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Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
RMA	repeated measures analysis
SPC	Summary of Product Characteristics
vs.	versus

1 Background

On 24 April 2013 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A12-18 (benefit assessment of dapagliflozin [1]).

In the commenting procedure on the assessment of dapagliflozin, on 5 April 2013 the pharmaceutical company (hereinafter abbreviated to "the company") submitted further data to the G-BA that went beyond the information in the dossier. These refer to data on Study D1690C00004 (comparison of dapagliflozin/metformin vs. glipizide/metformin). This study was already included in the company's dossier, but was not used by IQWiG to assess added benefit, as the comparator therapy (glipizide) did not correspond to the appropriate comparator therapy (ACT; glimepiride or glibenclamide) specified a priori by the G-BA.

The commission of the G-BA for the assessment of Study D1690C00004 reads as follows:

"In this context the data should be assessed with regard to the question as to whether the study and analyses submitted by the company for dapagliflozin/metformin versus glipizide/ metformin prove an added benefit of dapagliflozin/metformin."

In the following Chapter 2, in compliance with the commission, Study D1690C00004 is presented separately and assessed.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The decision on added benefit is made by the G-BA.

2 Assessment

According to the Summary of Product Characteristics (SPC), dapagliflozin is indicated in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as monotherapy or add-on combination therapy with other blood glucose-lowering drugs, including insulin [2].

Study D1690C00004 belongs to the subindication "combination with metformin" (dapagliflozin in combination with metformin, if metformin together with diet and exercise do not provide adequate glycaemic control; Module 4B of the original dossier on dapagliflozin [3]). The aim of the present addendum is therefore the assessment of added benefit of the drug dapagliflozin in combination with metformin versus glipizide in combination with metformin on the basis of Study D1690C00004.

As glipizide is no longer approved in Germany, the last SPC [4] effective for Germany was requested from the Federal Institute for Drugs and Medical Devices and used to answer the question as to whether glipizide was used in compliance with the approval status in Study D1690C00004.

The assessment was conducted based on patient-relevant outcomes.

2.1 Comparison of dapagliflozin/metformin versus glipizide/metformin: Study D1690C00004

Study D1690C00004 is not suitable for assessing treatment with dapagliflozin/metformin versus glipizide/metformin. This is particularly due to the fact that, both in the intervention arm (dapagliflozin) and in the control arm (glipizide), the treatments were not used in compliance with the approval status. This non-compliant use of treatments means that the effects observed in the study are not interpretable with regard to approval-compliant use and thus to the research question specified. This particularly applies to results on blood-glucose lowering and to hypoglycaemia.

Study D1690C00004 is described in more detail in the following text. Table 1 displays an overview of the design of Study D1690C00004. Table 2 describes the interventions used in Study D1690C00004.

Table 1: Characteristics of the studies included – RCT, direct comparison, dapagliflozin vs. glipizide (Study D1690C00004, dual combination with metformin)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
D1690C00004	RCT, double-blind, parallel, multi-centre	Adults with type 2 diabetes mellitus, Pretreatment with metformin as monotherapy or in combination with at most one other oral antidiabetic	Dapagliflozine + metformin (N = 406) Glipizide + metformin (N = 408) Thereof target population:[b] dapagliflozin + metformin (n = n.d.) glipizide + metformin (n = 354) Thereof dossier population:[c] dapagliflozin + metformin (n = 318) glipizide + metformin (n = 354)	Screening: 2 weeks Enrolment: 1 week Dose stabilization: 8 weeks Lead-in: 2 weeks Main treatment: 52 weeks Extension phase I: 52 weeks Extension phase II: 104 weeks Follow-up phase: 3 weeks	95 study centres in 10 countries in Europe, South Africa and Latin America 03/2008 – 12/2010 Extension phase II is still ongoing	Primary: HbA1c-change from start of study to Week 52 Secondary: Hypoglycaemia, adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for the present benefit assessment.

b: Relevant population for the assessment: (1) patients who were younger than 75 years at initiation of treatment with dapagliflozin and (2) patients without moderate to severe renal impairment (defined as creatinine clearance < 60 ml/min or estimated glomerular filtration rate < 60ml/min/1.73 m^2) or (3) patients not receiving loop diuretics.

c: The population used by the company for the assessment is composed as follows: patients of the target population minus patients of the dapagliflozin arm whose dapagliflozin dose was below 10 mg at the end of the titration phase.

N: number of randomized patients, n: relevant subpopulation, n.d.: no data; RCT: randomized controlled trial

Table 2: Characteristics of the interventions – RCT, direct comparison, dapagliflozin vs. glipizide (Study D1690C00004, dual combination with metformin)

Study	Intervention	Control	Concomitant therapy
D1690C00004	Dapagliflozin 2.5, 5 or 10 mg once daily Placebo for glipizide	Placebo for dapagliflozin Glipizide 5, 10, or 20 mg once or twice daily	Metformin[b] 1500, 2000, 2500 mg daily
	Blood-glucose target level The dose of dapagliflozin or glipizide was increased in 3-week intervals in the first 18 weeks of treatment, as long as the fasting blood-glucose levels were > 110 mg/dL[a], or if the highest tolerated dose had been reached. At the discretion of the investigator a dose-increase could be dispensed with if a patient had a risk of hypoglycaemia.		
a: Under consideration of self-measurement of patients and measurement in the study centre. b: Standardization of metformin dose according to specified scheme in the dose-stabilization or lead-in phase, see also following text. RCT: randomized controlled trial			

Study design

Study D1690C00004 was a company-sponsored randomized active-controlled double-blind approval study. Patients were to be investigated who did not achieve adequate glycaemic control, despite metformin monotherapy in a daily dose of ≥ 1500 mg. Patients with an HbA1c from 6.5% to ≤ 10% were eligible for study inclusion.

The study comprised a 2-week screening phase, a 1-week enrolment phase, an 8-week phase for stabilization of the metformin dose, a 2-week lead-in phase with administration of placebo and metformin, as well as a treatment phase. The treatment phase contained a main treatment phase (the first 52 weeks, including a titration phase of 18 weeks), an extension phase I (a further 52 weeks), and an extension phase II (a further 104 weeks, according to the company still ongoing). The overall treatment duration was 208 weeks.

During the enrolment phase the study population was recruited from several patient populations:

- Patients receiving metformin monotherapy in a dose of ≥ 1500 mg daily (Group 1)
- Patients receiving metformin monotherapy in a dose of < 1500 mg daily (Group 2)
- Patients receiving metformin therapy at any dose in combination with an oral antidiabetic. In this case the dose of the other antidiabetic was not allowed to exceed half of the maximum approved dose (Group 3).

Directly after the enrolment phase, patients in Group 1 entered the lead-in phase. The metformin dose of these patients was in each case specified as a standardized dose of

1500 mg, 2000 mg or 2500 mg daily, depending on the dose at the start of the study. In some cases the pre-existing dose was decreased (e.g. from 1700 mg daily to 1500 mg daily).

The dose-stabilization phase was planned for patients of Group 2 and 3. During the study period the current dose of metformin was adapted as follows: those patients who had received < 1500 mg metformin as monotherapy (Group 2) were switched to 1500 mg daily. Those patients who had received metformin in combination with a different oral antidiabetic had to discontinue the latter drug. Depending on the dose at the start of the study the metformin dose was specified as a standardized dose of 1500 mg, 2000 mg or 2500 mg daily. According to this scheme, dose reduction took place in patients with a metformin dose of > 2500 mg.

The algorithm used in the study for patient selection and for dose-finding of metformin was designed to include a patient population who, despite monotherapy with metformin in a dose ≥ 1500 mg daily, had inadequate glycaemic control. However, it was not suited to ensure that patients were included and then treated who, despite a maximum tolerated dose of metformin, had inadequate glycaemic control. This is because, on the one hand, patients receiving less than 50% of the maximum approved dose were included in the study (about 15% of patients). On the other, in some patients the metformin dose was reduced before the start of the study, even though a higher dose had apparently been tolerated beforehand.

At randomization, in addition to metformin patients received the following study medications: dapagliflozin 2.5 mg once daily or glipizide 5 mg once daily, in each case with administration of placebo of the other medication.

In the first 18 weeks of the main treatment phase, the dose of dapagliflozin was up-titrated in 3-week intervals from 2.5 mg to 5 mg and from 5 mg to 10 mg, as long as the fasting blood-glucose levels were above 110 mg/dL or the individual maximum tolerated dose had been reached.

In the first 18 weeks of the main treatment phase, the dose of glipizide was up-titrated in 3-week intervals from 5 mg to 10 mg and from 10 mg to 20 mg, as long as the fasting blood-glucose levels were above 110 mg/dL or the individual maximum tolerated dose had been reached.

In both treatment groups a dose increase could be dispensed with if a patient had a risk of hypoglycaemia.

The specifications described for the doses are not in compliance with the approval statuses of dapagliflozin and glipizide and lead to non-interpretability of the study results.

According to the SPC [2] the specified dose of dapagliflozin is 10 mg daily. Titration is not envisaged and thus the approach in Study D1690C00004 is not in compliance with the approval status. This could have caused distortion of the results on blood-glucose lowering, as well as on dose-dependent adverse events. In addition, treatment with a dose below 10 mg

daily is not in compliance with the approval status either. A dose reduction to 5 mg daily is recommended for patients with severe liver dysfunction. However, such patients were explicitly excluded from Study D1690C00004.

Titration in the glipizide arm was not in compliance with the approval status either. For patients whose dose was already 10 mg, the titration step was 10 mg (from 10 mg to 20 mg). However, according to the SPC for glipizide, dose adaptation should take place in steps of 2.5 mg to 5 mg [4]. This marked dose increase of 50% to 100% of the maximum dose can cause marked blood-glucose lowering leading to hypoglycaemia, which might not occur with a more cautious (and approval-compliant) titration. In addition, it is unclear whether in patients for whom a 20 mg dose was unsuitable because of hypoglycaemia, blood glucose could have been lowered further with 15 mg glipizide without the occurrence of hypoglycaemia.

Overall, despite a lack of approval, the dose in the dapagliflozin arm was titrated and in part a dose that was too low was chosen, whereas in the glipizide arm titration was not performed in compliance with the approval status and was too forceful.

In principle it is meaningful that a precise blood-glucose goal was specified in the study, not only for the glipizide arm but also for the dapagliflozin arm (see also Dossier Assessment A12-11 on linagliptin [5]). However, the precise approach in the study should represent the reality of treatment (appropriate titration; if possible with the respective drug, escalation through supplementation with a further drug or switch of treatment).

It should also be noted that the blood-glucose goal specified was very low (fasting blood glucose ≤ 110 mg/dl). Because of the study results on blood-glucose lowering to the near-normal level [6], current guidelines recommend this type of blood-glucose lowering only after an individual balancing of benefits and risks, and in principle target levels should be agreed upon under consideration of individual circumstances [7,8]. Such an individual adaptation was not envisaged in Study D1690C00004.

Total population versus target population versus dossier population

According to the SPC for dapagliflozin the use of dapagliflozin is not recommended for the following patient groups:

- Patients with moderate to severe renal impairment (creatinine clearance < 60ml/min or estimated glomerular filtration rate < 60 ml/min/1.73 m^2), or
- Patients who are 75 years and older at the start of treatment, or
- Patients receiving loop diuretics.

However, such patients were included in Study D1690C00004. In its dossier the company consequently stated that it had excluded the groups named above from the study population and had not considered them in the assessment. But closer consideration of this population

shows that the number of patient in the groups is unbalanced after exclusion of these patients (n = 318 in the dapagliflozin + metformin group; n = 354 in the glipizide + metformin group). The company's supplementary analyses show that in addition to patients who met the above criteria, the company also excluded those patients whose dapagliflozin dose was 2.5 mg or 5 mg at the end of the titration phase, even though it did not describe this in the dossier itself. It can be inferred from the available information that the proportion of these patients ranged from approximately 10 to over 15%. Because of this approach the treatment groups are no longer comparable, i.e. the structural equality between the intervention arm and control achieved through randomization is no longer given. The company did not present any analyses for the actual target population.

Characteristics of the population

Due to a lack of data for the target population, Table 3 presents the characteristics of the total population of Study D1690C00004.

Table 3: Characteristics of the study populations– RCT, direct comparison – dapagliflozin vs. glipizide (Study D1690C00004, dual combination with metformin)

Group	Dapagliflozin+metformin	Glipizide+metformin
N[a]	400	401
Age [years]: mean (SD)	58.1 (9.4)	58.6 (9.8)
Sex f/m [%]	44.8/55.3	45.1/54.9
Disease duration [years]: mean (SD)	6.1 (4.6)	6.6 (5.9)
HbA1c at start of study [%]:		
▫ mean (SD)	7.7 (0.9)	7.7 (0.9)
▫ min/max	6.2/11.6	5.7/10.3
HbA1c at start of study [%]: categories [n (%)]		
▫ < 8.0%	262 (65.5)	246 (61.3)
▫ ≥ 8.0% to < 9.0%	103 (25.8)	104 (25.9)
▫ ≥ 9.0%	35 (8.8)	51 (12.7)
Pretreatment with metformin at start of study [n (%)]		
▫ Monotherapy < 1500 mg daily	34 (8.4)	37 (9.1)
▫ Monotherapy ≥ 1500 mg daily	231 (56.9)	238 (58.3)
▫ OAD + metformin < 1500 mg daily	19 (4.7)	28 (6.9)
▫ OAD + metformin ≥ 1500 mg daily	122 (30.0)	104 (25.5)
▫ No OAD	0 (0.0)	1 (0.2)
▫ Daily metformin dose at enrolment [mg]: mean (SD)	1754.7 (474.6)	1756.1 (527.5)
▫ Daily metformin dose at randomization [mg]: mean (SD)	1892.9 (400.9)	1898.3 (413.3)
Ethnicity [n (%)]		
▫ White	327 (81.8)	323 (80.5)
▫ Asian	27 (6.8)	34 (8.5)
▫ Black/African American	26 (6.5)	24 (6.0)
▫ Other	20 (5.0)	20 (5.0)

a: Based on the full analysis set population (defined as all randomized subjects who took at least one dose of study medication, have a non-missing baseline value and at least one efficacy value in the treatment phase).
f: female; m: male; N: number of randomized and treated patients; OAD; oral antidiabetic drug; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

No relevant differences between treatment groups regarding age, sex, ethnicity, disease duration or HbA1c at the start of the study were evident for the total population. The patients were of a mean age of about 58 years. The proportion of women was about 45%. The disease duration was slightly over 6 years. Mainly patients classified as “white” participated in the study.

HbA1c (long-term marker for the average blood glucose level) had a mean value of 7.7% at the start of the study. However, despite a defined limit for HbA1c (> 6.5%), patients were included in the study whose HbA1c was 6.2% (dapagliflozin group) or even 5.7% (glipizide group). HbA1c was < 8.0% in about 63% of patients (65.5% in the dapagliflozin group and 61.3% in the glipizide group; only data for the total population). It cannot be inferred from the available documents how many patients had a baseline value of below 7%. According to protocol specifications the recruitment of patients with an HbA1c between > 6.5% and < 7% was to be stopped as soon as this patient cohort amounted to 25% of the total population. Thus according to current knowledge, for a relevant proportion of patients one cannot assume inadequate glycaemic control that would have required intensified therapy. Particularly in these patients intensified blood-glucose lowering therapy was associated with an increased risk of hypoglycaemia.

Summary

The non-approval-compliant use of the drugs in both study arms led to study results that are potentially distorted and not interpretable. In addition, the study also included patients for whom dapagliflozin is not approved. The analyses presented by the company to address this problem are unsuitable. It is also questionable in how many patients a maximum tolerated metformin dose was used and in how many patients treatment escalation because of inadequate glycaemic control was necessary at all.

Overall Study D1690C00004 provides no proof of an added benefit of dapagliflozin+metformin versus glipizide+metformin.

The results of Study D1690C00004 are presented in Appendix A as supplementary information.

2.2 Data sources for the study assessed

AstraZeneca. A 52-week international, multi-centre, randomised, parallel-group, double-blind, active-controlled, phase III study with a 52-week extension period to evaluate the efficacy and safety of dapagliflozin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycaemic control on metformin therapy alone: study D1690C00004; 52-week clinical study report errata list [unpublished]. 2010.

AstraZeneca. A 52-week international, multi-centre, randomized, parallel-group, double-blind, active-controlled, phase III study with a 52-week extension period to evaluate the efficacy and safety of dapagliflozin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone: report for the 52-week short-term treatment period; study D1690C00004; 52-week clinical study report [unpublished]. 2010.

AstraZeneca. A 52-week international, multi-centre, randomized, parallel-group, double-blind, active-controlled, phase III study with a 156-week extension period to evaluate the efficacy and safety of dapagliflozin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone: report for the 52-week short-term treatment period plus the 52-week long-term extension period I; study D1690C00004; 104-week clinical study report [unpublished]. 2011.

AstraZeneca. A 52-week international, multi-centre, randomized, parallel-group, double-blind, active-controlled, phase III study with a 156-week extension period to evaluate the efficacy and safety of dapagliflozin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone: report for the 52-week short-term treatment period plus the 52-week long-term extension period I; study D1690C00004; 104-week clinical study report errata list [unpublished]. 2012.

AstraZeneca, Bristol-Myers Squibb. Additional analyses of endpoints and subgroups for study: a 52-week international, multi-centre, randomized, parallel-group, double-blind, active-controlled, phase III study with a 156-week extension period to evaluate the efficacy and safety of dapagliflozin in combination with metformin compared with sulphonylurea in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone [unpublished]. 2012.

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Appendix A – supplementary presentation of results of D1690C00004

Blood-glucose lowering: HbA1c

The following Figure 1 shows the change in HbA1c (adjusted mean values according to HbA1c at the start of the study) during the 104-week treatment phase of Study D1690C00004 for the total population. The analyses of the change in HbA1c were conducted by means of repeated measurement analyses (RMA) (mixed models, adjusted according to baseline value). Figure 2 shows the course of absolute HbA1c values at each time point for the total population. No corresponding data were available for the target population.

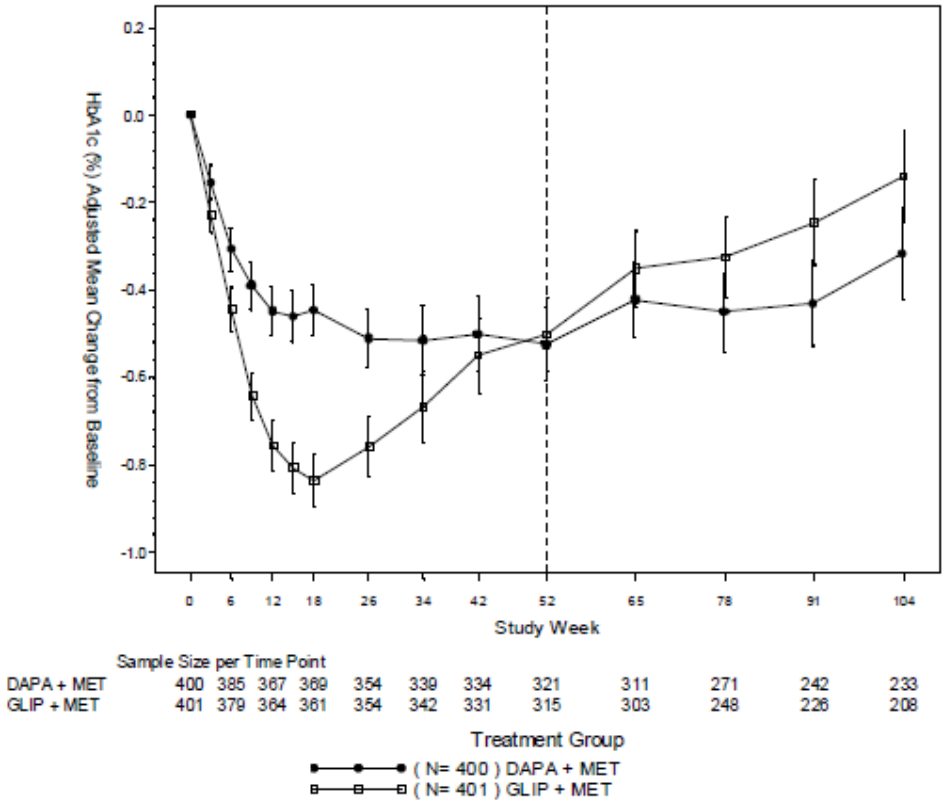

Figure 1: Change in HbA1c over the course of Study D1690C00004 (full analysis set, RMA, total population)

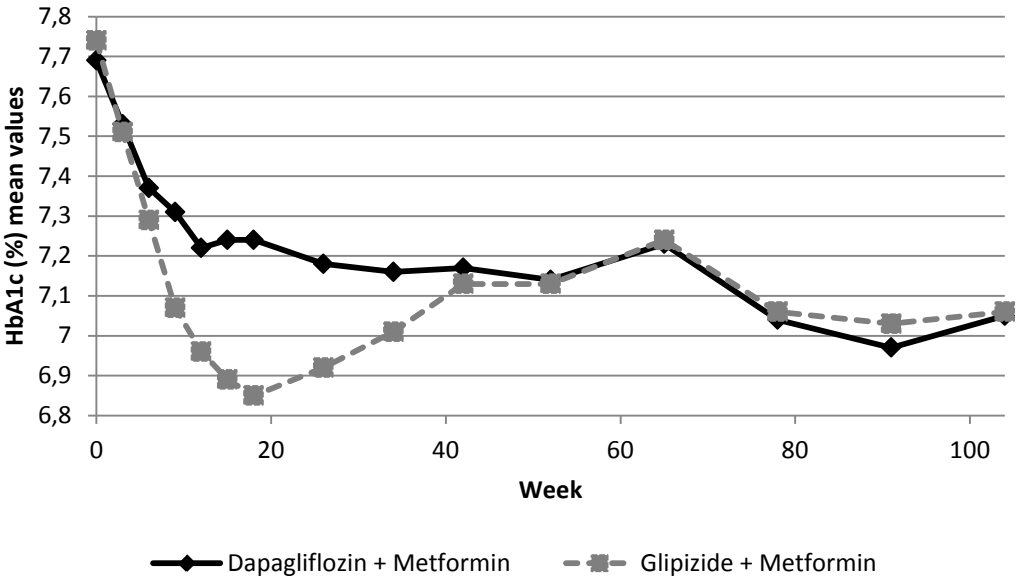

Figure 2: Change in HbA1c (mean values) over the course of Study D1690C00004 (full analysis set, total population)

If one considers the time course of change in HbA1c it is shown that in both treatment groups HbA1c decreases during the titration phase (first 18 weeks of the study).

However, the decrease in HbA1c is markedly less pronounced in the dapagliflozin group than in the glipizide group.

On the basis of the results presented, from Week 52 onwards differences in the course of mean values versus change in HbA1c were shown (in both groups the courses of the mean values approximate to each other and in both groups HbA1c still also decreases in the second half of the study, whereas the curves showing the change in HbA1c diverge markedly and also show an increase in both groups). This difference between the two observations can be explained by different analyses.

Hypoglycaemia

The company only presented data for the dossier population regarding the time course of all confirmed hypoglycaemic events (not only first events) and of the total number of hypoglycaemic events; independent of the general suitability of the study for reasons named in Section 2.1, these data are unsuitable (no randomized comparison). No information was available for the total population regarding the time course of all confirmed hypoglycaemic events.

Further outcomes

Results on mortality, as well as on cardiac and cerebral events could only be inferred from the data on adverse events. Study D1690C00004 was not designed to infer an advantage or non-

inferiority of dapagliflozin/metformin versus glipizide/metformin for these relevant outcomes. However, due to the deficiencies in study design described above, such data would also not be interpretable in the sense of an approval-compliant use of the drugs.

Data on health-related quality of life were not recorded in Study D1690C00004.

Data on other adverse events (including urinary tract infections, genital infections, serious adverse events and other events) may also be biased because of the non-approval-compliant use of the drugs.

The results of Study D1690C00004 (104 weeks) are presented in the following Table 4 for reasons of completeness.

Table 4: Results on the comparison of dapagliflozin versus glipizide (Study D1690C00004, dual combination with metformin, total population)

Outcome category **Outcome**	**Dapagliflozin+metformin**		**Glipizide+metformin**		**Dapagliflozin vs. glipizide**
	N[a]	**Patients with events n (%)**	**N[a]**	**Patients with events n (%)**	**Effect estimates [95% CI] p-value**
Mortality					
All-cause mortality	406	2 (0.5)	408	5 (1.2)	Peto OR[b]: 0.42 [0.10; 1.87] p = 0.289[c]
Cardiac events[d]	406	12 (3.0)	408	11 (2.7)	RR[b]: 1.10 [0.49; 2.46] p = 0.866
Cerebral events					
Nervous system disorders[e]	406	9 (2.2)	408	5 (1.2)	RR[b]: 1.81 [0.61; 5.35] p = 0.291
Health-related quality of life					
	not recorded				

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Table 4: Results on the comparison of dapagliflozin versus glipizide (Study D1690C00004, dual combination with metformin, total population) (continued)

Outcome category Outcome	Dapagliflozin+metformin		Glipizide+metformin		Dapagliflozin vs. glipizide
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	Effect estimates [95% CI] p-value
Adverse events					
Hypoglycaemia					
Severe hypoglycaemia[f]	406	0 (0.0)	408	3 (0.7)	0.14 [0.01, 2.77] p-value: n.d.
Confirmed symptomatic hypoglycaemia (blood glucose ≤ 0 mg/dl)[g]	No data were available for total population				
Change in HbA1c	See figures above for data on HbA1c during the course of the study				
Urinary tract infections[h]	406	55 (13.5)	408	37 (9.1)	RR[b]:1.49 [1.01; 2.21] p = 0.046
Genital infections[h]	406	60 (14.8)	408	12 (2.9)	RR[b]: 5.02 [2.75; 9.20] p < 0.001
Renal impairment or failure[h]	406	25 (6.2)	408	18 (4.4)	RR[b]: 1.40 [0.77; 2.52] p = 0.289
Volume depletion					
Hypotension, dehydration, hypovolaemia[h, i]	406	6 (1.5)	408	7 (1.7)	RR[b]:0.86 [0.29; 2.54] p = 0.852
Neoplasia[j]	406	15 (3.7)	408	12 (2.9)	RR[b]: 1.26 [0.60; 2.65] p = 0.563
Overall rate AE[k]	406	337 (83.0)	408	338 (82.8)	-
Overall rate SAE[k]	406	51 (12.6)	408	62 (15.2)	RR[b]: 0.83 [0.59; 1.17] p = 0.291
Treatment discontinuations due to AE[k]	406	40 (9.9)	408	31 (7.6)	RR[b]: 1.30 [0.83; 2.03] p = 0.266

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Table 4: Results on the comparison of dapagliflozin versus glipizide (Study D1690C00004, dual combination with metformin, total population) (continued)

Outcome category Outcome	Dapagliflozin+metformin			Glipizide+metformin			Dapagliflozin vs. glipizide
	N[a]	Patients with events n (%)		N[a]	Patients with events n (%)		Effect estimates [95% CI] p-value
Supplementary outcome "body weight"							
Weight reduction of at least 5%[l]	400	95 (23.8)		401	11 (2.8)		RR[b]: 8.66 [4.71; 15.91] p < 0.001
Change in body weight in kg[m]	N	Values at start of study mean (SD)	Change at end of study mean (SE)	N	Values at start of study mean (SD)	Change at end of study mean (SE)	Mean difference:
	400	88.4 (16.3)	-3.70 (0.2)	401	87.6 (17.0)	1.36 (3.8)	-5.1 (0.3) [-5.7, -4.4] p-value: n.d.

a: Corresponds to the safety analysis set population; unless otherwise noted. The safety analysis set population defined as all randomized subjects who took at least one dose of study medication and for whom safety information was available; patients who took a different study medication than that assigned through randomization were analysed in the group in the treatment group based on the treatment received.

b: Institute's calculation, asymptotic.

c: Institute's calculation, unconditional exact test (CSZ method according to [9]).

d: Serious cardiac events. MedDRA SOC "Cardiac disorders".

e: Serious cerebral events. MedDRA SOC "Nervous system disorders". An analysis of only ischaemic events, e.g. TIA or stroke, was not available.

f: Severe hypoglycaemia was defined as symptomatic hypoglycaemic events with capillary or plasma glucose levels below 3.0 mmol/l associated with severely impaired consciousness or behaviour, requiring external assistance, and rapid recovery after glucose or glucagon administration. There is a discrepancy regarding the information in Module 4B, where it is stated that confirmation of the blood-glucose level was not absolutely necessary.

g: Post-hoc LOCF analysis of the full analysis set population ((defined as all randomized subjects who took at least one dose of study medication, have a non-missing baseline value and at least one efficacy value in the treatment phase).

h: A predefined list of MedDRA PTs in the study protocol.

i: A separate analysis of volume depletion was not available.

j: MedDRA SOC: "Neoplasms benign, malignant and unspecified (incl. cysts and polyps)".

k: In this context serious hypoglycaemia (which were recorded as SAE) were also covered.

l: Analysis of the FAS population by means of logistic regression analysis; adjusted according to weight at the start of the study.

m: Adjusted mean values according to weight at start of the study (repeated measures analysis of the FAS population)

AE: adverse event; CI: confidence interval; CSZ; convexity, symmetry, z score; FAS: full analysis set; MedDRA: Medical Dictionary for Regulatory Activities,; N: number of analysed patients; n: number of patients with event; n.d.: no data; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SD: standard deviation; SE: standard error; SOC: system organ class; TIA: transient ischaemic attack; vs.: versus