IQWiG Reports – Commission No. A21-30

Semaglutide (type 2 diabetes mellitus) –

Addendum to Commission A20-93[1]

Addendum

Commission: A21-30
Version: 1.0
Status: 26 March 2021

[1] Translation of addendum A21-30 *Semaglutid (Diabetes mellitus Typ 2) – Addendum zum Auftrag A20-93* (Version 1.0; Status: 26 March 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Semaglutide (type 2 diabetes mellitus) – Addendum to Commission A20-93

Commissioning agency
Federal Joint Committee

Commission awarded on
10 March 2021

Internal Commission No.
A21-30

Address of publisher
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Keywords: Semaglutide, Diabetes Mellitus – Type 2, Benefit Assessment, NCT02863328, NCT02692716, NCT01720446

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List of abbreviations

Abbreviation	Meaning
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MCS	Mental Component Summary
PCS	Physical Component Summary
SF-36v2	Short Form 36 – version 2 Health Survey

1 Background

On 10 March 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-93 (Semaglutide – Benefit assessment according to §35a Social Code Book V) [1].

For research question B, benefit assessment A20-93 included the PIONEER 2 study for the assessment of the added benefit of semaglutide in combination with 1 other blood-glucose lowering drug (except insulin) in adults with type 2 diabetes mellitus in whom diet and exercise and treatment with 1 other blood-glucose lowering drug (except insulin) do not provide adequate glycaemic control. The study compares semaglutide with empagliflozin, each in combination with metformin. Relevant data for the other research questions of the benefit assessment (research questions A, C and D) were missing.

In its dossier, the pharmaceutical company (hereinafter referred to as "the company") investigated another research question in addition to the research questions of the benefit assessment: semaglutide in addition to standard therapy in the treatment of adult patients with inadequately controlled type 2 diabetes mellitus and high cardiovascular risk versus placebo in addition to a standard therapy. For this additional research question, the company presented the studies SUSTAIN 6 and PIONEER 6 in the dossier. 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 [2]).

In the PIONEER 2 and SUSTAIN 6 studies, the outcome "health-related quality of life" was recorded using the Short Form 36 – version 2 Health Survey (SF-36v2), while the outcome was not recorded in the PIONEER 6 study. Analyses on the basis of mean differences were available for the SF-36v2 for both the PIONEER 2 study and the SUSTAIN 6 study. After the oral hearing [3,4], the company submitted responder analyses for these studies with the commenting procedure; a response threshold of 15% of the scale range was used in these analyses. Therefore, the G-BA commissioned IQWiG with the assessment of these subsequently submitted analyses under consideration of the information provided in the dossier [5].

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

2 Assessment

2.1 Responder analyses subsequently submitted by the company for the outcome "health-related quality of life" recorded using SF-36v2

In accordance with the Institute's *General Methods* [6,7], the company presented post hoc analyses on 15% of the scale range conducted for the SF-36v2. In doing so, the company determined the response threshold of 15% of the scale range for the normalized values of the sum scores (Physical Component Summary [PCS] and Mental Component Summary [MCS]) taking into account the observed values of a norm sample from 2009. The approach is consistent with the approach described in dossier assessment A20-90 [8]. Thus, the analyses submitted by the company for the PIONEER 2 study are relevant for research question B (semaglutide in combination with 1 other blood glucose-lowering drug except insulin) of the present assessment and were therefore used. For the individual domains of the SF-36v2, the company presented analyses the response thresholds of which were determined on the basis of the same approach as for the total scores. These analyses are presented as supplementary information. The analyses presented for the SUSTAIN 6 study for the research question additionally addressed by the company (semaglutide in addition to standard therapy in patients at high cardiovascular risk) are described in Appendix A.

2.2 Research question B: semaglutide in combination with 1 other blood-glucose lowering drug (except insulin) - responder analyses subsequently submitted by the company

The responder analyses on PIONEER 2 subsequently submitted by the company for the outcome "health-related quality of life", recorded using the SF-36v2, refer to the proportion of patients with an improvement by at least 15% of the scale range at the end of treatment (week 52).

Risk of bias

For the risk of bias of the results based on the responder analyses on the outcome "health-related quality of life" recorded using the SF-36v2, there is no change in comparison with dossier assessment A20-93 [1]. Due to the lack of blinding in subjective recording of outcomes in the PIONEER 2 study, the risk of bias of the results on the outcome was rated as high.

Due to the outcome-specific high risk of bias, at most hints, e.g. of an added benefit, can be determined for the outcome "health-related quality of life measured with the SF-36v2".

Results

Table 1 summarizes 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 for the outcome "health-related quality of life measured with the SF-36v2". Where necessary, the data provided by the company were supplemented with the Institute's calculations.

Table 1: 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]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
PIONEER 2					
Health-related quality of life					
SF-36v2[c]					
Physical Component Summary (PCS)[d]	386	27 (7.0)	382	33 (8.6)	0.81 [0.50; 1.32]; 0.530
Mental Component Summary (MCS)[d]	386	39 (10.1)	382	44 (11.5)	0.88 [0.58; 1.32]; 0.544
Physical functioning[d]	386	59 (15.3)	383	58 (15.1)	1.01 [0.72; 1.41]
Physical role functioning[d]	386	56 (14.5)	382	83 (21.7)	0.67 [0.49; 0.91]
Physical pain[d]	386	99 (25.6)	383	108 (28.2)	0.91 [0.72; 1.15]
General health perception[d]	386	111 (28.8)	383	89 (23.2)	1.24 [0.97; 1.57]
Vitality[d]	386	78 (20.2)	383	77 (20.1)	1.01 [0.76; 1.33]
Social functioning[d]	386	58 (15.0)	383	55 (14.4)	1.05 [0.74; 1.47]
Emotional role functioning[d]	386	85 (22.0)	382	83 (21.7)	1.01 [0.78; 1.32]
Mental well-being[d]	386	51 (13.2)	383	59 (15.4)	0.86 [0.61; 1.21]

a. At the analysis date week 52, recordings were available for 94% and 93% of the randomized patients, respectively.
b. Institute's calculation (unconditional exact test [CSZ method according to [9]]).
c. In PIONEER 2, the acute version of the questionnaire was used with a recall period of 1 week.
d. Patients with an improvement by ≥ 15% of the scale range determined on the basis of the empirical minima and maxima from a 2009 norm sample, see information in Table 7.1 of the SF-36 manual [10]; this corresponds to an improvement of the following values: Physical Component Summary (PCS): ≥ 9.7 points, Mental Component Summary (MCS): ≥ 9.6 points, physical functioning: ≥ 5.8 points, physical role functioning: ≥ 5.3 points, physical pain: ≥ 5.9 points, general health perception: ≥ 6.6 points, vitality: ≥ 6.5 points, social functioning: ≥ 5.9 points, emotional role functioning: ≥ 6.9 points, mental well-being: ≥ 7.4 points.

CI: confidence interval; CSZ: convexity, symmetry, z-score; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SF-36v2: Short Form 36 – version 2 Health Survey

For the physical and the mental component summary of the SF-36v2, there was no statistically significant difference between the treatment groups on the basis of the responder analyses on the response threshold of 15% of the scale range. 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.

Subgroups and other effect modifiers

According to the methods described in the dossier assessment, no relevant effect modification by age or sex was identified for the outcome "health-related quality of life measured with the SF-36v2" on the basis of the responder analyses on the response threshold of 15% of the scale range.

Overall conclusion on added benefit

For the outcome "health-related quality of life measured with the SF-36v2", there is neither a statistically significant difference between the treatment groups nor a relevant effect modification by age or sex based on the responder analyses at the response threshold of 15% of the scale range. The conclusion on the added benefit of semaglutide for research question B (semaglutide in combination with 1 other blood-glucose lowering drug except insulin) from dossier assessment A20-93 is therefore not changed.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of semaglutide from dossier assessment A20-93.

The following Table 2 shows the result of the benefit assessment of semaglutide under consideration of dossier assessment A20-93 and the present addendum.

Table 2: 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[e] 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**[c]	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 G-BA decides on the added benefit.

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Anhang A Additional research question of the company - responder analyses subsequently submitted by the company

The responder analyses on SUSTAIN 6 subsequently submitted by the company for the outcome "health-related quality of life", recorded using the SF-36v2, refer to the proportion of patients with an improvement by at least 15% of the scale range at the analysis date week 104.

Table 3 shows the results for the outcome "health-related quality of life" measured with the SF-36v2 from the SUSTAIN 6 study. Where necessary, the data provided by the company were supplemented with the Institute's calculations.

Table 3: Results (health-related quality of life) – RCT, direct comparison: semaglutide vs. placebo

Study Outcome category Outcome	Semaglutide		Placebo		Semaglutide vs. placebo
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
SUSTAIN 6					
Health-related quality of life					
SF-36v2[c]					
Physical Component Summary (PCS)[d]	1466	192 (13.1)	1443	167 (11.6)	1.13 [0.93; 1.37]; 0.248
Mental Component Summary (MCS)[d]	1466	233 (15.9)	1443	215 (14.9)	1.07 [0.90; 1.26]; 0.533
Physical functioning[d]	1467	370 (25.2)	1443	344 (23.8)	1.06 [0.93; 1.20]
Physical role functioning[d]	1467	370 (25.2)	1443	334 (23.1)	1.09 [0.96; 1.24]
Physical pain[d]	1467	426 (29.0)	1443	386 (26.7)	1.09 [0.97; 1.22]
General health perception[d]	1467	435 (29.7)	1443	365 (25.3)	1.17 [1.04; 1.32]
Vitality[d]	1467	302 (20.6)	1443	256 (17.7)	1.16 [1.00; 1.35]
Social functioning[d]	1467	280 (19.1)	1443	264 (18.3)	1.04 [0.90; 1.21]
Emotional role functioning[d]	1466	389 (26.5)	1443	379 (26.3)	1.01 [0.89; 1.14]
Mental well-being[d]	1467	337 (23.0)	1443	260 (18.0)	1.27 [1.10; 1.47]

a. At the analysis date week 104, recordings were available for 89 % and 88 % of the randomized patients, respectively.
b. Institute's calculation (unconditional exact test [CSZ method according to [9]]).
c. In SUSTAIN 6, the standard version of the questionnaire was used with a recall period of 4 week.
d. Patients with an improvement by ≥ 15% of the scale range determined on the basis of the empirical minima and maxima from a 2009 norm sample, see information in Table 7.1 of the SF-36 manual [10]; this corresponds to an improvement of the following values: Physical Component Summary (PCS): ≥ 9.4 points, Mental Component Summary (MCS): ≥ 9.6 points, physical functioning: ≥ 5.7 points, physical role functioning: ≥ 5.4 points, physical pain: ≥ 6.1 points, general health perception: ≥ 7.1 points, vitality: ≥ 7.1 points, social functioning: ≥ 6.0 points, emotional role functioning: ≥ 6.3 points, mental well-being: ≥ 7.9 points.

CI: confidence interval; MCS: Mental Component Summary; n: number of patients with (at least 1) event; N: number of analysed patients; PCS: Physical Component Summary; RCT: randomized controlled trial; RR: relative risk; SF-36v2: Short Form 36 – version 2 Health Survey

Based on the SUSTAIN 6 study, statistically significant differences between the treatment groups were shown neither for the physical nor for the mental component summary of the SF-36v2. This resulted in no advantage or disadvantage of semaglutide compared with placebo, each in addition to standard therapy, for the outcome “health-related quality of life” measured with the SF-36v2.