IQWiG Reports – Commission No. A20-93

Semaglutide (type 2 diabetes mellitus) –

Benefit assessment according to §35a Social Code Book V[1] (new scientific findings)

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Semaglutid (Diabetes mellitus Typ 2) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 January 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
CI	confidence interval
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP	glucagon-like peptide
HbA1c	glycosylated haemoglobin A1c
IQWIG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PG	plasma glucose
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SF-36v2	Short Form 36 – version 2 Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
SGLT-2	sodium glucose co-transporter 2
SMQ	Standardized MedDRA Query
SPC	Summary of Product Characteristics
TIA	transient ischaemic attack

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug semaglutide. The pharmaceutical company (hereinafter referred to as "the company") submitted a first dossier for the early benefit assessment of the drug to be assessed on 30 October 2018. This benefit assessment was based on the results of the SUSTAIN 6 study on the subcutaneous administration of semaglutide. The G-BA has now requested a new benefit assessment because of new scientific findings including studies on oral administration, in particular the cardiovascular outcome study PIONEER 6. The present benefit assessment is based on a dossier compiled by the company, taking into account all available results for both administration forms. The dossier was sent to IQWiG on 2 November 2020.

Research question

The aim of the present report is the assessment of the added benefit of semaglutide in comparison with the appropriate comparator therapy (ACT) for the treatment of adults with type 2 diabetes mellitus in the following approved subindications:

- Monotherapy: in patients in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications.
- Combination therapy with other drugs for the treatment of diabetes mellitus: In patients in whom diet and exercise and treatment with other blood-glucose lowering drugs do not provide adequate glycaemic control.

In its specification of the ACT, the G-BA distinguished between different patient groups. This resulted in 4 research questions for the assessment, which are presented in Table 2.

Table 2: Research questions of the benefit assessment of semaglutide

Research question	Subindication[a]	ACT[b]
A	Monotherapy in adults in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications	▪ Sulfonylurea (glibenclamide or glimepiride)
B	Combination therapy in adults in whom diet and exercise and treatment with 1 other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control	▪ **Metformin + sulfonylurea (glibenclamide or glimepiride)** or ▪ **metformin + empagliflozin** or ▪ metformin + liraglutide[c] or ▪ human insulin[d]
C	Combination therapy in adults in whom diet and exercise and treatment with at least 2 other blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control	▪ **Human insulin + metformin** or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ **human insulin[e]**
D	Combination therapy in adults in whom diet and exercise and treatment with insulin (with or without 1 other blood-glucose lowering drug) do not provide adequate glycaemic control	▪ Optimization of the human insulin regimen (if applicable + metformin or empagliflozin[c] or liraglutide[c])

a. Subdivision of the therapeutic indication according to the G-BA.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of the cardiovascular risk factors, in particular antihypertensives, anticoagulants and/or lipid-lowering agents (for information on the operationalization see study protocols of the relevant studies for empagliflozin or liraglutide).
d. If metformin is contraindicated or not tolerated according to the SPC.
e. If, according to the SPC, metformin, empagliflozin[d] or liraglutide are contraindicated or not tolerated or are not sufficiently effective due to advanced type 2 diabetes mellitus.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

In its specification of the ACT options, the company followed the respective specification of the G-BA for the research questions presented in Table 2.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results for research question A: Monotherapy with semaglutide

In its dossier, the company provided no relevant data for the assessment of semaglutide as monotherapy in adults with type 2 diabetes mellitus in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due

to intolerance or contraindication. This resulted in no hint of an added benefit of semaglutide in comparison with the ACT. An added benefit is therefore not proven.

Results for research question B: semaglutide in combination with 1 other blood-glucose lowering drug (except insulin)

Semaglutide in combination with metformin

The study pool for the benefit assessment of semaglutide in adults in whom diet and exercise and treatment with 1 other blood-glucose lowering drug do not provide adequate glycaemic control consists of study NN9924-4223 (hereinafter referred to as PIONEER 2). The study compares semaglutide with empagliflozin, each in combination with metformin.

Study characteristics

The PIONEER 2 study is a 2-arm, randomized, active-controlled, unblinded study with a treatment duration of 52 weeks. The study included adults with type 2 diabetes mellitus who had inadequate glycaemic control despite at least 90 days of pretreatment with ≥ 1500 mg/day of metformin at unchanged doses. The proportion of glycosated haemoglobin (HbA1c value) had to range between ≥ 7.0% and ≤ 10.5% at baseline.

In accordance with the planning of the study, patients with cardiovascular disease or at high cardiovascular risk were not categorically excluded from the PIONEER 2 study. Patients with class IV cardiac failure according to the classification of the New York Heart Association (NYHA) were explicitly excluded (as defined in accordance with the approval), as were patients who had myocardial infarction, stroke or hospitalization due to unstable angina pectoris or transient ischaemic attack (TIA) within 180 days prior to study inclusion, and patients who had already been scheduled for coronary, peripheral or carotid revascularization at the time of screening. Patients with cardiovascular disease who did not meet any of these exclusion criteria and patients at high cardiovascular risk could be included in the study.

The PIONEER 2 study investigated the comparison of semaglutide with empagliflozin, each in combination with metformin (hereafter referred to as "semaglutide + metformin" or "empagliflozin + metformin"). Metformin was continued during the study, whereby the stable dose before the start of the study was maintained. For the study, a total of 821 patients were randomly assigned to treatment with semaglutide + metformin (N = 411) or empagliflozin + metformin (N = 410). Stratification was not performed.

In PIONEER 2, treatment with semaglutide and empagliflozin was essentially carried out in accordance with the respective Summary of Product Characteristics (SPCs).

Primary outcome of the study was the change in HbA1c after 26 weeks compared with baseline. Patient-relevant secondary outcomes were "all-cause mortality" and outcomes on morbidity, health-related quality of life and adverse events (AEs).

Risk of bias and overall assessment of the certainty of conclusions

The risk of bias across outcomes was rated as low for PIONEER 2. Due to the lack of blinding in subjective recording of outcomes or subjective request for treatment discontinuation, the risk of bias at outcome level was rated as high for the outcomes "health-related quality of life" measured using the Short Form 36 – version 2 Health Survey (SF-36v2), "discontinuation due to AEs", "symptomatic confirmed hypoglycaemia (plasma glucose [PG] < 56 mg/dL)", "genital infection", "urinary tract infection" and other specific AEs. At most hints, e.g. of an added benefit, can therefore be determined for these outcomes. For all other outcomes, the risk of bias was rated as low and at most indications can be derived.

Results

Mortality

- All-cause mortality

There was no statistically significant difference between the treatment groups for the outcome "all-cause mortality". This resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin; an added benefit is therefore not proven.

Morbidity

- Acute coronary syndrome

For the outcome "acute coronary syndrome", PIONEER 2 provides no usable data for a comparison of semaglutide + metformin with empagliflozin + metformin. This resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin; an added benefit is therefore not proven.

- Cerebrovascular event

A statistically significant difference in favour of semaglutide + metformin in comparison with empagliflozin + metformin was shown for the outcome "cerebrovascular event". This resulted in an indication of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin.

- Hospitalization due to cardiac failure

No statistically significant difference between the treatment groups was shown for the outcome "hospitalization due to cardiac failure". This resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin; an added benefit is therefore not proven.

- Renal disorders

For the outcome "renal disorders", operationalized using the Preferred Term (PT) "acute kidney injury" (serious adverse event [SAE]), there is no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin; an added benefit is therefore not proven.

- Diabetic retinopathies

For the outcome "diabetic retinopathies", PIONEER 2 provides no usable data for a comparison of semaglutide + metformin with empagliflozin + metformin. This resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin; an added benefit is therefore not proven.

Health-related quality of life

- SF-36v2 – Physical and Mental Component Summary

Based on the mean difference, a statistically significant difference to the disadvantage of semaglutide + metformin in comparison with empagliflozin + metformin was shown for the Physical Component Summary of the SF-36v2. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. However, the 95% confidence interval (CI) was not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the effect is relevant. No statistically significant difference between the treatment groups was shown for the Mental Component Summary of the SF-36v2. Overall, this resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin for the outcome "health-related quality of life measured with the SF-36v2"; an added benefit is therefore not proven.

Side effects

- SAEs, symptomatic confirmed hypoglycaemia (PG < 56 mg/dL), severe hypoglycaemia, acute pancreatitis, urinary tract infection, diabetic ketoacidosis

For the outcomes "SAEs", "symptomatic confirmed hypoglycaemia (PG < 56 mg/dl)", "acute pancreatitis", "urinary tract infection" and "diabetic ketoacidosis", there was no statistically significant difference between the treatment groups; for the outcome "severe hypoglycaemia", no events occurred in the PIONEER 2 study. Hence, there was no hint of greater or lesser harm from semaglutide + metformin in comparison with empagliflozin + metformin for each of these outcomes; greater or lesser harm is therefore not proven.

- Discontinuation due to AEs, specific AEs: gastrointestinal disorders (including: nausea)

For the outcomes "discontinuation due to AEs" and "gastrointestinal disorders (including nausea)", there was a statistically significant difference to the disadvantage of semaglutide + metformin in comparison with empagliflozin + metformin. Due to the high risk of bias, this resulted in a hint of greater harm from semaglutide + metformin in comparison with empagliflozin + metformin for each of these outcomes.

- Symptomatic confirmed hypoglycaemia (PG ≤ 70 mg/dL)

For the outcome "symptomatic confirmed hypoglycaemia (PG ≤ 70 mg/dL)", PIONEER 2 provides no usable data for a comparison of semaglutide + metformin with empagliflozin + metformin. This resulted in no hint of greater or lesser harm from semaglutide + metformin in comparison with empagliflozin + metformin; greater or lesser harm is therefore not proven.

- Genital infection

A statistically significant difference in favour of semaglutide + metformin in comparison with empagliflozin + metformin was shown for the outcome "genital infection". Due to the high risk of bias, this resulted in a hint of lesser harm from semaglutide + metformin in comparison with empagliflozin + metformin for the outcome „genital infection".

Semaglutide in combination with 1 other blood-glucose lowering drug (except metformin and insulin)

In its dossier, the company presented no relevant data for the combination of semaglutide with 1 other blood glucose-lowering drug (except metformin and insulin). This resulted in no hint of an added benefit of semaglutide in comparison with the ACT. An added benefit is therefore not proven.

Results for research question C: Semaglutide in combination with at least 2 other blood-glucose lowering drugs (except insulin)

In its dossier, the company provided no relevant data for the assessment of semaglutide in combination therapy in adults with type 2 diabetes mellitus in whom diet and exercise and treatment with at least 2 other blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control. This resulted in no hint of an added benefit of semaglutide in comparison with the ACT. An added benefit is therefore not proven.

Results for research question D: Semaglutide in combination with insulin (with or without 1 other blood glucose-lowering drug)

In its dossier, the company provided no relevant data for the assessment of semaglutide in combination therapy in adults with type 2 diabetes mellitus in whom diet and exercise and treatment with insulin (with or without 1 other blood-glucose lowering drug) do not provide adequate glycaemic control. This resulted in no hint of an added benefit of semaglutide in comparison with the ACT. An added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Based on the results presented, probability and extent of the added benefit of the drug semaglutide in comparison th the ACT are assessed as follows:

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Research question A: Monotherapy with semaglutide

As there are no relevant data for the assessment of the added benefit of semaglutide as monotherapy versus the ACT in adults with type 2 diabetes mellitus in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindication, an added benefit of semaglutide is not proven in this research question.

Research question B: semaglutide in combination with 1 other blood-glucose lowering drug (except insulin)

Semaglutide in combination with metformin

The overall consideration showed both positive and negative effects of semaglutide + metformin versus empagliflozin + metformin. The PIONEER 2 study was not designed to record patient-relevant cardiovascular outcomes and is therefore not suitable for this purpose. Accordingly, the positive effect for the outcome "cerebrovascular-related events" was only based on isolated patients with an event. Although the positive effect for the outcome "genital infection" was based on a larger proportion of patients with an event, there were also negative effects with the extent "considerable" for the outcome "gastrointestinal disorders" and the PT "nausea" contained therein. These events also contribute significantly to the negative effect for the outcome "discontinuation due to AEs".

In summary, an added benefit of semaglutide + metformin versus empagliflozin + metformin is not proven for adults with type 2 diabetes mellitus in whom diet and exercise and treatment with 1 other blood-glucose lowering drug (other than insulin) do not provide adequate glycaemic control.

Semaglutide in combination with 1 other blood-glucose lowering drug (except metformin and insulin)

Due to a lack of relevant data, an added benefit of semaglutide versus the ACT is not proven for semaglutide in combination with 1 other blood glucose-lowering drug (except metformin and insulin).

Research question C: Semaglutide in combination with at least 2 other blood-glucose lowering drugs (except insulin)

As there are no relevant data for the assessment of the added benefit of semaglutide in combination therapy versus the ACT in adults with type 2 diabetes mellitus in whom diet and exercise and treatment with at least 2 other blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control, an added benefit of semaglutide is not proven in this research question.

Research question D: Semaglutide in combination with insulin (with or without 1 other blood glucose-lowering drug)

As there are no relevant data for the assessment of the added benefit of semaglutide in combination therapy versus the ACT in adults with type 2 diabetes mellitus in whom diet and exercise and treatment with insulin (with or without 1 other blood-glucose lowering drug) do not provide adequate glycaemic control, an added benefit of semaglutide is not proven in this research question.

Summary

Table 3 shows a summary of probability and extent of the added benefit of semaglutide.

Table 3: Semaglutide – probability and extent of the added benefit in type 2 diabetes mellitus in adults

Research question	**Subindication**[a]	**ACT**[b]	**Probability and extent of added benefit**
A	Monotherapy in adults in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications	▪ Sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Combination therapy in adults in whom diet and exercise and treatment with 1 other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control	▪ **Metformin + sulfonylurea (glibenclamide or glimepiride) or** ▪ **metformin + empagliflozin** or ▪ metformin + liraglutide[c] or ▪ human insulin[d]	Added benefit not proven
C	Combination therapy in adults in whom diet and exercise and treatment with at least 2 other blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control	▪ **Human insulin + metformin** or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ **human insulin**[e]	Added benefit not proven
D	Combination therapy in adults in whom diet and exercise and treatment with insulin (with or without 1 other blood-glucose lowering drug) do not provide adequate glycaemic control	▪ Optimization of the human insulin regimen (if applicable + metformin or empagliflozin[c] or liraglutide[c])	Added benefit not proven

a. Subdivision of the therapeutic indication according to the G-BA.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of the cardiovascular risk factors, in particular antihypertensives, anticoagulants and/or lipid-lowering agents (for information on the operationalization see study protocols of the relevant studies for empagliflozin or liraglutide).
d. If metformin is contraindicated or not tolerated according to the SPC.
e. If, according to the SPC, metformin, empagliflozin[d] or liraglutide are contraindicated or not tolerated or are not sufficiently effective due to advanced type 2 diabetes mellitus.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Research question additionally investigated by the company (PIONEER 6 and SUSTAIN 6 studies)

In its dossier, the company investigated an additional research question E: Semaglutide in addition to standard therapy in the treatment of adult patients with type 2 diabetes mellitus and high cardiovascular risk in comparison with placebo in addition to a standard therapy. Thereby, the company defined standard therapy as antiglycaemic treatment according to the local standard based on individual goals of the high-risk population as well as the individual therapy of the cardiovascular disease. The company presented the SUSTANIN 6 study and the PIONEER 6 study for this research question. In its dossier, the company had already submitted the SUSTAIN 6 study for the early benefit assessment on 30 October 2018 (see dossier assessment A18-75).

PIONEER 6 is a randomized, placebo-controlled, double-blind study. Like the SUSTAIN 6 study, PIONEER 6 included adult patients with type 2 diabetes mellitus and a high cardiovascular risk. Thereby, the study investigated treatment with semaglutide in addition to ongoing antidiabetic standard therapy versus standard diabetes treatment.

Adult patients with type 2 diabetes mellitus and high cardiovascular risk are comprised by the therapeutic indication of semaglutide and therefore as a subgroup by the research questions mentioned above of the present benefit assessment. Therefore, the added benefit versus the respective ACT has to be proven also for these subpopulations. The company presented no such analyses, but due to the way they were conducted the PIONEER 6 and SUSTAIN 6 studies are not suitable for this purpose anyway.

However, due to the way they were conducted these two studies are also unsuitable for the comparison with standard therapy intended by the company:

- Blood glucose-lowering treatment was inadequate in a large proportion of patients. Adequate treatment escalation, particularly in the placebo arm, was not observed in both studies despite existing need of escalation of the patients. The available escalation options were not exhausted, although this was planned according to the study protocol. Moreover, it should be added that patients in SUSTAIN 6 were systematically under-treated with the comparator therapy during the first 12 weeks of the study.
- The large proportion of hypertensive patients whose systolic blood pressure was above the threshold value of 140 mmHg over the course of the study suggests that the options of drug adjustment to lower systolic blood pressure were not exhausted.

Moreover, with regard to blood-glucose lowering therapy, drugs defined by the G-BA as part of the ACT for patients at increased cardiovascular risk (empagliflozin, liraglutide), were hardly used in both studies.

Overall, it can therefore not be assumed for both aspects (blood-glucose lowering therapy, concomitant cardiovascular treatment) that the therapy used in the comparator group was an appropriate standard therapy.

2.2 Research question

The aim of the present report is the assessment of the added benefit of semaglutide in comparison with the ACT for the treatment of adults with type 2 diabetes mellitus in the following approved subindications:

- Monotherapy: in patients in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications.
- Combination therapy with other drugs for the treatment of diabetes mellitus: In patients in whom diet and exercise and treatment with other blood-glucose lowering drugs do not provide adequate glycaemic control.

In its specification of the ACT, the G-BA distinguished between different patient groups. This resulted in 4 research questions, which are presented in Table 4.

Table 4: Research questions of the benefit assessment of semaglutide

Research question	Subindication[a]	ACT[b]
A	Monotherapy in adults in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications	▪ Sulfonylurea (glibenclamide or glimepiride)
B	Combination therapy in adults in whom diet and exercise and treatment with 1 other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control	▪ **Metformin + sulfonylurea (glibenclamide or glimepiride) or** ▪ **metformin + empagliflozin** or ▪ metformin + liraglutide[c] or ▪ human insulin[d]
C	Combination therapy in adults in whom diet and exercise and treatment with at least 2 other blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control	▪ **Human insulin + metformin** or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ **human insulin[e]**
D	Combination therapy in adults in whom diet and exercise and treatment with insulin (with or without 1 other blood-glucose lowering drug) do not provide adequate glycaemic control	▪ Optimization of the human insulin regimen (possibly + metformin or empagliflozin[c] or liraglutide[c])

a. Subdivision of the therapeutic indication according to the G-BA.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of the cardiovascular risk factors, in particular antihypertensives, anticoagulants and/or lipid-lowering agents (for information on the operationalization see study protocols of the relevant studies for empagliflozin [3] or liraglutide [4]).
d. If metformin is contraindicated or not tolerated according to the SPC.
e. If, according to the SPC, metformin, empagliflozin or liraglutide are contraindicated or not tolerated or are not sufficiently effective due to advanced type 2 diabetes mellitus.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics

In its specification of the ACT options, the company followed the respective specification of the G-BA for the research questions presented in Table 4.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Choice of the ACT by the company

When choosing from the ACT options, the company first named all options specified by the G-BA. In its information on the research question, it restricted the patient populations for research questions B to D to patients without cardiovascular diseases. Accordingly, it did not take into account the ACT options that could have been considered for patients with cardiovascular

diseases: metformin in combination with liraglutide (research question B), human insulin in combination with empagliflozin or liraglutide (research question C) and optimization of the human insulin regime with additional administration of empagliflozin or liraglutide (research question D).

Moreover, for the intervention, the company assumed a combination of semaglutide with metformin for research question B, which is why, in its view, human insulin cannot be considered as an option for the ACT, as this is only suitable in the case of metformin intolerance or contraindication. The company presented no data for semaglutide in combination with other blood glucose-lowering drugs (except metformin and insulin).

The restriction of the ACT options by the company has no consequence for the benefit assessment insofar as the comparator therapy in the PIONEER 2 study presented by it corresponds to the ACT (see Section 2.4). No relevant studies are available for research questions A, C and D (see Sections 2.3, 2.5 and 2.6).

Deviating from the company's approach, the population relevant for the benefit assessment is not limited to patients without cardiovascular diseases. These patients are included in the therapeutic indication of semaglutide and thus as subgroups in the research questions mentioned above.

Research question additionally investigated by the company

In its dossier, the company investigated an additional research question E: Semaglutide in addition to standard therapy in the treatment of adult patients with type 2 diabetes mellitus and high cardiovascular risk, in whom diet and exercise do not provide adequate glycaemic control, versus placebo in addition to standard therapy. Thereby, the company defined standard therapy as individual background therapy for both type 2 diabetes mellitus and macrovascular concomitant diseases according to the corresponding National Health Care Guideline. For this research question, the company presented the studies PIONEER 6 [5-7] and SUSTAIN 6 [8-13].

Adult patients with type 2 diabetes mellitus and high cardiovascular risk are comprised by the therapeutic indication of semaglutide and therefore as a subgroup by all research questions of the present benefit assessment mentioned above. Therefore, the added benefit versus the respective ACT has to be proven also for this subpopulation. The company presented no such analyses, but due to the way they were conducted the PIONEER 6 and SUSTAIN 6 studies are not suitable for this purpose anyway. Moreover, the study is also unsuitable for the comparison with standard therapy intended by the company (see Appendix A of the full dossier assessment).

Due to the size and the outcomes investigated (particularly cardiovascular events and all-cause mortality), the studies PIONEER 6 and SUSTAIN 6 are described in Appendix A of the full dossier assessment.

2.3 Research question A: Monotherapy with semaglutide

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on semaglutide (status: 2 September 2020)
- bibliographical literature search on semaglutide (last search on 3 August 2020)
- search in trial registries/trial results databases for studies on semaglutide (last search on 24 August 2020)
- search on the G-BA website for semaglutide (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on semaglutide (last search on 11 November 2020)

The check of the completeness of the study pool identified no RCTs on the direct comparison of semaglutide versus the ACT for research question A: (Monotherapy with semaglutide). This assessment concurs with that of the company.

2.3.2 Results on added benefit

In its dossier, the company provided no relevant data for the assessment of semaglutide as monotherapy in adults with type 2 diabetes mellitus in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindication. This resulted in no hint of an added benefit of semaglutide in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

As there are no relevant data for the assessment of the added benefit of semaglutide as monotherapy versus the ACT in adults with type 2 diabetes mellitus in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindication, an added benefit of semaglutide is not proven in this research question. This assessment concurs with that of the company.

2.4 Research question B: semaglutide in combination with 1 other blood-glucose lowering drug (except insulin)

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on semaglutide (status: 2 September 2020)
- bibliographical literature search on semaglutide (last search on 3 August 2020)
- search in trial registries/trial results databases for studies on semaglutide (last search on 24 August 2020)
- search on the G-BA website for semaglutide (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on semaglutide (last search on 11 November 2020)

The check did not identify additional relevant studies investigating semaglutide in combination with metformin.

2.4.1.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] yes/no [citation])
NN9924-4223 (PIONEER 2[d])	Yes	Yes	No	No[e]	Yes [14,15]	Yes [16,17]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website.
d. Hereinafter, the study is referred to with this abbreviated form.
e. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the benefit assessment of semaglutide in adults in whom diet and exercise and treatment with 1 other blood-glucose lowering drug do not provide adequate glycaemic control consists of study NN9924-4223 (hereafter referred to as PIONEER 2). The study compares semaglutide with empagliflozin, each in combination with metformin. The study pool concurs with that of the company.

The company presented no relevant studies for the combination of semaglutide with 1 other blood glucose-lowering drug (except metformin and insulin) within research question B.

2.4.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PIONEER 2	RCT, unblinded, parallel	Adults (≥ 18 years) with inadequately controlled type 2 diabetes mellitus with ▪ stable metformin dose (≥ 1500 mg/day or maximum tolerated dose) ≥ 90 days prior to study inclusion ▪ HbA1c: ≥ 7.0% and ≤ 10.5% ▪ eGFR ≥ 60 mL/min/1.73 m²	Semaglutide + metformin (N = 411[b]) empagliflozin + metformin (N = 410)	Screening: 2 weeks treatment: 52 weeks (the first 8 weeks thereof being dose escalation) follow-up: 5 weeks	108 centres in Argentina, Brazil, Croatia, Greece, Hungary, Italy, Poland, Russia, Serbia, Spain, Thailand, USA 08/2016–03/2018 first data cut-off: 2 May 2018 second data cut-off: 5 July 2018	Primary: change in HbA1c at week 26 secondary: mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. 1 individual in the intervention arm was enrolled and randomized at 2 different study centers. The analysis only considered data from the first randomization.

AE: adverse event; eGFR: estimated glomerular filtration rate; HbA1c: glycosylated haemoglobin A1c; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study	Intervention	Comparison
PIONEER 2	Semaglutide 14 mg orally[a], once daily + metformin ≥ 1500 mg orally, daily, or maximum tolerated dose[b] semaglutide dose escalation: ▪ starting dose (week 0 to 4): 3 mg/day ▪ escalation (week 5 to 8): 7 mg/day ▪ maintenance dose (from week 9 onwards): 14 mg/day	Empagliflozin 25 mg orally[c] once daily + metformin ≥ 1500 mg orally, daily, or maximum tolerated dose[b] empagliflozin dose escalation: ▪ starting dose (week 0 to 8): 10 mg/day ▪ maintenance dose (from week 9 onwards): 25 mg/day[c]
	Pretreatment ▪ metformin at a stable dose for ≥ 90 days before study inclusion **Non-permitted pretreatment** ▪ additional drugs for the treatment of diabetes or obesity within 90 days before study inclusion, except for short-term treatment (≤ 14 days) with insulin for acute disease **Concomitant treatment** ▪ in case of persistent unacceptable hyperglycaemia[d], intensification of the background antidiabetic therapy and/or initiation of new antidiabetic drugs[e] was allowed from week 8 onwards	

a. Dose adjustments after dose escalation were not allowed during the study.
b. Maintenance of the stable dose at study inclusion; dose adjustment allowed in case of persistent unacceptable hyperglycaemia or safety concerns (up to the highest locally approved dosage).
c. For patients who tolerated empagliflozin and had an eGFR ≥ 60 mL/min/1.73 m², the dose was increased to a maintenance dose of 25 mg/day from week 9 onwards. During the study, dose reduction to 10 mg/day was allowed for patients in whom eGFR persistently reached values < 60 mL/min/1.73 m². If the eGFR value improved, the dose could be re-escalated during the study.
d. Depending on the time point within the study, defined as:
   ▫ week 8 to 13: FPG > 260 mg/dL
   ▫ week 14 to 25: FPG > 240 mg/dL
   ▫ from week 26 onwards: FPG > 200 mg/dL or HbA1c > 8.5%.
e. According to the investigator's assessment (GLP-1 receptor agonists, DPP-4 inhibitors and amylin analogues in the intervention arm or SGLT-2 inhibitors in the comparator arm).

DPP-4: dipeptidyl peptidase-4; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; GLP-1: glucagon-like peptide 1; HbA1c: glycosylated haemoglobin; RCT: randomized controlled trial; SGLT-2: sodium glucose co-transporter 2

Study characteristics

The PIONEER 2 study is a randomized, active-controlled, unblinded study with a treatment duration of 52 weeks. The study included adults with type 2 diabetes mellitus who had inadequate glycaemic control despite at least 90 days of pretreatment with ≥ 1500 mg/day of metformin at unchanged doses. The HbA1c value had to range between ≥ 7.0% and ≤ 10.5% at baseline.

In accordance with the planning of the study, patients with cardiovascular disease or at high cardiovascular risk were not categorically excluded from the PIONEER 2 study. Patients with

class IV cardiac failure according to the classification of the NYHA were generally excluded (as defined in accordance with the approval), as were patients who had myocardial infarction, stroke or hospitalization due to unstable angina pectoris or TIA within 180 days prior to study inclusion, and patients who had already been scheduled for coronary, peripheral or carotid revascularization at the time of screening. Patients with cardiovascular diseases who did not meet any of these exclusion criteria and patients at high cardiovascular risk could be included in the study.

The PIONEER 2 study investigated the comparison of semaglutide with empagliflozin, each in combination with metformin (hereafter referred to as "semaglutide + metformin" or "empagliflozin + metformin"). Metformin was continued during the study, whereby the stable dose before the start of the study was maintained. For the study, a total of 821 patients were randomly assigned to treatment with semaglutide + metformin (N = 411) or empagliflozin + metformin (N = 410) in a 1:1 ratio. Stratification was not performed.

Primary outcome of the study was the change in HbA1c after 26 weeks compared with baseline. Patient-relevant secondary outcomes were "all-cause mortality" and outcomes on morbidity, health-related quality of life and AEs.

Treatment with the study medication

In the PIONEER 2 study, administration of semaglutide and empagliflozin largely complied with the requirements of the SPC [18,19]. During the course of the study, the dose was increased to the respective approved maximum dose according to a fixed escalation schedule for both semaglutide and empagliflozin. Compared to the respective specifications according to the approval, the mandatory dose increase for all patients represents a forced therapy regimen. For semaglutide, the dose was increased from 3 mg/day to 7 mg/day and then to the maximum approved dose of 14 mg/day at 4-week intervals. According to the SPC [19], an increase in the daily dose of semaglutide from 7 mg to 14 mg is to be understood as an option to further improve glycaemic control. For empagliflozin, the starting dose of 10 mg/day was increased to the maximum approved dose of 25 mg/day after 8 weeks in patients who tolerated empagliflozin and had an estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m². According to the SPC [18], increase of the daily empagliflozin dose of 25 mg is also an option if tighter glycaemic control is needed. There is no information on whether there was need for further improvement of glycaemic control or tighter glycaemic control for the patients included before an increase to the maximum dose could be performed in the PIONEER 2 study.

For patients in PIONEER 2, both study arms were scheduled to continue their respective metformin therapy at a dosage of ≥ 1500 mg/day up to the locally approved maximum dosage, which is 3000 mg/day in Germany [20], in addition to the study medication. In Module 4 B of its dossier, the company addresses no information on the metformin dose the patients received in the PIONEER 2 study.

In case of persistent unacceptable hyperglycaemia, adjustments of the concomitant antidiabetic treatment following the escalation phase were allowed in the PIONEER 2 study (see Table 7). Concomitant antidiabetic treatment was to be adjusted at the investigator's discretion and according to local guidelines and standards, and was to be administered in addition to the study medication. The use of glucagon-like peptide (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors and amylin analogues was not allowed in the intervention arm, and sodium glucose co-transporter 2 (SGLT-2) inhibitors were prohibited in the comparator arm.

Patient characteristics

Table 8, Table 9 and Table 10 show the characteristics of the patients in the study included.

Table 8: Characteristics of the study population – RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study Characteristic Category	Semaglutide + metformin N = 411	Empagliflozin + metformin N = 410
PIONEER 2		
Age [years], mean (SD)	57 (10)	58 (10)
Sex [F/M], %	50/50	49/51
Family origin, n (%)		
Caucasian	355 (86)	353 (86)
African American	26 (6)	33 (8)
Asian	28 (7)	21 (5)
Other	2 (< 1)	3 (< 1)
Region, n (%)		
Europe	221 (54)	204 (50)
North America	115 (28)	127 (31)
South America	52 (13)	61 (15)
Asia	23 (6)	18 (4)
Body weight [kg], mean (SD)	91.9 (20.5)	91.3 (20.1)
BMI [kg/m²], mean (SD)	32.9 (6.3)	32.8 (5.9)
Duration of diabetes [years], mean (SD)	7.2 (5.8)	7.7 (6.3)
HbA1c [%], mean (SD)	8.1 (0.9)	8.1 (0.9)
HbA1c [%], n (%)		
≤ 7.5	134 (33)	131 (32)
> 7.5 – ≤ 8.0	94 (23)	98 (24)
> 8.0 – ≤ 8.5	55 (13)	58 (14)
> 8.5 – ≤ 9.0	51 (12)	47 (12)
> 9.0	77 (19)	76 (19)
FPG [mg/dL], mean (SD)	171.5 (41.8)	174.0 (45.2)
Treatment discontinuation, n (%)	73 (18)	45 (11)
Study discontinuation, n (%)	12 (3)	23 (6)

BMI: body mass index; FPG: fasting plasma glucose; F: female; HbA1c: glycosylated haemoglobin; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation

Table 9: Data on cardiovascular diseases or risk factors at study inclusion - RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study Characteristic	Patients with cardiovascular disease or cardiovascular risk factor[a] n (%)	
	Semaglutide + metformin N = 411	Empagliflozin + metformin N = 410
PIONEER 2		
Ischaemic heart disease	57 (14)	46 (11)
Myocardial infarction	29 (7)	22 (5)
Percutaneous coronary intervention	28 (7)	17 (4)
Bypass surgery	8 (2)	8 (2)
Cardiac failure	22 (5)	16 (4)
Left ventricular systolic dysfunction	4 (< 1)	6 (1)
Left ventricular diastolic dysfunction	6 (1)	15 (4)
Hypertension	298 (73)	305 (74)
Stroke	10 (2)	8 (2)
Transient ischaemic attack	4 (< 1)	8 (2)
Peripheral arterial disease in the upper or lower extremities	14 (3)	19 (5)

a. Several cardiovascular diseases or risk factors could be documented per patient.

n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial

Table 10: Information on the concomitant antidiabetic medication – RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study Characteristic Drug class Drug	Patients with concomitant antidiabetic medication n (%)	
	Semaglutide + metformin N = 411	Empagliflozin + metformin N = 410
PIONEER 2		
Concomitant medication at baseline		
Biguanide	411 (100)	410 (100)
Metformin	307 (75)	315 (77)
Metformin hydrochloride	104 (25)	95 (23)
Concomitant medication during the study[a]		
Additional medication[b]/rescue medication	52 (13)/31 (8)	56 (14)/44 (11)
Sulfonylureas	34 (8)/21 (5)	41 (10)/36 (9)
Biguanide	3 (< 1)/3 (< 1)	9 (2)/8 (2)
Insulin, short-acting	2 (< 1)/0 (0)	0 (0)/0 (0)
Insulin, intermediate-acting	6 (1)/3 (< 1)	1 (< 1)/0 (0)
Insulin, long-acting	6 (1)/4 (< 1)	2 (< 1)/1 (< 1)
DPP-4 inhibitors	5 (1)/0 (0)	5 (1)/3 (< 1)
GLP-1 receptor agonists	1 (< 1)/0 (0)	3 (< 1)/1 (< 1)
SGLT 2 inhibitors	3 (< 1)/1 (< 1)	4 (< 1)/0 (0)
Thiazolidinedione	0 (0)/0 (0)	1 (< 1)/0 (0)

a. Additional medication or intensification of ongoing medication (dose increase > 20%) within the planned treatment phase (from randomization to week 52); short-term administration of antidiabetic medication (≤ 21 days) was not considered as additional medication or rescue medication.
b. Includes both rescue medication administered in addition to the study medication and medication initiated after premature discontinuation of the study medication.

DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1; N: number of randomized patients; RCT: randomized controlled trial; SGLT-2: sodium glucose cotransporter 2

The demographic and clinical characteristics of the patients were largely balanced between the individual study arms.

The mean age of the patients in both study arms was 58 years. Half of the study population in both study arms were women. The mean HbA1c value at baseline was 8.1% in both study arms. In the intervention arm, slightly more patients (18%) discontinued the study medication than in the comparator arm (11%).

73% of the patients had hypertension at study inclusion. The proportion of patients with ischaemic heart disease was 13%. The further cardiovascular events were each present in up to 7% of the patients.

About 15% of the patients received additional antidiabetic medication during the study. Thereby, sulfonylureas were used most frequently (in 10% of the patients). During the course of the study, further antidiabetic drugs were only administered in isolated cases.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11:Risk of bias across outcomes (study level) - RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
PIONEER 2	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for PIONEER 2. This concurs with the company's assessment.

Limitations resulting from the unblinded study design are described in Section 2.4.2.2 under the outcome-specific risk of bias.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Acute coronary syndrome
  - Cerebrovascular event
  - Hospitalization due to cardiac failure
  - Renal disorders
  - Diabetic retinopathies
- Health-related quality of life
  - Measured using the SF-36v2

- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Symptomatic confirmed hypoglycaemia
    - PG < 56 mg/dL
    - PG ≤ 70 mg/dL
  - Severe hypoglycaemia (SAE)
  - Pancreatitis acute
  - Genital infections
  - Urinary tract infection (PT, AE)
  - Diabetic ketoacidosis (PT, SAE)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 B). The outcomes “change in HbA1c”, “change in body weight” and “change in body mass index (BMI)” are presented as supplementary information in this benefit assessment.

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of the outcomes – RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study	Outcomes																
	All-cause mortality	Acute coronary syndrome[a]	Cerebrovascular event[b]	Hospitalization due to cardiac failure	Renal disorders[c]	Diabetic retinopathies	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Symptomatic confirmed hypoglycaemia (PG < 56 mg/dL)	Symptomatic confirmed hypoglycaemia (PG ≤ 70 mg/dL)	Severe hypoglycaemia (SAEs)	Pancreatitis acute[d]	Genital infection[e]	Urinary tract infection (PT, AE)	Diabetic ketoacidosis (PT, SAE)	Further specific AEs[f]
PIONEER 2	Yes	No[g]	Yes	Yes	Yes	No[g]	Yes	Yes	Yes	Yes	No[h]	Yes	Yes	Yes	Yes	Yes	Yes

a. Comprises the following adjudicated events: acute myocardial infarction (STEMI or NSTEMI), silent myocardial infarction or hospitalization due to unstable angina pectoris.
b. Comprises the following adjudicated events: ischaemic or haemorrhagic stroke, stroke of unknown cause or TIA.
c. Deviating from the company, the outcome is based on the operationalization using the following events (MedDRA coding): "acute kidney injury (PT, SAEs)"; for explanation see Section 2.4.2.3. Moreover, deviating from the company, the outcome is assigned to the category "morbidity".
d. Deviating from the company, the outcome is based on the operationalization using adjudicated events based on 2 of 3 of the following criteria: 1st: abdominal pain characteristic for acute pancreatitis, 2nd: 3-fold increase in serum amylase and/or serum lipase, and 3rd: typical signs of pancreatitis acute by means of imaging techniques; for explanation see Section 2.4.2.3.
e. Post-hoc analysis on mycotic infections based on a PT/LLT collection compiled by the company based on the FDA approval of empagliflozin (MedDRA coding: balanitis, balanitis due to candida, balanoposthitis, candidiasis of the genital organs, genital infection, infection of the penis, infection of the urogenital tract, bacterial colpitis, fungal infection of the genital organs, fungal infection of the urogenital tract, scrotal abscess, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal fungal infection, vulvovaginitis, cervicitis).
f. The following events (MedDRA coding) are considered: "gastrointestinal disorders (SOC, AEs)", including "nausea (PT, AEs)".
g. No suitable operationalization available; for justification see Section 2.4.2.1.
h. The company presented no analyses on symptomatic confirmed hypoglycaemia (PG ≤ 70 mg/dL), although these were recorded in the PIONEER 2 study.

AE: adverse event; FDA: Food and Drug Administration; LLT: Lowest Level Term; MedDRA: Medical Dictionary for Regulatory Activities; NSTEMI: myocardial infarction without ST-segment elevation; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 – version 2 Health Survey; SOC: System Organ Class; STEMI: myocardial infarction with ST-segment elevation; TIA: transient ischaemic attack

- In Module 4 B, the company presents analyses on the composite outcome "adverse cardiovascular events", which is composed of the outcomes "acute coronary syndrome", "cerebrovascular event" and "hospitalization due to cardiac failure". In PIONEER 2, the events for these outcomes were collected based on the recording of AEs and adjudicated by an external blinded committee. The analyses submitted by the company on the component "acute coronary syndrome" and thus the analyses on adverse cardiovascular events as a whole are not usable for the present benefit assessment. "Acute coronary syndrome" was defined as acute myocardial infarction, silent myocardial infarction or hospitalization due to unstable angina pectoris. However, for silent myocardial infarctions and hospitalizations due to unstable angina pectoris, the extent to which the results were influenced by incidental findings without symptoms or by the health care context remains unclear. In Module 4 B, the company provides no information on the number of patients with individual events of the component "acute coronary syndrome". The analyses on the components "cerebrovascular event" and "hospitalization due to cardiac failure" submitted by the company are used separately for the present benefit assessment.
- In Module 4 B, the company presents analyses on the outcome "diabetic retinopathies and associated complications" based on a prespecified collection of PTs compiled by the company according to the Medical Dictionary for Regulatory Activities (MedDRA). The PIONEER 2 study included no dedicated recording of diabetic retinopathies. A PT collection on diabetic retinopathies and associated complications is not suitable to represent the outcome "diabetic retinopathies" and is therefore not used for the present benefit assessment.
- For hypoglycaemias that occurred in the PIONEER 2 study, the company only presents analyses on severe hypoglycaemias which were recorded as SAEs, and on symptomatic hypoglycaemias confirmed by a PG value of < 56 mg/dL in Module 4 B. The company did not present any analyses on symptomatic hypoglycaemia confirmed by a PG-value of ≤ 70 mg/dL, although these were also recorded in the PIONEER 2 study.

2.4.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias - RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study	Study level	Outcomes																
		All-cause mortality	Acute coronary syndrome[a]	Cerebrovascular event[b]	Hospitalization due to cardiac failure	Renal disorders[c]	Diabetic retinopathies	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Symptomatic confirmed hypoglycaemia (PG < 56 mg/dL)	Symptomatic confirmed hypoglycaemia (PG ≤ 70 mg/dL)	Severe hypoglycaemia (SAEs)	Pancreatitis acute[d]	Genital infection[e]	Urinary tract infection (PT, AE)	Diabetic ketoacidosis (PT, SAE)	Further specific AEs[f]
PIONEER 2	L	L	–[g]	L	L	L	–[g]	H[h]	L	H[h]	H[h]	–[i]	L	L	H[h]	H[h]	L	H[h]

a. Comprises the following adjudicated events: acute myocardial infarction (STEMI or NSTEMI), silent myocardial infarction or hospitalization due to unstable angina pectoris.
b. Comprises the following adjudicated events: ischaemic or haemorrhagic stroke, stroke of unknown cause or TIA.
c. Deviating from the company, the outcome is based on the operationalization using the following events (MedDRA coding): "acute kidney injury (PT, SAEs)"; for explanation see Section 2.4.2.3. Moreover, deviating from the company, the outcome is assigned to the category "morbidity".
d. Deviating from the company, the outcome is based on the operationalization using adjudicated events based on 2 of 3 of the following criteria: 1st: abdominal pain characteristic for acute pancreatitis, 2nd: 3-fold increase in serum amylase and/or serum lipase, and 3rd: typical signs of pancreatitis acute by means of imaging techniques; for explanation see Section 2.4.2.3.
e. Post-hoc analysis on mycotic infections based on a PT/LLT collection compiled by the company based on the FDA approval of empagliflozin (for details see Table 12).
f. The following events (MedDRA coding) are considered: "gastrointestinal disorders (SOC, AEs)", including "nausea (PT, AEs)".
g. No suitable operationalization available; for justification see Section 2.4.2.1.
h. Lack of blinding in subjective recording of outcomes or subjective request for treatment discontinuation.
h. The company presented no analyses on symptomatic confirmed hypoglycaemia (PG ≤ 70 mg/dL), although these were recorded in the PIONEER 2 study.

AE: adverse event; FDA: Food and Drug Administration; H: high; L: low; LLT: Lowest Level Term; MedDRA: Medical Dictionary for Regulatory Activities; NSTEMI: myocardial infarction without ST-segment elevation; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 – version 2 Health Survey; SOC: System Organ Class; STEMI: myocardial infarction with ST-segment elevation; TIA: transient ischaemic attack

For the PIONEER 2 study, the risk of bias for results on the outcomes “all-cause mortality”, “cerebrovascular event”, “hospitalization due to cardiac failure”, “renal disorders” and “SAEs” is rated as low. This concurs with the company’s assessment, which, however, summarizes the results on the outcomes “cerebrovascular event” and “hospitalization due to cardiac failure” under the composite outcome “adverse cardiovascular events” and determines the risk of bias only for the result on this superordinate outcome as a whole. For the outcome “renal disorders”, the company used a different operationalization for its assessment, but also assessed the risk of bias of the results for this operationalization as low.

For the present benefit assessment, the risk of bias of the results on the outcomes “severe hypoglycaemia”, “pancreatitis acute” and “diabetic ketoacidosis” is also assessed as low. This deviates from the company’s assessment. The company rated the risk of bias for the results on hypoglycaemia as high, irrespective of the operationalization. For the outcome “pancreatitis”, the company used a different operationalization for its assessment. For the consequential results, the company also assessed the risk of bias as high. In its assessment, the company did not consider the outcome “diabetic ketoacidosis” and thus presented no assessment of the risk of bias for this outcome.

Due to the lack of blinding in subjective recording of outcomes or subjective request for treatment discontinuation, the risk of bias was rated as high for the results on all other outcomes (“health-related quality of life” measured with the SF-36v2, “discontinuation due to AEs”, “symptomatic confirmed hypoglycaemia [PG < 56 mg/dL]”, “genital infection”, “urinary tract infection” and further specific AEs). This largely concurs with the company’s assessment. However, in its assessment, the company did not consider the outcomes “genital infection” and “urinary tract infection” and therefore presented no assessment of the risk of bias for the results of these outcomes.

2.4.2.3 Results

Table 14, Table 15 and Table 16 summarize the results on the comparison of semaglutide with empagliflozin, each in combination with metformin, in adults in whom diet and exercise and treatment with 1 other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control. Where necessary, calculations by the Institute are provided in addition to the data from the company’s dossier. Unless otherwise noted, the results refer to the entire observation period of the PIONEER 2 study. Tables on common AEs, SAEs and discontinuations due to AEs can be found in Appendix B.1 of the full dossier assessment.

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin (multipage table)

Study Outcome category Outcome	Semaglutide + metformin		Empagliflozin + metformin		Semaglutide + metformin vs empagliflozin + metformin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
PIONEER 2					
Mortality					
All-cause mortality	410	0 (0)	409	1 (0.2)	0.33 [0.01; 8.14]; 0.371
Morbidity					
acute coronary syndrome[b]				No usable data[c]	
cerebrovascular event[d]	411	0 (0)	410	4 (1.0)	0.11 [0.01; 2.05]; 0.046
hospitalization due to cardiac failure	411	2 (0.5)	410	1 (0.2)	2.00 [0.18; 21.92]; 0.683
renal disorders[e,f]	410	1 (0.2)	409	1 (0.2)	1.00 [0.06; 15.89][g]; > 0.999[h]
diabetic retinopathies				No usable data[c]	
Side effects					
AEs (supplementary information)	410	292 (71.2)	409	284 (69.4)	–
SAEs	410	28 (6.8)	409	37 (9.0)	0.75 [0.47; 1.21]; 0.248[h]
Discontinuation due to AEs	410	44 (10.7)	409	18 (4.4)	2.44 [1.43; 4.15]; < 0.001[h]
Symptomatic confirmed hypoglycaemia					
PG < 56 mg/dL	410	8 (2.0)	409	7 (1.7)	1.14 [0.42; 3.11]; 0.865[h]
PG ≤ 70 mg/dL				No data available[c]	
Severe hypoglycaemia (SAE)	410	0 (0)	409	0 (0)	–
pancreatitis acute[i]	410	1 (0.2)	409	1 (0.2)	1.00 [0.06; 15.89][g]; > 0.999[h]
Genital infection[j]	410	4 (1.0)[k]	409	31 (7.6)[k]	0.13 [0.05; 0.36][g]; < 0.001[h]
Urinary tract infection (PT, AE)	410	11 (2.7)	409	13 (3.2)	0.84 [0.38; 1.86]; 0.753[h]
diabetic ketoacidosis (PT, SAE)[f]	410	0 (0)	409	1 (0.2)	0.33 [0.01; 8.14][g]; 0.371[h]
Gastrointestinal disorders (SOC, AEs)	410	167 (40.7)	409	58 (14.2)	2.87 [2.20; 3.75]; < 0.001[h]
including nausea (PT, AEs)	410	81 (19.8)	409	10 (2.4)	8.08 [4.25; 15.36]; < 0.001[h]

Table 14: Results (mortality, morbidity, side effects) – RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin (multipage table)

Study Outcome category Outcome	Semaglutide + metformin		Empagliflozin + metformin		Semaglutide + metformin vs empagliflozin + metformin
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]

a. Unless stated otherwise, unconditional exact test (Barnard's test). Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. In case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
b. Comprises the following adjudicated events: acute myocardial infarction (STEMI or NSTEMI), silent myocardial infarction or hospitalization due to unstable angina pectoris.
c. For reasons, see Section 2.4.2.1 of the full dossier assessment.
d. Comprises the following adjudicated events: ischaemic or haemorrhagic stroke, stroke of unknown cause or TIA.
e. The following events (MedDRA coding) are considered: "acute kidney injury (PT, SAEs)".
f. Information was only provided on the events that occurred within the treatment phase. Events after discontinuation of the study medication were not recorded.
g. Institute's calculation of RR and CI (asymptotic). In case of 0 events in one study arm, the correction factor 0.5 was used for the calculation of effect and CI in both study arms.
h. Institute's calculation, unconditional exact test (CSZ method according to [21]).
i. Adjudicated events based on 2 of 3 of the following criteria: 1st: abdominal pain characteristic for acute pancreatitis, 2nd: 3-fold increase in serum amylase and/or serum lipase, and 3rd: typical signs of an acute pancreatitis by means of imaging techniques.
j. Post-hoc analysis on mycotic infections based on a PT/LLT collection compiled by the company based on the FDA approval of empagliflozin (for details see Table 12).
k. Institute's calculation from separate data by gender.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, Z-score; FDA: Food and Drug Administration; LLT: Lowest Level Term; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; NSTEMI: myocardial infarction without ST-segment elevation; PG: plasma glucose; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; STEMI: myocardial infarction with ST-segment elevation; TIA: transient ischaemic attack

Table 15: Results (health-related quality of life) – RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study Outcome category Outcome	Semaglutide + metformin			Empagliflozin + metformin			Semaglutide + metformin vs empagliflozin + metformin
	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]
PIONEER 2							
Health-related quality of life							
SF-36v2[c]							
Physical Component Summary (PCS)	411	50.00 (7.5)	0.44 (0.3)	410	49.31 (8.0)	1.44 (0.3)	-1.00 [-1.88; -0.12]; 0.026 Hedges' g: −0.14 [−0.28; −0.00]
Mental Component Summary (MCS)	411	49.76 (9.0)	0.23 (0.4)	410	50.13 (9.8)	0.02 (0.4)	0.20 [-0.93; 1.33]; 0.724
Physical functioning	411	49.04 (8.5)	0.47 (0.3)	410	49.01 (8.7)	1.09 (0.3)	-0.63 [-1.55; 0.30]
Physical role functioning	411	49.69 (8.0)	-0.64 (0.4)	410	49.38 (8.6)	0.76 (0.4)	-1.39 [-2.40; -0.38]
Bodily pain	411	50.98 (9.4)	-0.09 (0.5)	410	49.81 (10.3)	0.96 (0.5)	-1.05 [-2.34; 0.25]
general health perception	411	48.18 (7.9)	2.37 (0.4)	410	47.89 (8.5)	1.89 (0.4)	0.48 [-0.52; 1.48]
Vitality	411	53.43 (8.6)	0.79 (0.4)	410	53.09 (9.1)	1.16 (0.4)	-0.37 [-1.37; 0.64]
Social functioning	411	50.06 (8.0)	-0.33 (0.4)	410	50.25 (8.6)	-0.31 (0.4)	-0.02 [-1.17; 1.13]
Emotional role functioning	411	47.36 (10.5)	0.22 (0.5)	410	47.60 (10.4)	0.59 (0.5)	-0.37 [-1.65; 0.92]
Mental wellbeing	411	49.77 (9.1)	0.14 (0.4)	410	50.05 (10.1)	0.13 (0.4)	0.02 [-1.13; 1.16]

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. Mean and SE (change at week 52 per treatment group) as well as MD, CI and p-value (group comparison): ANCOVA with region and the corresponding value at baseline as variables. Imputation of missing values using multiple imputation.
c. Higher (increasing) values indicate better quality of life; positive effects (intervention minus control) indicate an advantage for the intervention.

ANCOVA: analysis of covariance; CI: confidence interval; MCS: Mental Component Summary; MD: mean difference; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36v2: Short Form 36 – version 2 Health Survey

Table 16: Results (supplementary outcomes: HbA1c, body weight and BMI) – RCT, direct comparison: semaglutide + metformin vs. empagliflozin + metformin

Study Outcome category Outcome	semaglutide + metformin			Empagliflozin + metformin			semaglutide + metformin vs empagliflozin + metformin
	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]
PIONEER 2							
Morbidity							
Supplementary information							
HbA1c [%]	411	8.14 (0.9)	-1.30 (0.0)	410	8.14 (0.9)	-0.89 (0.0)	-0.40 [-0.54; -0.27]; < 0.001
Body weight [kg]	411	91.93 (20.5)	-3.79 (0.3)	410	91.30 (20.1)	-3.62 (0.3)	-0.18 [-0.88; 0.53]; 0.623
BMI [kg/m²]	411	32.9 (6.3)	-1.4 (ND)	410	32.8 (5.9)	-1.3 (ND)	-0.1 [-0.3; 0.2]; 0.489

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. Mean and SE (change at week 52 per treatment group) as well as MD, CI and p-value (group comparison): ANCOVA with region and the corresponding value at baseline as variables. Imputation of missing values using multiple imputation.

ANCOVA: analysis of covariance; BMI: body mass index; HbA1c: glycosylated haemoglobin A1c; MD: mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error

Due to the high outcome-specific risk of bias, at most hints, e.g. of an added benefit, can be determined for the outcomes “health-related quality of life measured using the SF-36v2”, “discontinuation due to AEs”, “symptomatic confirmed hypoglycaemia (PG < 56 mg/dL)”, “genital infection”, “urinary tract infection” and further specific AEs. For all other outcomes, at most indications can be derived.

Mortality

All-cause mortality

Operationalization

In the PIONEER 2 study, deaths were recorded within the framework of AEs.

Result

There was no statistically significant difference between the treatment groups for the outcome “all-cause mortality”. This resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin; an added benefit is therefore not proven.

This concurs with the company’s assessment.

Morbidity

Acute coronary syndrome

For the outcome "acute coronary syndrome", PIONEER 2 provides no usable data for a comparison of semaglutide + metformin with empagliflozin + metformin. This resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin; an added benefit is therefore not proven.

This deviates from the assessment of the company in that the company used results on the outcome "acute coronary syndrome" from the PIONEER 2 study for its assessment. However, based on these analyses, the company also came to the conclusion that an added benefit is not proven for the outcome "acute coronary syndrome".

Moreover, the company considered cardiovascular morbidity as a whole and included the composite outcome "adverse cardiovascular events" and the individual components (acute coronary syndrome, cerebrovascular event and hospitalization due to heart failure). From the company's point of view, the overall assessment resulted in a hint of added benefit for cardiovascular morbidity.

Cerebrovascular event

A statistically significant difference in favour of semaglutide + metformin in comparison with empagliflozin + metformin was shown for the outcome "cerebrovascular-related events". This resulted in an indication of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin.

This deviates from the assessment of the company, which assumed a limited certainty of conclusions of the results for this outcome despite the low risk of bias, as only few cerebrovascular events were observed in the PIONEER 2 study. For this reason, the company derived an indication of added benefit for the outcome "cerebrovascular event".

Moreover, the company considered cardiovascular morbidity as a whole and derived a hint of added benefit (see description of its approach above for the outcome "acute coronary syndrome").

Hospitalization due to cardiac failure

No statistically significant difference between the treatment groups was shown for the outcome "hospitalization due to cardiac failure". This resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin; an added benefit is therefore not proven.

This corresponds to the assessment of the company for the outcome "hospitalization due to heart failure".

Moreover, the company considered cardiovascular morbidity as a whole and derived a hint of added benefit (see description of its approach above for the outcome "acute coronary syndrome").

Renal disorders

Operationalization

For the outcome "renal disorders", PIONEER 2 provides analyses on different operationalizations. One of them includes adjudicated events recorded under the Standardized MedDRA Query (SMQ) "acute renal failure". The adjudication was performed exclusively on the basis of laboratory values. Thereby, one of the following criteria had to be met: increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 µmol/l) within 48 hours; increase in serum creatinine by ≥ 1.5-times the baseline value known or suspected to have occurred within the previous 7 days; urine volume < 0.5 ml/kg/h over 6 hours. The patient relevance of the recorded events cannot be directly derived from this. This operationalization is therefore not included in the present benefit assessment.

The other available operationalization included in the present benefit assessment records SAEs that occurred under the PT "acute kidney injury". However, the analyses available for this PT from the PIONEER 2 study only include SAEs that occurred under treatment with the study medication. Events that occurred after discontinuation of the study medication are not included. However, it is assumed that the number of occurred events on the PT "acute kidney injury" (SAE) differs only slightly between the observation periods, and that the result for this outcome is not influenced to a relevant degree. This is due to the fact that for this outcome only isolated events occurred under treatment with the study medication. Moreover, between the entire observation period of the study and the period under treatment, the overall SAE rate differs only in 1 patient with event in the intervention arm. Therefore, analyses on the proportion of patients with SAEs of the PT "acute kidney injury" that occurred during treatment with the study medication are used for the present benefit assessment.

Result

For the outcome "renal disorders", operationalized using the PT "acute kidney injury" (SAE), there is no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin; an added benefit is therefore not proven.

This deviates from the company's approach insofar as the company used analyses on the proportion of patients with adjudicated events of the SMQ "acute renal failure" for its assessment. Besides, the company considered these analyses under the outcome category "side effects". On the basis of the operationalization used by it, the company also came to the conclusion that an added benefit is not proven.

Diabetic retinopathies

For the outcome "diabetic retinopathies", PIONEER 2 provides no usable data for a comparison of semaglutide + metformin with empagliflozin + metformin. This resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin; an added benefit is therefore not proven.

This deviates from the assessment of the company insofar as the company used results based on a predefined PT collection on diabetic retinopathies and associated complications from the PIONEER 2 study for its assessment. Moreover, the company allocated this outcome to the outcome category "side effects". On the basis of these analyses, the company also came to the conclusion that an added benefit is not proven.

Health-related quality of life

SF-36v2 – Physical and Mental Component Summary

Based on the mean difference, a statistically significant difference to the disadvantage of semaglutide + metformin in comparison with empagliflozin + metformin was shown for the Physical Component Summary of the SF-36v2. The standardized mean difference in the form of Hedges' g was considered to check the relevance of the result. The 95% CI of was not fully outside the irrelevance range of −0.2 to 0.2, however. It can therefore not be inferred that the effect is relevant. No statistically significant difference between the treatment groups was shown for the Mental Component Summary of the SF-36v2. Overall, this resulted in no hint of an added benefit of semaglutide + metformin in comparison with empagliflozin + metformin for the outcome "health-related quality of life measured with the SF-36v2"; an added benefit is therefore not proven.

This deviates from the company's approach insofar as the company also considered responder analyses on the response criteria "3.8 points" for the physical sum score and "4.6 points" for the physical sum score in addition to the mean differences. Independent of the analyses considered (mean differences or responder analyses) the company also came to the conclusion that an added benefit is not proven.

Side effects

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". This resulted in no hint of greater or lesser harm from semaglutide + metformin in comparison with empagliflozin + metformin; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of semaglutide + metformin in comparison with placebo + metformin was shown for the outcome "discontinuation due to

AEs". Due to the high risk of bias, this resulted in a hint of greater harm from semaglutide + metformin in comparison with empagliflozin + metformin for the outcome" discontinuation due to AEs".

This concurs with the company's assessment.

Symptomatic confirmed hypoglycaemia (PG < 56 mg/dL)

No statistically significant difference between the treatment groups was shown for the outcome "symptomatic confirmed hypoglycaemia (PG < 56 mg/dL)". This resulted in no hint of greater or lesser harm from semaglutide + metformin in comparison with empagliflozin + metformin; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Symptomatic confirmed hypoglycaemia (PG ≤ 70 mg/dL)

For the outcome "symptomatic confirmed hypoglycaemia (PG ≤ 70 mg/dL)", PIONEER 2 provides no usable data for a comparison of semaglutide + metformin with empagliflozin + metformin. This resulted in no hint of greater or lesser harm from semaglutide + metformin in comparison with empagliflozin + metformin; greater or lesser harm is therefore not proven.

The company did not use the outcome "symptomatic confirmed hypoglycaemia (PG ≤ 70 mg/dL)" in its assessment.

Severe hypoglycaemia

In the PIONEER 2 study, no events occurred for the outcome "severe hypoglycaemia". This resulted in no hint of greater or lesser harm from semaglutide + metformin in comparison with empagliflozin + metformin; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Pancreatitis acute

Operationalization

PIONEER 2 provides analyses on different operationalizations for the outcome "pancreatitis acute". One of them comprises the SMQ "acute pancreatitis". The other operationalization comprises adjudicated events based on the events recorded via the SMQ. At least 2 of the following 3 criteria had to be met for the adjudication: abdominal pain characteristic for acute pancreatitis; 3-fold increase in serum amylase and/or serum lipase; typical signs of an acute pancreatitis by means of imaging techniques. The analyses on the adjudicated events were used for the present benefit assessment.

Result

For the outcome "pancreatitis acute", no statistically significant difference between the treatment groups was shown on the basis of the adjudicated events. This resulted in no hint of

greater or lesser harm from semaglutide + metformin in comparison with empagliflozin + metformin; greater or lesser harm is therefore not proven.

This deviates from the company's approach insofar as the company used the analyses on the SMQ "pancreatitis acute" for its assessment. On the basis of the analyses on this operationalization, the company also came to the conclusion that greater or lesser harm is not proven.

Genital infections

A statistically significant difference in favour of semaglutide + metformin in comparison with empagliflozin + metformin was shown for the outcome "genital infection". Due to the high risk of bias, this resulted in a hint of lesser harm from semaglutide + metformin in comparison with empagliflozin + metformin for the outcome "genital infection".

The company did not consider the outcome "genital infection" in its assessment.

Urinary tract infection

No statistically significant difference between the treatment groups was shown for the outcome "urinary tract infection". This resulted in no hint of greater or lesser harm from semaglutide + metformin in comparison with empagliflozin + metformin; greater or lesser harm is therefore not proven.

The company did not consider the outcome "urinary tract infection" in its assessment.

Diabetic ketoacidosis

Operationalization

For the outcome "diabetic ketoacidosis", analyses from the PIONEER 2 study are only available for events that occurred under treatment with the study medication as SAEs under the PT "diabetic ketoacidosis" according to MedDRA. Events that occurred after discontinuation of the study medication are not included. However, it is assumed that the number of occurred events on the PT "diabetic ketoacidosis" (SAE) differs only slightly between the observation periods, and that the result for this outcome is not influenced to a relevant degree. This is due to the fact that for this outcome only isolated events occurred under treatment with the study medication. Moreover, between the entire observation period of the study and the period under treatment, the overall SAE rate differs only in 1 patient with event in the intervention arm. Therefore, analyses on the proportion of patients with SAEs of the PT "diabetic ketoacidosis" that occurred under treatment with the study medication are used for the outcome "diabetic ketoacidosis" in the present benefit assessment.

Result

There was no statistically significant difference between the treatment groups for the outcome "diabetic ketoacidosis". This resulted in no hint of greater or lesser harm from semaglutide +

metformin in comparison with empagliflozin + metformin; greater or lesser harm is therefore not proven.

The company did not consider the outcome "diabetic ketoacidosis" in its assessment.

Gastrointestinal disorders, including: nausea

For the outcome "gastrointestinal disorders" and the included event "nausea", there was a statistically significant difference to the disadvantage of semaglutide + metformin in comparison with empagliflozin + metformin. Due to the high risk of bias, this resulted in a hint of greater harm from semaglutide + metformin in comparison with empagliflozin + metformin for the outcome" gastrointestinal disorders" and for the included event "nausea".

This concurs with the company's assessment.

2.4.2.4 Subgroups and other effect modifiers

The following potential effect modifiers were considered in the present benefit assessment:

- age (≤ 65 years/> 65 years)
- sex (female/male)

In the PIONEER 2 study, no investigation of subgroup characteristics was planned according to the study design. In Module 4 B, the company presented post-hoc subgroup analyses for all outcomes except for the outcomes "renal disorders", "pancreatitis acute", "urinary tract infection", "genital infection" and "diabetic ketoacidosis". For the outcome "genital infection", the available data permitted only subgroup analyses for the characteristic "sex" by means of Institute's calculation. The PIONEER 2 study provides no subgroup analyses on a suitable characteristic for the investigation of the severity of the diseases.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

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

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below. Taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of the added benefit at outcome level

Based on the results presented in Section 2.4.2, the extent of the respective added benefit for adults in whom diet and exercise and treatment with 1 other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control is assessed at the outcome level (see Table 17).

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Discontinuation due to AEs

The events of the outcome "discontinuation due to AEs" are chiefly due to gastrointestinal events (see Table 39 of the full dossier assessment). Most of these events were non-serious/non-severe (see Table 37 and Table 38 of the full dossier assessment). However, it is unclear which gastrointestinal events (non-serious/non-severe or serious/severe) were included in the outcome "discontinuation due to AEs". Moreover, information on the assignment to the severity category is not available for the outcome "discontinuation due to AEs". Therefore, the outcome "discontinuation due to AEs" was assigned to the category of non-serious/non-severe side effects.

Genital infections

Information on the assignment to the severity category is not available for the outcome "genital infection". Therefore, the outcome was assigned to the category non-serious/non-severe side effects.

Gastrointestinal disorders (including: nausea)

Most of the events that occurred under the outcome "gastrointestinal disorders (including: nausea)" were non-serious/non-severe. Therefore, the cited outcomes were assigned to the category non-serious/non-severe side effects.

Table 17: Extent of added benefit at outcome level: semaglutide + metformin vs. empagliflozin + metformin (multipage table)

Outcome category **outcome**	**Semaglutide + metformin vs. empagliflozin + metformin** **proportion of events (%) or mean change** **effect estimation [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0.2% RR: 0.33 [0.01; 8.14] p = 0.371	Lesser benefit/added benefit not proven
Morbidity		
Acute coronary syndrome	No usable data	Lesser benefit/added benefit not proven
Cerebrovascular event	0% vs. 1.0% RR: 0.11 [0.01; 2.05] p = 0.046 probability: "indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "minor"[c]
Hospitalization due to cardiac failure	0.5% vs. 0.2% RR: 2.00 [0.18; 21.92] p = 0.683	Lesser benefit/added benefit not proven
Renal disorders	0.2% vs. 0.2% RR: 1.00 [0.06; 15.89] p > 0.999	Lesser benefit/added benefit not proven
Diabetic retinopathies	No usable data	Lesser benefit/added benefit not proven
Health-related quality of life		
SF-36v2		
Physical Component Summary (PCS)	Mean change: 0.44 vs. 1.44 MD: -1.00 [-1.88; -0.12] p = 0.026 Hedges' g: -0.14 [-0.28; -0.00][d]	Lesser benefit/added benefit not proven
Mental Component Summary (MCS)	Mean change: 0.23 vs. 0.02 MD: 0.20 [-0.93; 1.33] p = 0.724	Lesser benefit/added benefit not proven
Side effects		
SAEs	6.8% vs. 9.0% RR: 0.75 [0.47; 1.21] p = 0.248	Greater/lesser harm not proven
Discontinuation due to AEs	10.7% vs. 4.4% RR: 2.44 [1.43; 4.15] RR: 0.41 [0.24; 0.70][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

Table 17: Extent of added benefit at outcome level: semaglutide + metformin vs. empagliflozin + metformin (multipage table)

Outcome category **outcome**	**Semaglutide + metformin vs. empagliflozin + metformin** **proportion of events (%) or mean change** **effect estimation [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Symptomatic confirmed hypoglycaemia		
PG < 56 mg/dL	2.0% vs. 1.7% RR: 1.14 [0.42; 3.11] p = 0.865	Greater/lesser harm not proven
PG ≤ 70 mg/dL	No data available	Greater/lesser harm not proven
Severe hypoglycaemia (SAE)	0% vs. 0%	Greater/lesser harm not proven
Pancreatitis acute	0.2% vs. 0.2% RR: 1.00 [0.06; 15.89] p = 0.999	Greater/lesser harm not proven
Genital infection	1.0% vs. 7.6% RR: 0.13 [0.05; 0.36] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 lesser harm, extent: "considerable"
Urinary tract infection (PT, AE)	2.7 % vs. 3.2 % RR: 0.84 [0.38; 1.86] p = 0.753	Greater/lesser harm not proven
Diabetic ketoacidosis (PT, SAE)	0% vs. 0.2% RR: 0.33 [0.01; 8.14] p = 0.371	Greater/lesser harm not proven
Gastrointestinal disorders (SOC, AEs)	40.7% vs. 14.2% RR: 2.87 [2.20; 3.75] RR: 0.35 [0.27; 0.45][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
including: nausea (PT, AEs)	19.8% vs. 2.4% RR: 8.08 [4.25; 15.36] RR: 0.12 [0.07; 0.24][e] p < 0.001 probability: "hint"	

Table 17: Extent of added benefit at outcome level: semaglutide + metformin vs. empagliflozin + metformin (multipage table)

Outcome category **outcome**	**Semaglutide + metformin vs. empagliflozin + metformin** **proportion of events (%) or mean change** **effect estimation [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. The p-value serves for the assessment of the extent. Due to the proximity of the p-value to the significance threshold of 0.05, the extent is estimated to be "minor". d. If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be inferred. e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. AE: adverse event; CI: confidence interval; CIu: upper limit of the confidence interval; MCS: Mental Component Summary; MD: mean difference; PCS: Physical Component Summary; PG: plasma glucose; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SF-36v2: Short Form (36) – version 2 Health Survey; SOC: System Organ Class		

2.4.3.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of semaglutide + metformin compared with empagliflozin + metformin

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ cerebrovascular event: indication of added benefit – extent: "minor"	–
Non-serious/non-severe side effects ▪ genital infection: hint of lesser harm – extent: "considerable"	Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of greater harm – extent: "considerable" ▪ gastrointestinal disorders (SOC, AEs, including: nausea [PT, AEs]): in each case hint of greater harm - extent: "considerable"
AEs: adverse events; PT: preferred term; SOC: system organ class	

The overall consideration showed both positive and negative effects of semaglutide + metformin versus empagliflozin + metformin. The PIONEER 2 study was not designed to record patient-relevant cardiovascular outcomes and is therefore not suitable for this purpose. Accordingly, the positive effect for the outcome "cerebrovascular-related events" was only

based on isolated patients with an event. Although the positive effect for the outcome "genital infection" was based on a larger proportion of patients with an event, there were also negative effects with the extent "considerable" for the outcome "gastrointestinal disorders" and the PT "nausea" contained therein. These events contribute significantly to the negative effect for the outcome "discontinuation due to AEs".

In summary, an added benefit of semaglutide + metformin versus empagliflozin + metformin is not proven for adults with type 2 diabetes mellitus in whom diet and exercise and treatment with 1 other blood-glucose lowering drug (other than insulin) do not provide adequate glycaemic control.

Due to a lack of relevant data, an added benefit of semaglutide versus the ACT is not proven for semaglutide in combination with 1 other blood glucose-lowering drug (except metformin and insulin).

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit of semaglutide (orally) compared with the ACT empagliflozin for the combination therapy with 1 other blood-glucose lowering drug (except insulin).

2.5 Research question C: Semaglutide in combination with at least 2 other blood-glucose lowering drugs (except insulin)

2.5.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on semaglutide (status: 2 September 2020)
- bibliographical literature search on semaglutide (last search on 3 August 2020)
- search in trial registries/trial results databases for studies on semaglutide (last search on 24 August 2020)
- search on the G-BA website for semaglutide (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on semaglutide (last search on 11 November 2020)

The check of the completeness of the study pool identified no RCTs on the direct comparison of semaglutide versus the ACT for research question C (semaglutide in combination with at least 2 other blood-glucose lowering drugs [except insulin]). This assessment concurs with that of the company.

2.5.2 Results on added benefit

In its dossier, the company provided no relevant data for the assessment of semaglutide in combination therapy in adults with type 2 diabetes mellitus in whom diet and exercise and treatment with at least 2 other blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control. This resulted in no hint of an added benefit of semaglutide in comparison with the ACT. An added benefit is therefore not proven.

2.5.3 Probability and extent of added benefit

As there are no relevant data for the assessment of the added benefit of semaglutide in combination therapy versus the ACT in adults with type 2 diabetes mellitus in whom diet and exercise and treatment with at least 2 other blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control, an added benefit of semaglutide is not proven in this research question. This assessment concurs with that of the company.

2.6 Research question D: Semaglutide in combination with insulin (with or without 1 other blood glucose-lowering drug)

2.6.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on semaglutide (status: 2 September 2020)
- bibliographical literature search on semaglutide (last search on 3 August 2020)
- search in trial registries/trial results databases for studies on semaglutide (last search on 24 August 2020)
- search on the G-BA website for semaglutide (last search on 5 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on semaglutide (last search on 11 November 2020)

The check of the completeness of the study pool identified no RCTs on the direct comparison of semaglutide versus the ACT for research question D: (semaglutide in combination with insulin [with or without 1 other blood-glucose lowering drug]). This assessment concurs with that of the company.

2.6.2 Results on added benefit

In its dossier, the company provided no relevant data for the assessment of semaglutide in combination therapy in adults with type 2 diabetes mellitus in whom diet and exercise and treatment with insulin (with or without 1 other blood-glucose lowering drug) do not provide

adequate glycaemic control. This resulted in no hint of an added benefit of semaglutide in comparison with the ACT. An added benefit is therefore not proven.

2.6.3 Probability and extent of added benefit

As there are no relevant data for the assessment of the added benefit of semaglutide in combination therapy versus the ACT in adults with type 2 diabetes mellitus in whom diet and exercise and treatment with insulin (with or without 1 other blood-glucose lowering drug) do not provide adequate glycaemic control, an added benefit of semaglutide is not proven in this research question. This assessment concurs with that of the company.

2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of semaglutide in comparison with the ACT is summarized in Table 19.

Table 19: Semaglutide – probability and extent of the added benefit for type 2 diabetes mellitus in adults

Research question	Subindication[a]	ACT[b]	Probability and extent of added benefit
A	Monotherapy in adults in whom diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications	▪ Sulfonylurea (glibenclamide or glimepiride)	Added benefit not proven
B	Combination therapy in adults in whom diet and exercise and treatment with 1 other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control	▪ **Metformin + sulfonylurea (glibenclamide or glimepiride)** or ▪ **metformin + empagliflozin** or ▪ metformin + liraglutide[c] or ▪ human insulin[d]	Added benefit not proven
C	Combination therapy in adults in whom diet and exercise and treatment with at least 2 other blood-glucose lowering drugs (except insulin) do not provide adequate glycaemic control	▪ **Human insulin + metformin** or ▪ human insulin + empagliflozin[c] or ▪ human insulin + liraglutide[c] or ▪ **human insulin[e]**	Added benefit not proven
D	Combination therapy in adults in whom diet and exercise and treatment with insulin (with or without 1 other blood-glucose lowering drug) do not provide adequate glycaemic control	▪ Optimization of the human insulin regimen (if applicable + metformin or empagliflozin[c] or liraglutide[c])	Added benefit not proven

a. Subdivision of the therapeutic indication according to the G-BA.
b. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
c. Empagliflozin or liraglutide only for patients with manifest cardiovascular disease who receive further medication for the treatment of the cardiovascular risk factors, in particular antihypertensives, anticoagulants and/or lipid-lowering agents (for information on the operationalization see study protocols of the relevant studies for empagliflozin [3] or liraglutide [4]).
d. If metformin is contraindicated or not tolerated according to the SPC.
e: If, according to the SPC, metformin, empagliflozin or liraglutide are contraindicated or not tolerated or are not sufficiently effective due to advanced type 2 diabetes mellitus.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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

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