IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Assessment of the LEADER study on liraglutide[1]

Executive Summary

[1] Translation of the executive summary of the rapid report *Bewertung der Studie LEADER zu Liraglutid* (Version 1.0; Status: 23 August 2017). 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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This rapid report was prepared in collaboration with external experts. The rapid report was subject to an external review.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139 b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". An external expert was involved in the present assessment to answer specific questions in the course of the project and to conduct an external review of the rapid report. The Institute received the completed *Form for disclosure of potential conflicts of interest* from the external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external expert is presented in Appendix E of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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IQWiG thanks the external expert for his collaboration in the project.

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[2] Due to legal data protection regulations, employees have the right not to be named.

1 Executive summary

On 8 March 2017, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct an assessment of the long-term study LEADER on liraglutide in the therapeutic indication of type 2 diabetes mellitus. The results of the LEADER study are intended to provide insight into the relevance of liraglutide regarding the determination of the appropriate comparator therapy (ACT) in the therapeutic indication of type 2 diabetes mellitus in the framework of the early benefit assessment according to §35a Social Code Book V.

Research question

The goal of the present research was

- the assessment of the long-term study LEADER in the therapeutic indication of type 2 diabetes mellitus regarding patient-relevant outcomes.

Methods

For the assessment, the pharmaceutical company Novo Nordisk Pharma GmbH (hereinafter referred to as "the company") was requested to provide the clinical study report (CSR) and publications on the LEADER study. In addition, the company was requested to provide subgroup analyses and analyses on hypoglycaemic events that were not contained in the CSR. Information from the ClinicalTrials.gov trial registry and from the publications and result reports on the LEADER study cited at ClinicalTrials.gov were additionally used.

The patient-relevant outcomes of the categories "mortality", "morbidity", "health-related quality of life" and "side effects" were assessed for the investigation.

Data extraction was conducted in standardized tables. To evaluate the certainty of results, the risk of bias at study and outcome level was assessed and rated as low or high respectively.

The results were investigated for potential effect modifiers, i.e. clinical factors influencing the effects.

Results

The company provided the complete documents and analyses on the LEADER study requested.

The LEADER study was a randomized, placebo-controlled, double-blind study sponsored by the company. It included adult patients with type 2 diabetes mellitus who had an HbA1c value of $\geq 7.0\%$ and were at least 50 years of age. Patients aged 50 years or older had to have concomitant cardiovascular disease; for patients aged 60 years or older, the presence of at least 1 risk factor for cardiovascular disease was sufficient. A total of 9340 patients were randomly assigned in a ratio of 1:1 to treatment with liraglutide 0.6 mg or to placebo, each of which was administered in addition to the ongoing antidiabetic therapy.

Except for the outcome “health status”, the risk of bias was rated as low for all further patient-relevant outcomes of the LEADER study. Despite the mainly low risk of bias at study and outcome level, the certainty of conclusions of the study is low because the study requirements of treatment escalation to lower blood glucose and blood pressure were not sufficiently implemented in the majority of the patients in the course of the study. Hence the certainty of conclusions for each individual patient-relevant outcome of the LEADER study is also low. Furthermore, the forced titration of liraglutide was conducted contrary to the information provided in the Summary of Product Characteristics (SPC) of liraglutide.

All-cause mortality

A statistically significant difference in favour of liraglutide was shown for the outcome “all-cause mortality”.

Morbidity

Major adverse cardiovascular event

A statistically significant difference in favour of liraglutide was shown for the outcome “major adverse cardiovascular event (MACE)”, which consists of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke. This also applied to the individual component “cardiovascular death”. No statistically significant difference between both treatment groups was shown for the components “nonfatal myocardial infarction” and “nonfatal stroke”. There was an effect modification for the outcome “MACE” and for the component “stroke”, however (see below).

There were no statistically significant differences for further patient-relevant outcomes from the categories of mortality and morbidity recorded in the LEADER study. However, there was an effect modification for each of the outcomes “hospitalization for cardiac failure” and “stroke” (see below).

Health-related quality of life

The outcome “health-related quality of life” was not assessed in the LEADER study.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome “serious adverse event (SAE)”. However, late complications of the disease (such as cardiac disorders) were also recorded in the recording of SAEs, showing a statistically significant difference in favour of liraglutide. SAE data without late disease complications were not available. Hence, the overall rate of SAEs can only be interpreted to a limited extent. The consideration of frequent SAEs showed no notable difference between the treatment groups for further specific SAEs (without late complications), however.

Serious adverse event or non-serious medical event of special interest

For the outcome "SAE or non-serious medical event of special interest (MESI)", a statistically significant difference to the disadvantage of liraglutide was shown for gastrointestinal disorders overall and for the individual events "diarrhoea", "nausea" and "vomiting".

Discontinuation due to serious adverse events or non-serious medical events of special interest

A statistically significant difference in favour of the comparator treatment was shown for the outcome "discontinuation due to SAE or non-serious MESI". Treatment discontinuation due to an SAE or a non-serious MESI was more common in the liraglutide arm. This also applied to discontinuation due to gastrointestinal disorders and to discontinuation due to nausea. There was also an effect modification for this outcome (see below).

Hypoglycaemia

Hypoglycaemic events could be reported during the entire course of the study.

A statistically significant difference in favour of liraglutide was shown for the outcome "symptomatic hypoglycaemia with a plasma glucose level of < 56 mg/dL".

No statistically significant differences between the treatment groups were shown for the outcomes "symptomatic hypoglycaemia with a plasma glucose level of ≤ 70 mg/dL" and "severe hypoglycaemia".

Pancreatitis

No statistically significant difference between the treatment groups was shown for the outcome "pancreatitis".

Subgroup analyses in the LEADER study on renal function and on cardiovascular risk

There were effect modifications for patient-relevant outcomes for the 2 factors "patients' renal function" (estimated glomerular filtration rate [eGFR] calculated as modification of diet in renal disease [MDRD]) and "cardiovascular risk".

Subgroup of patients with eGFR < 60 mL/min/1.73 m^2

For the patient group with eGFR < 60 (calculated as MDRD) and existing cardiovascular disease, there was in each case a statistically significant difference in favour of liraglutide for the outcome "MACE", the individual component "nonfatal stroke" and the outcome "all strokes".

For the patient population with the same impairment of renal function without manifest cardiovascular disease (i.e. patients who have only risk factors for cardiovascular disease), there was a consistent result with only imprecise results, however, due to the low number of patients (44 patients in the liraglutide group and 42 patients in the comparator group). In the present assessment, a joint conclusion is therefore drawn for the patient population with

severely impaired renal function (eGFR < 60), irrespective of the presence of a manifest cardiovascular disease.

Subgroup of patients with eGFR ≥ 60 mL/min/1.73 m²

For the patient group with eGFR ≥ 60 (calculated as MDRD), there was a statistically significant difference to the disadvantage of liraglutide for the outcome "discontinuation due to SAEs or non-serious MESIs" – irrespective of an existing cardiovascular disease or the presence of risk factors for such diseases.

For each of the outcomes "MACE", "nonfatal stroke" and "all strokes", no statistically significant differences between the treatment groups were shown for the patient group with eGFR ≥ 60.

Effect modification for the outcome "hospitalization due to cardiac failure"

A statistically significant difference in favour of liraglutide was shown for the outcome "hospitalization due to cardiac failure" for the patient group with cardiovascular disease, irrespective of renal function.

Summary of the results

Patient group with eGFR < 60 mL/min/1.73 m²

The results for patients with renal function disorder of stage 3 or greater (eGFR < 60 mL/min/1.73 m^2) are shown in Table 1.

Table 1: Positive and negative effects of liraglutide + antidiabetic standard therapy in comparison with placebo + antidiabetic standard therapy in the LEADER study for the patient group with eGFR < 60 mL/min/1.73 m2 (calculated with MDRD)

Positive effects	**Negative effects**
Mortality ▪ all-cause mortality	
Morbidity ▪ MACE[a] ▪ nonfatal stroke ▪ all strokes ▪ hospitalization due to cardiac failure[b]	
Side effects ▪ symptomatic hypoglycaemia (plasma glucose < 56 mg/dL)	Side effects ▪ SAE or non-serious MESI ▫ gastrointestinal disorder (diarrhoea, nausea, vomiting)
a: Composite outcome, consisting of the individual components "cardiovascular death", "nonfatal myocardial infarction" and "nonfatal stroke". b: Only applies to the patient group with cardiovascular disease. eGFR: estimated glomerular filtration rate; MACE: major adverse cardiovascular event; MDRD: modification of diet in renal disease; MESI: medical event of special interest; SAE: serious adverse event	

Overall, in the LEADER study, the advantages of liraglutide notably outweigh the disadvantages in patients with eGFR < 60 mL/min/1.73 m^2.

Patient group with eGFR ≥ 60 mL/min/1.73 m^2

The results for patients with renal function disorder of stage 1 or 2 or without renal function disorder (eGFR ≥ 60 mL/min/1.73 m^2) are shown in Table 2.

Table 2: Positive and negative effects of liraglutide + antidiabetic standard therapy in comparison with placebo + antidiabetic standard therapy in the LEADER study for the patient group with eGFR ≥ 60 mL/min/1.73 m2 (calculated with MDRD)

Positive effects	**Negative effects**
Mortality ▪ all-cause mortality	
Morbidity ▪ hospitalization due to cardiac failure[a]	
Side effects ▪ symptomatic hypoglycaemia (plasma glucose < 56 mg/dL)	Side effects ▪ SAE or non-serious MESI ▫ gastrointestinal disorder (diarrhoea, nausea, vomiting) ▪ discontinuation due to SAE or non-serious MESI
a: Only applies to the patient group with cardiovascular disease. eGFR: estimated glomerular filtration rate; MACE: major adverse cardiovascular event; MDRD: modification of diet in renal disease; MESI: medical event of special interest; SAE: serious adverse event	

Overall, in the LEADER study, the advantages of liraglutide outweigh the disadvantages also in patients with eGFR ≥ 60 mL/min/1.73 m^2.

Limitations of the LEADER study

In the overall consideration, it is not apparent for the LEADER study that the requirements of lowering blood glucose and blood pressure mandated by the study protocol were sufficiently adhered to and that the treatment was adequately escalated in the course of the study. Since the treatment escalation was supposed to be based on regional standards, this was potentially due to regional differences in the type and quality of clinical practice. Among other things, it was not guaranteed that insulin therapy was supported by a structured training and treatment programme as mandated by the disease management programme for type 2 diabetes mellitus in Germany. The characteristic “region” showed no effect modification for the primary outcome of the LEADER study. However, due to the different standards of care in the individual countries, the regions formed in the LEADER study were unsuitable to uncover a difference. The Franek 2016 publication on the LEADER study, for example, showed that, within the region of Europe, treatment differs notably between West and East European countries.

Since the intervention group received forced titration of liraglutide, the lowering of HbA1c values was notably less pronounced in the comparator group than in the liraglutide group at any time point of the study, despite identical specifications for both treatment groups to reach the target HbA1c and optimize standard therapy. Furthermore, the forced titration of liraglutide was conducted contrary to the information provided in the SPC of liraglutide. The lowering of systolic blood pressure was also consistently more pronounced in the intervention group than in the control group. Overall, it is unclear whether the effects on cardiovascular outcomes observed in the study were caused by liraglutide or by the different qualities of treatment in the treatment groups. In contrast, the rate of hypoglycaemia was lower in the intervention group than in the control group, despite the forced titration of liraglutide and the overall greater lowering of blood-glucose. Hence, a substance-specific effect of liraglutide can be assumed for this outcome.

Conclusion

Results of the LEADER study on patient-relevant outcomes

The positive and negative effects of liraglutide in addition to antidiabetic standard therapy resulting from the LEADER study differ depending on the extent of renal function disorder at the start of the study.

In patients with eGFR < 60 mL/min/1.73 m^2, the advantages of liraglutide regarding mortality, cardiovascular and cerebrovascular morbidity, hospitalization due to cardiac failure (for the latter outcome only in patients with cardiovascular disease) and symptomatic hypoglycaemic events (plasma glucose < 56 mg/dL) notably outweighed the disadvantages regarding the occurrence of gastrointestinal adverse events in the LEADER study.

Also in patients with eGFR ≥ 60 mL/min/1.73 m^2, the advantages of liraglutide regarding mortality, hospitalization due to cardiac failure (for the latter outcome only in patients with cardiovascular disease) and symptomatic hypoglycaemic events (plasma glucose < 56 mg/dL) outweighed the disadvantages regarding the occurrence of gastrointestinal adverse events and discontinuations due to SAEs or non-serious MESIs in the LEADER study.

Consequences of the limitations of the LEADER study for the interpretation of the results

The major limitations of the LEADER study have to be taken into account when considering the observed advantages of liraglutide.

It is not apparent that the requirements of lowering blood glucose and blood pressure mandated by the study protocol were sufficiently adhered to and that the treatment was adequately escalated in the course of the study. Despite identical specifications for both treatment groups to reach the target HbA1c and optimize standard therapy, the lowering of HbA1c values was notably less pronounced in the comparator group than in the liraglutide group at any time point of the study. The lowering of systolic blood pressure was also consistently more pronounced in the intervention group than in the control group.

Overall, it remains unclear whether the effects on cardiovascular outcomes observed in the study were caused by liraglutide or by the different quality of treatment in the treatment groups. In contrast, the rate of hypoglycaemia was lower in the intervention group than in the control group, despite the forced titration of liraglutide and the overall greater lowering of blood-glucose. Hence, a substance-specific effect of liraglutide can be assumed for this outcome.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-09-assessment-of-the-leader-study-on-liraglutide-rapid-report.7790.html.