Tirzepatide
(Type 2 diabetes mellitus 1)

Addendum to Project A23-112
(dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
AESI	adverse event of special interest
BMI	body mass index
eGFR	estimated glomerular filtration rate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP1	glucagon-like peptide
HbA1c	glycosylated haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MACE	major adverse cardiovascular event
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Physical Component Summary
PT	Preferred Term
SGB	Sozialgesetzbuch (Social Code Book)
SGLT2	sodium-glucose cotransporter 2
SOC	System Organ Class
SPC	Summary of Product Characteristics

1 Background

On 26 March 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-112 (Tirzepatide – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprised the assessment of the SURPASS-4 study for the population of insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous drug therapy, consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated (referred to as research question c2 by the pharmaceutical company [hereinafter referred to as "the company"] in the dossier, corresponds to research question 6 of the dossier assessment), as well as the assessment of the SURPASS-6 study for the population of insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous insulin regimen in addition to diet and exercise (referred to as research question d1 by the company in the dossier, corresponds to research question 7 of the dossier assessment). Each assessment takes into account the information in the dossier [2] and the analyses (fasting blood glucose categories and frequency of severe or non-severe symptomatic confirmed hypoglycaemic episodes; analysis of the glycosylated haemoglobin A1c (HbA1c) corridors over time; summaries of the insulin dose assessments) subsequently submitted by the company in the commenting procedure [3] for the studies.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

As explained in detail in the dossier assessment [4], the analyses for the subpopulations c2 of the SURPASS-4 study (see research question 6 of the dossier assessment) and d1 of the SURPASS-6 study (see research question 7 of the dossier assessment) presented by the company were not used for the benefit assessment. This is mainly due to the fact that no patient-specific target values for the glycated haemoglobin A1c (HbA1c) had been agreed. However, according to the National Disease Management Guideline Type 2 Diabetes Mellitus [5], the agreement of individualized target ranges for the HbA1c value, taking into account various factors such as age, physical condition, comorbidities, time since diabetes diagnosis, treatment adherence, treatment level and risk of hypoglycaemic episodes and other adverse effects, is explicitly recommended. For the SURPASS-4 study, different treatment goals were also specified between the treatment groups with strict titration to a fasting blood glucose value of < 100 mg/dL in the comparator arm only. This leads to an unfair and uninterpretable comparison within the study, e.g. with regard to the frequency of hypoglycaemic episodes occurring during the study. Also in the SURPASS-6 study, patients had to titrate their fasting blood glucose values to a fixed target range between 100 to 125 mg/dL by adjusting the insulin dose, however, this was equally required in both study arms.

In its comments, the company subsequently submitted different analyses for the SURPASS-4 study and the SURPASS-6 study respectively, from which, according to the company, it can be inferred that hypoglycaemic episodes occurred independently of the fasting blood glucose value or the respective titration target of the studies and that individualized treatment was possible in the studies. However, for the assessment of a connection between fasting blood glucose levels and the occurrence of hypoglycaemic episodes, the analyses presented by the company can only be interpreted to a limited extent. In addition, the data do not allow any conclusions as to whether treatment was carried out in compliance with the guidelines on the basis of individualized target values. Therefore, the points of criticism listed in the dossier assessment and thus the assessment that the studies SURPASS-4 and SURPASS-6 are not suitable for the benefit assessment remain valid. This is explained in more detail in the following Section 2.1.

In accordance with the commission, Section 2.2 presents the results of the SURPASS-4 study for the population of insulin-naive adults with type 2 diabetes mellitus with manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous drug therapy, consisting of at least 2 blood glucose-lowering drugs in addition to diet and exercise, and for whom insulin therapy is indicated; Section 2.3 shows the results of the SURPASS-6 study for the population of insulin-experienced adults with type 2 diabetes mellitus without manifest cardiovascular disease who have not achieved adequate glycaemic control with their previous insulin regimen in addition to diet and exercise.

2.1 Analyses on the studies SURPASS-4 and SURPASS-6 subsequently submitted by the company

2.1.1 Fasting blood glucose categories and frequency of severe or non-severe symptomatic confirmed hypoglycaemic episodes.

With its comments on dossier assessment A23-112, the company presented analyses for the studies SURPASS-4 and SURPASS-6 on the occurrence of hypoglycaemic episodes at the individual visits depending on the fasting blood glucose categories < 100 mg/dL, ≥ 100 to ≤ 125 mg/dL and > 125 mg/dL. For the SURPASS-6 study, data are only available for the total population of the study.

2.1.1.1 SURPASS-4 study

The subsequently submitted analyses on the SURPASS-4 study show that the strict titration target of < 100 mg/dL in the comparator arm of the study was implemented during the course of the study in a relevant proportion of patients for whom data on fasting blood glucose levels were available at the respective time points. In the intervention arm, in contrast, a significantly lower proportion of patients had a fasting blood glucose level of < 100 mg/dL (intervention vs. comparator arm at baseline: 1% vs. 9%; at Week 16: 12% vs. 40%; at Week 52: 27% vs. 42%). However, it should be noted that the proportion of patients for whom corresponding data are available varies over the course of the study. At Week 24, for example, data are only available for around 90 patients in each of the study arms. In addition, not all events that occurred in the study are shown for the outcome of non-severe confirmed symptomatic hypoglycaemic episodes (plasma glucose [PG] < 54 mg/dL).

Severe hypoglycaemic episodes did not occur in the subpopulation of the SURPASS-4 study pretreated with metformin + sodium-glucose cotransporter 2 (SGLT2). Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL) in the present subpopulation of patients for whom data on fasting blood glucose levels were available (1 vs. 10 events) occurred significantly more often in the comparator arm. However, a total of 2 vs. 16 patients with event were recorded in the study, and it remains unclear to which fasting blood glucose category the events not included in the analyses should be assigned. Furthermore, it remains unclear whether recurrent events are also included in the analyses, i.e. it remains unclear whether patients with multiple events are included in the analysis.

Of the hypoglycaemic episodes that occurred in patients for whom information on the fasting blood glucose category was available (1 vs. 10 events), 6 of the 10 events (60%) in the comparator arm occurred in patients who had belonged to the fasting blood glucose category < 100 mg/dL at the last visit. In addition, 1 event (10%) was recorded in the fasting blood glucose category of ≥ 100 to ≤ 125 mg/dL and 3 events (30%) in the fasting blood glucose category of > 125 mg/dL. The proportion of patients in the respective category stabilized

overall over the course of the study at around 40% in the lowest category and around 30% in each of the higher categories (in relation to the comparator arm).

The company argued that the results showed no obvious connection between the occurrence of non-severe hypoglycaemic episodes and the fasting blood glucose category, and that these were therefore not influenced by the titration target < 100 mg/dL. However, for the assessment of a connection between fasting blood glucose levels and the occurrence of hypoglycaemic episodes, the analyses presented by the company can only be interpreted to a limited extent. This is due to the fact that the data refer to the value recorded during the last visit, and not to a measurement immediately before the event. It is therefore unclear which fasting blood glucose category the patients were to be assigned to immediately before the event. Furthermore, it is not clear from the data whether or which adjustments were made to the insulin dose before and after the respective visit in order to achieve the titration target. In addition, fasting blood glucose values during the course of the study were not available for all patients. Nevertheless, the analyses show that the majority of non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL) (60% of events) in the comparator arm occurred in patients who were assigned to the fasting blood glucose category < 100 mg/dL at their last visit. Even if the values refer to the last visit before the occurrence of the event and not to the last previous measurement immediately before the occurrence of the hypoglycaemic episode, the accumulation of events in the fasting blood glucose category < 100 mg/dL exclusively in the comparator arm of the study suggests that the strict titration target in this arm may have promoted the occurrence of hypoglycaemic episodes overall. The company presented no corresponding analyses for non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL), so that it is not possible to assess in how far a similar data constellation exists here. In particular the results on hypoglycaemic episodes from the SURPASS-4 study are still not interpretable overall due to the different titration targets in the study arms.

2.1.1.2 SURPASS-6 study

The comparison of the proportions of patients in the respective fasting blood glucose categories between the two studies clearly shows that without the specification of a strict titration target of < 100 mg/dL in the comparator arm of the SURPASS-6 study, the proportion of patients in the < 100 mg/dL category over the course of the study is lower compared to the SURPASS-4 study. In SURPASS-6, for example, 20% of patients in the comparator arm for whom corresponding data were available fell into this category at Week 24, while this applied to 39% in the intervention arm. In SURPASS-4, however, at Week 24, 42% in the comparator arm and 23% in the intervention arm fell into the < 100 mg/dL category.

Overall, significantly fewer severe hypoglycaemic episodes occurred in the intervention arm during the course of the SURPASS-6 study under treatment with tirzepatide + insulin glargine

± metformin than under treatment with insulin lispro + insulin glargine ± metformin (4 vs. 27 events). A total of 2 vs. 25 patients with at least 1 event were recorded in the study for the outcome of severe hypoglycaemic episodes. Based on the data comparison, it can be assumed that recurring events were recorded. However, as information on the fasting blood glucose categories is not available for all patients in the total population, it remains unclear whether the analyses subsequently submitted comprise all patients with at least 1 event.

Of the hypoglycaemic episodes that occurred in patients for whom information on the fasting blood glucose category was available (4 vs. 27 events), 5 of the 27 events (18.5%) occurred in patients who had a fasting blood glucose level of < 100 mg/dL at the last visit. 7 events (25.9%) occurred in patients who had a fasting blood glucose level of 100 to 125 mg/dL at the last visit. 15 events (55.6%) occurred in the group of patients with a fasting blood glucose level of 125 mg/dL. For non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL), the distribution of events across the categories was similar to that for severe hypoglycaemic episodes, with significantly more events occurring overall in the individual categories. In both the intervention and the comparator arm, the events were distributed across all fasting blood glucose categories (< 100 mg/dL: 29.3% and 26.0%; 100 to 125 mg/dL: 28.3% and 23.8%; > 125 mg/dL: 42.4% and 50.1% in the intervention and the comparator arm). Over the majority of the study period, around one-third of patients in the intervention arm were allocated to each category, while around half of patients in the comparator arm were allocated to the highest category and around one quarter to each of the lower categories. In contrast to the SURPASS-4 study, there was no accumulation of events in the < 100 mg/dL category that only affected the comparator arm. The company also did not provide any analyses for the SURPASS-6 study on the frequency of non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL) at the individual visits depending on the fasting blood glucose categories.

The company argued that, based on the data subsequently submitted, hypoglycaemic episodes occurred regardless of the fasting blood glucose level or the titration target of 100 to 125 mg/dL. However, as already described for the SURPASS-4 study, the data for the assessment of a correlation between the fasting blood glucose level and the event could only be interpreted to a limited extent. As described in Section 3, this is particularly due to the fact that the data refer to the value recorded during the last visit, and not to a measurement immediately before the event.

2.1.2 Analysis of the HbA1c corridors over time

With its comments on benefit assessment A23-112, the company presented analyses on the time course of the HbA1c corridors for the studies SURPASS-4 and SURPASS-6. In doing so, it considered the number of patients in the corridors < 6.5%, ≥ 6.5% to < 7.5%, ≥ 7.5% to ≤ 8.5% and > 8.5% per visit.

In the SURPASS-4 study, 47.7% of patients in the intervention arm and 36.1% in the comparator arm had a baseline HbA1c level of > 8.5%. These are above the target corridor for an individualized HbA1c target value described in the German National Care Guideline for Type 2 Diabetes Mellitus [5]. With the initiation of the intervention or comparator therapy, a shift in HbA1c towards lower values can be observed over the course of the study. At Week 52, the proportion of patients with an HbA1c level of > 8.5% had reduced to 1.0% and 6.5% respectively. Only individual patients had baseline HbA1c values below the target corridor of 6.5% to 8.5% described in the German National Care Guideline, whereas at Week 52, 61.4% of the patients in the intervention arm and 36.4% in the comparator arm had such values.

A similar development of the distribution across different HbA1c corridors could be observed in the course of the SURPASS-6 study. The majority of patients in the intervention arm (58.9%) were in the HbA1c category of > 8.5% at the start of the study. At Week 52, the majority of patients in the intervention arm (56.2%) were in the lowest HbA1c category < 6.5%, and only 7.4% were in the highest HbA1c category of > 8.5%. Also in the comparator arm, the proportion of patients with HbA1c levels of > 8.5% decreased over the course of the study: at baseline, the proportion was 58.9%, at Week 52 it was still 22.7%. Meanwhile, the proportion of patients in the lowest HbA1c category of < 6.5% had increased from 0.3% at baseline to 18.2% at Week 52.

The company argued that the distribution of patients across different HbA1c corridors would illustrate the possibilities for treatment individualization in the studies. However, the fact that the patients were generally in different HbA1c categories during the course of the study does not allow any conclusions to be drawn that previously agreed individualized HbA1c target values in accordance with the German National Care Guideline [5] were being aimed for. The HbA1c category in which the patients found themselves during the course of the study or at Week 52 is not necessarily the most suitable target category for them individually. In addition, the individualized target value may also change during the course of the study.

Contrary to the company's argumentation, the distribution of HbA1c levels in the course of the study therefore does not allow any conclusions to be drawn as to whether guideline-compliant therapy was carried out on the basis of individualized target values.

2.1.3 Summaries of the insulin dose assessments

With its comments on benefit assessment A23-112, the company presented summaries of the insulin dose assessment for the comparator arm of the subpopulation of the SURPASS-4 study pretreated with metformin + SGLT2 inhibitor and for the two treatment arms of the presented subpopulation of the SURPASS-6 study.

As described in benefit assessment A23-112, in the comparator arm of the SURPASS-4 study, the insulin glargine dose was adjusted at one-week intervals based on measurements of the

fasting blood glucose and the corresponding target value of < 100 mg/dL. Corresponding dose adjustments were largely carried out in the present subpopulation. However, in the implementation, 57% of patients deviated from the titration scheme for insulin glargine by their own decision. The main reason here (46%) was the fear of hypoglycaemic episodes. Furthermore, 46% of the patients deviated from the titration scheme for insulin glargine according to the investigator's decision. With 38.5%, the most common reason for the investigator's decision was also the risk of hypoglycaemic episodes.

The SURPASS-6 study shows a similar constellation with regard to insulin dose deviations in the comparator arm, with a total of around 70% of patients deviating from the insulin lispro titration regimen by their own decision and around 22% by the investigator's decision. The most common reason for dose deviations was also the fear of hypoglycaemic episodes (43.8%; patient's decision) or the risk of hypoglycaemic episodes (16.8%; investigator's decision).

According to the company, this shows the possibility of individualized therapy adjustment in the course of the studies despite the titration targets for the SURPASS-6 study and the comparator arm of the SURPASS-4 study. Although dose adjustments were basically possible and a certain proportion deviated from the specified insulin titration regimen due to a patient-specific decision, this does not represent an individualization of the therapy in the sense of guideline-compliant therapy taking into account individualized target values. Thus, the point of criticism remains that, at the start of the study and in its further course, the definition of the HbA1c target value as the superordinate treatment goal was not based on an individualized basis and did not take into account other factors such as age, physical condition, comorbidities, time since diabetes diagnosis, etc.

2.2 Study SURPASS-4 (population c2 or research question 6 of the dossier assessment)

2.2.1 Study characteristics

A detailed characterization of the SURPASS-4 study can be found in dossier assessment A21-112 [4] and its Appendix B. As described in benefit assessment A23-112, patients received 5 mg, 10 mg or 15 mg tirzepatide according to their randomization following a dose escalation phase. During escalation (Weeks 0 to 24), there was a one-time option to reduce to the next lower maintenance dose (5 mg or 10 mg) if gastrointestinal symptoms occurred, depending on the investigator's decision. Further individualized dose adjustments were not permitted. However, according to the Summary of Product Characteristics (SPC) [6], the dose of tirzepatide can be increased or adjusted as required, with 5 mg, 10 mg and 15 mg being the recommended maintenance doses. As in the dossier, the pooled results of the 3 tirzepatide dose arms are presented versus the comparator arm in this addendum.

The subpopulation presented by the company comprised patients with type 2 diabetes mellitus who were pretreated with metformin + SGLT2 inhibitor (empagliflozin or

dapagliflozin). Detailed information on prior antidiabetic therapies of the subpopulation is not available. As described in dossier assessment A23-112, it is unclear whether all drug measures other than insulin (e.g. by adding a glucagon-like peptide [GLP-1] receptor agonist such as liraglutide) had already been exhausted for these patients and therefore insulin therapy might not yet have been indicated. Information on prior therapies for the entire study population (N = 2002) shows that < 2% of patients had received liraglutide prior to study inclusion. It may therefore have been possible for patients to intensify their treatment using a triple combination of metformin + SGLT2 inhibitor (empagliflozin or dapagliflozin) + GLP-1 receptor agonist (e.g. liraglutide) before the start of insulin administration.

Characteristics of the population of the SURPASS-4 study (subpopulation pretreated with metformin + SGLT2 inhibitor)

Table 1 shows the characteristics of the subpopulation of the SURPASS-4 study presented by the company for research question 6. Table 2 shows the characteristics of the cardiovascular diseases or risk factors of the subpopulation presented by the company.

Table 1: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor: (multipage table)

Study characteristic category	Tirzepatide, pooled + metformin + SGLT2 inhibitor N[a] = 107	Insulin glargine + metformin + SGLT2 inhibitor N[a] = 122
SURPASS-4		
Age [years], mean (SD)	61 (9)	63 (9)
Sex [F/M], %	35/65	26/74
Body weight [kg], mean (SD)	92.9 (18.4)	90.6 (18.1)
BMI [kg/m^2], mean (SD)	32.9 (5.8)	32.3 (5.3)
Family origin, n (%)		
White	91 (85)	106 (88)
Native American or Alaskans	4 (4)	6 (5)
Asian	8 (8)	6 (5)
Black or African American	1 (< 1)	1 (< 1)
Multiple family origins	2 (2)	2 (2)
Native Hawaiians/Pacific Islanders	1 (< 1)	0 (0)
Missing	0 (0)	1 (< 1)[b]
Geographical region, n (%)		
OECD country	46 (43)	45 (37)
Non-OECD country	61 (57)	77 (63)

Table 1: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor: (multipage table)

Study characteristic category	**Tirzepatide, pooled + metformin + SGLT2 inhibitor** **N[a] = 107**	**Insulin glargine + metformin + SGLT2 inhibitor** **N[a] = 122**
Duration of diabetic disease [years], mean (SD)	10.8 (7.4)	11.8 (7.9)
Systolic blood pressure (mmHg), mean (SD)	130.3 (18.1)	132.8 (14.7)
Diastolic blood pressure (mmHg), mean (SD)	78.1 (9.4)	77.7 (9.0)
Fasting serum glucose [mg/dL], median [min; max]	159.4 [99; 347]	146.5 [41; 265]
HbA1c [%], mean (SD)	8.5 (0.8)	8.3 (0.8)
HbA1c [%], n (%)		
≤ 8.5	56 (52)	78 (64)
> 8.5	51 (48)	44 (36)
UACR [mg/g], median [min; max]	21.1 [1; 3090.4]	12.4 [1; 2424.9]
UACR category, n (%)		
Macroalbuminuria (> 300 mg/g)	6 (5.9)	7 (5.9)
Microalbuminuria (≥ 30 to ≤ 300 mg/g)	31 (30.4)	35 (29.4)
Normal (< 30 mg/g)	65 (63.7)	77 (64.7)
eGFR [CKD-EPI; mL/min/1.73 m^2], mean (SD)	85.1 (20.8)	83.0 (18.0)
eGFR (mL/min/1.73 m^2), n (%)		
< 60	14 (13)	14 (12)
≥ 60	93 (87)	108 (89)
≥ 1 antihypertensive therapy at the start of the study, n (%)	99 (93)	113 (93)
≥ 1 lipid-lowering therapy at the start of the study, n (%)	94 (88)	106 (87)
Treatment discontinuation, n (%)[c]	13 (12.1)[b]	20 (16.4)[b]
Study discontinuation, n (%)[d]	8 (7.5)[b]	16 (13.1)[b]

a. Number of randomized patients.
b. Institute's calculation.
c. Common reasons for treatment discontinuation in the intervention vs. comparator arm were: withdrawal of consent (1 patient vs. 10 patients), adverse events (4 patients vs. 3 patients).
d. Common reason for study discontinuation in the intervention arm vs. the comparator arm were: withdrawal of consent (1 patient vs. 8 patients), death (3 patients vs. 4 patients).

BMI: body mass index; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: estimated glomerular filtration rate; f: female; HbA1c: glycosylated haemoglobin A1c; m: male; max: maximum; min: minimum; mmHg: millimetres of mercury; n: number of patients in the category; OECD: Organization for Economic Co-operation and Development; RCT: randomized controlled trial; SD: standard deviation; SGLT2: sodium-glucose cotransporter 2; UACR: urine albumin-creatinine ratio

Table 2: Data on cardiovascular diseases or risk factors at study inclusion - RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor

Study characteristic	**Tirzepatide, pooled + metformin + SGLT2 inhibitor** **N[a] = 107**	**Insulin glargine + metformin + SGLT2 inhibitor** **N[a] = 122**
SURPASS-4		
Hypertension, n (%)	94 (88)	105 (86)
Dyslipidaemia, n (%)	92 (86)	102 (84)
Peripheral arterial occlusive disease, n (%)	29 (27)	23 (19)
Atrial fibrillation, n (%)	8 (8)	8 (7)
Retinopathy, n (%)	12 (11)	16 (13)
History of myocardial infarction, n (%)	37 (35)	60 (49)
Condition after coronary revascularization, n (%)	38 (36)	55 (45)
History of hospitalization for unstable angina pectoris, n (%)	9 (8)	11 (9)
History of hospitalization for heart failure, n (%)	9 (8)	7 (6)
History of stroke, n (%)	14 (13)	13 (11)
Condition after arterial revascularization of the lower extremities, n (%)	5 (5)	3 (3)
Condition after carotid revascularization, n (%)	1 (< 1)	0 (0)
History of TIA, n (%)	7 (7)	10 (8)
Diabetic dyslipidaemia or other lipid metabolism diseases requiring treatment, n (%)	76 (71)	91 (75)
Known coronary artery disease, n (%)	48 (45)	64 (53)
First-degree relatives with known coronary artery disease, n (%)	12 (11)	10 (8)
First-degree relatives with known cerebrovascular disease, n (%)	4 (4)	8 (7)
Pre-existing cardiovascular disease[b], n (%)	94 (88)	110 (90)

a. Number of randomized patients.
b. Defined by a history of at least one of the following: myocardial infarction, coronary revascularization; hospitalization for unstable angina pectoris or heart failure, stroke or TIA, peripheral arterial occlusive disease, condition after arterial revascularization of the lower extremities, carotid revascularization or known coronary artery disease.

n: Number of patients with the characteristic; RCT: randomized controlled trial; SGLT2: sodium-glucose cotransporter 2; TIA: transient ischaemic attack

The patient characteristics of the subpopulation of the SURPASS-4 study presented by the company for research question 6 are largely balanced between the intervention and the comparator arm. Most of the patients were of White family origin (85% and 88% respectively) and the majority (around 60%) came from a non-OECD country. The mean age was 61 years

in the intervention arm and 63 years in the comparator arm. With 35%, more women were included in the intervention arm than in the comparator arm, in which the proportion of women was 26%. The mean duration of type 2 diabetes mellitus was comparable between the treatment arms (10.8 to 11.8 years). The median fasting serum glucose in the intervention arm was 159.4 mg/dL at baseline, which was higher than in the comparator arm (146.5 mg/dL). With 8.5% and 8.3% respectively, the mean HbA1c value was comparable between the treatment arms, but the intervention arm included fewer patients (52%) with an HbA1c value ≤ 8.5% than the comparator arm (64%). According to the company, cardiovascular disease was present in approx. 89% of patients in the subpopulation at the start of the study.

In the subpopulation of the open-label study SURPASS-4 presented by the company, more patients discontinued treatment or the study in the comparator arm than in the intervention arm. Half of the treatment and study discontinuations in the comparator arm were due to patients withdrawing their consent. In the present data situation, in which overall a low proportion of patients had discontinued treatment or the study, this has no consequences for the assessment of the risk of bias.

Information on the course of the study

Table 3 shows the mean/median treatment duration and the mean/median follow-up duration of the subpopulation of the SURPASS-4 study pretreated with metformin + SGLT2 inhibitor presented by the company.

Table 3: Information on the course of the study - RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor (multipage table)

Study **duration of the study phase** **outcome category** **outcome**	**Tirzepatide, pooled + metformin + SGLT2 inhibitor** **N = 107**	**Insulin glargine + metformin + SGLT2 inhibitor** **N = 122**
SURPASS-4		
Treatment duration [weeks]		
Until the visit at Week 52		
Median [Q1; Q3]	52.1 [51.7; 52.3]	52.1 [51.3; 52.4]
Mean (SD)	49.7 (9.5)	48.2 (12.2)
Overall		
Median [Q1; Q3]	78.9 [68.0; 88.9]	75.1 [67.0; 85.4]
Mean (SD)	75.6 (19.9)	70.4 (22.3)

Table 3: Information on the course of the study - RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor (multipage table)

Study **duration of the study phase** **outcome category** **outcome**	**Tirzepatide, pooled + metformin + SGLT2 inhibitor** **N = 107**	**Insulin glargine + metformin + SGLT2 inhibitor** **N = 122**
Observation period [days][a]		
All-cause mortality[b]		
Median [Q1; Q3]	581 [512; 646]	567 [506; 637]
Mean (SD)	580.2 (109.6)	551.6 (143.4)
Morbidity		
Health status (EQ-5D VAS)		
Median [Q1; Q3]	365 [364; 369]	365 [360; 370]
Mean (SD)	364.2 (43.4)	350.9 (70.4)
End-stage renal disease		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Diabetic retinopathy[c]		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Myocardial infarction		
Median [Q1; Q3]	576 [505; 645]	566 [502; 637]
Mean (SD)	566.7 (133.1)	539.5 (163.2)
Hospitalization due to unstable angina pectoris		
Median [Q1; Q3]	581 [512; 646]	567 [506; 637]
Mean (SD)	580.2 (109.6)	547.7 (148.2)
Hospitalization for heart failure		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Cerebrovascular events[d]		
Median [Q1; Q3]	ND	ND
Mean (SD)	ND	ND
Side effects		
Median [Q1; Q3]	581 [512; 646]	567 [506; 637]
Mean (SD)	580.2 (109.6)	551.7 (143.5)

a. Information on how the observation period was calculated is not available.
b. Deaths were recorded under AEs.
c. Recorded as part of the AEs.
d. Including cerebrovascular insult, stroke and TIA.

AE: adverse event; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; SGLT2: sodium-glucose cotransporter 2; VAS: visual analogue scale

As described in benefit assessment A23-112, the SURPASS-4 study comprised a fixed treatment phase of 52 weeks and a variable treatment phase from Week 52 to Week 104. In addition, AEs were followed up for 4 weeks (at most until Week 108). The SURPASS-4 study ended when the last randomized patient had completed Week 52, at least 300 patients of the pooled tirzepatide arm had been treated for 78 weeks and at least 1 event of the composite cardiovascular outcome (death from a cardiovascular cause, myocardial infarction, stroke or hospitalization due to unstable angina pectoris) had occurred in approximately 110 patients.

The median duration of treatment over the period of the fixed and variable treatment phases was roughly comparable between the study arms, totalling approximately 79 weeks in the intervention arm and 75 weeks in the comparator arm.

In the SURPASS-4 study, the outcome of health status (EQ-5D VAS) was only recorded at baseline and at Week 52 or in the event of premature discontinuation of the study. The median observation period for this outcome is therefore significantly shorter than for other outcomes of the SURPASS-4 study; it was 365 days in both the intervention and the comparator arm. With 576 to 581 days and 566 to 577 days respectively, the observation periods for the other morbidity outcomes for which corresponding data were available, for all-cause mortality, and for the outcomes in the side effects category were also roughly comparable in the intervention and the comparator arm.

Wherever possible, the latest available observation time points were considered for the assessment of the SURPASS-4 study. For the outcome “health status” (EQ-5D VAS), this corresponded to the visit at Week 52. For all other outcomes, the analyses at Week 104 were considered or, for outcomes that were recorded under AEs, the analyses at Week 108.

In the SURPASS-4 study, the morbidity outcomes of HbA1c and body weight, which were presented as supplementary information, were recorded both at the visits of the fixed treatment phase up to Week 52 and at the visits of the variable treatment phase from Week 52 to Week 104 as well as during the follow-up of AEs (at most until Week 108). Due to the small number of patients included in the analyses at later observation time points, the results for Week 52 are shown in Table 7.

2.2.2 Results of the SURPASS-4 study

2.2.2.1 Presented outcomes

This addendum presents the following patient-relevant outcomes for the subpopulation of the SURPASS-4 study presented by the company:

- Mortality
  - All-cause mortality

- Morbidity
  - Myocardial infarction
  - Hospitalization for unstable angina pectoris
  - Hospitalization for heart failure
  - Cerebrovascular events
  - End-stage renal disease
  - Diabetic retinopathies
  - Health status, recorded using the EQ-5D VAS
- Health-related quality of life
- Side effects
  - Serious adverse events (SAEs)
  - Discontinuation due to adverse events (AEs)
  - Pancreatitis
  - Non-severe confirmed symptomatic hypoglycaemic episodes
    - PG < 54 mg/dL
    - PG ≤ 70 mg/dL
  - Severe hypoglycaemic episodes
  - Other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used additional outcomes in the dossier (Module 4 C) [7]. The outcomes “change in HbA1c”, “change in body weight” and “change in body mass index (BMI)” are presented as supplementary information in this addendum.

Table 4 shows the outcomes for which data were available in the SURPASS-4 study.

Table 4: Matrix of outcomes – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor

Study	Outcomes															
	All-cause mortality	Myocardial infarction	Hospitalization for unstable angina pectoris	Hospitalization for heart failure	Cerebrovascular events	End-stage renal disease[a]	Diabetic retinopathies[b]	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Discontinuation due to AEs	Pancreatitis[c]	Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)	Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)	Severe hypoglycaemic episodes[d]	Further specific AEs[e]
SURPASS-4	Yes	Yes	Yes	Yes	Yes	No[f]	Yes	Yes	No[g]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Defined as eGFR < 15 mL/min/1.73 m², renal transplant or start of chronic dialysis.
b. Events confirmed by funduscopy that were recorded as part of the AE survey on the basis of a PT list compiled by the company.
c. Operationalized by adjudicated events based on the events recorded by the SMQ "acute pancreatitis" and the PT "chronic pancreatitis".
d. Hypoglycaemia that met at least one of the following criteria: emergency department stay or (prolonged) hospitalization; assistance by medical staff; treatment with glucagon or intravenous glucose; leads to disability or permanent damage to the patient; recovered/subsided with sequelae; seizure or loss of consciousness; leads to death or was life-threatening.
e. The following (MedDRA-coded) events were considered: gastrointestinal disorders (SOC, AEs), including nausea (PT, AEs), vomiting (PT, AEs), diarrhoea (PT, AEs).
f. No data are available on the frequency of events that occurred in this outcome.
g. Health-related quality of life was not recorded in the SURPASS-4 study.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; N: no; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SGLT2: sodium-glucose cotransporter 2; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale; Y: yes

Notes on outcomes

Composite renal outcome

For the outcome category of morbidity, the company presented analyses on a composite renal outcome consisting of the individual components "new onset of macroalbuminuria", "reduction of the estimated glomerular filtration rate (eGFR) by ≥ 40% compared to baseline", "renal death" and "end-stage renal disease" (consisting of eGFR < 15 mL/min/1.73 m², renal transplant or initiation of chronic dialysis). The composite renal outcome is not presented in this addendum, as the individual components are not of comparable clinical significance or severity. Results on the outcome of end-stage renal disease consisting of an eGFR < 15 mL/min/1.73 m², a renal transplant or the initiation of chronic dialysis would be relevant for the present addendum. However, in the dossier, the company did not present analyses on the individual components of the composite outcome for the subpopulation of the SURPASS-4 study. Therefore, no data on the outcome "end-stage renal disease" are available for the addendum.

Severe cardiovascular events

This research question 6 includes patients with type 2 diabetes mellitus and manifest cardiovascular disease. The occurrence of severe cardiovascular events is fundamentally relevant when considering the patient population in question. In the SURPASS-4 study, serious cardiovascular events were recorded as an adverse event of special interest (AESI). The company presented separate analyses for the events "death from a cardiovascular cause", "myocardial infarction", "hospitalization due to unstable angina pectoris", "hospitalization for heart failure", "coronary intervention and cerebrovascular events". In addition, the company presented the composite outcome "major adverse cardiovascular event (MACE) 4", which comprises the components "death from a cardiovascular cause", "myocardial infarction", "stroke" and "hospitalization due to unstable angina pectoris". In principle, a combined analysis of severe cardiovascular events is to be preferred. However, under "hospitalizations", the operationalization chosen by the company only included hospitalizations due to unstable angina pectoris. This is not appropriate. Rather, the analysis of a composite outcome should also include further severe cardiovascular events that might lead to hospitalization in patients with manifest cardiovascular disease, such as cardiac failure. In the following, the individual components "myocardial infarction", "hospitalization due to unstable angina pectoris", "hospitalization for heart failure" and "cerebrovascular events" are therefore used to assess severe cardiovascular events. The component "death from a cardiovascular cause" is taken into account via "all-cause mortality".

2.2.2.2 Risk of bias

The risk of bias across outcomes was rated as low for the SURPASS-4 study. Limitations resulting from the open-label study design are described below under the outcome-specific risk of bias.

The risk of bias of the results on the outcomes of all-cause mortality, myocardial infarction, hospitalization due to unstable angina pectoris or heart failure, cerebrovascular events, SAEs, pancreatitis and diabetic retinopathies was rated as low.

There is also a high risk of bias for the results of the outcome "health status" (recorded using the EQ-5D VAS) due to lack of blinding in subjective recording of outcomes.

The results of the outcome of discontinuation due to AEs also have a high risk of bias due to the lack of blinding in the case of a subjective decision to discontinue treatment. Results on non-serious and non-severe specific AEs (gastrointestinal disorders including diarrhoea, nausea and vomiting as well as the AEs "non-severe confirmed symptomatic hypoglycaemic episodes" [PG < 54 mg/dL or PG ≤ 70 mg/L]) have a high risk of bias due to the lack of blinding.

For the outcome of end-stage renal disease, the risk of bias is not assessed, as no data are available for this outcome.

2.2.2.3 Results

Table 5, Table 6 and Table 7 summarize the results on the comparison of tirzepatide + metformin + SGLT2 inhibitor with insulin glargine + metformin + SGLT2 inhibitor in insulin-naive patients with type 2 diabetes mellitus at an increased cardiovascular risk in the SURPASS-4 study. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

If available, the Kaplan-Meier curves on the time-to-event analyses are presented in Appendix A.1, and the results on common AEs, SAEs, and discontinuations due to AEs are presented in Appendix B.1 of the full dossier assessment.

Table 5: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor (multipage table)

Study outcome category outcome	Tirzepatide + metformin + SGLT2 inhibitor		Insulin glargine + metformin + SGLT2 inhibitor		Tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
SURPASS-4					
Mortality					
All-cause mortality	107	3 (2.8)	122	4 (3.3)	0.86 [0.20; 3.74]; 0.867
Morbidity					
Diabetic retinopathies[b]	107	1 (0.9)	122	1 (0.8)	1.14 [0.07; 18.01]; 0.992
Health status (EQ-5D VAS - improvement at Week 52[c])	107	24 (22.4)	122	20 (16.4)	1.37 [0.80; 2.33]; 0.261
Health-related quality of life					
Outcome not recorded					
Side effects					
AEs (supplementary information)	107	74 (69.2)	122	76 (62.3)	–
SAEs	107	18 (16.8)	122	19 (15.6)	1.08 [0.60; 1.95]; 0.808
Discontinuation due to AEs	107	7 (6.5)	122	7 (5.7)	1.14 [0.41; 3.15]; 0.816
Pancreatitis[e]	107	0 (0)	122	0 (0)	–
Non-severe confirmed symptomatic hypoglycaemic episodes					
PG < 54 mg/dL	107	2 (1.9)	122	16 (13.1)	0.14 [0.03; 0.61]; 0.002
PG ≤ 70 mg/dL	107	6 (5.6)	122	40 (32.8)	0.17 [0.08; 0.39]; < 0.001
Severe hypoglycaemia[f]	107	0 (0)	122	0 (0)	–
Gastrointestinal disorders (SOC, AEs)	107	44 (41.1)	122	12 (9.8)	4.18 [2.33; 7.49]; < 0.001
Including:					
Nausea (PT, AE)	107	23 (21.5)	122	3 (2.5)	8.74 [2.70; 28.30]; < 0.001
Vomiting (PT, AE)	107	11 (10.3)	122	2 (1.6)	6.27 [1.42; 27.66]; 0.005
Diarrhoea (PT, AE)	107	19 (17.8)	122	4 (3.3)	5.42 [1.90; 15.42]; 0.001

Table 5: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor (multipage table)

Study **outcome category** **outcome**	**Tirzepatide + metformin + SGLT2 inhibitor**		**Insulin glargine + metformin + SGLT2 inhibitor**		**Tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**

a. Institute's calculation of effect, CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [8]).
b. Events confirmed by funduscopy that were recorded as part of the AE survey on the basis of a PT list compiled by the company.
c. An EQ-5D VAS score increase by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range 0 to 100).
d. Patients with only one baseline value and no post-baseline value were included in the analysis as non-responders. For patients with post-baseline values but no value at Week 52, this value was imputed using LOCF.
e. Operationalized by adjudicated events based on the events recorded by the SMQ "acute pancreatitis" and the PT "chronic pancreatitis".
f. Hypoglycaemia that met at least one of the following criteria: emergency department stay or (prolonged) hospitalization; assistance by medical staff; treatment with glucagon or intravenous glucose; leads to disability or permanent damage to the patient; recovered/subsided with sequelae; seizure or loss of consciousness; leads to death or was life-threatening.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SGLT 2: sodium-glucose cotransporter 2; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Table 6: Results (morbidity, time to event) – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor

Study **outcome category** **outcome**	**Tirzepatide + metformin + SGLT2 inhibitor**		**Insulin glargine + metformin + SGLT2 inhibitor**		**Tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value[a]**
SURPASS-4					
Morbidity					
Myocardial infarction	107	NA 4 (3.7)	122	NA 3 (2.5)	1.47 [0.33; 6.55]; 0.617
Hospitalization for unstable angina pectoris	107	NA 0 (0)	122	NA 2 (1.6)	NC; ND
Hospitalization for heart failure	107	NA 0 (0)	122	NA 0 (0)	–
Cerebrovascular events[b]	107	NA 0 (0)	122	NA 0 (0)	–
End-stage renal disease[c]				ND	

a. Cox proportional hazards model, unstratified.
b. Including cerebrovascular insult, stroke and TIA.
c. Defined as eGFR < 15 mL/min/1.73 m², renal transplant or start of chronic dialysis.

CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; SGLT2: sodium-glucose cotransporter 2

Table 7: Results (supplementary outcomes: HbA1c; body weight; BMI, continuous) – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor

Study outcome category outcome	Tirzepatide + metformin + SGLT2 inhibitor			Insulin glargine + metformin + SGLT2 inhibitor			Tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor
	N[a]	values at baseline mean (SD)	change at Week 52 mean (SE)[b]	N[a]	values at baseline mean (SD)	change at Week 52 mean (SE)[b]	MD [95% CI]; p-value[b]
SURPASS-4							
Morbidity							
HbA1c (%) (supplementary information)	ND	8.5 (0.8)	-2.27 (0.1)	ND	8.3 (0.8)	-1.39 (0.1)	-0.88 [-1.13; -0.63]; < 0.001
Body weight (kg) (supplementary information)	ND	92.9 (18.4)	-9.74 (0.8)	ND	90.6 (18.1)	1.18 (0.4)	-10.92 [-12.76; -9.08]; < 0.001
BMI (kg/m^2) (supplementary information)					ND		

a. Number of patients considered in the analysis for the calculation of the effect estimation, the values at time points after the start of the study may be based on other patient numbers.
b. Effect, CI and p-value: mixed-effects model repeated measures (MMRM).

BMI: body mass index; CI: confidence interval; HbA1c: glycosylated haemoglobin A1c; MD: mean difference; MMRM: mixed-effects model repeated measures; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SGLT2: sodium/glucose cotransporter 2

Mortality

All-cause mortality

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality.

Morbidity

Myocardial infarction

There was no statistically significant difference between the treatment arms for the outcome "myocardial infarction".

Hospitalization for unstable angina pectoris

The effect estimation for the outcome of hospitalization due to unstable angina pectoris is not possible. In the study, events only occurred in 2 patients in the comparator arm.

Hospitalization for heart failure

In the subpopulation of the SURPASS-4 study pretreated with metformin + SGLT2 inhibitor, there were no events in the outcome of hospitalization due to heart failure.

Cerebrovascular events

In the subpopulation of the SURPASS-4 study pretreated with metformin + SGLT2 inhibitor, no events occurred in the outcome of cerebrovascular events.

End-stage renal disease

For the outcome of end-stage renal disease, no data are available on the frequency of occurrence in the subpopulation pretreated with metformin + SGLT2 inhibitor.

Diabetic retinopathies

No statistically significant difference between treatment arms was shown for the outcome of diabetic retinopathies.

Health status (EQ-5D VAS)

For the outcome of health status, recorded using the EQ-5D VAS, no statistically significant difference was found between treatment groups.

Health-related quality of life

Health-related quality of life was not recorded in the SURPASS-4 study.

Side effects

SAEs

No statistically significant difference between treatment groups was found for the outcome of SAEs.

Discontinuation due to AEs

No statistically significant difference between treatment groups was found for the outcome of discontinuation due to AEs.

Specific AEs

Pancreatitis

In the subpopulation of the SURPASS-4 study pretreated with metformin + SGLT2 inhibitor, no events occurred in the outcome “pancreatitis”.

Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL and PG ≤ 70 mg/dL)

For the outcomes of non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL) and non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL), there were statistically significant differences between the treatment arms in favour of tirzepatide + metformin + SGLT2 inhibitor. These are presented here as commissioned. However, it should be noted that the comparison in the SURPASS-4 study is unfair and uninterpretable, and therefore the results on hypoglycaemic episodes in particular cannot be interpreted (for a detailed explanation, see Section 2.1.1.1).

Severe hypoglycaemia

In the subpopulation of the SURPASS-4 study pretreated with metformin + SGLT2 inhibitor, no events occurred in the outcome of severe hypoglycaemic episodes.

Gastrointestinal disorders (AE) (including nausea [AE], vomiting [AE] and diarrhoea [AE])

For each of the gastrointestinal disorders outcomes (AE) (including nausea ([AE]), vomiting ([AE]) and diarrhoea ([AE]), there were statistically significant differences between the treatment arms to the disadvantage of tirzepatide + metformin + SGLT2 inhibitor.

2.2.2.4 Subgroups and other effect modifications

For this addendum, the following potential effect modifiers were considered for the subpopulation of the SURPASS-4 study pretreated with metformin + SGLT2 inhibitor:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)

The selected characteristics were defined a priori. In SURPASS-4, subgroup analyses were only predefined for the outcomes “change in HbA1c”, “change in body weight” and “AEs”. For further outcomes listed in Module 4 C, the company presented post hoc subgroup analyses. The SURPASS-4 study provides no subgroup analyses on a suitable characteristic for the investigation of the severity of the diseases.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Following the methods described above, no relevant effect modification was identified for the present research question.

2.2.3 Summary of the results

Overall, the commissioned assessment showed advantages of tirzepatide + metformin + SGLT2 inhibitor over insulin glargine + metformin + SGLT2 inhibitor for the following outcomes:

- Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)
- Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)

However, it should be noted that the comparison in the SURPASS-4 study is unfair and uninterpretable, and therefore the results on hypoglycaemic episodes in particular cannot be interpreted (for a detailed explanation, see Section 2.1.1.1).

Disadvantages of tirzepatide + metformin + SGLT2 inhibitor compared to insulin glargine + metformin + SGLT2 inhibitor were shown for the following outcomes:

- Gastrointestinal disorders (AE), including nausea (AE), vomiting (AE) and diarrhoea (AE)

2.3 Study SURPASS-6 (population d1 or research question 7 of the dossier assessment)

2.3.1 Study characteristics

A detailed characterization of the SURPASS-6 study can be found in dossier assessment A21-112 [4] and its Appendix B. As described in benefit assessment A23-112, patients received 5 mg, 10 mg or 15 mg tirzepatide according to their randomization following a dose escalation phase. a. Individualized dose adjustments were not allowed. However, according to the SPC [6], the dose of tirzepatide can be increased or adjusted as required, with 5 mg, 10 mg and 15 mg being the recommended maintenance doses. As in the dossier, the pooled results of the 3 tirzepatide dose arms are presented versus the comparator arm in this addendum.

Characteristics of the SURPASS-6 study population (subpopulation without manifest cardiovascular disease)

Table 8 shows the characteristics of the subpopulation of the SURPASS-6 study presented by the company for research question 7. It comprises patients with type 2 diabetes mellitus and without manifest cardiovascular disease.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin (multipage table)

Study characteristic **category**	**Tirzepatide, pooled + insulin glargine ± metformin** **N[a] = 584**	**Insulin lispro + insulin glargine ± metformin** **N[a] = 587**
SURPASS-6		
Age [years], mean (SD)	58 (10)	58 (10)
Sex [F/M], %	61/39	58/42
Family origin, n (%)		
White	549 (94)	553 (94)
Native American or Alaskans	1 (< 1)	1 (< 1)
Asian	2 (< 1)	3 (< 1)
Black or African American	26 (5)	22 (4)
Multiple family origins	6 (1)	8 (1)
Geographical region, n (%)		
Europe	149 (26)	159 (27)
Latin America	365 (63)	353 (60)
United States	70 (12)	75 (13)
Geographical region according to OECD, n (%)		
Non-OECD country	367 (63)	362 (62)
OECD country	217 (37)	225 (38)
Body weight [kg], mean (SD)	90.1 (18.5)	90.5 (18.3)
BMI [kg/m^2], mean (SD)	33.2 (5.4)	33.2 (5.2)
Duration of diabetic disease [years], mean (SD)	13.1 (7.0)	13.6 (7.4)
Use of metformin, n (%)		
No	91 (16)	85 (15)
Yes	493 (84)	502 (86)
Fasting serum glucose [mg/dL], median [min; max]	151.2 [45.0; 383.0]	149.0 [43.0; 396.3]
HbA1c (%), mean (SD)	8.8 (1.0)	8.8 (1.0)
HbA1c [%], n (%)		
≤ 8.5	240 (41)	241 (41)
> 8.5	344 (59)	346 (59)
Treatment discontinuation, n (%)	ND[b]	ND[b]
Study discontinuation, n (%)	ND[c]	ND[c]

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin (multipage table)

Study characteristic category	Tirzepatide, pooled + insulin glargine ± metformin	Insulin lispro + insulin glargine ± metformin
	N[a] = 584	N[a] = 587

a. Number of randomized patients.
b. In the total population, 69 patients in the intervention arm and 88 patients in the comparator arm discontinued treatment. Common reason for treatment discontinuation in the intervention arm vs. the comparator arm were: withdrawal of consent (16 patient vs. 51 patients), side effects (39 patients vs. 6 patients).
c. In the total population, 36 patients in the intervention arm and 88 patients in the comparator arm discontinued the study. Common reason for study discontinuation in the intervention arm vs. the comparator arm were: withdrawal of consent (11 patient vs. 52 patients) and death (7 patients vs. 11 patients).

BMI: Body-Mass-Index; f: female; HbA1c: glycosylated haemoglobin A1c; m: male; max: maximum; min: minimum; n: number of patients in the category; ND: no data; OECD: Organisation for Economic Co-operation and Development; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the subpopulation of patients without manifest cardiovascular disease (approx. 82% of all patients in SURPASS-6) are largely balanced between the pooled tirzepatide arm and the comparator arm. The patients' mean age at study entry was 58 years; about 60% were female, and a vast majority of 94% were of White family origin. A large proportion of patients (> 60%) came from non-OECD countries (Brazil, Argentina, Romania, Russia). At the start of the study, the patients had a body weight of around 90 kg and an average HbA1c value of 8.8%; average time since diabetes diagnosis was around 13 years. The majority of patients were taking metformin at the start of the study (84% and 86% respectively).

Data on study or treatment discontinuations are only available for the total population of SURPASS-6. Both treatment discontinuations (69 vs. 88 patients) and study discontinuations (36 vs. 88 patients) occurred more frequently in the comparator than in the intervention arm. The most common reason in the comparator arm as opposed to the intervention arm was the withdrawal of consent (52 patients as opposed to 11 patients). Since the subpopulation with type 2 diabetes mellitus and without manifest cardiovascular disease comprised about 82% of the total study population, it is assumed that similar differences exist in the subpopulation. This is taken into account in the outcome-specific assessment of the risk of bias.

2.3.2 Results of the SURPASS-6 study

2.3.2.1 Presented outcomes

This addendum presents the following patient-relevant outcomes for the subpopulation of the SURPASS-6 study presented by the company:

- Mortality
  - All-cause mortality
- Morbidity
  - Myocardial infarction
  - Hospitalization for unstable angina pectoris
  - Hospitalization for heart failure
  - Cerebrovascular events
  - End-stage renal disease
  - Diabetic retinopathies
  - Health status (EQ-5D VAS)
- Health-related quality of life
  - Measured using the SF-36v2
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Pancreatitis
  - Non-severe confirmed symptomatic hypoglycaemic episodes
    - PG < 54 mg/dL
    - PG ≤ 70 mg/dL
  - Severe hypoglycaemic episodes
  - Other specific AEs, if any

The choice of patient-relevant outcomes deviates from that made by the company, which used additional outcomes in its dossier (Module 4 D) [7]. The outcomes “change in HbA1c”, “change in body weight” and “change in BMI” are presented as supplementary information in this addendum.

Table 9 shows for which outcomes data were available in the SURPASS-6 study.

Table 9: Matrix of outcomes – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin

Study	Outcomes															
	All-cause mortality	Myocardial infarction	Hospitalization for unstable angina pectoris	Hospitalization for heart failure	Cerebrovascular events	End-stage renal disease[a]	Diabetic retinopathies[b]	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Pancreatitis[c]	Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)	Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)	Severe hypoglycaemic episodes[d]	Further specific AEs[e]
SURPASS-6	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Consisting of eGFR < 15 mL/min/1.73 m², renal transplant or initiation of chronic dialysis.
b. Events confirmed by funduscopy that were recorded as part of the AE survey on the basis of a PT list compiled by the company.
c. Operationalized by adjudicated events based on the events recorded by the SMQ "acute pancreatitis" and the PT "chronic pancreatitis".
d. Hypoglycaemia that met at least one of the following criteria: emergency department stay or (prolonged) hospitalization; assistance by medical staff; treatment with glucagon or intravenous glucose; leads to disability or permanent damage to the patient; seizure or loss of consciousness; leads to death or was life-threatening.
e. The following (MedDRA-coded) events were considered: gastrointestinal disorders (SOC, AEs), including nausea (PT, AEs), vomiting (PT, AEs), diarrhoea (PT, AEs).

AE: adverse event; eGFR: estimated glomerular filtration rate; MedDRA: Medical Dictionary for Regulatory Activities; n: no; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form-36 Health Survey Version 2; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale; Y: yes

Notes on outcomes

Composite renal outcome

For the outcome category of morbidity, the company presented analyses on a composite renal outcome consisting of the individual components "new onset of macroalbuminuria", "reduction in the eGFR by ≥ 40% compared to baseline", "renal death" and "end-stage renal disease" (consisting of eGFR < 15 mL/min/1.73 m², renal transplant or initiation of chronic dialysis). The composite renal outcome is not presented in this addendum, as the individual components are not of comparable clinical significance or severity. Events were reported in particular in the individual component of new onset of macroalbuminuria, which, however, is of lesser clinical significance or severity than the other individual components of the outcome. Results on the outcome of end-stage renal disease consisting of an eGFR < 15 mL/min/1.73 m², a renal transplant or the initiation of chronic dialysis are presented for this addendum.

Severe cardiovascular events

In the SURPASS-6 study, severe cardiovascular events were recorded as AESI. The company presented separate analyses for the operationalizations "death from a cardiovascular cause", "myocardial infarction", "hospitalization due to unstable angina pectoris", "hospitalization for heart failure", "coronary intervention" and "cerebrovascular events". In addition, the company presents results on severe cardiovascular events for the outcome of MACE. For these results, it is not clear from the information in Module 4 D of the dossier whether it represents a composite outcome of the aforementioned components. In principle, a combined analysis of serious cardiovascular events is to be preferred. However, due to the uncertainty, the individual severe cardiovascular events "myocardial infarction", "hospitalization due to unstable angina pectoris", "hospitalization for heart failure" and "cerebrovascular events" are presented below. The coronary intervention component is not shown here, as it remains unclear whether the cardiovascular event underlying the intervention is not already covered by the events mentioned before. The component "death from a cardiovascular cause" is taken into account via "all-cause mortality".

2.3.2.2 Risk of bias

The risk of bias across outcomes was rated as low for the SURPASS-6 study. Limitations resulting from the open-label study design are described below under the outcome-specific risk of bias.

The risk of bias of the results on the outcomes of all-cause mortality, SAEs, severe hypoglycaemic episodes, end-stage renal disease, myocardial infarction, hospitalization due to unstable angina pectoris, hospitalization for heart failure, cerebrovascular events, pancreatitis and diabetic retinopathies was rated as low.

There is a high risk of bias in the results for the outcomes of health status (recorded using the EQ-5D VAS) and health-related quality of life (recorded using the SF-36v2) due to a lack of blinding in subjective recording of outcomes and a large difference between the treatment groups in terms of imputed values (approx. 10 percentage points).

The results of the outcome of discontinuation due to AEs also have a high risk of bias due to the lack of blinding in the case of subjective decision on treatment discontinuation. Results on non-serious and non-severe specific AEs (non-severe confirmed symptomatic hypoglycaemic episodes [PG < 54 mg/dL or PG ≤ 70 mg/L]; gastrointestinal disorders including diarrhoea, nausea, vomiting) have a high risk of bias due to the lack of blinding.

2.3.2.3 Results

Table 10, Table 11 and Table 12 summarize the results on the comparison of tirzepatide + insulin glargine ± metformin versus insulin lispro + insulin glargine ± metformin in patients with type 2 diabetes mellitus and without manifest cardiovascular disease in the SURPASS-6 study. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

Kaplan-Meier curves for outcomes with time-to-event analyses are not available. Results on common AEs, SAEs and discontinuations due to AEs can be found in Appendix B.2 of the full dossier assessment.

Table 10: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin (multipage table)

Study outcome category outcome	Tirzepatide, pooled + insulin glargine ± metformin		Insulin lispro + insulin glargine ± metformin		Tirzepatide, pooled + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
SURPASS-6					
Mortality					
All-cause mortality	584	3 (0.5)	584	10 (1.7)	0.30 [0.08; 1.08]; 0.053[a]
Morbidity					
Diabetic retinopathies[b]	584	6 (1.0)	584	8 (1.4)	0.75 [0.26; 2.15]; 0.683[a]
Health status (EQ-5D VAS - improvement at Week 52[c])	584	155 (26.5)	584	86 (14.7)	1.80 [1.42; 2.29]; < 0.001[d]

Table 10: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin (multipage table)

Study outcome category outcome	Tirzepatide, pooled + insulin glargine ± metformin		Insulin lispro + insulin glargine ± metformin		Tirzepatide, pooled + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value
Health-related quality of life					
SF-36v2 (improvement at Week 52)					
Physical Component Summary (PCS)[e]	584	59 (10.1)	584	43 (7.4)	1.37 [0.94; 2.00]; 0.120[d]
Mental Component Summary (MCS)[e]	584	97 (16.6)	584	61 (10.5)	1.59 [1.18; 2.14]; 0.003[d]
Physical functioning[e]	584	112 (19.2)	584	68 (11.6)	1.63 [1.23; 2.14][f]
Physical role functioning[e]	584	148 (25.3)	584	100 (17.1)	1.45 [1.16; 1.82][f]
Physical pain[e]	584	161 (27.6)	584	111 (19.0)	1.42 [1.15; 1.75][f]
General health perception[e]	584	180 (30.8)	584	110 (18.8)	1.63 [1.33; 2.00][f]
Vitality[e]	584	121 (20.7)	584	82 (14.0)	1.44 [1.12; 1.86][f]
Social functioning[e]	584	114 (19.5)	584	78 (13.4)	1.41 [1.08; 1.83][f]
Emotional role functioning[e]	584	150 (25.7)	584	112 (19.2)	1.35 [1.09; 1.68][f]
Mental well-being[e]	584	136 (23.3)	584	100 (17.1)	1.33 [1.06; 1.67][f]
Side effects					
AEs (supplementary information)	584	423 (72.4)	584	318 (54.5)	–
SAEs	584	28 (4.8)	584	59 (10.1)	0.47 [0.31; 0.73]; < 0.001[a]
Discontinuation due to AEs	584	33 (5.7)	584	16 (2.7)	2.06 [1.15; 3.71]; 0.013[a]
Pancreatitis[g]	584	0 (0.0)	584	0 (0.0)	–
Non-severe confirmed symptomatic hypoglycaemic episodes					
PG < 54 mg/dL	584	46 (7.9)	584	250 (42.8)	0.18 [0.14; 0.25]; < 0.001[a]
PG ≤ 70 mg/dL	584	139 (23.8)	584	371 (63.5)	0.37 [0.32; 0.44]; < 0.001[a]
Severe hypoglycaemia[h]	584	2 (0.3)	584	22 (3.8)	0.09 [0.02; 0.38]; < 0.001[a]
Gastrointestinal disorders (SOC, AEs)	584	260 (44.5)	584	51 (8.7)	5.10 [3.86; 6.73]; < 0.001[a]
Including:					
Nausea (PT, AE)	584	124 (21.2)	584	7 (1.2)	17.71 [8.34; 37.60]; < 0.001[a]
Vomiting (PT, AE)	584	59 (10.1)	584	4 (0.7)	14.75 [5.39; 40.34]; < 0.001[a]
Diarrhoea (PT, AE)	584	80 (13.7)	584	15 (2.6)	5.33 [3.11; 9.15]; < 0.001[a]

Table 10: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin (multipage table)

Study outcome category outcome	Tirzepatide, pooled + insulin glargine ± metformin		Insulin lispro + insulin glargine ± metformin		Tirzepatide, pooled + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value

a. Institute's calculation of effect, CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [8]).

b. Events confirmed by funduscopy that were recorded as part of the AE survey on the basis of a PT list compiled by the company.

c. An EQ-5D VAS score increase by ≥ 15 points from baseline is considered a clinically relevant improvement (scale range 0 to 100).

d. RR and CI unadjusted, p-value using Fisher's exact test. Patients with only one baseline value and no post-baseline value were included in the analysis as non-responders. For patients with post-baseline values but no value at Week 52, this value was imputed using LOCF.

e. Patients with an improvement by ≥ 15% of the scale range, determined using the empirical minima and maxima from a 2009 norm sample, see information in Table 7.1 of the SF-36 manual [9]; this corresponds to an improvement of the following values:

- Physical Component Summary (PCS): ≥ 9.7 points (scale range from 10.8 to 75.5),
- Mental Component Summary (MCS): ≥ 9.6 points (scale range from 5.6 to 69.7),
- Physical functioning: ≥ 5.8 points, physical role functioning: ≥ 5.3 points, physical pain: ≥ 5.9 points, general health perception: ≥ 6.6 points, vitality: ≥ 6.5 points, social functioning: ≥ 5.9 points, emotional role functioning: ≥ 6.9 points, psychological well-being: ≥ 7.4 points[e].

f. RR and CI from adjusted model with LOCF. The adjusted model contains the variables "treatment", "country/pooled country", "HbA1c value at baseline" (≤ 8.5%/> 8.5%) and "treatment with metformin at baseline" (yes/no).

g. Operationalized by adjudicated events based on the events recorded using the SMQ "acute pancreatitis" and the PT "chronic pancreatitis".

h. Hypoglycaemia that met at least one of the following criteria: emergency department stay or (prolonged) hospitalization; assistance by medical staff; treatment with glucagon or intravenous glucose; leads to disability or permanent damage to the patient; seizure or loss of consciousness; leads to death or was life-threatening.

AE: adverse event; CI: confidence interval; HbA1c: glycosylated haemoglobin A1c; LOCF: last observation carried forward; MCS: Mental Component Summary; MedDRA: Medical Dictionary of Drug Regulatory Activities; n: Number of patients with (at least 1) event; N: number of analysed patients; PCS: Physical Component Summary; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form-36 Health Survey Version 2; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

Table 11: Results (morbidity, time to event) – RCT, direct comparison: tirzepatide, pooled + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin

Study **outcome category** **outcome**	**Tirzepatide, pooled + insulin glargine ± metformin**		**Insulin lispro + insulin glargine ± metformin**		**Tirzepatide, pooled + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin**
	N	**median time to event in months [95% CI]** **patients with event n (%)**	**N**	**median time to event in months [95% CI]** **patients with event n (%)**	**HR [95% CI]; p-value**
SURPASS-6					
Morbidity					
Myocardial infarction	584	NA 0 (0)	584	NA 4 (0.7)	NC; ND
Hospitalization due to unstable angina pectoris	584	NA 0 (0)	584	NA 1 (0.2)	NC; ND
Hospitalization for heart failure	584	NA 0 (0)	584	NA 1 (0.2)	NC; ND
Cerebrovascular events[a]	584	4 (0.7)	584	1 (0.2)	3.89 [0.43; 34.79]; 0.225[b]
End-stage renal disease[c]	584	NA 0 (0)	854	NA 0 (0)	–

a. Including cerebrovascular insult, stroke and TIA.
b. Effect estimates and methods unclear, discrepancy between results table and methods section in M 4 D.
c. Consisting of eGFR < 15 mL/min/1.73 m^2, renal transplant or initiation of chronic dialysis.

CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial

Table 12: Results (supplementary outcomes: HbA1c, body weight, BMI, continuous) – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin

Study outcome category outcome	Tirzepatide, pooled + insulin glargine ± metformin			Insulin lispro + insulin glargine ± metformin			Tirzepatide, pooled + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin
	N[a]	values at baseline mean (SD)	change at Week 52 mean (SE)	N[a]	values at baseline mean (SD)	change at Week 52 mean (SE)	MD [95% CI]; p-value
SURPASS-6							
Morbidity							
HbA1c (%) (supplementary information)	584	8.82 (1.0)	-2.20 (0.1)[b]	584	8.84 (1.0)	-1.16 (0.1)[b]	-1.04 [-1.20; -0.89]; < 0.001[b]
Body weight (kg) (supplementary information)	584	90.09 (18.5)	-9.11 (0.3)[c]	584	90.48 (18.3)	3.77 (0.3)[c]	-12.88 [-13.67; -12.09]; < 0.001[c]
BMI (kg/m^2)[d] (supplementary information)	708	33.3 (5.4)	-3.6 (0.1)[e]	694	33.0 (5.2)	1.4 (0.1)[e]	-5.0 [-5.2; -4.8]; < 0.001[e]

a. Number of patients considered in the analysis for the calculation of the effect estimation, the values at time points after the start of the study may be based on other patient numbers.
b. MMRM with treatment, visit, interaction of treatment and visit, country/pooled country, treatment with metformin at baseline (yes/no) as fixed effects and baseline HbA1c value as covariate.
c. MMRM with treatment, visit, interaction of treatment and visit, country/pooled country, HbA1c value at baseline (≤ 8.5%/> 8.5%), treatment with metformin at baseline (yes / no) as fixed effects and baseline body weight as covariates.
d. Data for the total study population. The subpopulation of patients without manifest cardiovascular disease relevant for the research question comprises approx. 82% of the total study population.
e. MMRM with baseline value, treatment, visit, interaction of treatment and visit, pooled country, HbA1c value at baseline (≤ 8.5%/> 8.5%), treatment with metformin at baseline (yes / no) as fixed effects.

BMI: body mass index; CI: confidence interval; HbA1c: glycosylated haemoglobin A1c; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality".

Morbidity

Myocardial infarction

The effect estimation for the outcome of myocardial infarction is not possible. In the study, events only occurred in 4 patients in the comparator arm.

Hospitalization due to unstable angina pectoris

The effect estimation for the outcome of hospitalization due to unstable angina pectoris is not possible. In the study, an event only occurred in 1 patient in the comparator arm.

Hospitalization for heart failure

The effect estimation for the outcome of hospitalization for heart failure is not possible. In the study, an event only occurred in 1 patient in the comparator arm.

Cerebrovascular events

No statistically significant difference between treatment arms was shown for the outcome of cerebrovascular events.

Diabetic retinopathies

No statistically significant difference between treatment arms was shown for the outcome of diabetic retinopathies.

End-stage renal disease

In the SURPASS-6 study, no events occurred in the outcome of end-stage renal disease in the subpopulation of patients with type 2 diabetes mellitus and without manifest cardiovascular disease.

Health status (EQ-5D VAS)

A statistically significant difference between the treatment arms in favour of tirzepatide + insulin glargine ± metformin was shown for the outcome of health status, recorded using the EQ-5D VAS.

Health-related quality of life (SF-36v2)

No statistically significant difference between treatment arms was shown for the Physical Component Summary (PCS) of the SF-36v2.

A statistically significant difference between the treatment arms in favour of tirzepatide + insulin glargine ± metformin was shown for the Mental Component Summary (MCS) of the SF-36v2.

Side effects

SAEs

A statistically significant difference between the treatment arms in favour of tirzepatide + insulin glargine ± metformin was shown for the outcome of SAE. It should be noted that severe hypoglycaemic episodes (2 vs. 22 patients with at least 1 event in the intervention or the comparator arm) were recorded via the SAEs.

Discontinuation due to AEs

A statistically significant difference between the treatment arms to the disadvantage of tirzepatide + insulin glargine ± metformin was shown for the outcome "discontinuation due to AEs".

Specific AEs

Pancreatitis

No pancreatitis events occurred in the subpopulation of patients with type 2 diabetes mellitus and without manifest cardiovascular disease.

Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL and PG ≤ 70 mg/dL), severe hypoglycaemic episodes

For each of the outcomes of non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL), non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL) and severe hypoglycaemic episodes, there were statistically significant differences between the treatment arms in favour of tirzepatide + insulin glargine ± metformin.

Gastrointestinal disorders (AE) (including nausea [AE], vomiting [AE] and diarrhoea [AE])

For each of the outcomes of gastrointestinal disorders (AE) (including nausea [AE], vomiting [AE] and diarrhoea [AE]), there were statistically significant differences between the treatment arms to the disadvantage of tirzepatide + insulin glargine ± metformin.

2.3.2.4 Subgroups and other effect modifications

For this addendum, the following potential effect modifiers were considered for the subpopulation with type 2 diabetes mellitus and without manifest cardiovascular disease in the SURPASS-6 study:

- age (< 65 years versus ≥ 65 years)
- sex (female versus male)

The selected characteristics were defined a priori. In SURPASS-6, subgroup analyses were only predefined for the outcomes of change in HbA1c and change in body weight. For further outcomes listed in Module 4 D, the company presented post hoc subgroup analyses. The

SURPASS-6 study provides no subgroup analyses on a suitable characteristic for the investigation of the severity of the diseases.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Following the methods described above, no relevant effect modification was identified for the present research question.

2.3.3 Summary of the results

Overall, advantages of tirzepatide + insulin glargine ± metformin over insulin lispro + insulin glargine ± metformin were shown for the following outcomes:

- Health status (EQ-5D VAS)
- MCS of the SF-36v2
- SAEs
  - Severe hypoglycaemic episodes
- Non-severe confirmed symptomatic hypoglycaemic episodes (PG < 54 mg/dL)
- Non-severe confirmed symptomatic hypoglycaemic episodes (PG ≤ 70 mg/dL)

Disadvantages of tirzepatide + insulin glargine ± metformin versus insulin lispro + insulin glargine ± metformin were shown for the following outcomes:

- Discontinuation due to AEs
- Gastrointestinal disorders (AE), including nausea (AE), vomiting (AE) and diarrhoea (AE)

2.4 Summary

Compared with dossier assessment A23-112 [4], the analyses subsequently submitted by the company with the comments did not change the conclusion on the added benefit of tirzepatide compared with the ACT specified by the G-BA.

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The reference list contains citations provided by the company in which bibliographical information may be missing.

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Appendix A Kaplan-Meier curves

A.1 SURPASS-4 study

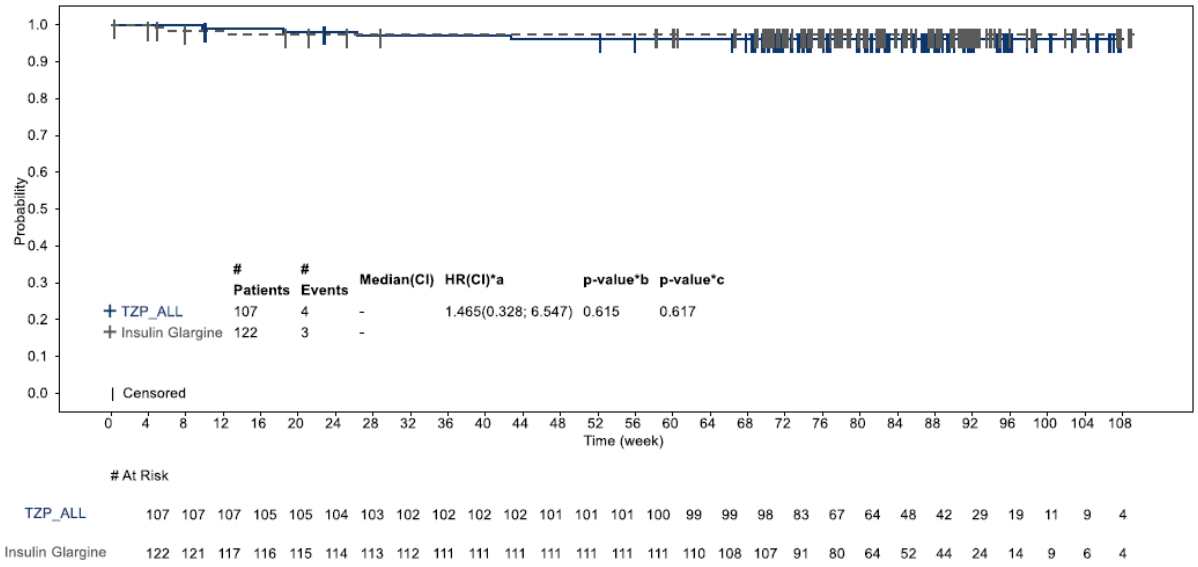

Figure 1: Kaplan-Meier curves for the outcome of myocardial infarction – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor, SURPASS-4 study

Appendix B Results on side effects

The tables below present events for Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOCs) and Preferred Terms (PTs) for the overall rates of AEs and SAEs, each on the basis of the following criteria:

- overall rate of AEs (irrespective of severity): events which occurred in at least 10% of patients in one study arm
- Overall rates of SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity: events which occurred in at least 10 patients and in at least 1% of patients in 1 study arm

A complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided for the outcome of discontinuation due to AEs.

B.1 SURPASS-4 study

Table 13: Common AEsa – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor

Study	Patients with event n (%)	
	tirzepatide, pooled + metformin + SGLT2 inhibitor N = 107	insulin glargine + metformin + SGLT2 inhibitor N = 122
SURPASS-4		
Overall AE rate[b]	74 (69.2)	76 (62.3)
SOC[c]		
Cardiac disorders	11 (10.3)	12 (9.8)
Gastrointestinal disorders	44 (41.1)	12 (9.8)
General disorders and administration site conditions	14 (13.1)	12 (9.8)
Infections and infestations	28 (26.2)	37 (30.3)
Injury, poisoning and procedural complications	6 (5.6)	13 (10.7)
Investigations	14 (13.1)	13 (10.7)
Metabolism and nutrition disorders	11 (10.3)	10 (8.2)
Musculoskeletal and connective tissue disorders	8 (7.5)	19 (15.6)
Nervous system disorders	14 (13.1)	16 (13.1)
Surgical and medical procedures	10 (9.4)	8 (6.6)
PT[c]		
Diarrhoea	19 (17.7)	4 (3.3)
Nausea	23 (21.5)	3 (2.5)
Vomiting	11 (10.3)	2 (1.6)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. AEs were recorded until the end of the safety follow-up (Week 108) at the latest.
c. MedDRA version 23.1; SOC and PT notation taken from Module 4 C without adaptation.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SGLT2: sodium-glucose cotransporter 2; SOC: System Organ Class

Table 14: Common SAEsa – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor

Study	**Patients with event n (%)**	
	tirzepatide, pooled + metformin + SGLT2 inhibitor N = 107	**insulin glargine + metformin + SGLT2 inhibitor N = 122**
SURPASS-4		
Overall rate of SAEs[b]	18 (16.8)	19 (15.6)
SOC[c]		
Cardiac disorders	7 (6.5)	7 (5.7)

a. Events which occurred in ≥ 5% of the patients in at least 1 study arm.
b. For SAEs, no PTs (according to MedDRA) met the criterion for presentation. AEs were recorded until the end of the safety follow-up (Week 108) at the latest.
c. MedDRA version 23.1; SOCs taken from Module 4 C without adaptation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SGLT2: sodium-glucose cotransporter 2; SOC: System Organ Class

Table 15: Discontinuation due to AEs – RCT, direct comparison: tirzepatide + metformin + SGLT2 inhibitor vs. insulin glargine + metformin + SGLT2 inhibitor

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**tirzepatide, pooled + metformin + SGLT2 inhibitor** **N = 107**	**insulin glargine + metformin + SGLT2 inhibitor** **N = 122**
SURPASS-4[b]		
Total rate of discontinuations due to AEs	7 (6.5)	7 (5.7)
Cardiac disorders	1 (0.9)	3 (2.5)
Acute myocardial infarction	1 (0.9)	0 (0)
Angina unstable	0 (0)	1 (0.8)
Cardiac failure congestive	0 (0)	1 (0.8)
Cardiogenic shock	0 (0)	1 (0.8)
Gastrointestinal disorders	3 (2.8)	0 (0)
Abdominal pain	2 (1.9)	0 (0)
Nausea	1 (0.9)	0 (0)
Infections and infestations	2 (1.9)	0 (0)
COVID-19 pneumonia	1 (0.9)	0 (0)
Cellulitis	1 (0.9)	0 (0)
Investigations	1 (0.9)	0 (0)
Weight decreased	1 (0.9)	0 (0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0 (0)	3 (2.5)
Invasive ductal breast carcinoma	0 (0)	1 (0.8)
Laryngeal squamous cell carcinoma	0 (0)	1 (0.8)
Lung adenocarcinoma	0 (0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (0.8)
Pulmonary embolism	0 (0)	1 (0.8)

b. MedDRA version 23.1; SOC and PT notation taken from Module 4 C without adaptation.
AEs were recorded until the end of the safety follow-up (Week 108) at the latest.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SGLT2: sodium-glucose cotransporter 2; SOC: System Organ Class

B.2 SURPASS-6 study

Table 16: Common AEsa – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin (multipage table)

Study	Patients with event n (%)	
	tirzepatide, pooled + insulin glargine ± metformin N = 584	insulin lispro + insulin glargine ± metformin N = 584
SURPASS-6		
Overall AE rate	423 (72.4)	318 (54.5)
SOC[b]		
Blood and lymphatic system disorders	15 (2.6)	12 (2.1)
Cardiac disorders	16 (2.7)	25 (4.3)
Eye disorders	12 (2.1)	17 (2.9)
Gastrointestinal disorders	260 (44.5)	51 (8.7)
General disorders and administration site conditions	48 (8.2)	37 (6.3)
Hepatobiliary disorders	15 (2.6)	10 (1.7)
Infections and infestations	136 (23.3)	161 (27.6)
Injury, poisoning and procedural complications	29 (5.0)	28 (4.8)
Investigations	51 (8.7)	30 (5.1)
Metabolism and nutrition disorders	105 (18.0)	69 (11.8)
Musculoskeletal and connective tissue disorders	50 (8.6)	62 (10.6)
Nervous system disorders	60 (10.3)	60 (10.3)
Psychiatric disorders	23 (3.9)	19 (3.3)
Renal and urinary disorders	34 (5.8)	37 (6.3)
Respiratory, thoracic and mediastinal disorders	17 (2.9)	17 (2.9)
Skin and subcutaneous tissue disorders	33 (5.7)	11 (1.9)
Surgical and medical procedures	13 (2.2)	15 (2.6)
Vascular disorders	26 (4.5)	20 (3.4)

Table 16: Common AEsa – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin (multipage table)

Study	Patients with event n (%)	
	tirzepatide, pooled + insulin glargine ± metformin N = 584	insulin lispro + insulin glargine ± metformin N = 584
PT[b]		
Abdominal distension	15 (2.6)	1 (0.2)
Abdominal pain	21 (3.6)	1 (0.2)
Abdominal pain upper	19 (3.3)	2 (0.3)
Alopecia	10 (1.7)	0 (0)
Anaemia	10 (1.7)	9 (1.5)
Arthralgia	8 (1.4)	23 (3.9)
Asthenia	10 (1.7)	3 (0.5)
Back pain	15 (2.6)	14 (2.4)
COVID 19	62 (10.6)	65 (11.1)
Constipation	26 (4.5)	1 (0.2)
Decreased appetite	77 (13.2)	1 (0.2)
Diarrhoea	80 (13.7)	15 (2.6)
Dizziness	21 (3.6)	7 (1.2)
Dyslipidaemia	7 (1.2)	13 (2.2)
Dyspepsia	57 (9.8)	4 (0.7)
Eructation	23 (3.9)	0 (0)
Flatulence	22 (3.8)	1 (0.2)
Gastritis	11 (1.9)	3 (0.5)
Gastrooesophageal reflux disease	14 (2.4)	4 (0.7)
Headache	13 (2.2)	14 (2.4)
Hyperglycaemia	6 (1.0)	15 (2.6)
Hypertension	13 (2.2)	16 (2.7)
Hypoglycaemia	3 (0.5)	25 (4.3)
Influenza	16 (2.7)	11 (1.9)
Lipase increased	16 (2.7)	6 (1.0)
Microalbuminuria	6 (1.0)	13 (2.2)
Nasopharyngitis	8 (1.4)	13 (2.2)
Nausea	124 (21.2)	7 (1.2)
Oedema peripheral	3 (0.5)	13 (2.2)
Pain in extremity	11 (1.9)	11 (1.9)
Urinary tract infection	19 (3.3)	20 (3.4)
Vomiting	59 (10.1)	4 (0.7)
Weight decreased	16 (2.7)	0 (0)

Table 16: Common AEsa – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin (multipage table)

Study	**Patients with event n (%)**	
	tirzepatide, pooled + insulin glargine ± metformin	**insulin lispro + insulin glargine ± metformin**
	N = 584	**N = 584**
a. Events that occurred in ≥ 10 patients in at least one study arm. b. MedDRA version 25.1; SOC and PT notation taken from Module 4 D without adaptation. AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class		

Table 17: Common SAEsa – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin

Study	**Patients with event n (%)**	
	tirzepatide, pooled + insulin glargine ± metformin	**insulin lispro + insulin glargine ± metformin**
	N = 584	**N = 584**
SURPASS-6		
Overall SAE rate	28 (4.8)	59 (10.1)
SOC[b]		
Infections and infestations	10 (1.7)	11 (1.9)
Metabolism and nutrition disorders	4 (0.7)	24 (4.1)
PT[b]		
Hypoglycaemia	3 (0.5)	24 (4.1)
a. Events that occurred in ≥ 10 patients in at least one study arm. b. MedDRA version 25.1; SOC and PT notation taken from Module 4 D without adaptation. MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class		

Table 18: Discontinuations due to AEs – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin (multipage table)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**tirzepatide, pooled + insulin glargine ± metformin N = 584**	**insulin lispro + insulin glargine ± metformin N = 584**
SURPASS-6		
Overall rate of discontinuations due to AEs	33 (5.7)	16 (2.7)
Gastrointestinal disorders	20 (3.4)	0 (0)
Nausea	9 (1.5)	0 (0)
Vomiting	5 (0.9)	0 (0)
Dyspepsia	2 (0.3)	0 (0)
Gastritis	2 (0.3)	0 (0)
Diarrhoea	1 (0.2)	0 (0)
Gastrooesophageal reflux disease	1 (0.2)	0 (0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0 (0)	5 (0.9)
Lung neoplasm malignant	0 (0)	2 (0.3)
Breast cancer	0 (0)	1 (0.2)
Glioblastoma	0 (0)	1 (0.2)
Oral neoplasm	0 (0)	1 (0.2)
General disorders and administration site conditions	3 (0.5)	1 (0.2)
Death	1 (0.2)	1 (0.2)
Asthenia	1 (0.2)	0 (0)
Fatigue	1 (0.2)	0 (0)
Infections and infestations	0 (0)	4 (0.7)
COVID-19	0 (0)	3 (0.5)
COVID-19 pneumonia	0 (0)	1 (0.2)
Investigations	2 (0.3)	1 (0.2)
Pancreatic enzymes increased	1 (0.2)	0 (0)
Weight decreased	1 (0.2)	0 (0)
Weight increased	0 (0)	1 (0.2)
Metabolism and nutrition disorders	3 (0.5)	0 (0)
Decreased appetite	2 (0.3)	0 (0)
Food intolerance	1 (0.2)	0 (0)

Table 18: Discontinuations due to AEs – RCT, direct comparison: tirzepatide + insulin glargine ± metformin vs. insulin lispro + insulin glargine ± metformin (multipage table)

Study	**Patients with event n (%)**	
SOC[a] PT[a]	**tirzepatide, pooled + insulin glargine ± metformin N = 584**	**insulin lispro + insulin glargine ± metformin N = 584**
Cardiac disorders	1 (0.2)	1 (0.2)
Acute coronary syndrome	1 (0.2)	0 (0)
Myocardial infarction	0 (0)	1 (0.2)
Injury, poisoning and procedural complications	1 (0.2)	1 (0.2)
Skull fracture	0 (0)	1 (0.2)
Spinal fracture	1 (0.2)	0 (0)
Endocrine disorders	1 (0.2)	0 (0)
Inappropriate antidiuretic hormone secretion	1 (0.2)	0 (0)
Musculoskeletal and connective tissue disorders	0 (0)	1 (0.2)
Back pain	0 (0)	1 (0.2)
Nervous system disorders	0 (0)	1 (0.2)
Ischaemic stroke	0 (0)	1 (0.2)
Psychiatric disorders	1 (0.2)	0 (0)
Nervousness	1 (0.2)	0 (0)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (0.2)
Respiratory failure	0 (0)	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.2)	0 (0)
Alopecia	1 (0.2)	0 (0)

a. MedDRA version 25.1; SOCs and PTs taken from Module 4 D.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class