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1 **Empagliflozin for Patients with Presumed Resistant Hypertension: a Post Hoc Analysis of the**
2 **EMPA-REG OUTCOME Trial**

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38 **Abstract**

39 *Background:* Type 2 diabetes (T2D) and resistant hypertension (rHT) often coexist, greatly increasing
40 risk of target-organ damage and death. We explored the effects of empagliflozin in patients with and
41 without presumed resistant hypertension (prHT) in a post hoc analysis of EMPA-REG OUTCOME
42 (NCT01131676).

43 *Methods:* Overall, 7020 patients received empagliflozin 10mg, 25mg, or placebo with median follow-
44 up of 3.1 years. We defined baseline prHT as ≥ 3 classes of antihypertensive drugs including a diuretic
45 and uncontrolled BP (SBP ≥ 140 and/or diastolic BP [DBP] ≥ 90 mmHg), or ≥ 4 classes of
46 antihypertensive, including a diuretic, and controlled BP. We explored the effect of empagliflozin on
47 CV death, heart failure hospitalization (HHF), 3-point major adverse cardiac events (3P-MACE), all-
48 cause death, and incident/worsening nephropathy by Cox regression and BP over time by a mixed-
49 repeated-measures-model analysis.

50 *Results:* 1579 (22.5%) patients had prHT. The mean difference in change in SBP from baseline to
51 week 12 versus placebo was -4.5 (95% CI, -5.9 to -3.1) mmHg ($p < 0.001$) in prHT and -3.7 (-4.5, -2.9)
52 mmHg ($p < 0.001$) in patients without prHT. SBP was more frequently controlled ($< 130/80$ mmHg)
53 with empagliflozin than with placebo. Patients with prHT had 1.5 to 2-fold greater risk of HHF,
54 incident/worsening nephropathy and CV death compared to those without prHT. Empagliflozin
55 improved all outcomes in patients with and without prHT (interaction $P > 0.1$ for all outcomes).

56 *Conclusions:* Empagliflozin induced a clinically relevant reduction in SBP and consistently improved
57 all outcomes regardless of prHT status. Due to these dual effects, empagliflozin should be considered
58 for patients with hypertension and T2D.

59

60 *Key-words:* resistant hypertension; type 2 diabetes; empagliflozin.

61

62 INTRODUCTION

63 Cardiovascular (CV) risk in patients with diabetes is graded and continuous across the entire range of
64 blood pressure (BP). International recommendations support the start of antihypertensive treatment in
65 persons with diabetes who have high blood pressure with a treatment goal of reducing systolic blood
66 pressure (SBP) to <130 mmHg.¹⁻³ A subset (5–30%) of patients with high BP may have resistant
67 hypertension (rHT) defined (by European guidelines) as a seated office SBP \geq 140 mmHg or diastolic
68 blood pressure (DBP) \geq 90 mmHg on maximally tolerated doses of \geq 3 antihypertensive agents
69 (including a diuretic) or when BP control is achieved but requires \geq 4 medications.³ Diabetes increases
70 the risk of developing rHT.⁴ Furthermore, the concomitant existence of diabetes and rHT is associated
71 with a major increase in the risk of target-organ damage (including heart failure [HF], atrial
72 fibrillation, myocardial infarction [MI], stroke, chronic kidney disease [CKD]) and ultimately death.³⁻⁸

73 Spironolactone is recommended as 4th line therapy for rHT; notwithstanding, a large
74 proportion of patients with rHT remain uncontrolled and/or may have a formal contraindication or
75 intolerance (e.g., advanced CKD, hyperkalemia) to spironolactone, therefore additional strategies are
76 urgently needed.^{5,9}

77 Empagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor, which, compared with
78 placebo, reduced time to first HF hospitalization, incident or worsening nephropathy, and death (CV
79 and all-cause) in patients with type 2 diabetes mellitus (T2D) and CV disease in the EMPA-REG
80 OUTCOME trial.¹⁰ SGLT2-inhibitors also reduce blood pressure,¹¹ and in the EMPA-REG BP trial
81 empagliflozin (compared with placebo) reduced mean SBP by 3–5 mmHg and DBP by 1–2 mmHg at
82 week 12.^{12,13} However, the effect of empagliflozin in patients with rHT is yet to be studied.

83 The aim of the present study is to assess the BP-lowering effects of empagliflozin in patients
84 with and without rHT (rHT versus no-rHT), and whether the treatment effect of empagliflozin on CV,
85 renal and HF outcomes are consistent in those with and without rHT; as rHT was a presumptive post-
86 hoc diagnosis in this population, we refer to it as presumed resistant hypertension (prHT) throughout
87 the manuscript (please see also the methods section).

88

89 METHODS

90 The methods of the EMPA-REG OUTCOME trial have been previously described.¹⁰ In short, 7020
91 patients with T2D and established CV disease were assigned to receive either 10 mg or 25 mg of
92 empagliflozin or placebo once daily. The primary composite outcome was death from CV causes,
93 nonfatal MI, or nonfatal stroke (3P-MACE), as analyzed in the pooled empagliflozin group versus the
94 placebo group. Other outcomes were CV death, hospitalization for HF, the composite of CV death or
95 hospitalization for HF, incident/worsening nephropathy, and all-cause death. These outcomes were
96 also assessed in the present analysis. The median follow-up time was 3.1 years.

97 Because of the sensitive nature of the data collected for this study, requests to access the
98 dataset from qualified researchers trained in human subject confidentiality protocols may be sent to
99 Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance.

100 **Definition of Resistant Hypertension and Blood Pressure Assessment**

101 In this post hoc analysis, we defined prHT at baseline as the use of ≥ 3 classes of antihypertensive
102 drugs, including a diuretic, and uncontrolled BP (SBP ≥ 140 and/or DBP ≥ 90 mmHg), or use of ≥ 4
103 classes of antihypertensive drugs, including a diuretic, and SBP < 140 and DBP < 90 mmHg. “True”
104 rHT definition requires a BP that remains above goal in spite of the concurrent use of 3
105 antihypertensive agents of different classes, with (ideally) one of the 3 agents being a diuretic, with all
106 agents prescribed at maximally tolerated doses; and (ideally) also requires ambulatory confirmation of
107 high BP.³ Typically, a clinic BP of 140/90 mmHg corresponds to home BP values of 135/85 mmHg
108 and to ambulatory blood pressure monitoring values defined as a daytime SBP/DBP of 135/85 mmHg,
109 a night-time SBP/DBP of 120/70 mmHg, and a 24-hour SBP/DBP of 130/80 mmHg². For this reason,
110 we used the 140/90 mmHg cutoff in our rHT definition, as it may better reflect “true” rHT (i.e., be
111 more specific). As our study is a post hoc analysis of an outcome trial, we cannot ascertain whether all
112 of the patients herein included have ‘true’ rHT (despite using a cutoff of office BP $> 140/90$ mmHg).
113 In consequence, throughout the manuscript whenever rHT is referred to, it should be considered as
114 prHT.

115 Blood pressure was measured in the seated position after at least 5 minutes of rest with a
116 calibrated automatic sphygmomanometer and in the presence of the study physician and/or nurse at

117 each study site, taking the average of 3 consecutive measurements with a between-measurement
118 interval of at least 1 minute.

119

120 **Statistical Analysis**

121 Patients` baseline characteristics were derived in the prHT versus no-prHT groups, and continuous
122 variables are presented as mean±standard deviation (SD), and categorical variables are presented as
123 number (n) and proportion (%). Effects on blood pressure (SBP, DBP) were evaluated using a mixed
124 effect model repeat measurement (MMRM) model, which included subject as a random effect,
125 baseline glycated hemoglobin (HbA1c) and baseline of the endpoint (SBP or DBP) as linear
126 covariates and their interaction with visit in addition to baseline estimated glomerular filtration rate
127 (eGFR) category, geographic region, baseline body mass index (BMI) category. Treatment, resistant
128 hypertension at baseline and visit were also entered as fixed effects as well as all 2- and 3-way
129 interactions thereof. Additionally, the model included a fixed categorical effect for ‘time of
130 randomization’ to account for each patient’s theoretical ability to ‘reach’ certain weeks in this study
131 arising from the study design. A similar MMRM model was applied for the evaluation of effects on
132 weight and HbA1c. We furthermore explored the proportion of patients that achieved SBP <130
133 mmHg during the trial. We then evaluated the treatment effects (pooled empagliflozin arms versus
134 placebo) on time to first 3P-MACE, CV death, hospitalization for HF, the composite of CV death or
135 HF hospitalization, incident/worsening nephropathy, and all-cause death, in those with and without
136 prHT by Cox regression models. The Cox model included the interaction of presence of prHT at
137 baseline by treatment to evaluate the treatment effect in patients with and without prHT at baseline
138 separately. The model further included covariate terms for age, gender, BMI, HbA1c, eGFR, region,
139 resistant hypertension at baseline, and treatment. All analyses are post hoc and not adjusted for
140 multiplicity. All statistical analyses were performed using SAS Software, Version 9.4.

141

142 **RESULTS**

143 **Baseline Characteristics**

144 Overall, 1579 (22.5%) patients had prHT (as defined in the methods section); these patients had
145 longer diabetes duration (>10 y: 63% versus 55%) and more concomitant diseases, including HF (17%
146 versus 8%), retinopathy (27% versus 21%) and macroalbuminuria (15% versus 10%), as well as lower
147 mean eGFR ($68 \text{ mL/min/1.73 m}^2 \pm 21 \text{ (SD)}$ versus $76 \text{ mL/min/1.73 m}^2 \pm 21 \text{ (SD)}$). The mean baseline
148 SBP/DBP \pm SD was $142\pm 18/78\pm 11 \text{ mmHg}$ in prHT versus $133\pm 16/76\pm 10 \text{ mmHg}$ in no-prHT, and
149 patients with prHT used more antihypertensive treatments, including mineralocorticoid receptor
150 antagonists ([MRAs] Table 1). More patients with prHT added antihypertensive medications
151 including beta blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers
152 during the trial, compared to those with no-prHT. Fewer patients added concomitant medications in
153 the empagliflozin versus placebo arms in both prHT and no-prHT groups. Addition of MRAs was
154 balanced between treatments in patients with prHT (Table 2).

155

156 **Blood Pressure Control**

157 Systolic and diastolic BP were consistently reduced by empagliflozin in patients with prHT or no-
158 prHT. Overall, the treatment effect of empagliflozin on SBP was consistent in patients with and
159 without prHT throughout the trial (Figure 1). The mean difference (95% CI) of SBP change from
160 baseline to week 12 with empagliflozin versus placebo was $-4.5 \text{ (-5.9 to -3.1) mmHg}$ in prHT versus -
161 $3.7 \text{ (-4.5 to -2.9) mmHg}$ in no-prHT; a difference that was sustained during the follow-up (Figure 1).
162 These changes were generally comparable between empagliflozin doses (Supplemental Figure 1). The
163 differences in change in DBP from baseline to week 12 for empagliflozin versus placebo were smaller
164 as compared to SBP in patients with and without prHT: $-1.7 \text{ (-2.5 to -0.9) mmHg}$ in prHT versus -1.2
165 $\text{ (1.7 to -0.8) mmHg}$ in no-prHT; a difference that was also sustained during the follow-up
166 (Supplemental Figure 2).

167 The proportion of patients with prHT that achieved SBP <130 mmHg was higher with
168 empagliflozin (versus placebo) throughout the follow-up (e.g., 38% versus 26% at week 12; Figure 2,
169 Supplemental Figure 3 and Supplemental Table 1. Similarly, more patients without prHT treated with
170 empagliflozin achieved SBP <130 mmHg compared with placebo (Figure 2, Supplemental Table 1).

171

173 **Outcome Events**

174 In both placebo- and empagliflozin-treated patients, patients with prHT were generally at increased
175 risk for all outcomes compared to patients with no-prHT – with the only exception of all-cause
176 mortality in the placebo group which only showed a weak trend in this respect (HR 1.13, 95% CI,
177 0.82–1.56) for prHT versus no prHT). For example, in placebo-treated patients, the hazard ratio for
178 3P-MACE was 1.31 (95% CI, 1.01–1.71) (Table 3).

179

180 **Treatment Effects on Outcomes and HbA1c**

181 Empagliflozin (versus placebo) consistently reduced the risk for all outcomes regardless of baseline
182 prHT status (*P* value for interaction >0.1 for all outcomes; Figure 3). HbA1c levels and weight were
183 reduced by empagliflozin treatment in patients with and without prHT (Supplemental Figures 4 and 5).

184

185 **Adverse Events**

186 For most AEs, incidence rates in patients with prHT were higher compared to patients with no-prHT
187 irrespective of treatment (Supplemental Table 2). Empagliflozin-treated prHT patients experienced
188 numerically fewer serious adverse events compared with placebo-treated prHT patients (45.7% versus
189 52.1%). Furthermore, rates of hyperkalemia were lower with empagliflozin than placebo, irrespective
190 of prHT status, whereas incidence rates of genital infection were increased with empagliflozin in both
191 subgroups.

192

193 **DISCUSSION**

194 In this analysis, treatment with empagliflozin resulted in early reductions in SBP in patients with T2D
195 with and without prHT (-4.5 mmHg compared with placebo in patients with prHT at week 12) with
196 sustained BP reduction throughout the follow-up. A higher proportion of empagliflozin-treated
197 patients achieved a SBP <130 mmHg compared with those receiving placebo. Independent of
198 treatment arm, patients with prHT had higher incidence of major CV (including HF) events compared
199 to those with no-prHT after multivariable adjustment for risk factors including age and eGFR .
200 Treatment with empagliflozin reduced major CV events irrespective of the patients` prHT status.

201 Treatment with empagliflozin has consistently been shown to reduce BP in patients with T2D,
202 thereby improving the BP control in this population.¹¹⁻¹³ Reductions in major CV events and death
203 with empagliflozin are likely explained by a multitude of mechanisms, including osmotic diuresis
204 following increased urinary glucose excretion, improved glycemic control, weight loss, reduced
205 arterial stiffness, and, importantly, a reduction in plasma volume.¹⁴⁻¹⁶ Although a mediation analysis
206 identified changes in markers of plasma volume as the most important mediators of the reduction of
207 CV death in empagliflozin treated patients and showed that SBP and DBP had only negligible
208 mediating effects,¹⁶ it is well established that BP control is important to improve outcomes in patients
209 with T2D and CVD.

210 In the EMPA-REG OUTCOME trial, patients with prHT represented 22% of the study
211 population, supporting the high prevalence of rHT in patients with diabetes also reported in
212 population-based cohorts.¹⁷ Patients with rHT have high CV risk, which poses additional difficulties
213 in the BP control, where a low BP target (SBP <130 mmHg) is desirable.¹⁸ The Action to Control
214 Cardiovascular Risk in Diabetes blood pressure trial (ACCORD-BP)¹⁹ tested the effect of a target
215 SBP <120 mmHg on major adverse cardiac effects among high-risk persons with type 2 diabetes
216 (n=4733). Although this trial did not show a reduction in the primary composite outcome of MI,
217 stroke or CV death, a reduction in stroke rate, a prespecified secondary outcome, was observed.¹⁹
218 Subsequent large meta-analyses strongly support intensive BP-lowering strategies over standard
219 regimens for CV protection in persons with diabetes, with benefits seen even at SBP values <120
220 mmHg.^{20, 21} The Systolic Blood Pressure Intervention Trial (SPRINT), also supports a target of <120
221 mmHg among patients at high risk for CV events but without diabetes²². In order to achieve an
222 adequate BP control in rHT patients, multiple drugs and drug-combinations are often used. In rHT
223 patients participating in the PATHWAY-2 trial²³, spironolactone started at 25 mg daily, and up-
224 titrated to 50 mg, reduced home SBP at 12 weeks by a mean of -8.7 (-9.7 to -7.7) mmHg, compared
225 with placebo, and was more effective than alternative fourth-line drugs (bisoprolol or doxazosin) by a
226 mean SBP margin of -4.3 (-5.1 to -3.4) mmHg. In the present study, treatment with empagliflozin
227 resulted in a -4.5 (-5.9 to -3.1) mmHg greater reduction in SBP at week 12 compared with placebo in
228 patients with prHT, suggesting that empagliflozin may have additional BP-lowering benefit on top of

229 standard of care²⁴. The differences in trial design and populations preclude comparisons of BP effects
230 between spironolactone and empagliflozin (e.g., PATHWAY-2 was a “cross-over” trial, enrolling
231 only patients with resistant hypertension and where only 14% of the patients had T2D). Interestingly,
232 in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
233 (TOPCAT) trial, that enrolled patients with heart failure and preserved ejection fraction, of which 32%
234 had diabetes, spironolactone reduced SBP by -6.1 (-8.9 to -3.3) mmHg at 16 weeks in those with
235 prHT.²⁵ Together these results suggest that there may exist a potential interest in associating these
236 drugs (spironolactone and empagliflozin) for the treatment of rHT in patients with T2D. These drugs
237 showed morbidity and mortality reductions across different populations, and patients treated with
238 empagliflozin had lower rates of hyperkalemia during the follow-up, which may be of particular
239 interest when used concomitantly with an MRA. Analogously, another emerging treatment option is
240 potassium binding. For example, the AMBER study (patiromer versus placebo to enable
241 spironolactone use in patients with resistant hypertension and chronic kidney disease) showed that
242 patiromer enabled more patients to continue treatment with spironolactone with less hyperkalaemia²⁶
243 The findings reported in the present study are also concordant with those of the EMPA-REG BP trial
244 where, compared with placebo, empagliflozin reduced ambulatory SBP by 3.4 (-4.8 to -2.1) mmHg
245 and 4.2 (-5.5 to -2.8) mmHg in the 10 mg and 25 mg formulations, respectively in patients with T2D
246 and hypertension.¹² The BP-lowering effect of empagliflozin was retained in patients who were
247 receiving one or multiple antihypertensive medications.¹³ The BP-lowering properties of
248 empagliflozin, may likely be extended to a class effect, as dapagliflozin also reduced office BP in
249 patients receiving background antihypertensive treatment,²⁷ and canagliflozin also reduced BP,
250 especially in patients with baseline SBP >140 mmHg.²⁸

251

252 **Clinical and Research Implications**

253 These findings may have major clinical and research implications as empagliflozin could be a
254 therapeutic option for BP control in patients with hypertension and T2D, providing survival and renal
255 protection benefits beyond its BP-lowering effects. As patients treated with empagliflozin had lower
256 rates of hyperkalemia in our analysis as well as in previous analyses from EMPA-REG OUTCOME,²⁹

257 future studies may evaluate the benefit of empagliflozin in reducing hyperkalemia risk in rHT patients
258 treated with MRAs.

259

260 **Limitations**

261 Our analysis has some limitations. First, since it is post-hoc and non-prespecified, and the trial was
262 not powered for subgroup analyses, the results must be regarded as hypothesis generating. Although
263 blood pressure measurement was standardized, this was not a dedicated blood pressure trial, blood
264 pressure was measured in the presence of the study personnel and sphygmomanometers might have
265 been different between study sites; therefore, the precision of the values reported may be reduced.
266 However, this imprecision was not systematic and may even reinforce the robustness of our findings
267 (i.e., with variability similar to a ‘real-world’ setting). Finally, the American Heart Association (AHA)
268 uses an inclusive definition of rHT: “rHT is defined as blood pressure (BP) that remains above goal in
269 spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, 1 of the 3 agents
270 should be a diuretic and all agents should be prescribed at optimal dose amounts”.⁹ The presence of
271 ‘true’ rHT is difficult to ascertain in non-HT studies, due to the difficulty in confirming adherence to
272 therapy and performing 24-hour ambulatory blood pressure measurements: such assessments were not
273 performed within the framework of a cardiovascular outcome trial. Furthermore, doses of anti-
274 hypertensive treatments were not captured.

275

276 **CONCLUSIONS**

277 Empagliflozin induced a clinically relevant reduction in SBP and consistently improved all outcomes
278 regardless of the prHT status. Acknowledging that this is a post-hoc analysis, the consistent findings
279 suggest that due to the optimal dual effect of BP control and CV event reduction, empagliflozin
280 should be considered a therapeutic option for patients with hypertension and T2D.

281

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432

433

Figure Legends

Figure 1. Change from baseline in systolic blood pressure over time in patients a) with presumed resistant hypertension and b) no presumed resistant hypertension at baseline including all data up until individual trial termination: mixed effect repeated measurement model results.

*MMRM model on the overall population including subject as random effect and, among others, treatment, visit, and presumed resistant hypertension at baseline as well as their corresponding 2- and 3-way interactions as fixed effects (for details on other fixed effects and linear covariates, see “statistical analysis” section).

Figure 2. Proportion of patients a) with presumed resistant hypertension and b) without presumed resistant hypertension who achieved systolic blood pressure <130 mmHg during the trial in empagliflozin and placebo groups.

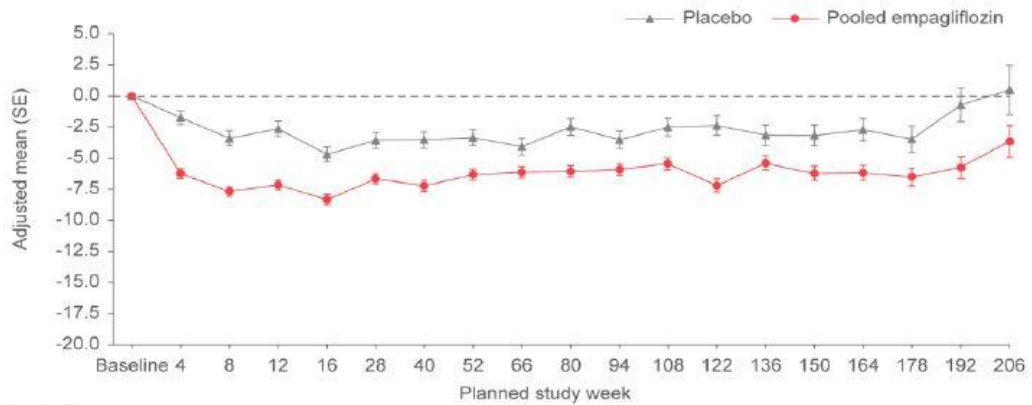
Figure 3. Treatment effects of empagliflozin versus placebo on outcomes in patients with or without presumed resistant hypertension.

*Based on a Cox regression model with terms for age sex, baseline BMI category, baseline HbA1c category, baseline eGFR category, geographical region, treatment, presumed resistant hypertension and treatment by presumed resistant hypertension interaction.

†excludes fatal stroke

Figure 1

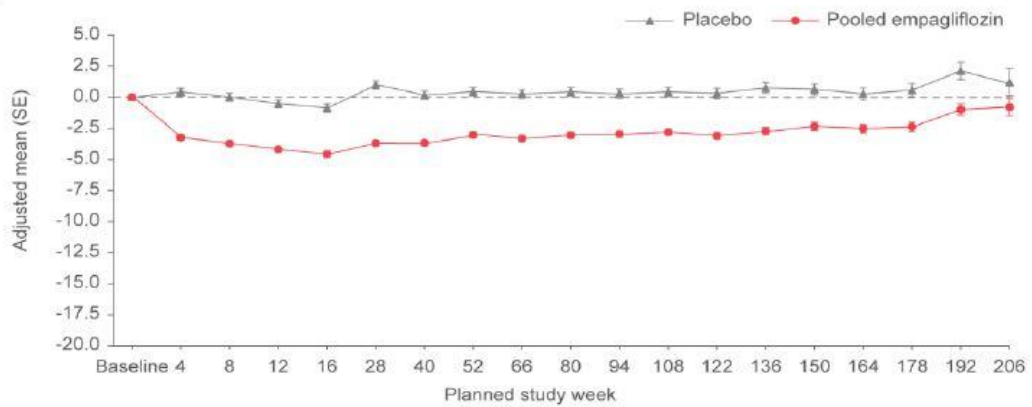
A) rHT



No. with data at visit

Placebo	515	509	494	489	496	489	474	473	458	445	435	383	321	275	244	218	157	90	40
Pooled empagliflozin	1053	1039	1015	1003	1020	1011	1000	985	964	949	943	834	700	596	524	452	333	206	98

B) No rHT



No. with data at visit

Placebo	1807	1777	1748	1712	1739	1714	1687	1660	1615	1579	1539	1388	1171	999	882	763	578	360	131
Pooled empagliflozin	3592	3528	3469	3418	3477	3445	3390	3358	3290	3248	3195	2897	2427	2082	1877	1652	1299	840	317

Figure 2

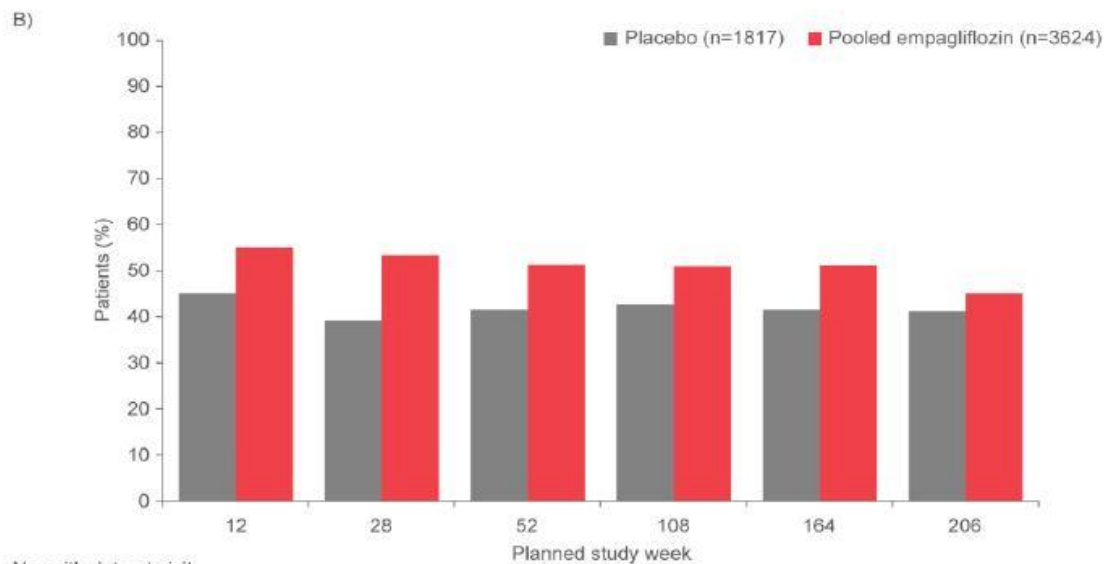
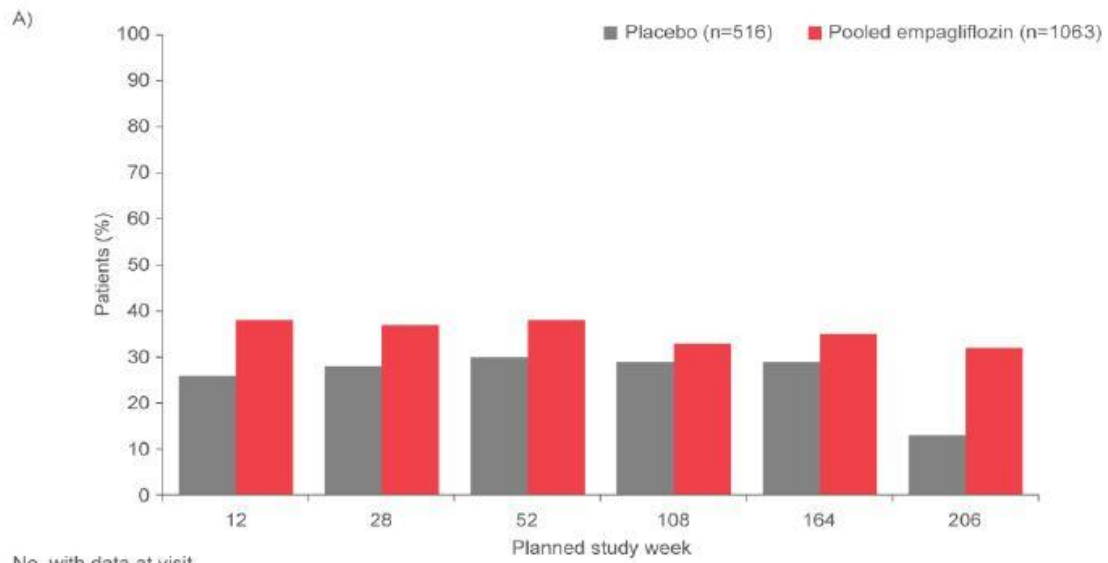


Figure 3

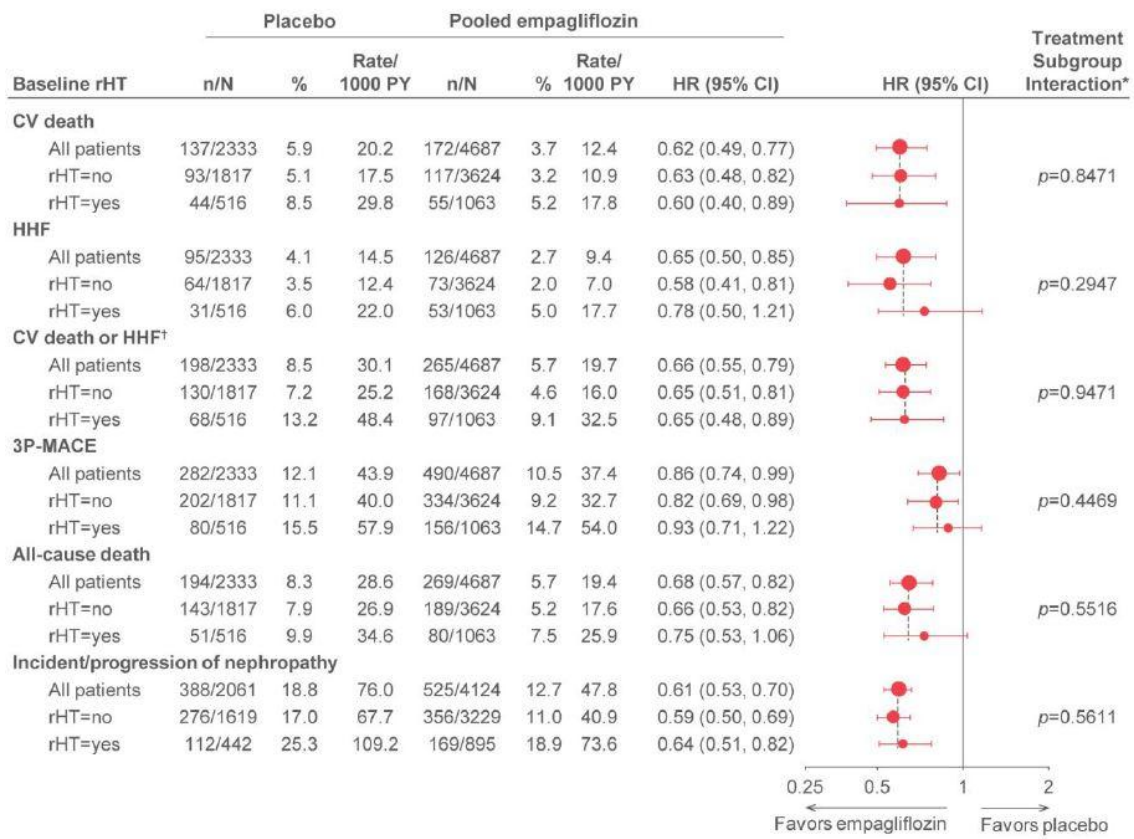


Table 1. Baseline Characteristics and Baseline Medication use by presumed Resistant Hypertension status

Characteristic	No Resistant Hypertension N=5441	Resistant Hypertension N=1579
Female sex	1543 (28.4)	461 (29.2)
Age, years	62.7±8.7	64.8±8.3
Body mass index, kg/m ²	30.2±5.2	32.2±5.1
Time since T2D diagnosis, years		
≤1	143 (2.6)	37 (2.3)
>1-5	906 (16.7)	177 (11.2)
>5-10	1382 (25.4)	364 (23.1)
>10	3010 (55.3)	1001 (63.4)
LDL-C, mg/dL	86.5±36.3	82.4±33.7
eGFR, mL/min/1.73 m ²	75.8±21.4	68.1±20.5
<60	1239 (22.8)	580 (36.7)
Previous stroke, n (%)	1256 (23.1)	381 (24.1)
CAD*, n (%)	4065 (74.7)	1243 (78.7)
Heart failure, n (%)	433 (8.0)	273 (17.3)
HbA1c, %	8.1±0.9	8.1±0.8
SBP, mm Hg	133.4±16.1	142.4±18.2
DBP, mm Hg	76.4±9.6	77.6±10.7
Retinopathy, n (%)	1127 (20.7)	419 (26.5)
Urine albumin-to-creatinine ratio, mg/g, median (Q1, Q3)	16.8 (6.2, 62.8)	25.2 (7.1, 116.7)
Micro albuminuria†	1514 (27.8)	499 (31.6)
Macro albuminuria†	532 (9.8)	237 (15.0)
Left ventricular hypertrophy‡	101 (2.2)	39 (2.9)
Uric acid (mg/dL)	5.8±1.6	6.6±1.8
Baseline medication use		
Antihypertensive drugs	5088 (93.5)	1579 (100.0)
Beta blockers	3197 (58.8)	1357 (85.9)
Diuretics	1456 (26.8)	1579 (100.0)
ACE inhibitors/angiotensin receptor blockers	4140 (76.1)	1526(96.6)
Mineralocorticoid receptor antagonists	170 (3.1)	271 (17.2)
Statins	4097 (75.3)	1306 (82.7)
Anti-platelets	4645 (85.4)	1377 (87.2)
Metformin	4057 (74.6)	1136 (71.9)
Insulin	2447 (45.0)	940 (59.5)

All data are n (%) or mean±SE unless otherwise noted. “Resistant hypertension” was a post-hoc presumptive diagnosis. ACE indicates angiotensin converting enzyme; CAD, coronary artery disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

*Coronary artery disease defined as any of the components of history of myocardial infarction, coronary artery bypass graft, multivessel coronary artery disease, single vessel coronary artery disease. †defined as microalbuminuria UACR 30 to ≤300 mg/g; macroalbuminuria UACR >300 mg/g. ‡defined on ECG as RV5/V6 + SV1/V2 >3.5 mV or RaVL ≥1.3 mV plus ≥1 of the following: left atrial abnormality, left axis deviation, and ST- and/or T-wave changes consistent with LVH.

Table 2. Anti-Coagulants, Lipid-Lowering, Antihypertensive and Antihypertensive Drugs Introduced Post-Baseline by presumed Resistant Hypertension status

	No Resistant Hypertension N=5441		Resistant Hypertension N=1579	
	Placebo n=1817	All Empagliflozin n=3624	Placebo n=516	All Empagliflozin n=1063
Anti-hypertensive	882 (48.5)	1550 (42.8)	308 (59.7)	538 (50.6)
Beta blockers	362 (19.9)	627 (17.3)	119 (23.1)	231 (21.7)
Diuretics	426 (23.4)	608 (16.8)	182 (35.3)	291 (27.4)
Mineralocorticoid receptor antagonists	89 (4.9)	86 (2.4)	47 (9.1)	91 (8.6)
ACE inhibitors/angiotensin receptor blockers	533 (29.3)	922 (25.4)	169 (32.8)	302 (28.4)
Statins	446 (24.5)	896 (24.7)	155 (30.0)	249 (23.4)
Anti-platelets	395 (21.7)	732 (20.2)	123 (23.8)	243 (22.9)

All data are n (%). “Resistant hypertension” was a post-hoc presumptive diagnosis. ACE indicates angiotensin-converting enzyme.

Table 3. Association of Outcomes with presumed Resistant Hypertension at Baseline

	Placebo			Empagliflozin		
	No resistant hypertension N=1817	Resistant hypertension N=516		No Resistant Hypertension N=3624	Resistant Hypertension N=1063	
	No of Patients With Events (%)	No of Patients With Events (%)	HR* (95% Confidence Interval) Resistant Hypertension vs No Resistant Hypertension	No of Patients With Events (%)	No of Patients With Events (%)	HR* (95% Confidence Interval) Resistant Hypertension vs No Resistant Hypertension
CV death	93 (5.1)	44 (8.5)	1.50 (1.04–2.16)	117 (3.2)	55 (5.2)	1.43 (1.03–1.98)
HHF	64 (3.5)	31 (6.0)	1.50 (0.97–2.32)	73 (2.0)	53 (5.0)	2.02 (1.41–2.91)
CV death or HHF†	130 (7.2)	68 (13.2)	1.68 (1.25–2.26)	168 (4.6)	97 (9.1)	1.70 (1.32–2.19)
3P-MACE	202 (11.1)	80 (15.5)	1.31 (1.01–1.71)	334 (9.2)	156 (14.7)	1.49 (1.23–1.81)
All-cause mortality	143 (7.9)	51 (9.9)	1.13 (0.82–1.56)	189 (5.2)	80 (7.5)	1.28 (0.98–1.67)
Incident/worsening nephropathy	276 (17.0)	112 (25.3)	1.55 (1.24–1.93)	356 (11.0)	169 (18.9)	1.68 (1.40–2.03)

*HR by multivariable Cox regression with the following variables: age, sex, region, HbA1c (category), BMI (category), eGFR (category), treatment, rHT, and treatment by resistant hypertension interaction. “Resistant hypertension” was a post-hoc presumptive diagnosis. †excluding fatal stroke.

	No resistant hypertension		Resistant hypertension	
n/N (%)	Placebo n=1817	Empagliflozin n=3624	Placebo n=516	Empagliflozin n=1063
Week 12	770/1712 (45.0)	1869/3419 (54.7)	129/489 (26.4)	379/1004 (37.7)
Week 28	672/1714 (39.2)	1842/3446 (53.5)	139/489 (28.4)	371/1012 (36.7)
Week 52	688/1660 (41.4)	1724/3359 (51.3)	142/473 (30.0)	371/986 (37.6)
Week 108	590/1388 (42.5)	1480/2897 (51.1)	110/383 (28.7)	271/835 (32.5)
Week 164	319/763 (41.8)	846/1652 (51.2)	64/218 (29.4)	156/452 (34.5)
Week 206	54/131 (41.2)	143/317 (45.1)	5/40 (12.5)	31/98 (31.6)

Supplemental Table 1. Number of patients with systolic blood pressure <130 mm Hg over time by presumed resistant hypertension at baseline, including all data up until individual trial termination.

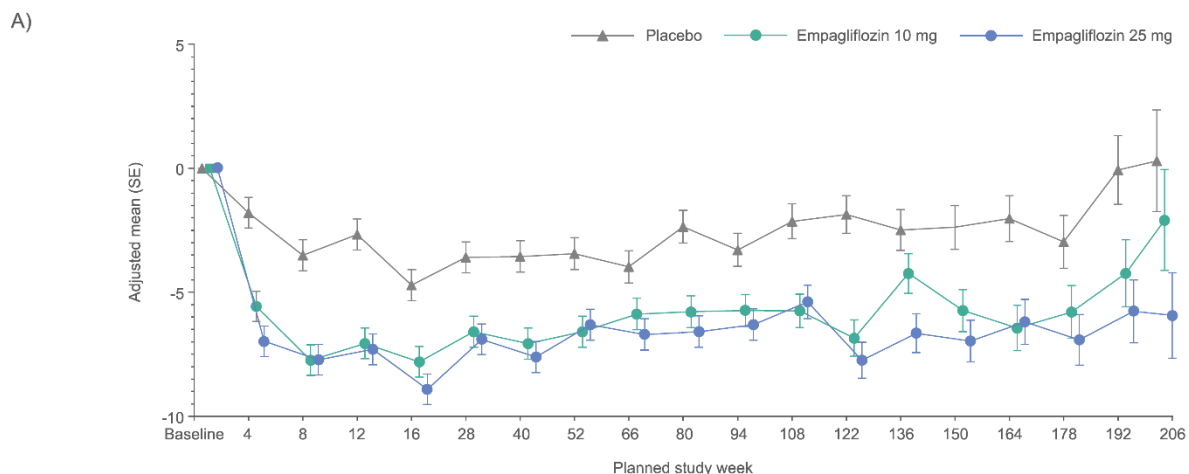
	Placebo				Empagliflozin			
	Without rHT (n=1817)		With rHT (n=516)		Without rHT (n=3624)		With rHT (n=1063)	
	N (%)	Incidence rate/100 patient- years	N (%)	Incidence rate/100 patient- years	N (%)	Incidence rate/100 patient-years	N (%)	Incidence rate/100 patient- years
Any AE	1654 (91.0)	165.34	485 (94.0)	246.44	3249 (89.7)	143.03	981 (92.3)	174.90
SAE	719 (39.6)	20.36	269 (52.1)	30.20	1303 (36.0)	17.30	486 (45.7)	24.42
Severe hypoglycemic episode requiring assistance	26 (1.4)	-	10 (1.9)	-	43 (1.2)	-	20 (1.9)	-
Genital infection	27 (1.5)	0.60	15 (2.9)	1.20	240 (6.6)	2.67	61 (5.7)	2.38
Volume depletion	82 (4.5)	1.86	33 (6.4)	2.70	162 (4.5)	1.77	77 (7.2)	3.01
Acute kidney injury	29 (1.6)	0.64	8 (1.6)	0.64	25 (0.7)	0.27	20 (1.9)	0.76
Hyperkalemia*	59 (3.2)	1.33	19 (3.7)	1.53	72 (2.0)	0.77	21 (2.0)	0.80

Supplemental Table 2. Frequency of key relevant adverse events by presumed resistant hypertension at baseline.

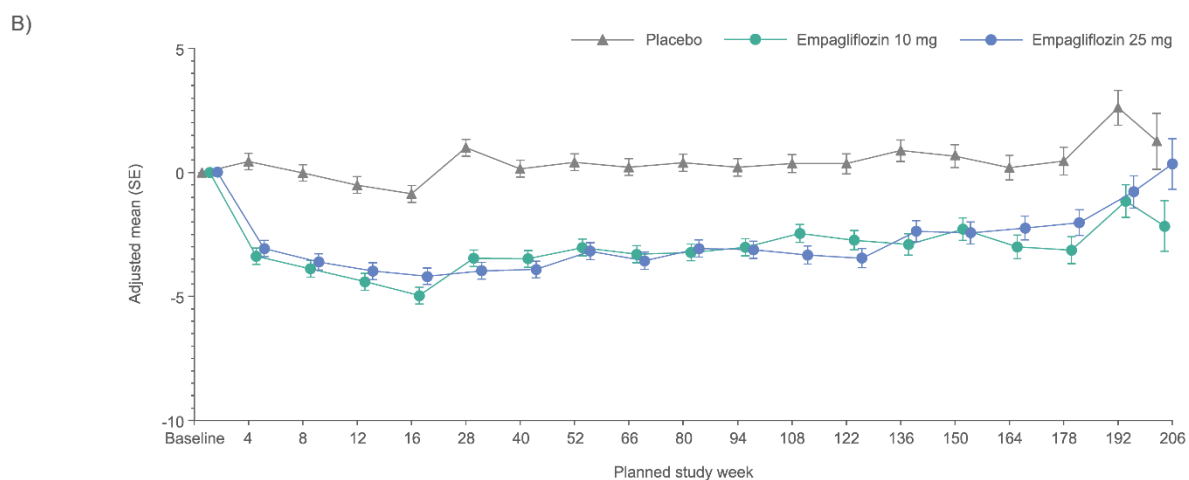
AE indicates adverse event; rHT, resistant hypertension; SAE, serious adverse event.

*Hyperkalemia defined by the MedDRA terms hyperkalemia and blood potassium increase.

Supplemental Figure 1. Change from baseline in systolic blood pressure over time up until individual trial termination in patients a) with presumed resistant hypertension and b) without presumed resistant hypertension: mixed effect repeated measurement model results in individual dose groups.



No. with data at visit	
Placebo	515 509 494 489 496 489 474 473 458 445 435 383 321 275 244 218 157 90 40
Empagliflozin 10 mg	527 522 510 509 509 504 497 491 479 468 468 411 349 292 258 222 160 96 40
Empagliflozin 25 mg	526 517 505 494 511 507 503 494 485 481 475 423 351 304 266 230 173 110 58

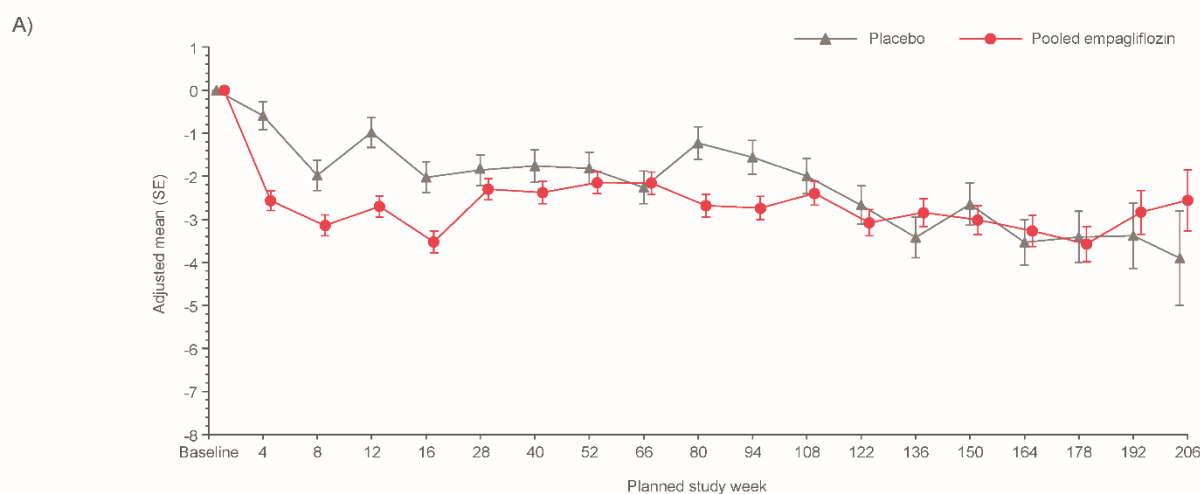


No. with data at visit	
Placebo	1807 1777 1748 1712 1739 1714 1687 1660 1615 1579 1539 1388 1171 999 882 763 578 360 131
Empagliflozin 10 mg	1795 1758 1727 1715 1741 1731 1696 1683 1646 1627 1604 1442 1207 1035 931 812 630 422 159
Empagliflozin 25 mg	1797 1770 1742 1703 1736 1714 1694 1675 1644 1621 1591 1455 1220 1047 946 840 669 418 158

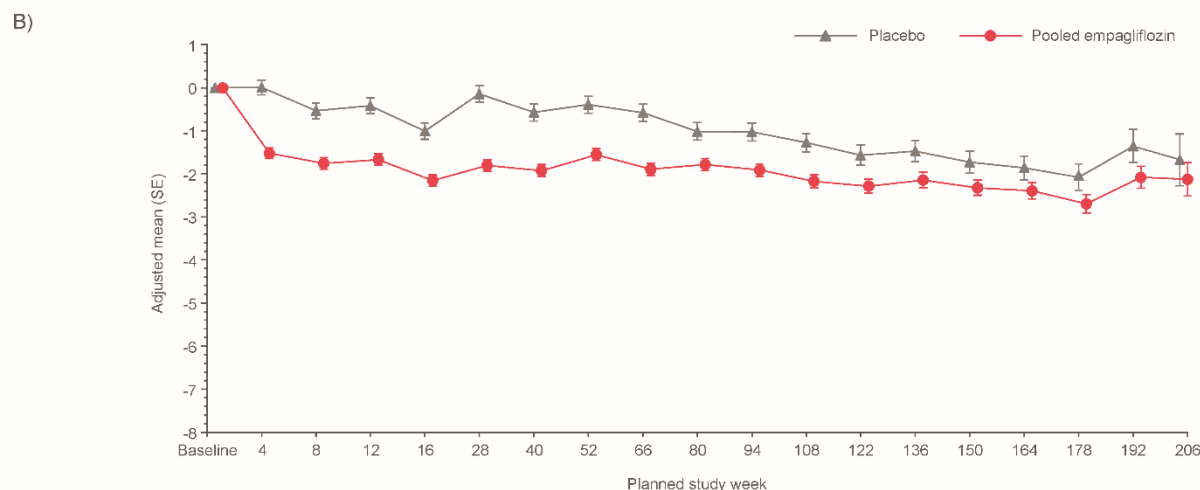
MMRM model on the overall population including subject as random effect and, among others, treatment, visit, and presumed resistant hypertension at baseline as well as their corresponding 2- and

3-way interactions as fixed effects (for details on other fixed effects and linear covariates, see “statistical analysis” section).

Supplemental Figure 2. Change from baseline in diastolic blood pressure over time up until individual trial termination in patients a) with presumed resistant hypertension and b) without presumed resistant hypertension: mixed effect model repeated measurement model results.



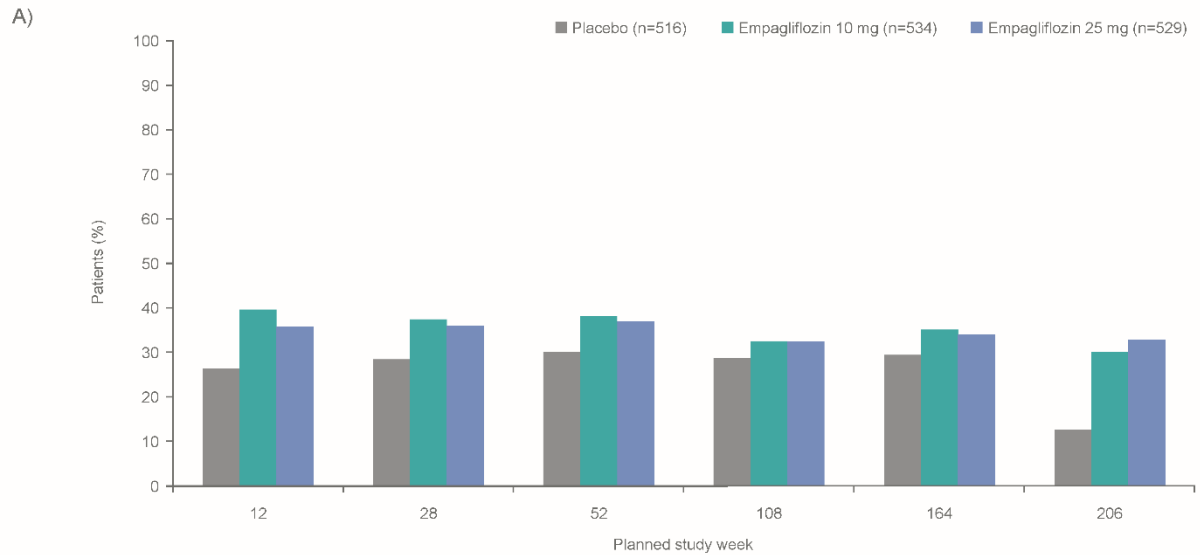
No. with data at visit	
Placebo	515 509 494 489 496 489 474 473 458 445 435 383 321 275 244 218 157 90 40
Pooled empagliflozin	1053 1039 1015 1003 1020 1011 1000 985 964 949 943 834 700 596 524 452 333 206 98



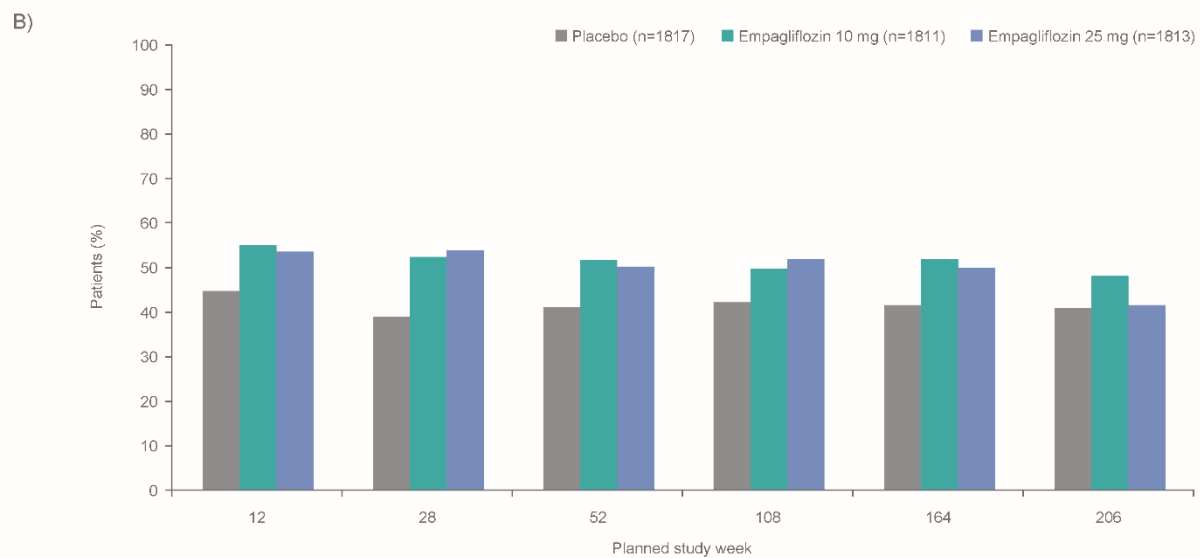
No. with data at visit	
Placebo	1807 1777 1748 1712 1739 1714 1687 1660 1615 1579 1539 1388 1171 999 882 763 578 360 131
Pooled empagliflozin	3592 3528 3469 3418 3477 3445 3390 3358 3290 3248 3195 2897 2427 2082 1877 1652 1299 840 317

MMRM model on the overall population including subject as random effect and, among others, treatment, visit, and presumed resistant hypertension at baseline as well as their corresponding 2- and 3-way interactions as fixed effects (for details on other fixed effects and linear covariates, see “statistical analysis” section).

Supplemental Figure 3. Proportion of patients a) with presumed resistant hypertension and b) without presumed resistant hypertension who achieved systolic blood pressure <130 mm Hg during the trial in the placebo group and the two separate empagliflozin doses.

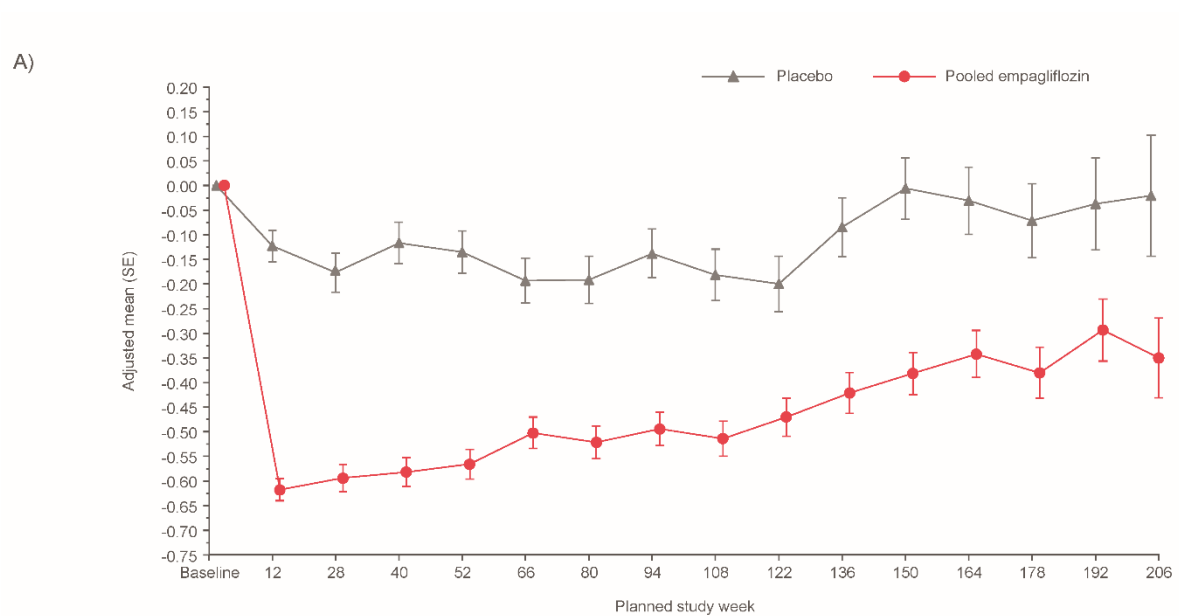


No. with data at visit	12	28	52	108	164	206
Placebo	489	489	473	383	218	40
Empagliflozin 10 mg	510	505	492	412	222	40
Empagliflozin 25 mg	494	507	494	423	230	58

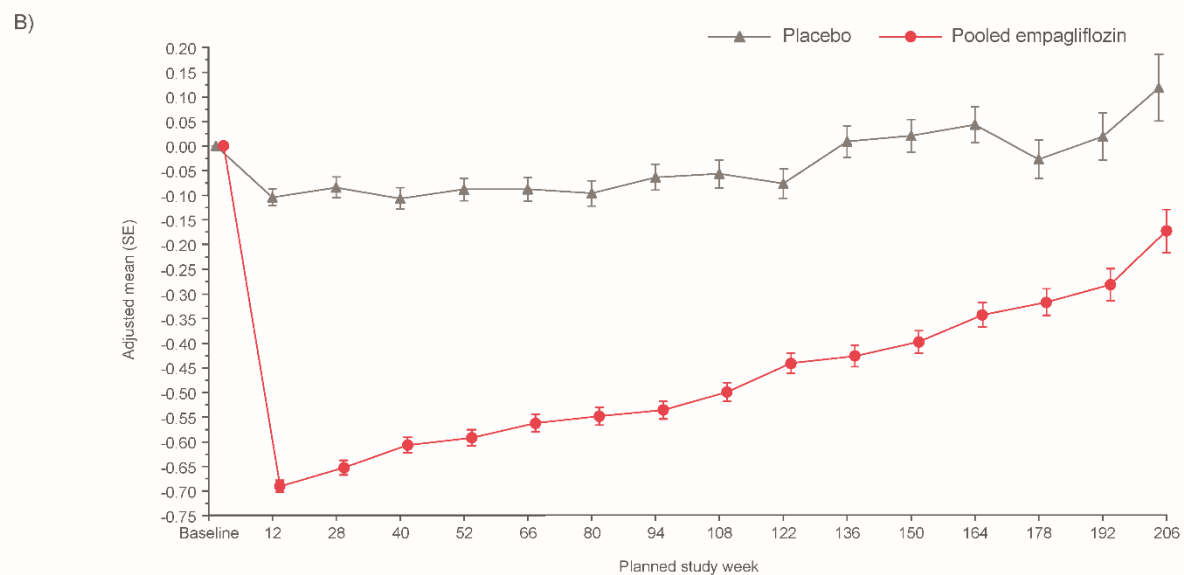


No. with data at visit	12	28	52	108	164	206
Placebo	1712	1714	1660	1388	763	131
Empagliflozin 10 mg	1715	1731	1683	1442	812	159
Empagliflozin 25 mg	1704	1715	1676	1455	840	158

Supplemental Figure 4. Change in HbA1c levels (%) from baseline over time in patients a) with presumed resistant hypertension and b) without presumed resistant hypertension: mixed effect repeated measurement model results.



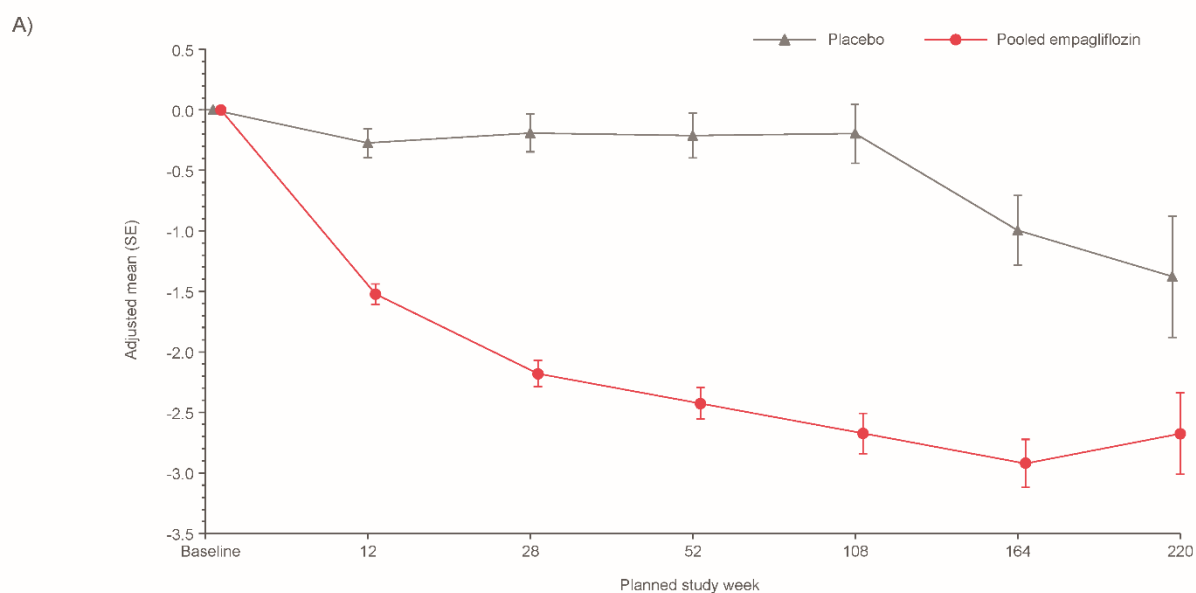
No. with data at visit	Baseline	12	28	40	52	66	80	94	108	122	136	150	164	178	192	206
Placebo	510	505	483	466	468	454	440	432	373	311	267	241	215	150	85	37
Pooled empagliflozin	1043	1034	1001	973	974	958	938	937	814	681	584	516	437	317	196	85



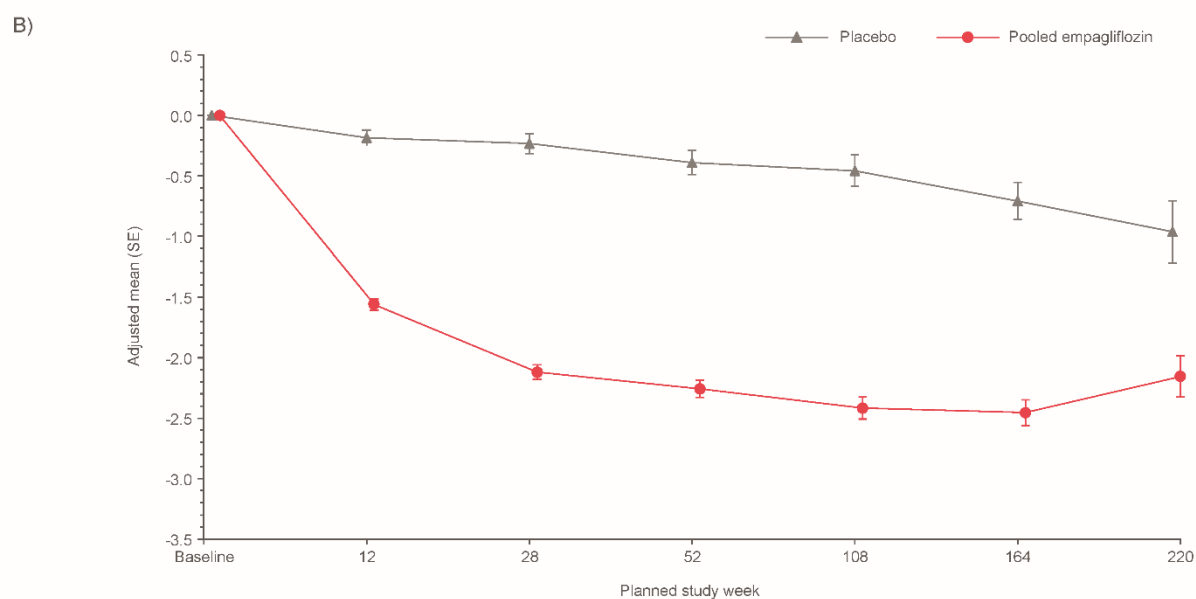
No. with data at visit	Baseline	12	28	40	52	66	80	94	108	122	136	150	164	178	192	206
Placebo	1784	1767	1705	1667	1645	1609	1568	1535	1368	1145	974	868	747	555	335	114
Pooled empagliflozin	3549	3518	3429	3329	3331	3265	3214	3165	2833	2379	2040	1838	1612	1227	790	280

MMRM model on the overall population including subject as random effect and, among others, treatment, visit, and presumed resistant hypertension at baseline as well as their corresponding 2- and 3-way interactions as fixed effects (for details on other fixed effects and linear covariates, see “statistical analysis” section).

Supplemental Figure 5. Change in body weight (Kg) from baseline in patients a) with presumed resistant hypertension and b) without presumed resistant hypertension: mixed effect repeated measurement model results.



No. with data at visit		Baseline	12	28	52	108	164	220
Placebo	509	417	489	475	348	272	86	
Pooled empagliflozin	1038	864	1012	989	760	575	195	



No. with data at visit		Baseline	12	28	52	108	164	220
Placebo	1776	1498	1726	1663	1250	967	339	
Pooled empagliflozin	3535	2920	3452	3363	2591	2058	777	

MMRM model on the overall population including subject as random effect and, among others, treatment, visit, and presumed resistant hypertension at baseline as well as their corresponding 2- and 3-way interactions as fixed effects (for details on other fixed effects and linear covariates, see “statistical analysis” section).

