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

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Abbreviation	Meaning
CI	confidence interval
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
HbA1c	glycosylated haemoglobin
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
RR	relative risk
SAE	serious adverse event

1   Background

On 6 August 2013 the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A13-16 (benefit assessment of vildagliptin) [1].

In the commenting procedure on the assessment of vildagliptin, the pharmaceutical company (hereinafter abbreviated to "the company") submitted further data to the G-BA that went beyond the information in the dossier.

These refer to expanded analyses of the study LAF237A2308:

- on the time course of the hypoglycaemias

- on subgroups of patients with baseline HbA1c value ($\geq 7\%/< 7\%$)

- on a subpopulation of patients with stable 2 mg glimepiride dosage (without further titration in the course of the study)

- on HbA1c-adjusted analyses of the risk of hypoglycaemia

The study LAF237A2308 (on the comparison of vildagliptin plus metformin versus glimepiride plus metformin) was already contained in the company's dossier. However, IQWiG did not use it for the assessment of the added benefit because of the specifications on the titration of glimepiride [1].

The commission of the G-BA for the assessment of the data presented in the company's comment reads as follows:

"The G-BA therefore commissions IQWiG to analyse these data with regard to the question as to whether they can be validly assessed for the interpretation of the occurrence of hypoglycaemias in relation to HbA1c values under consideration of an approval-compliant dosage and titration."

In the following Chapter 2, the additional analyses for the study LAF237A2308 are presented and assessed according to the commission.

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

2 Assessment

Introductory note

The study LAF237A2308 was conducted in the subindication "combination with metformin for the treatment of adult patients with type 2 diabetes mellitus with inadequate glycaemic control despite monotherapy with maximum tolerated doses of metformin (research question A2 of the dossier assessment A13-16 [1]).

After randomization, patients received either vildagliptin 50 mg twice a day or glimepiride 2 mg, 4 mg or 6 mg once a day with the respective placebo of the other drug (double-dummy) in addition to continued metformin. The metformin dose remained unchanged. The initial dose of glimepiride was 2 mg a day and was up-titrated by 2 mg steps as long as the fasting blood glucose levels were above 100 mg/dl and the titration was not contraindicated because of the risk of hypoglycaemia according to the investigator's assessment. Hence glimepiride could not be used in the study LAF237A2308 as it is in reality. In fact, 1 mg and 3 mg dosages were not available to the investigators. The study design made it therefore impossible to conduct a treatment optimized for the individual patient by using the options of an approval-compliant use of glimepiride. Further information on the design of the study LAF237A2308 can be found in the dossier assessment A13-16 [1].

None of the analyses presented by the company with the comments addressed the problem mentioned above. However, because of the design of the study, no analyses are conceivable that would allow reliable conclusions on a treatment optimized for the individual patient by using all glimepiride dosages that are available. So even considering the supplementary analyses presented by the company, the study LAF237A2308 is therefore unsuitable for the assessment of the added benefit of vildagliptin versus a comparator therapy with glimepiride that uses all possibilities of approval-compliant administration. The following assessment of the data subsequently submitted is therefore solely conducted with regards to the research question investigated in the study, i.e. the comparison of vildagliptin with glimepiride without using the glimepiride dosages of 1 mg and 3 mg and under unilateral specification of a treatment goal of 100 mg/dl (fasting blood glucose) for glimepiride.

2.1 Analyses on the time course of hypoglycaemias

With the comments, the company presented analyses of the study LAF237A2308 on the time course of hypoglycaemias during the 104-week treatment phase.
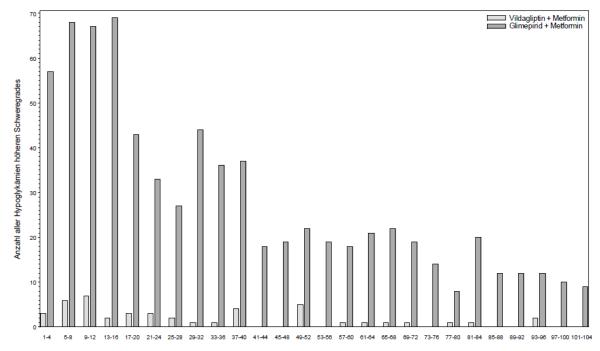
The analyses referred to hypoglycaemias classified as serious or significant. Symptomatic events were rated as "serious" when the assistance of another party was required, either with ("Grade 2") or without ("suspected Grade 2") confirmation by blood glucose measurement (blood glucose < 50 mg/dl). Symptomatic events confirmed by blood glucose measurement (blood glucose < 50 mg/dl) were rated as "significant" when the patient was able to treat himself or herself ("Grade 1"), but the event resulted in an adjustment of the dosage of the study medication, in treatment discontinuation, or in further drug or non-drug intervention.

The vast majority of the events of the combined outcome (800 out of 815, 98.2%) were "significant" events, which did not require assistance of another party, i.e. non-severe hypoglycaemias. Hence only conclusions on non-severe hypoglycaemias could be derived from the analyses presented by the company.

Figure 1 shows the course of the number of hypoglycaemias classified as "serious" or "significant" during the 104-week treatment phase with vildagliptin plus metformin or glimepiride plus metformin. Figure 2 shows the corresponding course of the HbA1c mean value.
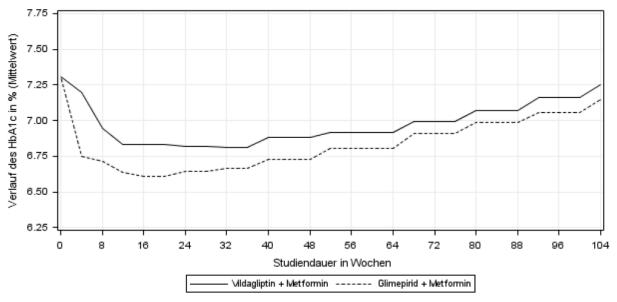
It emerged that the number of hypoglycaemias was noticeably high under glimepiride particularly in the first 16 weeks. This corresponds to the rapid decrease of the HbA1c value to the minimum mean value in week 16 (approximately 6.6%). Hypoglycaemias already occurred up to week 4 in a large proportion of patients, i.e. under the lowest glimepiride dosage used in the study (2 mg/day). Hence these hypoglycaemias could not be explained directly by the titration, but rather by the initial dose of glimepiride used, which was not the minimum dose (1 mg/day).

In the further course of the study, the number of hypoglycaemias decreased considerably. But hypoglycaemias still occurred continuously (e.g. in the second year). However, the greater reduction of blood-glucose under glimepiride remained apparent until the end of the study, even though it was less pronounced (and therefore of questionable relevance). It remained unclear to what extent the difference observed with regards to hypoglycaemias was caused by the more pronounced reduction of blood glucose.

y-axis: Number of all hypoglycaemias with higher grade of severity

Figure 1: Course of the hypoglycaemias classified as "serious" or "significant" during the 104-week treatment phase in the study LAF237A2308

x-axis: Study duration in weeks
y-axis: Course of HbA1c in % (mean value)

Figure 2: Course of the HbA1c value (mean value) during the 104-week treatment phase in the study LAF237A2308 (ITT population, LOCF analysis)

2.2   Subgroup analyses according to baseline HbA1c value

With the comments, the company presented analyses in a subpopulation of the study LAF237A2308 with a baseline HbA1c value of $\geq 7\%$.

According to the company, the aim of these analyses was to show that the advantage of vildagliptin plus metformin versus glimepiride plus metformin in the study LAF237A2308 did not depend on the baseline HbA1c value, and particularly also applied to patients with a baseline HbA1c value of $\geq 7\%$. The company primarily addressed the outcomes "hypoglycaemias", "body weight" and "adverse events". The company did not present any corresponding analyses for further patient-relevant outcomes such as cardiac and cerebral morbidity, which were presented in the dossier assessment A13-16. For this reason and because of the objective formulated in the G-BA's commission (interpretation of the results on hypoglycaemias), only the analyses on hypoglycaemias in relation to the reduction of blood glucose are considered in the following text.

The company presented analyses on different hypoglycaemia operationalizations. In addition to the operationalizations (Grade 2, suspected Grade 2, Grade 1 hypoglycaemias with specific treatment requirements ["significant" hypoglycaemias]) described in Section 2.1, these were the following:

- Grade 1 hypoglycaemias without specific treatment requirements

- Hypoglycaemias classified as serious adverse event (SAE)

- Hypoglycaemias classified as severe adverse event

None of the operationalizations presented was suitable to distinguish severe hypoglycaemias from non-severe hypoglycaemias with sufficient certainty, because none of the operationalizations required the presence of severe symptoms (e.g. neurological dysfunctions, coma) that could only be resolved using medical interventions (e.g. glucose infusion). This also applied to hypoglycaemias classified as SAEs, which, deviating from the general definition of SAEs, also included hypoglycaemias that required assistance of another party that did not have to involve medical interventions. The considerations below therefore only refer to non-severe hypoglycaemias (Grade 1[3]).

The results on non-severe hypoglycaemias are presented in Table 1. Figure 3 shows the occurrence of non-severe hypoglycaemias over the course of the study, Figure 4 shows the mean HbA1c value over the course of the study.

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[3] The vast majority of Grade 1 hypoglycaemias were hypoglycaemias with specific treatment requirements ("significant" hypoglycaemias): 51 out of 58 events under vildagliptin (87.9%) and 749 out of 799 events under glimepiride (93.7%).

Table 1: Subgroups: non-severe confirmed hypoglycaemias according to baseline HbA1c value at the start of the study (≥ 7%/< 7%), RCT, direct comparison: therapeutic strategy "vildagliptin plus metformin" vs. therapeutic strategy "glimepiride plus metformin" (study LAF237A2308)

Outcome Characteristic Subgroup	Therapeutic strategy "vildagliptin plus metformin"		Therapeutic strategy "glimepiride plus metformin"		Vildagliptin + metformin vs. glimepiride + metformin	
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]	p-value
Non-severe confirmed hypoglycaemias (blood glucose < 50 mg/dl)						
Total population	1539	34 (2.2)	1520	266 (17.5)	0.13 [0.09; 0.18]	< 0.001
Baseline HbA1c value						
≥ 7%	1051	16 (1.5)	1011	158 (15.6)	0.10 [0.06; 0.16]	< 0.001
< 7%	488	18 (3.7)	509	108 (21.2)	0.17 [0.11; 0.28][b]	< 0.001
					Interaction	0.103[c]

a: ITT population: defined as all randomized patients who received at least one dose of the study medication and who had at least one efficacy assessment after the start of the study (post-baseline) during the dual therapy (assessments during the emergency treatment were not considered).
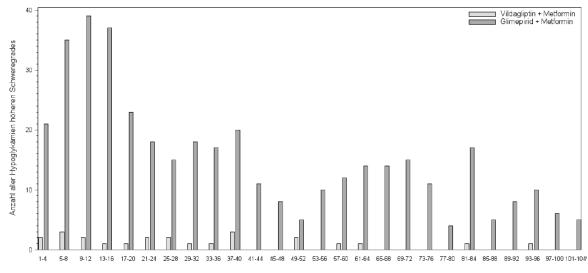b: Institute's calculation of RR, asymptotic.
c: Institute's calculation.
CI: confidence interval; ITT: intention to treat; N: number of analysed patients; n: number of patients with event; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Non-severe hypoglycaemias were statistically significantly more common under glimepiride than under vildagliptin both in patients with a baseline HbA1c value of < 7% and in patients with a baseline HbA1c value of ≥ 7%. The effects in both groups and in the total population were large. However, there was an indication of an interaction: The effect was even more pronounced in patients with a baseline HbA1c value of ≥ 7% (relative risk [RR]: 0.10; 95% confidence interval [CI] [0.06; 0.16]) than in patients with an HbA1c value of < 7% (RR: 0.17; 95% CI [0.11; 0.28]). In contrast, the absolute risk of hypoglycaemia in both treatment groups was higher in patients with a baseline HbA1c value of < 7% than in patients with an HbA1c value of ≥ 7%, as was to be expected.

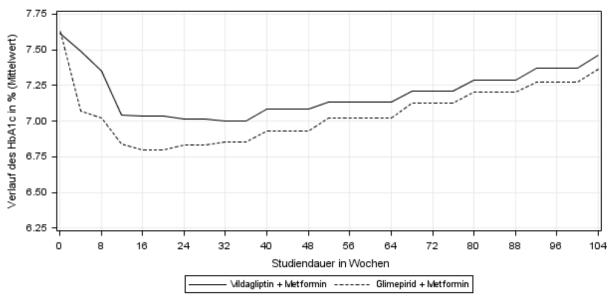The analyses on the time course of the hypoglycaemias and the HbA1c values showed a similar course for patients with a baseline HbA1c value of ≥ 7% (Figure 3, Figure 4) as in the total population (Figure 1, Figure 2).

In summary, it can be assumed that the results of the study LAF237A2308 on the outcome "non-severe hypoglycaemias" can be used equally for patients with a baseline HbA1c value of ≥ 7% and of <7%.

y-axis: Number of hypoglycaemias with higher grade of severity

Figure 3: Course of the hypoglycaemias classified as "serious" or "significant" during the 104-week treatment phase in the study LAF237A2308 – patients with a baseline HbA1c value of ≥ 7%

x-axis: Study duration in weeks
y-axis: Course of HbA1c in % (mean value)

Figure 4: Course of the HbA1c value (mean value) during the 104-week treatment phase in the study LAF237A2308 (ITT population, LOCF analysis) – patients with a baseline HbA1c value of ≥ 7%

2.3 Subpopulation with stable glimepiride dose of 2 mg

With the comments, the company presented analyses in a subpopulation of the study LAF237A2308 with stable glimepiride dose of 2 mg/day (or glimepiride placebo of 2 mg/day).

According to the company, the aim of these analyses was to show that the titration scheme chosen in the study (from 2 mg/day to 4 mg/day; from 4 mg/day to 6 mg/day) did not influence the study results on hypoglycaemias because the corresponding effects in the subpopulation with stable glimepiride dosage are comparable to the ones of the total population.

In the study arm with vildagliptin plus metformin, glimepiride placebo was given at a stable dose of 2 mg a day to 263 patients in total. In the glimepiride arm, 417 patients received 2 mg glimepiride a day.

The grouping variable (glimepiride dose) was not determined at the start of the study, but only arose in the course of the study and therefore depended on the treatment. This also explains the marked imbalance regarding the number of patients between the groups. The analyses of this subpopulation presented therefore did no longer constitute a randomized comparison of vildagliptin with glimepiride because the groups to be compared were formed on the basis of a non-random self-selection by the patients (individual treatment response). Hence the structural equality of the vildagliptin group in comparison with the glimepiride group was no longer guaranteed in this type of analysis, and the results could therefore no longer be interpreted.

2.4 HbA1c-adjusted analyses of the risk of hypoglycaemia

With the comments, the company presented further analyses, in which it investigated the risk of hypoglycaemia (at week 18) of vildagliptin plus metformin versus glimepiride plus metformin depending on the last HbA1c value measured.

The analysis was aimed at considering the risk of occurrence of a hypoglycaemia after adjustment for the HbA1c value last measured to demonstrate that the advantage of vildagliptin in hypoglycaemias is independent from the present HbA1c value.

Analyses of hypoglycaemias with adjustment for the HbA1c value last measured are only of limited suitability to draw conclusions on the effects of treatments on the risk of hypoglycaemias. The results of this kind of analyses (adjusted for values based on follow-up information) are subject to a high risk of bias because the adjusting factor (the HbA1c value last measured) is an entity arising in the course of the study [2]. Similarly to the analyses of the subpopulation with stable glimepiride dose of 2 mg, it cannot be excluded and is shown by the data that the treatment influenced the adjusting characteristic (here: HbA1c value last measured). In addition, the analyses presented were limited to the time of 18 weeks after the

start of the study. Moreover, the HbA1c value is suitable for assessing the mean reduction of blood glucose in the course of the study, and therefore for answering the question whether similar reduction of blood glucose between the treatment groups over the study period could be assumed. But it is unsuitable as adjusting factor at the level of the individual patient because the current HbA1c value of a patient only allows to draw limited conclusions on the current blood glucose level.

In the present case, the study effects were already to be regarded as uncertain because it was unclear to what extent the different reductions of blood glucose contributed to the difference regarding hypoglycaemias. The analyses presented by the company were unsuitable to reduce this uncertainty for the reasons mentioned above.

3 Data sources for the study assessed

Novartis. A multicenter, randomized, double-blind, active controlled study to compare the long-term effect of treatment with LAF237 50 mg bid to glimepiride up to 6 mg daily as add-on therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: study LAF237A 2308; full clinical study report [unpublished]. 2008.

Novartis. Weitere Unterlagen zu Vildagliptin und Vildagliptin/Metformin: Zusatzauswertungen zu Studie LAF237A2308 [unpublished]. 2013.

Novartis. Zusatzauswertungen der Teilpopulation von Patienten mit konstanter 2 mg Glimepirid-Behandlung während der Studie LAF237A2308 [unpublished]. 2013.

Novartis. Zusatzauswertungen von Patienten mit Hypoglykämien pro Zeitintervall der Studie LAF237A2308 [unpublished]. 2013.

Novartis. Zusatzauswertungen der Teilpopulation von Patienten mit HbA$_{1c}$-Ausgangswert von 7 und höher zu Beginn der Studie LAF237A2308 [unpublished]. 2013.

Novartis. Zusatzauswertungen zu den Studien LAF237A2308, LAF237A2310, LAF237A23135 und LAF237AFR03 [unpublished]. 2013.

Novartis Pharma. Vildagliptin (Galvus, Jalra, Xiliarx): Dossier zur Nutzenbewertung gemäß § 35a SGB V; Modul 4A; Diabetes mellitus Typ 2; medizinischer Nutzen und medizinischer Zusatznutzen; Patientengruppen mit therapeutisch bedeutsamem Zusatznutzen [online]. 25 March 2013 [accessed: 27 August 2013]. URL: http://www.g-ba.de/downloads/92-975-303/2013-03-25_Modul4A_Vildagliptin.pdf.

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