IQWiG Reports – Commission No. A13-31

Addendum to Commission A13-17 (vildagliptin/metformin)[1]

Addendum

Commission: A13-31
Version: 1.0
Status: 29 August 2013

[1] Translation of addendum A13-31 "Addendum zum Auftrag A13-17 (Vildagliptin/Metformin)" (Version 1.0; Status: 29 August 2013). 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:
Addendum to Commission A13-17 (vildagliptin/metformin)

Commissioning agency:
Federal Joint Committee

Commission awarded on:
6 August 2013

Internal Commission No.:
A13-31

Address of publisher:
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Keywords: vildagliptin/metformin, diabetes mellitus – type 2, benefit assessment

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

Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
AE	adverse event
CCV	cardiovascular and cerebrovascular
CI	confidence interval
DSC-R	Diabetes Symptom Checklist-Revised
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)
ITT	intention to treat
MCS	Mental Component Summary
OR	odds ratio
PCS	Physical Component Summary
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SF-36	Short Form (36) Health Survey

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 A13-17 (benefit assessment of vildagliptin/metformin) [1].

The study LAF237A2308 presented by the pharmaceutical company (hereinafter abbreviated to "the company") could not be used in the original benefit assessment for the assessment of vildagliptin/metformin because it was unclear how many patients received the metformin dose of $\geq$ 1700 mg/day, which concurs with the approval of the fixed combination vildagliptin/metformin, and because the company did not prove that the results of the study were independent from the metformin dose administered.

In the commenting procedure on the assessment of vildagliptin/metformin, the company submitted further data to the G-BA that went beyond the information in the dossier. These refer to analyses for the subpopulation of the patients of the study LAF237A2308 who were treated with a metformin dose of 1700 mg/day to 3000 mg/day.

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 assess the data submitted in the comment."

In the following Chapter 2, the expanded 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 following assessment is solely conducted to clarify the question whether the data of the total population of the study LAF237A2308 can be used for the assessment of the fixed combination vildagliptin/metformin or whether conclusions on the fixed combination can only be drawn on the basis of the data of the subpopulation with a metformin dose of ≥ 1700 mg/day. The question whether the study LAF237A2308 is generally suitable for the assessment of the added benefit is not assessed. You can find further information on this in the assessments A13-17 (vildagliptin/metformin) [1] and A13-16 (vildagliptin) [2] with the result that, due to its design, the study LAF237A2308 is unsuitable for the assessment of the added benefit of vildagliptin or vildagliptin/metformin versus a comparator therapy in which all options of approval-compliant administration of glimepiride or glimepiride/metformin are used.

Assessment

The distribution of the patients according to the metformin dose in the study LAF237A2308 is presented in Table 1.

Table 1: Distribution of the patients according to the metformin dose in the study LAF237A2308

	Therapeutic strategy "vildagliptin/metformin" N[a] = 1553	**Therapeutic strategy "glimepiride plus metformin" N[a] = 1546**
Metformin dose	**n (%)**	**n (%)**
< 1700 mg/day	389[b] (25.0)	417[b] (27.0)
≥ 1700 mg/day	1164 (75.0)	1129 (73.0)

a: Safety population (SAF): defined as all randomized patients who received at least one dose of the study medication and who had at least one safety assessment after the start of the study (post-baseline).
b: Institute's calculation.
N: number of analysed patients; n: number of patients in the dose category

The majority of patients of the study LAF237A2308 received the approval-compliant metformin dose of ≥ 1700 mg/day (approximately 74% of the patients). The company did not present any patient characteristics for the patients with the approval-compliant metformin dose of ≥ 1700 mg/day.

IQWiG conducted subgroup analyses for the characteristic "metformin dose (< 1700 mg/day / ≥ 1700 mg/day)" to answer the present research question. The results of these subgroup analyses are presented below together with the ones of the total population of the study LAF237A2308 (from the dossier assessment for vildagliptin A13-16 [2]). The data subsequently submitted by the company were, where necessary, supplemented by the

Institute's calculations. The tables contain results on the overall rate of adverse events (AEs) and on the change in body weight as additional information.

The odds ratio (OR) offers a good approximation of the relative risk (RR) in low numbers of events. Hence in event rates of ≤ 1% (in at least one cell), the Peto OR instead of the RR was calculated as effect measure and used for the assessment.

Table 2 and Table 3 present the results for the comparison of vildagliptin/metformin versus glimepiride plus metformin. The forest plots of the subgroup analyses can be found in Appendix A.

Table 2: Results (dichotomous outcomes) – RCT, direct comparison: therapeutic strategy "vildagliptin/metformin" vs. therapeutic strategy "glimepiride plus metformin" (LAF237A2308)

Outcome category **Outcome** **Population**	**Therapeutic strategy "vildagliptin/ metformin"**		**Therapeutic strategy "glimepiride plus metformin"**		**Vildagliptin/ metformin vs. glimepiride + metformin**
	N[a]	**Patients with events n (%)**	**N[a]**	**Patients with events n (%)**	**RR/Peto OR [95% CI]; p-value**
Mortality					
All-cause mortality					
Total population	1553	7 (0.5)[b]	1546	6 (0.4)	1.16 [0.39; 3.45]; 0.787[c]
< 1700 mg/day[d]	389	0 (0)	417	2 (0.5)	0.14 [0.01; 2.32]; n.c.[c]
≥ 1700 mg/day	1164	7 (0.6)	1129	4 (0.4)	1.68 [0.51; 5.48]; 0.392[c]
				Interaction	p = 0.111[e]
Morbidity					
Cardiovascular and cerebrovascular morbidity (CCV)[f]					
Total population	1553	59 (3.8)	1546	60 (3.9)	0.98 [0.69; 1.39]; 0.926[g]
< 1700 mg/day				n.d.	
≥ 1700 mg/day				n.d.	
Cardiac morbidity[h]					
Total population	1553	42 (2.7)	1546	42 (2.7)	1.00 [0.65; 1.52]; > 0.999[g]
< 1700 mg/day				n.d.	
≥ 1700 mg/day				n.d.	
Cerebral morbidity[i]					
Total population	1553	32 (2.1)	1546	29 (1.9)	1.10 [0.67; 1.81]; 0.796[g]
< 1700 mg/day				n.d.	
≥ 1700 mg/day				n.d.	

(continued)

Table 2: Results (dichotomous outcomes) – RCT, direct comparison: therapeutic strategy "vildagliptin/metformin" vs. therapeutic strategy "glimepiride plus metformin" (LAF237A2308) (continued)

Outcome category Outcome Population	Therapeutic strategy "vildagliptin/ metformin"		Therapeutic strategy "glimepiride plus metformin"		Vildagliptin/ metformin vs. glimepiride + metformin
	N[a]	Patients with events n (%)	N[a]	Patients with events n (%)	RR [95% CI]; p-value
Adverse events					
Hypoglycaemias					
Severe hypoglycaemias[j]	No evaluable data				
Non-severe confirmed hypoglycaemias[k] (blood glucose < 50 mg/dl)					
Total population	1539[l]	34 (2.2)	1520[l]	266 (17.5)	0.13 [0.09; 0.18]; < 0.001
< 1700 mg/day[d]	386[l]	4 (1.0)	409[l]	67 (16.4)	0.06 [0.02; 0.17]; n.c.
≥ 1700 mg/day	1153[l]	30 (2.6)	1111[l]	199 (17.9)	0.15 [0.10; 0.21]; < 0.001
				Interaction	p = 0.122[e]
Change in HbA1c	See Figure 3 and Figure 4 for data on HbA1c during the course of the study				
Pancreatitis[m]					
Total population	1553	6 (0.4)	1546	6 (0.4)	1.00 [0.32; 3.09]; > 0.999
< 1700 mg/day				n.d.	
≥ 1700 mg/day				n.d.	
Renal impairment[n]					
Total population	1553	97 (6.2)	1546	89 (5.8)	1.08 [0.82; 1.43]; 0.597[g]
< 1700 mg/day				n.d.	
≥ 1700 mg/day				n.d.	
Overall rate AEs[o]					
Total population	1553	1291 (83.1)	1546	1335 (86.4)	n.c.
< 1700 mg/day[d]	389	317 (81.5)	417	357 (85.6)	n.c.
≥ 1700 mg/day	1164	974 (83.7)	1129	978 (86.6)	n.c.
				Interaction	n.c.
Overall rate SAEs[o]					
Total population	1553	236 (15.2)	1546	253 (16.4)	0.93 [0.79; 1.09]; 0.38
< 1700 mg/day[d]	389	57 (14.7)	417	63 (15.1)	0.97 [0.70; 1.35]
≥ 1700 mg/day	1164	179 (15.4)	1129	190 (16.8)	0.91 [0.76; 1.10]
				Interaction	p = 0.758[e]

(continued)

Table 2: Results (dichotomous outcomes) – RCT, direct comparison: therapeutic strategy "vildagliptin/metformin" vs. therapeutic strategy "glimepiride plus metformin" (LAF237A2308) (continued)

Outcome category **Outcome** **Population**	**Therapeutic strategy "vildagliptin/ metformin"**		**Therapeutic strategy "glimepiride plus metformin"**		**Vildagliptin/ metformin vs. glimepiride + metformin**
	N[a]	**Patients with events n (%)**	**N[a]**	**Patients with events n (%)**	**RR [95% CI]; p-value**
Discontinuations due to AEs[o]					
Total population	1553	130 (8.4)	1546	166 (10.7)	0.78 [0.63; 0.97]; 0.03
< 1700 mg/day[d]	389	32 (8.2)	417	45 (10.8)	0.76 [0.50; 1.17]
≥ 1700 mg/day	1164	98 (8.4)	1129	121 (10.7)	0.79 [0.61; 1.01]
				Interaction	p = 0.906[e]

a: Safety population (SAF): defined as all randomized patients who received at least one dose of the study medication and who had at least one assessment after the start of the study (post-baseline).
b: In the dossier assessment on Commission A13-16 (vildagliptin), 11 deaths were documented in the total population, although only 7 deaths were reported in the dossier. It could be inferred from the clinical study report that another 4 patients died after study discontinuation. The metformin dose of these patients was unclear, however. The Institute therefore dispensed with a presentation of the 4 additional deaths.
c: Institute's calculation: asymptotic estimate and CI, Peto OR due to low event rates; Fisher's exact test for p-value.
d: Institute's calculation of the number of patients and the number of patients with event.
e: Institute's calculation (see Appendix A)
f: Outcome with a choice of HLGTs and PTs defined a priori in the following areas: ACS, heart rhythm disorders, decompensated cardiac failure, death, peripheral vascular disorders, stroke, syncope, TIA; events were confirmed by independent and blinded CCV adjudication committee.
g: Institute's calculation: asymptotic estimate and CI for RR; Fisher's exact test for p-value.
h: serious cardiac events; recorded using MedDRA SOC "cardiac disorders".
i: serious cerebral events; recorded using MedDRA SOC "nervous system disorders".
j: Results on severe hypoglycaemias could not be derived from the available operationalizations (see also assessments A13-16 (vildagliptin) [2] and A13-30 (addendum on the assessment of vildagliptin) [3].
k: Non-serious hypoglycaemias are symptomatic Grade-1 hypoglycaemias with a blood glucose value of < 50 mg/dl in which the patient is able to treat himself or herself.
l: Intention-to-treat (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).
m: Includes the following MedDRA PTs: pancreatitis, pancreatitis acute, and pancreatitis chronic.
n: MedDRA SOC “renal and urinary disorders”.
o: Hypoglycaemic events were also included here. In the overall rate of SAEs, this applied to 1 versus 13 patients with hypoglycaemias in the total population. Regarding the outcome "discontinuations due to AEs", 0 versus 14 patients in the total population discontinued treatment due to hypoglycaemias. Without these patients with event, there is an effect of 0.85 [0.68; 1.06].

ACS: acute coronary syndrome; AE: adverse event; CCV: cardiovascular and cerebrovascular; CI: confidence interval; HbA1c: glycosylated haemoglobin; HLGT: High Level Group Term; MedDRA: Medical Dictionary for Regulatory Activities; N: Number of analysed patients; n: number of patients with event; n.c.: not calculated; n.d.: no data; OR: odds ratio; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; TIA: transient ischaemic attack; vs.: versus

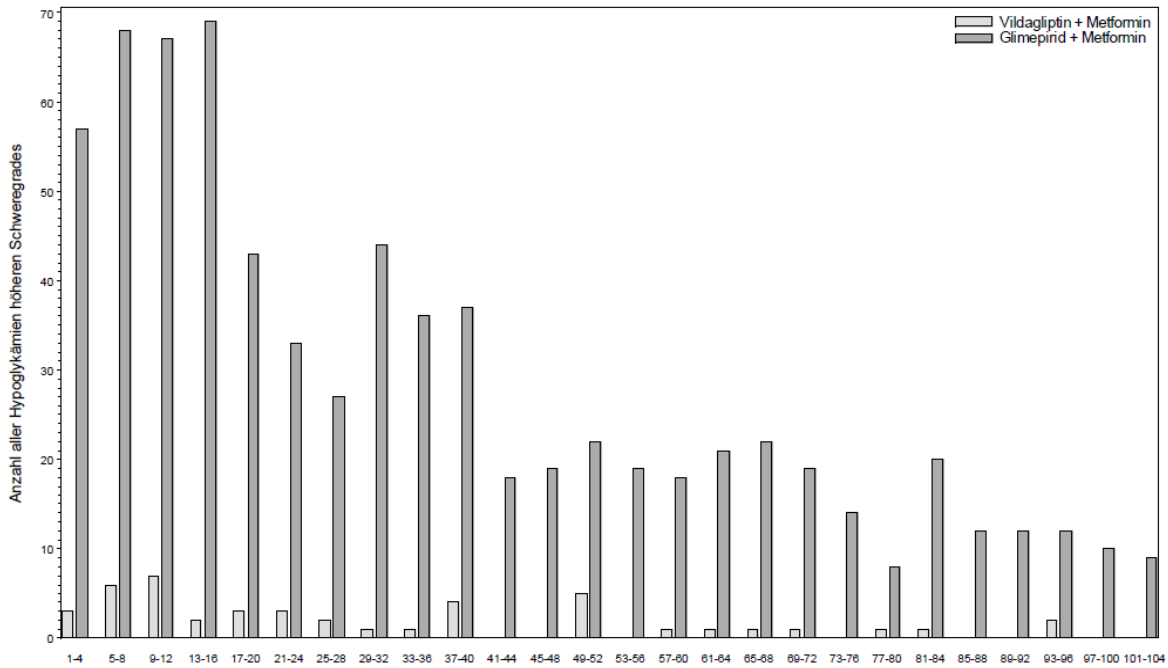
Table 3: Results (continuous outcomes) – RCT, direct comparison: therapeutic strategy "vildagliptin/metformin" vs. therapeutic strategy "glimepiride plus metformin" (LAF237A2308)

Outcome category Outcome Population	Therapeutic strategy "vildagliptin/metformin"			Therapeutic strategy "glimepiride plus metformin"			Vildagliptin/ metformin vs. glimepiride + metformin
	N[a]	Values at start of study mean (SE)	Change at end of study mean (SE)	N[a]	Values at start of study mean (SE)	Change at end of study mean (SE)	Difference [95% CI]; p-value
Morbidity							
Symptoms[b]							
Total population	1322	18.22 (0.43)	0.15 (0.34)	1289	17.84 (0.41)	0.35 (0.34)	-0.20 [-1.14; 0.73]; 0.67[c]
< 1700 mg/day	323[d]	n.d.	n.d.	334[d]	n.d.	n.d.	-0.23 [-0.85; 0.39][e]
≥ 1700 mg/day	999	5.40 (0.15)	0.02 (0.12)	955	5.35 (0.14)	0.21 (0.12)	-0.19 [-0.51; 0.13][c]
						Interaction	p = 0.914[f]
Health-related quality of life							
SF-36: PCS[g]							
Total population	1347	48.48 (0.25)	20.45 (0.03)	1301	48.50 (0.26)	20.43 (0.03)	0.02 [-0.06; 0.09]; 0.68[c]
< 1700 mg/day	334[d]	n.d.	n.d.	333[d]	n.d.	n.d.	0.02 [-0.13; 0.17][e]
≥ 1700 mg/day	1013	28.08 (0.04)	-0.01 (0.03)	968	28.07 (0.04)	-0.04 (0.03)	0.02 [-0.06; 0.11][c]
						Interaction	p > 0.999[f]
SF-36: MCS[g]							
Total population	1347	49.00 (0.32)	31.68 (0.04)	1301	49.40 (0.30)	31.66 (0.04)	0.03 [-0.08; 0.14]; 0.63[c]
< 1700 mg/day	334[d]	n.d.	n.d.	333[d]	n.d.	n.d.	0.02 [-0.17; 0.21][e]
≥ 1700 mg/day	1013	17.59 (0.05)	-0.14 (0.05)	968	17.72 (0.05)	-0.18 (0.05)	0.04 [-0.08; 0.17][c]
						Interaction	p = 0.863[f]
Supplementary outcome "body weight"							
Body weight							
Total population	1539	89.42 (0.46)	-0.26 (0.11)	1520	88.76 (0.46)	1.19 (0.11)	-1.45 [-1.74; -1.16]; < 0.001[c]
< 1700 mg/day	386[d]	n.d.	n.d.	409[d]	n.d.	n.d.	-1.17 [-1.65; -0.68][e]; n.c.
≥ 1700 mg/day	1153	88.86 (0.53)	-0.35 (0.12)	1111	89.25 (0.54)	1.20 (0.12)	-1.55 [-1.87; -1.22]; < 0.001[c]
						Interaction	p = 0.199[f]

(continued)

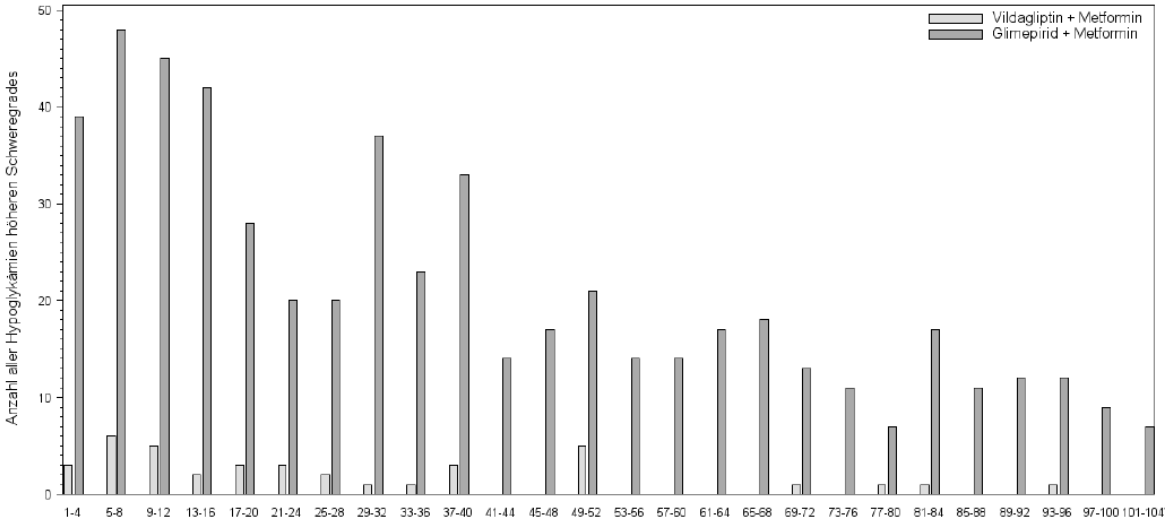
Table 3: Results (continuous outcomes) – RCT, direct comparison: therapeutic strategy "vildagliptin/metformin" vs. therapeutic strategy "glimepiride plus metformin" (LAF237A2308) (continued)

a: Number of patients with observations at the start and end of the study.
b: Recorded with the symptom scale DSC-R; higher values indicate a higher perceived burden of disease (of physical and psychological symptoms associated with type 2 diabetes mellitus and its complications).
c: Adjusted mean values, standard errors, confidence intervals and p-values result from the ANCOVA model (with treatment as factor and baseline scale value as covariate, or weight to baseline and pooled centre as covariables).
d: Institute's calculation.
e: Institute's calculation from data on total population and subpopulation (metformin dose ≥ 1700 mg/day): effect was estimated as weighted difference of the effects of total population and subpopulation and under assumption of the same variances in the subpopulations.
f: Institute's calculation (see Appendix A)
g: Higher values indicate higher health-related quality of life.
CI: confidence interval; DSC-R: Diabetes Symptom Checklist-Revised; MCS: Mental Component Summary; N: number of analysed patients; n.c.: not calculated; n.d.: no data; PCS: Physical Component Summary; RCT: randomized controlled trial; SE: standard error; SF-36: Short Form (36) Health Survey; vs.: versus



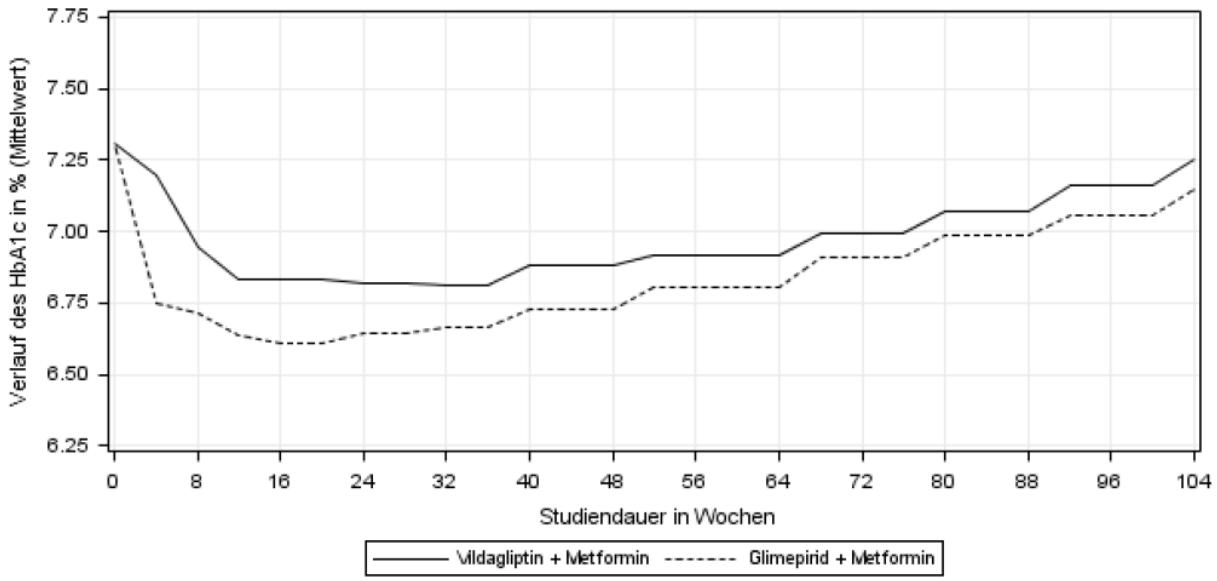
y-axis: Number of all hypoglycaemias with higher grade of severity

Figure 1: Course of the hypoglycaemias classified as "serious" or "significant" during the 104-week treatment phase (study LAF237A2308) – total population



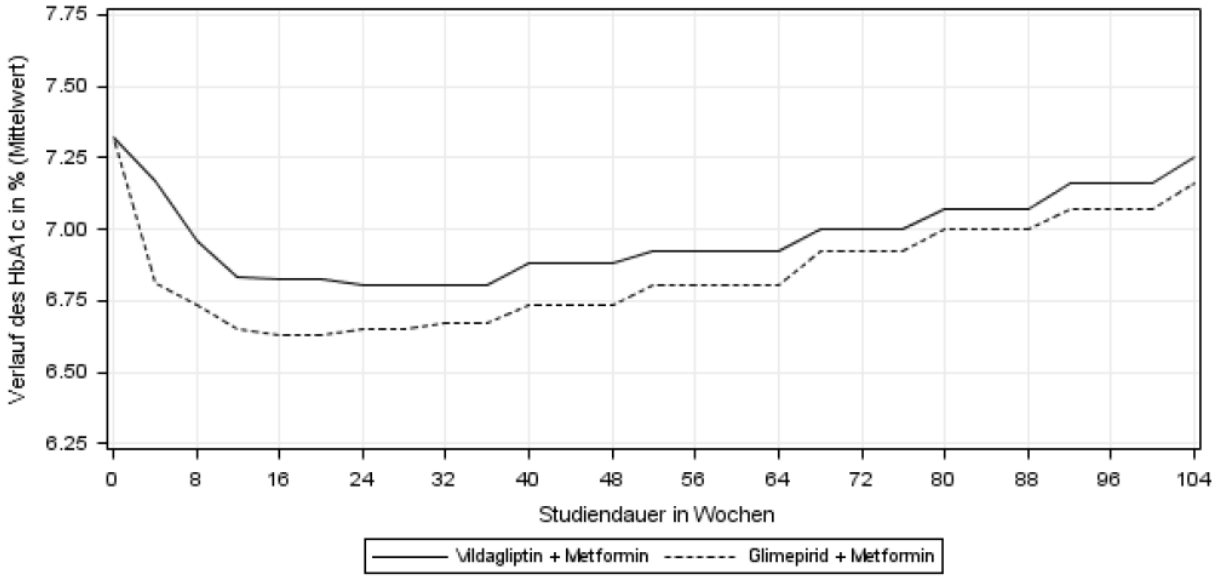
y-axis: Number of all hypoglycaemias with higher grade of severity

Figure 2: Course of the hypoglycaemias classified as "serious" or "significant" during the 104-week treatment phase (study LAF237A2308) – patients with a metformin dose of 1700–3000 mg/day



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

Figure 3: Course of the HbA1c value (mean value) during the 104-week treatment phase (study LAF237A2308, ITT population, LOCF analysis) – total population



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 (study LAF237A2308, ITT population, LOCF analysis) – patients with a metformin dose of 1700–3000 mg/day

The subgroup analyses for the characteristic "metformin dose" showed neither indications nor proof of an interaction for the outcomes "overall rate of SAEs", "discontinuations due to AEs", "health-related quality of life" and "disease-specific symptoms" ($p \geq 0.2$). Moreover, the effect estimates of the patient group with a metformin dose of ≥ 1700 mg/day and of the total population showed in the same direction and were of similar magnitude.

The subgroup analysis on the metformin dose for the outcome "all-cause mortality" resulted in an indication of effect modification ($p = 0.111$). The effects in the groups with different metformin doses showed in different directions, but the results were not statistically significant. Overall, the indication of interaction did not have any consequences for the assessment.

The company did not present any data for the outcomes "cardiac morbidity" and "cerebral morbidity" and the combined outcome "cardiovascular and cerebrovascular morbidity (CCV)", as well as for the outcomes on particular AEs (renal impairment and pancreatitis) for the relevant subpopulation with a metformin dose of ≥ 1700 mg/day. It was unclear for these outcomes whether there was an effect modification. In all outcomes, the result in the total population was not statistically significant.

The subgroup analysis on the metformin dose for the outcome "non-severe confirmed hypoglycaemias (blood glucose < 50 mg/dl)" resulted in an indication of effect modification ($p = 0.122$). Non-severe hypoglycaemias were statistically significantly more common under glimepiride plus metformin than under vildagliptin/metformin both in patients with a metformin dose of < 1700 mg/day and in patients with a metformin dose of ≥ 1700 mg/day. The effects in both groups and in the total population were large. The effect was even more pronounced in patients with a metformin dose of < 1700 mg/day (RR: 0.06; 95% confidence interval [CI] [0.02; 0.17]) than in patients with a metformin dose of ≥ 1700 mg/day (RR: 0.15; 95% CI [0.10; 0.21]). The effect of the total population (RR: 0.13; 95% CI [0.09; 0.18]) was comparable to the effect in the subpopulation with a metformin dose of ≥ 1700 mg/day. The analyses on the time course of the hypoglycaemias and the HbA1c mean values also showed a similar course for patients with a metformin dose of ≥ 1700 mg/day as in the total population.

Summary

It can be assumed for most outcomes that there was no effect modification from the metformin dose or that this was not relevant for the assessment. The presence of an effect modification could not be assessed for some outcomes on morbidity and on specific AEs because the company did not present any data on this. The result in the total population was not statistically significant in any of these outcomes. Overall, it seems possible to also draw conclusions on the fixed combination vildagliptin/metformin from the available data on the total population of the study LAF237A2308.

3 Data sources for the study assessed

Novartis. 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: 28 August 2013]. URL: http://www.g-ba.de/downloads/92-975-308/2013-03-25_Modul4A_Vildagliptin-Metformin.pdf.

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

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

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

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.

4 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vildagliptin/Metformin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-17 [online]. 27 June 2013 [accessed: 20 August 2013]. (IQWiG-Berichte; Volume 179). URL: https://www.iqwig.de/download/A13-17_Vildagliptin-Metformin_Nutzenbewertung-35a-SGB-V.pdf.

2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Vildagliptin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-16 [online]. 27 June 2013 [accessed: 12 August 2013]. (IQWiG-Berichte; Volume 178). URL: https://www.iqwig.de/download/A13-16_Vildagliptin_Nutzenbewertung-35a-SGB-V.pdf.

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Addendum zum Auftrag A13-16 (Vildagliptin): Auftrag A13-30. Köln: IQWiG; 2013. (IQWiG-Berichte; Volume 188).

Appendix A – Forest plots of the subgroup analyses for the characteristic "metformin dose", vildagliptin/metformin versus glimepiride plus metformin

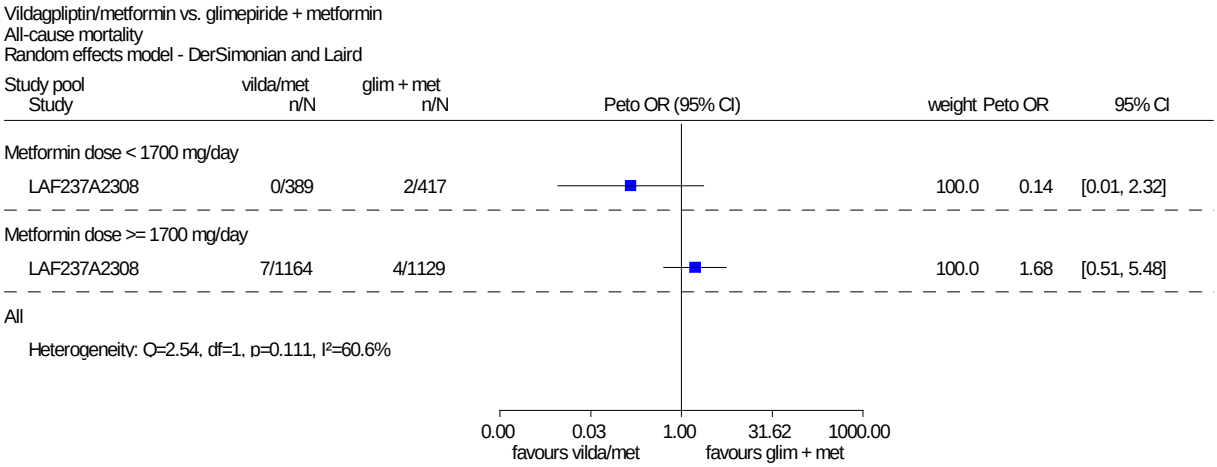


Figure 5: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) all-cause mortality – RCT, direct comparison: vildagliptin/metformin versus glimepiride plus metformin

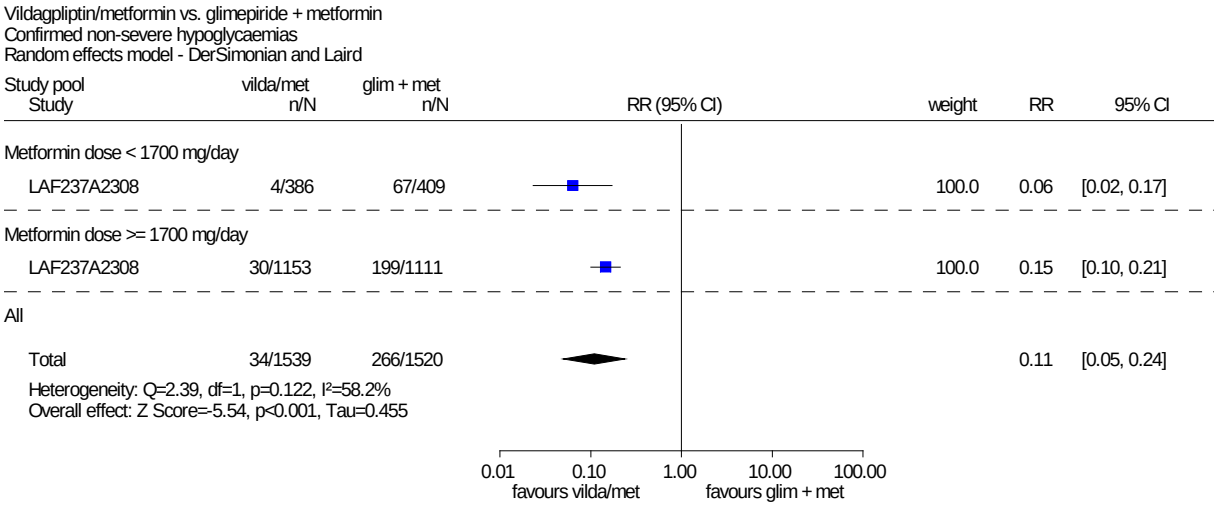


Figure 6: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) confirmed non-severe hypoglycaemias (plasma glucose ≤ 56 mg/dl) – RCT, direct comparison: vildagliptin/metformin versus glimepiride plus metformin

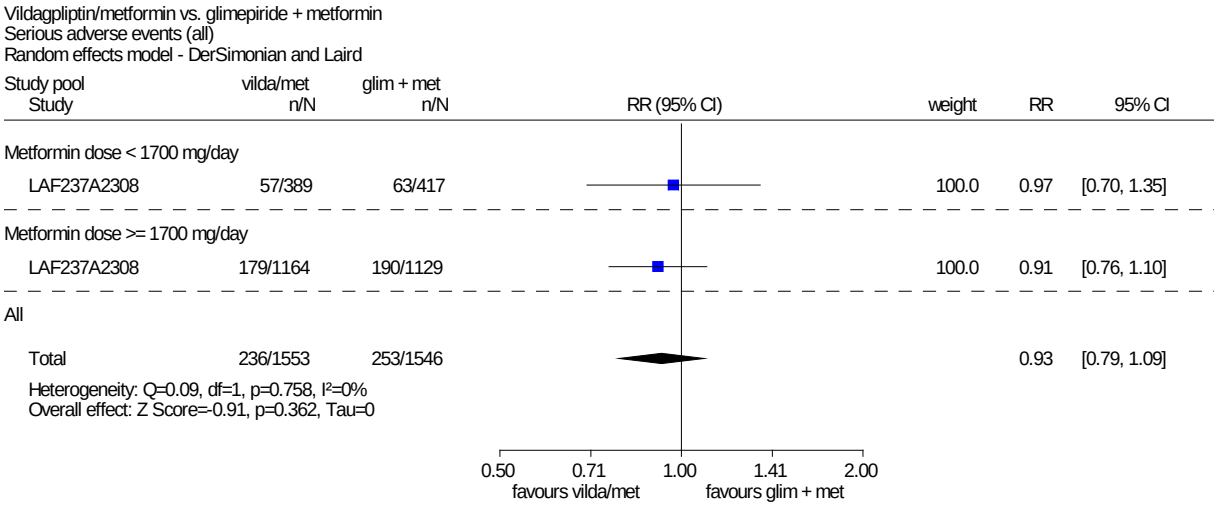


Figure 7: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) overall rate of SAEs – RCT, direct comparison: vildagliptin/metformin versus glimepiride plus metformin

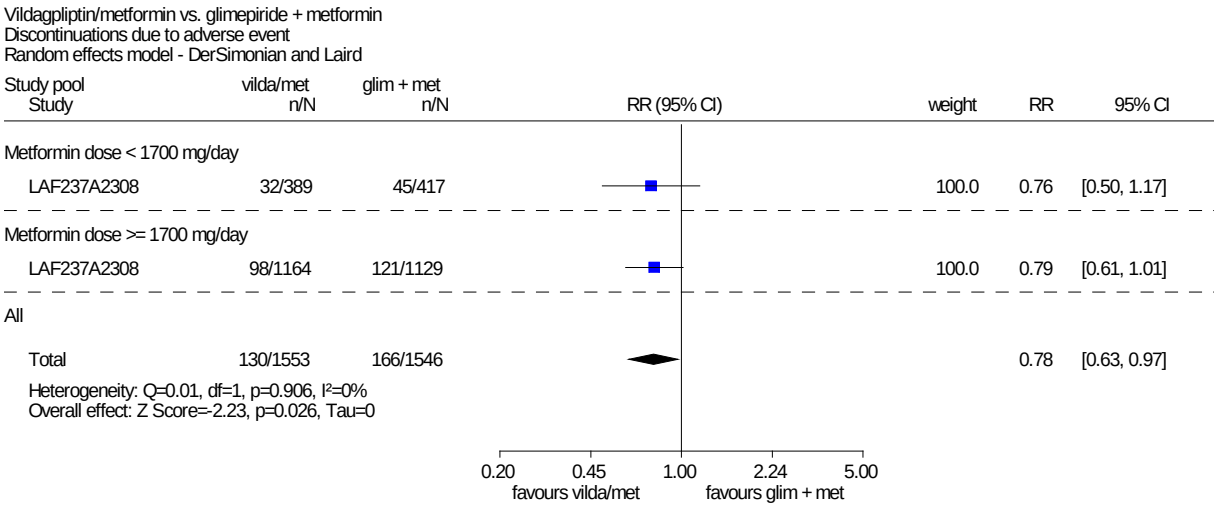


Figure 8: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) treatment discontinuations due to AEs – RCT, direct comparison: vildagliptin/metformin versus glimepiride plus metformin

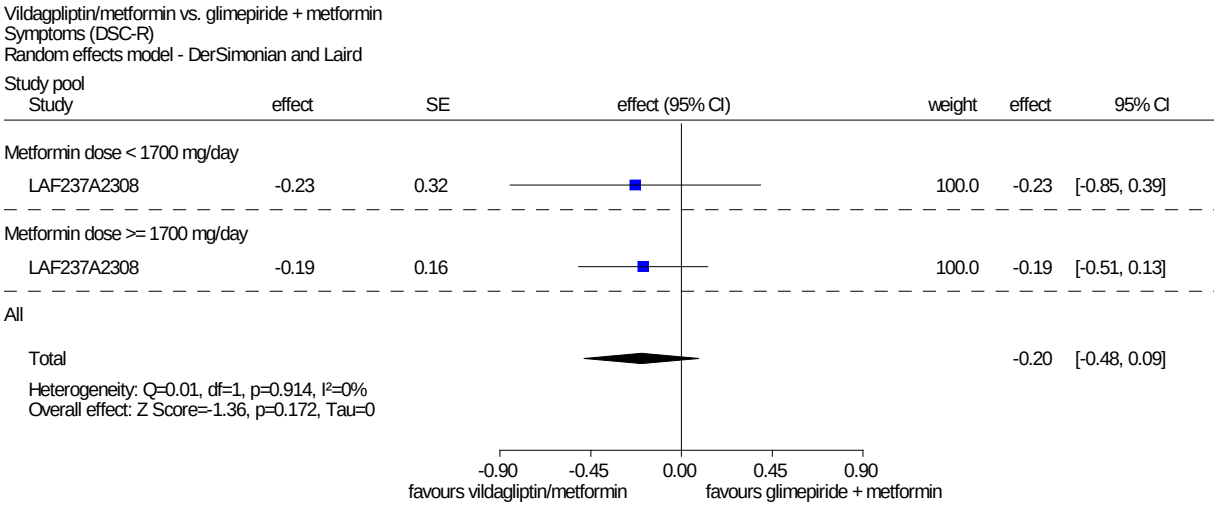


Figure 9: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) symptomatic (DSC-R) – RCT, direct comparison: vildagliptin/metformin versus glimepiride plus metformin

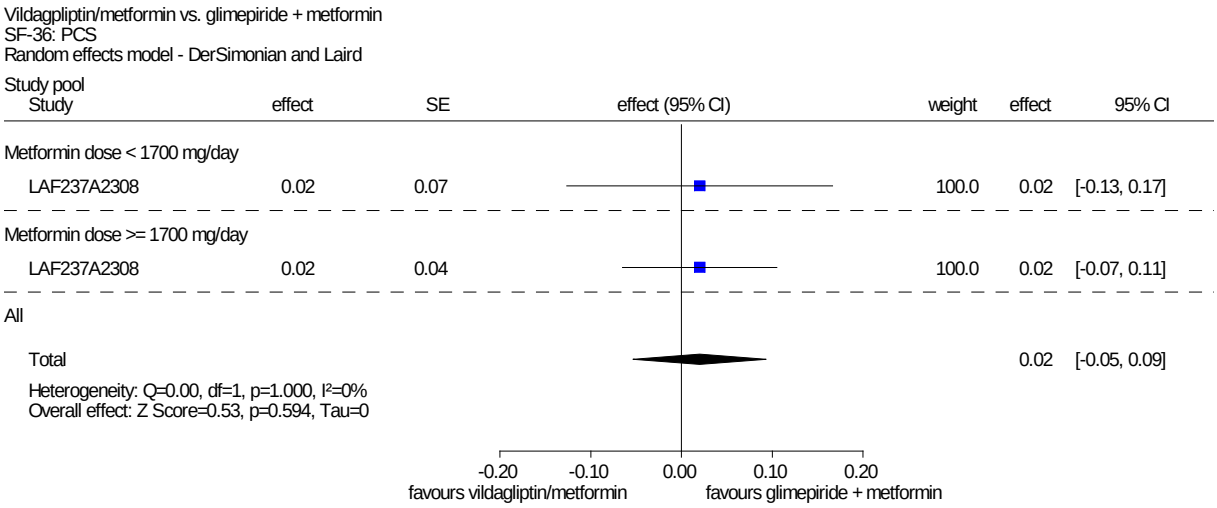


Figure 10: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) health-related quality of life (SF-36 PCS) – RCT, direct comparison: vildagliptin/metformin versus glimepiride plus metformin

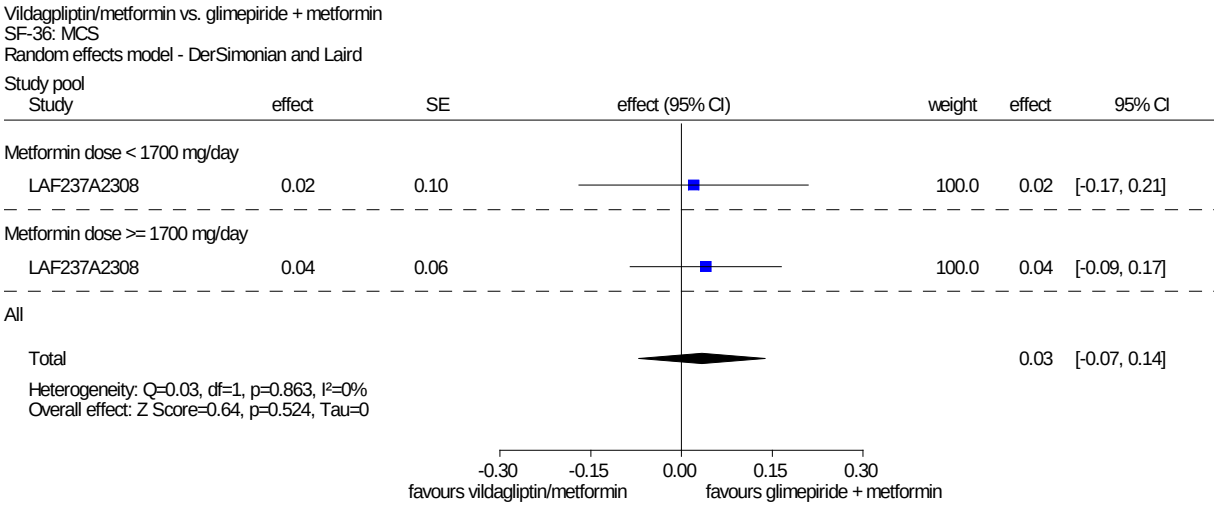


Figure 11: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) health-related quality of life (SF-36 MCS) – RCT, direct comparison: vildagliptin/metformin versus glimepiride plus metformin