122	434	426	Yes	
			V2	59	172	124	438	433	Yes	
			V3	64	168	116	426	439	Yes	
			V4	58	182	116	434	426	Yes	
			V5	57	170	116	422	410	Yes	
			V6	65	162	122	426	443	Yes	
			V7	60	170	118	424	424	Yes	
			V8	60	166	120	414	414	Yes	
			V9	61	172	122	432	434	Yes	
	EM-01-004	PP	V0	68	152	80	394	418	Yes	
			V1	68	152	82	390	414	Yes	
			V2	73	152	82	386	425	Yes	
			V3	69	152	80	396	424	Yes	

Treatment	Patient	Highest population	Visit	Heart Rate (bpm)	PQ interval (ms)	QRS duration (ms)	QT time (ms)	QTc time (ms)	Sinus rhythm (yes/no)	If no sinus rythm, specification
			V4	74	154	78	378	419	Yes	
			V5	69	150	82	394	422	Yes	
			V6	70	156	80	370	399	Yes	
			V7	69	152	78	388	415	Yes	
			V8	66	154	82	386	404	Yes	
			V9	64	148	78	392	404	Yes	
	EM-01-006	Full-analysis set	V0	60	154	88	414	414	Yes	

3.5.6 *Cardiac MRI*

Table 21: Listing of cardiac MRI (Part 1) - All Patients

Treatment	Patient	Highest population	Visit	CI (l/min/m^2)	CO (l/min)	EF (%)	ECV (%)	EDV (ml)	EDV/BSA (ml/m^2)	EF (%)	ESV (ml)	ESV / BSA (m /m^2)	MTG (%)
Empagliflozin	EM-01-002	PP	V1	3.63	6.47	67.43	0.24	161.3	90.68	67.43	52.54	29.54	3.6
			V8	3.74	6.5	66.15	0.2516	150.29	86.45	66.15	50.88	29.27	2.2
	EM-01-005	PP	V1	3.44	6.79	70.17	.	144.65	73.29	70.17	43.15	21.86	0.95
			V8	3.43	6.75	69.75	.	143.73	73.04	69.75	43.47	22.09	1.05
	EM-01-007	PP	V1	2.6	5.03	61.87	0.283	125.09	64.74	61.87	47.69	24.68	2.43
			V8	2.46	4.64	63.92	0.276	124.95	66.35	63.92	45.09	23.94	1.69
Glimepiride	EM-01-001	ITT	V1	3.31	6.47	68.37	0.269	121.55	62.2	68.37	38.44	19.67	2.3
	EM-01-003	PP	V1	1.81	3.96	53.11	0.2654	132.44	60.58	53.11	62.1	28.41	4.8
			V8	2.42	5.37	60.54	0.287	137.99	62.31	60.54	54.46	24.59	1.73
	EM-01-004	PP	V1	2.77	4.89	59	0.2599	115.97	65.61	59	47.55	29.17	1.1
			V8	3.02	5.33	62.71	0.2718	115.27	65.21	62.71	42.98	24.32	.
	EM-01-006	Full-analysis set											

Table 22: Listing of cardiac MRI (Part 2) - All Patients

Treatment	Patient	Highest population	Visit	MyoMasse (diast) (g)	MyoMasse/BSA (diast) (g/m^2)	SV (ml)	SV/BSA (ml/m^2)	T1 RT B postc (ms)	T1 RT B prec (ms)	T1 RT Myo postc (ms)	T1 RT Myo prec (ms)
Empagliflozin	EM-01-002	PP	V1	102.38	57.56	108.77	61.15	254.4	1583.6	427.6	992.5
			V8	99.84	57.43	99.41	57.19	266	1585.5	429.3	978.8
	EM-01-005	PP	V1	88.89	45.04	101.5	51.42	.	1593	.	977
			V8	88.72	45.09	100.26	50.95	.	1500.3	.	932.1
	EM-01-007	PP	V1	89.05	46.09	77.39	40.05	195.8	1608.6	339	1031.6
			V8	75.59	40.14	79.86	42.41	199	1572	335	1003
Glimepiride	EM-01-001	ITT	V1	89.32	45.71	83.11	42.53	294	1525	448.4	978.4
	EM-01-003	PP	V1	120.47	55.11	70.34	32.18	225.3	1619.5	365.5	951.3
			V8	122.48	55.31	83.53	37.72	249.8	1632.9	377.3	968.7
	EM-01-004	PP	V1	87.23	49.35	68.42	38.71	198.3	1565.3	345.6	966.2
			V8	77.19	43.67	72.28	40.89	190.3	1616.1	328.5	995.1
	EM-01-006	Full-analysis set									

3.5.7 *Clinical Chemistry*

Table 23: Listing of Clinical Chemistry (Part 1) - All Patients

Treatment	Patient	Highest population	Visit	GPT [ALAT] (U/l)	GOT [ASAT] (U/l)	ß-HCG (mIE/ml)	HbA1c (%)	Hematocrit (%)	Hemoglobin (g/dl)	INR	MCH (pg)	MCV (fl)	aPTT (s)	Bilirubin direct (mg/dl)	Bilirubin indirect (ml/dl)
Empagliflozin	EM-01-002	PP	V0	31.9	26.4	<5	6.66	38.5	13	<0.6	28.8	85.4	27.1	0.36	0.73
			V1	25.6	21.8		6.62	40.4	13.5		28.5	85.4		0.27	0.54
			V2	25.9	25		6.55	38.8	13.1		28.8	85.3		0.31	0.67
			V3	24.7	25.5		6.47	37.6	12.8		29.4	86.2		0.33	0.64
			V4	32.3	28.8		6.61	42.3	14		28.8	87		0.39	0.67
			V5	25.5	29.2		6.61	43.6	14.1		28.4	87.9		0.26	0.52
			V6	27.2	26.2		6.46	42	13.8		28.4	86.4		0.38	0.78
			V7	23.6	24.6		6.63	41.5	13.9		28.7	85.7		0.36	0.66
			V8	27	28.7		6.47	39.8	13.2		28.4	85.8		0.29	0.47
			V9	35.1	38.2		6.64	38.5	13.1		29.2	85.7		0.34	0.66
	EM-01-005	PP	V0	30.5	28.1	<5	7.56	44.8	14.9	1.05	30	90.3	28.8	0.18	0.31
			V1	24.7	21		7.53	43.9	14.5		30.2	91.5		0.16	0.32
			V2	24.8	23.3		7.42	44.9	14.8		30	90.9		0.14	0.26
			V3	23.9	25.1		7.49	45.8	14.9		29.7	91.4		>34	.
			V4	26.5	22		6.93	46.1	15.5		30.3	90		0.23	0.5
			V5	24.8	28.4		6.99	42.3	14.1		30.3	91		0.11	0.39
			V6	28.5	21.7		7	44.2	14.4		29	88.9		0.16	0.23
			V7	26.4	25.3		7.48	41.5	13.7		29.1	88.1		0.21	0.39
			V8	27.2	26.4		7.57	41.2	13.5		28.8	88		0.2	0.43
			V9	22.2	24.4		8.16	40.7	13.9		29.8	87.3		0.18	0.31
	EM-01-007	PP	V0	28	25.6	<5	8.9	36.9	12.9	1	30.8	88.1	32.5	0.18	0.19
			V1	32.5	30		8.96	35.8	12.5		31.1	89.1		0.18	0.26
			V2	29.4	25.4		8.93	39	13.2		31	91.5		0.18	0.22

Treatment	Patient	Highest population	Visit	GPT [ALAT] (U/l)	GOT [ASAT] (U/l)	ß-HCG (mIE/ml)	HbA1c (%)	Hematocrit (%)	Hemoglobin (g/dl)	INR	MCH (pg)	MCV (fl)	aPTT (s)	Bilirubin direct (mg/dl)	Bilirubin indirect (ml/dl)
			V3	33.9	29.4		8.63	40.9	13.8		30.8	91.3		0.19	0.23
			V4	27.9	25.2		8.43	39.9	13.6		30.8	90.5		0.15	0.17
			V5	29.7	32.5		8.75	42.8	14.3		30	89.9		.	.
			V8	25.9	21.8		9.2	38.9	13.4		30.7	89		0.22	0.24
			V9	26.9	21.5		10.29	38.6	13.2		30.1	88.1		0.2	0.31
Glimepiride	EM-01-001	ITT	V0	60.5	46	<5	7.88	39.4	12.9	<0.6	27.7	84.7	23.5	0.15	0.18
			V1	65.3	51.1		7.97	38.8	12.8		28.4	86.2		0.17	0.2
			V2	70.7	50.3		7.98	38.4	12.6		28.1	85.5		0.14	0.18
			V3	87.1	63.9		7.72	40	13.1		28.4	86.6		0.13	0.09
			V4	63.2	43.4		7.03	39.9	13.1		28.7	87.3		0.17	0.19
			V5	59	38.1		7.08	40	12.8		27.3	85.3		0.12	0.18
			V6	57.5	35.2		7	41.9	13.4		27.3	85.3		0.15	0.21
			V9	64.1	36.3		7.54	40.7	12.9		27	85.1		0.15	0.18
	EM-01-003	PP	V0	43.1	19.6	.	8.06	41.7	14	0.96	29	86.3	26.1	0.16	0.22
			V1	34.6	18.7		7.63	39.8	13.4		29.4	87.3		0.17	0.18
			V2	34.5	18.9		7.37	40.8	13.7		29.8	88.7		0.11	0.14
			V3	42	22.4		7.11	43	14.2		29.2	88.3		0.1	0.16
			V4	37.7	19.4		7.05	42.3	14		29.3	88.5		0.13	0.17
			V5	34.6	23.3		6.64	44.5	14.5		29.2	89.5		0.11	0.15
			V6	38.2	18.9		6.93	42.5	14.1		29.4	88.5		0.12	0.17
			V7	35.2	23		6.91	42	14.2		30	88.6		0.13	0.19
			V8	36.6	26		6.89	39.8	13.1		29.3	89		0.1	0.12
			V9	40.1	23.7		7.8	41.9	13.5		28.7	89.1		0.11	0.16
	EM-01-004	PP	V0	16.5	20.9	<5	6.51	36.8	12.1	1.02	29.2	88.9	28.1	0.19	0.29
			V1	14.8	19.4		6.2	38.4	12.9		30.3	90.1		0.23	0.35
			V2	18	17.1		6	38.8	12.9		29.9	90		0.14	0.23
			V3	20.1	21.4		5.81	39.5	12.7		29	90.2		0.19	0.35
			V4	19.1	18.6		6.01	39.5	13		29.5	89.6		0.15	0.23

Treatment	Patient	Highest population	Visit	GPT [ALAT] (U/l)	GOT [ASAT] (U/l)	ß-HCG (mIE/ml)	HbA1c (%)	Hematocrit (%)	Hemoglobin (g/dl)	INR	MCH (pg)	MCV (fl)	aPTT (s)	Bilirubin direct (mg/dl)	Bilirubin indirect (ml/dl)
			V5	18.2	19.2		6.19	40.1	13		29.1	89.7		0.17	0.22
			V6	17.6	19.5		5.86	37.1	12.2		29.3	89		0.22	0.31
			V7	18.6	18.5		5.81	39.1	12.8		29.4	89.9		0.14	0.16
			V8	20.9	16		5.84	38.2	12.3		29.1	90.5		0.12	0.17
			V9	17.7	19.1		6.03	38.9	12.9		29.7	89.6		0.24	0.37
	EM-01-006	Full-analysis set	V0	27.4	21.3	<5	7.19	34.2	10.7	1.04	24.3	77.7	28.3	0.12	0.1

Table 24: Listing of Clinical Chemistry (Part 2) - All Patients

Treatment	Patient	Highest population	Visit	Bilirubin total (mg/dl)	Creatinine (mg/dl)	eGFR (ml/min)	Erythrocytes (pl^{-1})	Fasting glucose (mg/dl)	g-GT (U/l)	Leucocytes (nl^{-1})	Lipase (U/l)
Empagliflozin	EM-01-002	PP	V0	1.09	0.57	>80	4.51	147	17.9	6.19	34.9
			V1	0.81	0.66	>80	4.73	146	18	7.24	46.1
			V2	0.98	0.67	>80	4.55	139	14.9	5.43	37.9
			V3	0.97	0.66	>80	4.36	152	14.2	4.46	38.4
			V4	1.06	0.73	79.52	4.86	137	14.9	6.32	39.7
			V5	0.78	0.71	>80	4.96	130	13.9	4.55	52.3
			V6	1.16	0.64	>80	4.86	137	13.3	4.91	34.1
			V7	1.02	0.69	>80	4.84	132	14.2	5.66	38.8
			V8	0.76	0.63	>80	4.64	121	12.3	5.82	52.2
			V9	1	0.68	>80	4.49	129	11.7	5.64	41.1
	EM-01-005	PP	V0	0.49	0.83	71.64	4.96	151	49.4	7.1	33.5
			V1	0.48	0.8	74.75	4.8	130	42.1	6.37	32.1
			V2	0.4	0.84	70.66	4.94	168	46.5	7.11	36.4
			V3	0.25	0.83	71.64	5.01	145	45	7.22	37.5
			V4	0.73	0.74	>80	5.12	132	38.8	7.37	35.8

Treatment	Patient	Highest population	Visit	Bilirubin total (mg/dl)	Creatinine (mg/dl)	eGFR (ml/min)	Erythrocytes (pl^{-1})	Fasting glucose (mg/dl)	g-GT (U/l)	Leucocytes (nl^{-1})	Lipase (U/l)
			V5	0.5	0.84	70.66	4.65	128	40.4	7.21	42.8
			V6	0.39	0.81	73.68	4.97	155	42.3	6.41	36.6
			V7	0.6	0.77	78.12	4.71	195	52.5	5.99	32
			V8	0.63	0.81	73.68	4.68	168	59.3	6.1	33.4
			V9	0.49	0.8	74.75	4.66	187	52.3	6.45	36.1
	EM-01-007	PP	V0	0.37	0.62	>80	4.19	171	49.7	4.73	43.9
			V1	0.44	0.61	>80	4.02	181	46.3	6.55	46.3
			V2	0.4	0.63	>80	4.26	152	40.1	3.92	53.5
			V3	0.42	0.67	>80	4.48	157	40.4	4.22	61.2
			V4	0.32	0.66	>80	4.41	152	45.9	4.56	61.1
			V5	0.46	0.71	>80	4.76	161	40.2	4.73	51.8
			V8	0.46	0.69	>80	4.37	168	39.5	5.74	60.2
			V9	0.51	0.68	>80	4.38	244	42.1	4.49	55.5
Glimepiride	EM-01-001	ITT	V0	0.33	0.64	>80	4.65	159	48.4	6.92	32.8
			V1	0.37	0.59	>80	4.5	200	60.6	8.26	40.3
			V2	0.32	0.73	>80	4.49	176	52.9	6.95	45.7
			V3	0.22	0.68	>80	4.62	177	51.4	7.36	40.9
			V4	0.36	0.7	>80	4.57	164	42.9	7.13	36.9
			V5	0.3	0.74	>80	4.69	162	43.7	7.3	71.2
			V6	0.36	0.76	>80	4.91	166	41.5	6.21	31.7
			V9	0.33	0.63	>80	4.78	194	47.6	6.16	37.7
	EM-01-003	PP	V0	0.38	0.85	>80	4.83	153	22.6	7.25	31.8
			V1	0.35	0.85	>80	4.56	136	21.3	7.56	27.9
			V2	0.27	0.78	>80	4.6	128	21.4	6.32	37.8
			V3	0.26	0.95	77.71	4.87	155	26.1	6.51	32.8
			V4	0.3	0.87	>80	4.78	151	22	6.54	33.9
			V5	0.26	1.05	69.24	4.97	135	20.8	7.76	37.5
			V6	0.29	0.94	78.67	4.8	138	21.4	7.22	35

Treatment	Patient	Highest population	Visit	Bilirubin total (mg/dl)	Creatinine (mg/dl)	eGFR (ml/min)	Erythrocytes (pl^{-1})	Fasting glucose (mg/dl)	g-GT (U/l)	Leucocytes (nl^{-1})	Lipase (U/l)
			V7	0.32	1.07	67.74	4.74	144	22.5	6.59	31.9
			V8	0.22	0.83	>80	4.47	130	21.2	6.47	30.5
			V9	0.27	0.88	>80	4.7	219	21.2	6.44	32.4
	EM-01-004	PP	V0	0.48	0.82	71.6	4.14	122	21.8	7.47	27.8
			V1	0.58	0.75	79.37	4.26	94	18.6	5.93	31.8
			V2	0.37	0.77	76.73	4.31	119	18.9	6.25	35.6
			V3	0.54	0.88	65.77	4.38	108	16.7	6.75	36.3
			V4	0.38	0.87	66.64	4.41	123	16.4	5.85	38.6
			V5	0.39	0.82	71.35	4.47	93	16.3	5.89	39.2
			V6	0.53	0.74	>80	4.17	107	15.4	6.01	33.1
			V7	0.3	0.86	67.54	4.35	133	17.4	6.12	43.7
			V8	0.29	0.73	>80	4.22	137	14.3	5.68	43.2
			V9	0.61	0.85	68.46	4.34	103	17.5	6.11	30.8
	EM-01-006	Full-analysis set	V0	0.22	0.74	76.51	4.4	155	22.9	5.06	35.9

Table 25: Listing of Clinical Chemistry (Part 3) - All Patients

Treatment	Patient	Highest population	Visit	Potassium (mmol/l)	Sodium (mmol/l)	Thrombocytes (nl^{-1})	Urea (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Cholesterol (mg/dl)	Fasting insulin (µU/ml)	hs-CRP (mg/dl)	Triglycerides (mg/dl)
Empagliflozin	EM-01-002	PP	V0	4	143	346	26.1						
			V1	4.17	143	336	28	52.7	78	148	5.7	0.016	85.5
			V2	4.23	139	352	31.3						
			V3	4.84	142	344	21.1						
			V4	4.32	.	373	38.8						
			V5	3.98	144	365	25.1						
			V6	4.09	143	367	25.6						
			V7	4.57	138	378	32.7						

Treatment	Patient	Highest population	Visit	Potassium (mmol/l)	Sodium (mmol/l)	Thrombocytes (nl^{-1})	Urea (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Cholesterol (mg/dl)	Fasting insulin (µU/ml)	hs-CRP (mg/dl)	Triglycerides (mg/dl)
			V8	4.39	141	345	42.9	64.5	68	147	4.5	0.026	73.7
			V9	4.26	140	341	38.7						
	EM-01-005	PP	V0	4.57	140	263	24.3						
			V1	4.66	140	267	32	42.5	119	210	7.3	0.288	240.6
			V2	4.78	142	265	34.1						
			V3	4.6	145	268	48.4						
			V4	4.58	140	273	33.7						
			V5	5.5	139	290	30.2						
			V6	4.72	139	261	33.2						
			V7	4.4	140	253	34						
			V8	4.83	140	250	27.2	48.5	140	237	8.6	0.487	242
			V9	4.93	140	262	30						
	EM-01-007	PP	V0	5.13	138	148	21.4						
			V1	4.85	139	149	16.3	77.2	132.2	222	10.8	0.53	276.9
			V2	5.22	139	162	20.5						
			V3	4.44	142	175	36.9						
			V4	4.69	139	156	31.1						
			V5	5.08	140	140	30.8						
			V8	5	139	151	21.9	80.4	146.58	247	12.5	1.1	274.8
			V9	4.73	138	157	23.9						
Glimepiride	EM-01-001	ITT	V0	4.35	142	288	33.5						
			V1	4.99	140	287	24.4	47.2	139	236	11.9	0.829	249.6
			V2	4.39	138	259	37						
			V3	5.31	139	304	35.3						
			V4	4.76	141	285	26.8						
			V5	4.91	140	290	47.6						
			V6	4.51	140	296	27						
			V9	4.5	142	278	29.9						

Treatment	Patient	Highest population	Visit	Potassium (mmol/l)	Sodium (mmol/l)	Thrombocytes (nl^{-1})	Urea (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	Cholesterol (mg/dl)	Fasting insulin (µU/ml)	hs-CRP (mg/dl)	Triglycerides (mg/dl)
	EM-01-003	PP	V0	4.96	139	224	35.6						
			V1	5.07	140	238	28.9	46.7	117	182	8.2	0.161	89.8
			V2	5.56	139	237	34.5						
			V3	5.43	140	232	37.2						
			V4	5.62	140	249	34.6						
			V5	5.78	140	258	46.1						
			V6	5.06	140	261	40.3						
			V7	5.03	141	256	34.6						
			V8	4.79	142	255	39	57.9	133	212	6.9	0.164	103.9
			V9	5.11	140	250	36.8						
	EM-01-004	PP	V0	4.57	143	274	37.8						
			V1	4.59	141	260	41.7	66.1	101	183	6.8	0.104	78
			V2	4.84	144	279	45						
			V3	4.62	142	275	38.5						
			V4	4.93	144	267	33.2						
			V5	5.1	145	283	31.9						
			V6	4.74	144	250	41.7						
			V7	4.72	142	282	34.4						
			V8	4.6	143	321	47.8	57	91	162	8.7	<0.6	68.6
			V9	4.84	143	290	39.3						
	EM-01-006	Full-analysis set	V0	4.29	139	291	27.3						

3.5.8 *Termination*

Table 26: Listing of Termination - All Patients

Treatment	Patient	Highest population	Date of last study drug intake	Has the blind been broken?	Termination status	If patient prematurely stopped treatment, provided reason	Explanation
Empagliflozin	EM-01-002	PP	2016-12-15	No	The patient completed the treatment period according to protocol	.	
	EM-01-005	PP	2017-08-02	No	The patient completed the treatment period according to protocol	.	
	EM-01-007	PP	2017-09-26	No	The patient terminated treatment in week 15 with all end of trial measurements	Other (please explain in explanation / comment field)	Study paused due to organizational reasons
Glimepiride	EM-01-001	ITT	2016-10-18	No	The patient prematurely stopped the treatment period	Adverse event	weight gain during study participation annoyed the patient so much that she decided to stop
	EM-01-003	PP	2017-02-19	No	The patient completed the treatment period according to protocol	.	
	EM-01-004	PP	2017-04-12	No	The patient completed the treatment period according to protocol	.	
	EM-01-006	Full-analysis set		No	The patient prematurely stopped before treatment period	Adverse event	During baseline MRI, Patient experienced a strong coughing attack. MRI was not possible. Study drug was never taken.

3.5.9 *Adverse Events*

Table 27: Listing of Adverse Events (without MedDRA) - All Patients

Treatment	Patient	Highest population	AE Term	Additional comment	AE intensity grade	Serious	Start date of AE	End date of AE	Duration of AE (in days)	Outcome	Reporter causality to study drug	Action taken regarding study medication
Empagliflozin	EM-01-002	PP	hematoma left abdomen		Grade 1	No	01/07/2016	21/07/2016	21	Recovered	No	None
			back pain		Grade 1	No	23/07/2016	25/07/2016	3	Recovered	No	None
			headache		Grade 2	No	05/09/2016	05/09/2016	1	Recovered	No	None
			vaginal fungal infection	Treatment with clotrimazol for 12 days.	Grade 2	No	12/09/2016	23/09/2016	12	Recovered	Yes	None
			back pain		Grade 2	No	24/11/2016	05/12/2016	12	Recovered	No	None
			vaginal fungal infection		Grade 2	No	16/10/2016	25/11/2016	41	Recovered	Yes	None
	EM-01-005	PP	hypotension with vertigo		Grade 2	No	11/06/2017	14/06/2017	4	Recovered	No	Drug interrupted (temporarily)
	EM-01-007	PP	Fatigue	Typical Situation, happens every year at this season.	Grade 2	No	01/08/2017	01/09/2017	32	Recovered	No	None
			lumbago		Grade 2	No	04/09/2017	07/09/2017	4	Recovered	No	None
Glimepiride	EM-01-001	ITT	headache		Grade 1	No	30/06/2016	30/06/2016	1	Recovered	No	None
			hematoma left abdomen		Grade 2	No	30/06/2016	15/07/2016	16	Recovered	No	None
			abdominal pain (right side)		Grade 1	No	10/07/2016	12/07/2016	3	Recovered	No	None
			headache		Grade 3	No	10/09/2016	16/09/2016	7	Recovered	No	None
			severe upper abdominal pain	Abdominal pain was accompanied by mild diarrhoe for 2 days (30/10/16-01/11/16).	Grade 3	No	01/11/2016	01/11/2016	1	Recovered	No	None
			weight gain*	weight gain during study participation annoyed the patient so much that she decided to stop*	Grade 1*	No*	24/08/2016*	02/11/2016*	71*	Recovered*	Yes*	terminated*
	EM-01-004	PP	hypoglycemia	measured Glucose Level was 3.2 mmol/l.	Grade 1	No	02/11/2016	02/11/2016	1	Recovered	Yes	None

Treatment	Patient	Highest population	AE Term	Additional comment	AE intensity grade	Serious	Start date of AE	End date of AE	Duration of AE (in days)	Outcome	Reporter causality to study drug	Action taken regarding study medication
			dental surgery		Grade 2	No	24/04/2017	04/05/2017	11	Recovered	No	None
	EM-01-006	Full-analysis set	coughing	Study drug was not taken, interuption of participation was before start of study drug.	Grade 2	no	19/06/2017	19/06/2017	1	Recovered	No	None

* Due to an accidental omission, this AE was not recorded in the eCRF during the study conduct by the study physicians. This omission was not detected by external monitoring. Therefore, this AE is not contained in the electronic study database. However, this AE was recorded as termination reason for patient EM-01-001 and is therefore recorded in Table 26 which is based on the electronic database. For reasons of completeness, the study coordinator decided to consider this AE in Tables 12, 13, 27 and 28 as well.

Table 28: Listing of Adverse Events (with MedDRA) - All Patients

Treatment	Patient	Highest population	AE Term	Additional comment	Start date of AE	End date of AE	Duration of AE	MedDRA SOC Term	MedDRA PT Term
Glimepiride	EM-01-001	ITT	headache		30/06/2016	30/06/2016	1	Nervous system disorders	Headache
Glimepiride	EM-01-001	ITT	hematoma left abdomen		30/06/2016	15/07/2016	16	Injury, poisoning and procedural complications	Administration site haematoma
Glimepiride	EM-01-001	ITT	abdominal pain (right side)		10/07/2016	12/07/2016	3	Gastrointestinal disorders	Abdominal pain
Glimepiride	EM-01-001	ITT	headache		10/09/2016	16/09/2016	7	Nervous system disorders	Headache
Glimepiride	EM-01-001	ITT	severe upper abdominal pain	Abdominal pain was accompanied by mild diarrhoe for 2 days (30/10/16-01/11/16).	01/11/2016	01/11/2016	1	Gastrointestinal disorders	Abdominal pain upper
Glimepiride*	EM-01-001*	ITT*	weight gain*	weight gain during study participation annoyed the patient so much that she decided to stop*	24/08/2016*	02/11/2016*	71*	Metabolism and nutrition disorders*	abnormal weight gain*

Treatment	Patient	Highest population	AE Term	Additional comment	Start date of AE	End date of AE	Duration of AE	MedDRA SOC Term	MedDRA PT Term
Empagliflozin	EM-01-002	PP	hematoma left abdomen		01/07/2016	21/07/2016	21	Injury, poisoning and procedural complications	Administration site haematoma
Empagliflozin	EM-01-002	PP	back pain		23/07/2016	25/07/2016	3	Musculoskeletal and connective tissue disorders	Back pain
Empagliflozin	EM-01-002	PP	headache		05/09/2016	05/09/2016	1	Nervous system disorders	Headache
Empagliflozin	EM-01-002	PP	vaginal fungal infection	Treatment with clotrimazol for 12 days.	12/09/2016	23/09/2016	12	Infections and infestations	Vulvovaginal mycotic infection
Empagliflozin	EM-01-002	PP	back pain		24/11/2016	05/12/2016	12	Musculoskeletal and connective tissue disorders	Back pain
Empagliflozin	EM-01-002	PP	vaginal fungal infection		16/10/2016	25/11/2016	41	Infections and infestations	Vulvovaginal mycotic infection
Glimepiride	EM-01-004	PP	hypoglycemia	measured Glucose Level was 3.2 mmol/l.	02/11/2016	02/11/2016	1	Metabolism and nutrition disorders	Hypoglycaemia
Glimepiride	EM-01-004	PP	dental surgery		24/04/2017	04/05/2017	11	Surgical and medical procedures	Dental operation
Empagliflozin	EM-01-005	PP	hypotension with vertigo		11/06/2017	14/06/2017	4	Vascular disorders	Hypotension
Glimepiride	EM-01-006	Full-analysis set	coughing	Study drug was not taken, interuption of participation was before start of study drug.	19/06/2017	19/06/2017	1	Respiratory, thoracic and mediastinal disorders	Cough
Empagliflozin	EM-01-007	PP	Fatigue	Typical Situation, happens every year at this season.	01/08/2017	01/09/2017	32	General disorders and administration site conditions	Fatigue
Empagliflozin	EM-01-007	PP	lumbago		04/09/2017	07/09/2017	4	Musculoskeletal and connective tissue disorders	Back pain

* Due to an accidental omission, this AE was not recorded in the eCRF during the study conduct by the study physicians. This omission was not detected by external monitoring. Therefore, this AE is not contained in the electronic study database. However, this AE was recorded as termination reason for patient EM-01-001 and is therefore recorded in Table 26 which is based on the electronic database. For reasons of completeness, the study coordinator decided to consider this AE in Tables 12, 13, 27 and 28 as well.

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
CI	Confidence interval
CL	Confidence limit
ITT	Intention-to-treat
MIN	Minimum
MAX	Maximum
PP	Per-protocol
SAE	Serious adverse event
SD	Standard deviation