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Addendum to Commission A13-03 (sitagliptin/metformin)[1]

Addendum

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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
ACT	appropriate comparator therapy
AE	adverse event
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
HbA1c	glycosylated haemoglobin A1c
IQWiG	*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk

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 A13-03 ([1], fixed combination of sitagliptin and metformin, hereinafter referred to as "sitagliptin/metformin").

The studies P803 and P024 presented by the pharmaceutical company (hereinafter abbreviated to "the company") could not be used in the original benefit assessment for the assessment of the added benefit of sitagliptin/metformin because it was unclear how many patients received a metformin dose of ≥ 1700 mg/day, which concurs with the approval of the fixed combination sitagliptin/metformin, and because the company did not prove that the results of the studies were independent from the metformin dose administered. However, it was noted in the assessment report: "In case of a proof that the results of both studies do not depend on the metformin dose, the results cited in the dossier assessment A13-02 could also be used for the fixed combination sitagliptin/metformin."

In the commenting procedure on the assessment of sitagliptin/metformin, the company submitted further data to the G-BA that went beyond the information in the dossier. These refer to separate analyses of the data according to metformin exposition:

- Patients with a metformin dose of < 1700 mg/day
- Patients with an approval-compliant metformin dose of ≥ 1700 mg/day

These data were presented for the 2 studies P803 (comparison of sitagliptin plus metformin versus glimepiride plus metformin) and P024 (comparison of sitagliptin plus metformin versus glipizide plus metformin).

The commission of the G-BA for the assessment of the added benefit of the fixed combination of sitagliptin and metformin reads as follows: "Assessment of the documents submitted in the commenting procedure, particularly with regards to the study population with a minimum dosage of 1700 mg metformin."

In Chapter 2, the documents subsequently submitted are presented and assessed according to the commission, considering the same outcomes as for the assessment of the free combination of sitagliptin and metformin [2].

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

The distribution of the patients according to the metformin dose in the 2 studies P803 and P024 is presented in Table 1.

Table 1: Distribution of the patients according to the metformin dose in the studies P803 and P024

	Study P803		Study P024	
	Sitagliptin/ metformin N^a = 516	Glimepiride plus metformin N^a = 518	Sitagliptin/ metformin N^a = 588	Glipizide plus metformin N^a = 584
Metformin dose	**n (%)**	**n (%)**	**n (%)**	**n (%)**
< 1700 mg/day	185 (35.9)	178 (34.4)	158 (26.9)	157 (26.9)
≥ 1700 mg/day	324 (62.8)	333 (64.3)	429 (73.0)	427 (73.1)
n.d.	7 (1.4)	7 (1.4)	1 (0.2)	0 (0.0)
a: All randomized patients according to the allocated treatment arm. N: number of analysed patients; n: number of patients in the dose category; n.d.: no data				

The majority of patients in both studies received an approval-compliant metformin dose of ≥ 1700 mg/day (64% of the patients in the study P803 und 73% of the patients in the study P024). Due to the low number of patients without data on the metformin dose, the results of the subgroup analyses for the characteristic "metformin dose" are presented below only for patients for whom data on the metformin dose are available. The company did not present any patient characteristics for the patients with an approval-compliant metformin dose of ≥ 1700 mg/day.

The results from the subgroup analyses for the characteristic "metformin dose" on the comparison of sitagliptin/metformin versus glimepiride plus metformin (as operationalization of the appropriate comparator therapy [ACT] specified by the G-BA, research question A1 of the assessment A13-03) are presented in Section 2.1. The results from the subgroup analyses for the characteristic "metformin dose" on the comparison additionally commissioned by the G-BA (sitagliptin/metformin versus glipizide plus metformin, research question A2 of the assessment A13-03) are presented in Section 2.2. The results for the total population from the assessment report and for the free combination of sitagliptin plus metformin [2] and – if provided by the company – the results from the subgroup analyses for the characteristic "metformin dose" are presented. 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.

2.1 Research question A1: sitagliptin/metformin versus sulfonylurea (glibenclamide, glimepiride) plus metformin

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

Table 2: Results (dichotomous outcomes) – RCT, direct comparison: sitagliptin/metformin vs. glimepiride plus metformin

Study **Outcome category** Outcome Population	**Sitagliptin/ metformin**		**Glimepiride plus metformin**		**Sitagliptin/metformin vs. glimepiride plus metformin**
	N[a]	**Patients with events n (%)**	**N[a]**	**Patients with events n (%)**	**RR/Peto-OR[b] [95% CI]; p-value[c]**
P803					
Mortality					
All-cause mortality					
Total population	516	0 (0)	518	1 (0.2)	0.14 [0.00; 6.85]; p > 0.999
< 1700 mg/day	185	0 (0)	178	1 (0.7)	0.13 [0.00; 6.56]
≥ 1700 mg/day	324	0 (0)	333	0 (0)	n.c.
				Interaction[d]	n.c.
Morbidity					
Cardiac morbidity[e]					
Total population	516	2 (0.4)	518	2 (0.4)	1.00 [0.14; 7.15]; p > 0.999[f]
< 1700 mg/day		n.d.		n.d.	—
≥ 1700 mg/day		n.d.		n.d.	—
Cerebral morbidity[g]					
Total population	516	1 (0.2)	518	2 (0.4)	0.51 [0.05; 4.96]; p = 0.584[f]
< 1700 mg/day		n.d.		n.d.	—
≥ 1700 mg/day		n.d.		n.d.	—
AEs					
Hypoglycaemias					
Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)					
Total population	516	3 (0.6)	518	33 (6.4)	0.18 [0.09; 0.35]; p < 0.001[f]
< 1700 mg/day	185	0 (0)	178	10 (5.6)	0.12 [0.04; 0.43]
≥ 1700 mg/day	324	3 (0.9)	333	22 (6.6)	0.21 [0.10; 0.47]
				Interaction[d]	p = 0.476

(continued)

Table 2: Results (dichotomous outcomes) – RCT, direct comparison: sitagliptin/metformin vs. glimepiride plus metformin (continuation)

Study **Outcome category** Outcome Population	**Sitagliptin/ metformin**		**Glimepiride plus metformin**		**Sitagliptin/metformin vs. glimepiride plus metformin**
	N[a]	**Patients with events n (%)**	**N[a]**	**Patients with events n (%)**	**RR/Peto-OR[b] [95% CI]; p-value[c]**
Severe hypoglycaemias					
Total population	516	1 (0.2)	518	3 (0.6)	0.37 [0.05; 2.62]; p = 0.624[f]
< 1700 mg/day	185	0 (0)	178	0 (0)	n.c.
≥ 1700 mg/day	324	1 (0.3)	333	3 (0.9)	0.38 [0.05; 2.68]
				Interaction[d]	n.c.
Change in HbA1c	Neither data on the course of HbA1c nor on the difference between the start and the end of the study were available for patients with a metformin dose of ≥ 1700 mg/day.				
Pancreatitis					
Total population	516	1 (0.2)	518	0 (0)	7.42 [0.15; 373.83]; p = 0.499[f]
< 1700 mg/day		n.d.		n.d.	—
≥ 1700 mg/day		n.d.		n.d.	—
Renal impairment[h]					
Total population	516	0 (0)	518	0 (0)	n.c.
< 1700 mg/day		n.d.		n.d.	—
≥ 1700 mg/day		n.d.		n.d.	—
Overall rate AEs[i]					
Total population	516	244 (47.3)	518	291 (56.2)	n.c.
< 1700 mg/day	185	87 (47.0)	178	95 (53.4)	n.c.
≥ 1700 mg/day	324	152 (46.9)	333	193 (58.0)	n.c.
				Interaction[d]	n.c.
Overall rate SAEs[i]					
Total population	516	16 (3.1)	518	11 (2.1)	1.46 [0.68; 3.12]; p = 0.338[f]
< 1700 mg/day	185	5 (2.7)	178	3 (1.7)	1.60 [0.39; 6.61]
≥ 1700 mg/day	324	11 (3.4)	333	8 (2.4)	1.41 [0.58; 3.47]
				Interaction[d]	p = 0.883
Treatment discontinuations due to AEs[i]					
Total population	516	10 (1.9)	518	2 (0.4)	3.86 [1.24; 12.05]; 0.020
< 1700 mg/day	185	3 (1.6)	178	0 (0)	7.19 [0.74; 69.61]
≥ 1700 mg/day	324	6 (1.9)	333	2 (0.6)	2.83 [0.70; 11.38]
				Interaction[d]	p = 0.492

(continued)

Table 2: Results (dichotomous outcomes) – RCT, direct comparison: sitagliptin/metformin vs. glimepiride plus metformin (continuation)

a: All randomized patients according to the allocated treatment arm, or number of patients with a metformin dose of ≥ 1700 mg/day.
b: Peto OR provided in event numbers ≤ 1% in at least one cell.
c: Fisher's exact test.
d: Institute's calculation, meta-analysis with random effects according to DerSimonian and Laird. Missing observations were not considered.
e: Serious cardiac events. MedDRA SOC “cardiac disorders”, without deaths.
f: Institute's calculation.
g: Serious cerebral events. MedDRA SOC “nervous system disorders”, without deaths.
h: Serious renal events. MedDRA SOC “renal and urinary disorders”, without deaths.
i: Hypoglycaemias were also recorded here, with hypoglycaemias occurring neither in the SAEs nor in the treatment discontinuations due to AEs.

AE: adverse event; CI: confidence interval; HbA1c: glycosylated haemoglobin A1c; 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; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class according to MedDRA; vs.: versus

Table 3: Results (continuous outcomes) – RCT, direct comparison: sitagliptin/metformin vs. glimepiride plus metformin

Study **Outcome category** Outcome Population	**Sitagliptin/metformin**			**Glimepiride plus metformin**			**Sitagliptin/ metformin vs. glimepiride plus metformin**
P803							
Health-related quality of life							
EQ-5D (VAS)							
	N[a]	**Change at end of study mean (SD)**		**N[a]**	**Change at end of study mean (SD)**		**Hedges' g [95% CI]; p-value[c]**
< 1700 mg/day	173	2.1 (8.1)		167	4.3 (7.9)		-0.27[d] [-0.49; -0.06] p = 0.011
≥ 1700 mg/day	309	2.0 (7.9)		320	1.6 (8.1)		0.05 [-0.11; 0.21] p = 0.531
						Interaction	p = 0.016
Supplementary outcome "body weight"							
Body weight							
	N[a]	**Values at start of study mean (SD)**	**Change at end of study mean (SD)**	**N[a]**	**Values at start of study mean (SD)**	**Change at end of study mean (SD)**	**Hedges' g [95% CI]; p-value[c]**
Change in body weight at week 30							
Total population	465	80.6 (15.2)	-0.8 (3.0)	461	82.2 (16.8)	1.2 (2.8)	-2.0 [-2.3; -1.6]; p < 0.001
< 1700 mg/day	165	n.d.	-0.8 (2.4)	161	n.d.	0.9 (2.8)	n.c.
≥ 1700 mg/day	294	n.d.	-0.8 (3.2)	294	n.d.	1.3 (2.8)	n.c.

a: Unless stated otherwise, LOCF analysis of the ITT population. Includes all patients according to their randomization who received at least one dose of the study medication and for whom a baseline and at least one further measurement were available or, out of this, number of patients with a metformin dose of ≥ 1700 mg/day.
b: Adjusted for country and baseline value.
c: Cochran-Mantel-Haenszel test.
d: Negative values mean disadvantage of sitagliptin/metformin.
CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; ITT: intention to treat; LOCF: last observation carried forward; N: number of analysed patients; n.c.: not calculated; n.d.: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

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

could not be finally assessed for the outcomes "all-cause mortality" and "overall rate of SAEs" due to the small number of events.

The subgroup analyses on health-related quality of life for the characteristic "metformin dose" showed proof of an interaction ($p = 0.016$). This did not result in different conclusions for patients with a metformin dose of ≥ 1700 mg/day versus those with a metformin dose of < 1700 mg/day. The result was not statistically significant in the patient group with a metformin dose of ≥ 1700 mg/day. In the patient group with a metformin dose of < 1700 mg/day, the result was statistically significant to the disadvantage of sitagliptin, but the upper limit of the 95% confidence interval of the standardized mean difference was -0.06 and thus above the irrelevance threshold of -0.2 [3].

The company provided no subgroup analyses for the characteristic "metformin dose" for the outcomes "cardiac morbidity", "cerebral morbidity", "renal impairment" and "pancreatitis". Since no more than 2 patients in each treatment arm had an event in the total population, an effect modification could also not have been assessed for these outcomes.

Neither indications nor proof of an interaction were shown for the outcomes "symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)" and "severe hypoglycaemias" ($p \geq 0.2$). The company did not provide data on the courses of glycosylated haemoglobin A1c value (HbA1c values) or the HbA1c values at the start and end of the study in the subpopulations. Since there were no relevant differences between subpopulations and total population in the remaining outcomes, however, this did not raise fundamental doubts about the interpretation of the results on hypoglycaemias in the subpopulations.

Summary

It can be assumed for most outcomes that there was no effect modification by the metformin dose or that this was not relevant for the assessment. Overall, it seems possible to use the analyses of the total population of the study P803 presented in the dossier assessment A13-02 also for the assessment of the fixed combination sitagliptin/metformin versus glimepiride plus metformin.

2.2 Research question A2: sitagliptin/metformin versus glipizide plus metformin

The results for the comparison of sitagliptin/metformin versus glipizide plus metformin are presented in Table 4. The forest plots of the subgroup analyses for the characteristic "metformin dose" can be found in Appendix B.

Table 4: Results – RCT, direct comparison: combination sitagliptin/metformin vs. glipizide plus metformin

Study **Outcome category** Outcome Population	**Sitagliptin/metformin**		**Glipizide plus metformin**		**Sitagliptin/ metformin vs. glipizide plus metformin**
	N[a]	**Patients with events n (%)**	**N[a]**	**Patients with events n (%)**	**RR/Peto-OR[b] [95% CI]; p-value[c]**
P024[d]					
Mortality					
All-cause mortality					
Total population	588	1 (0.2)	584	8 (1.4)	0.21 [0.06; 0.77]; p = 0.021
< 1700 mg/day	158	1 (0.6)	157	1 (0.6)	0.99 [0.06; 15.96]
≥ 1700 mg/day	429	0 (0)	427	7 (1.6)	0.13 [0.03; 0.59]
				Interaction[e]	p = 0.210
Morbidity					
Cardiac morbidity[f]					
Total population	588	15 (2.6)	584	11 (1.9)	1.35 [0.63; 2.92]; p = 0.553[g]
< 1700 mg/day		n.d.		n.d.	—
≥ 1700 mg/day		n.d.		n.d.	—
Cerebral morbidity[h]					
Total population	588	2 (0.3)	584	8 (1.4)	0.30 [0.09; 1.03]; p = 0.064[g]
< 1700 mg/day		n.d.		n.d.	—
≥ 1700 mg/day		n.d.		n.d.	—
Health-related quality of life				Not recorded	
AEs					
Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl) week 0 to 52					
Total population	588	4 (0.7)	584	44 (7.5)	0.17 [0.10; 0.31]; p < 0.001
< 1700 mg/day	158	0 (0)	157	14 (8.9)	0.12 [0.04; 0.36]
≥ 1700 mg/day	429	4 (0.9)	427	30 (7.0)	0.20 [0.10; 0.40]
				Interaction[e]	p = 0.443
Symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl) week 0 to 104					
Total population	588	5 (0.9)	584	48 (8.2)	0.18 [0.10; 0.32]; < 0.001
< 1700 mg/day	158	0 (0)	157	14 (8.9)	0.12 [0.04; 0.36]
≥ 1700 mg/day	429	5 (1.2)	427	34 (8.0)	0.21 [0.11; 0.40]
				Interaction[e]	p = 0.404

(continued)

Table 4: Results – RCT, direct comparison: combination sitagliptin/metformin vs. glipizide plus metformin (continuation)

Study **Outcome category** Outcome Population	**Sitagliptin/metformin**		**Glipizide plus metformin**		**Sitagliptin/ metformin vs. glipizide plus metformin**
	N[a]	**Patients with events n (%)**	**N[a]**	**Patients with events n (%)**	**RR/Peto-OR[b] [95% CI]; p-value[c]**
Severe hypoglycaemias week 0 to 52					
Total population	588	1 (0.2)	584	7 (1.2)	0.22 [0.05; 0.88]; p = 0.038[g]
< 1700 mg/day	158	0 (0)	157	3 (1.9)	0.13 [0.01; 1.29]
≥ 1700 mg/day	429	1 (0.2)	427	4 (0.9)	0.30 [0.05; 1.73]
				Interaction[e]	p = 0.581
Severe hypoglycaemias week 0 to 104					
Total population	588	1 (0.2)	584	9 (1.5)	0.20 [0.06; 0.69]; p = 0.011[g]
< 1700 mg/day	158	0 (0)	157	3 (1.9)	0.13 [0.01; 1.29]
≥ 1700 mg/day	429	1 (0.2)	427	6 (1.4)	0.24 [0.05; 1.04]
				Interaction[e]	p = 0.678
Change in HbA1c	Neither data on the course of HbA1c nor on the difference between the start and the end of the study were available for patients with a metformin dose of ≥ 1700 mg/day.				
Pancreatitis					
Total population	588	2[k] (0.3[g])	584	0 (0)	7.35 [0.46; 117.67]; p = 0.500[g]
< 1700 mg/day		n.d.		n.d.	—
≥ 1700 mg/day		n.d.		n.d.	—
Renal impairment[i]					
Total population	588	4 (0.7)	584	4 (0.7)	0.99 [0.25; 3.99]; p > 0.999[g]
< 1700 mg/day		n.d.		n.d.	—
≥ 1700 mg/day		n.d.		n.d.	—
Overall rate AEs[l]					
Total population	588	452 (76.9)	584	480 (82.2)	n.c.
< 1700 mg/day	158	126 (79.7)[j]	157	136 (86.6)[j]	n.c.
≥ 1700 mg/day	429	334 (77.9)[j]	427	348 (81.5)[j]	n.c.
Overall rate SAEs[l,m]					
Total population	588	64 (10.9)	584	73 (12.5)	0.87 [0.64; 1.19]; p = 0.414[g]
< 1700 mg/day	158	16 (10.1)	157	16 (10.2)	0.99 [0.52; 1.92]
≥ 1700 mg/day	429	48 (11.2)	427	57 (13.3)	0.84 [0.58; 1.20]
				Interaction[e]	p = 0.656

(continued)

Table 4: Results – RCT, direct comparison: combination sitagliptin/metformin vs. glipizide plus metformin (continuation)

Study **Outcome category** Outcome Population	**Sitagliptin/metformin**			**Glipizide plus metformin**			**Sitagliptin/ metformin vs. glipizide plus metformin**
	N[a]	**Patients with events n (%)**		**N[a]**	**Patients with events n (%)**		**RR/Peto-OR[b] [95% CI]; p-value[c]**
Treatment discontinuations due to AEs[m]							
Total population	588	23 (3.9)		584	29 (5.0)		0.79 [0.46; 1.35]; p = 0.398[g]
< 1700 mg/day	158	6 (3.8)[j]		157	10 (6.4)[j]		0.60 [0.22; 1.60]
≥ 1700 mg/day	429	25 (5.8)[j]		427	25 (5.6)[j]		1.00 [0.58; 1.70]
					Interaction[e]		p = 0.372
	N[n]	**Values at start of study mean (SD)**	**Change at end of study mean (SD)**	**N[n]**	**Values at start of study mean (SD)**	**Change at end of study mean (SD)**	**ΔLSM[o] [95% CI]; p-value**
Supplementary outcome							
Body weight week 52							
Total population	547[p]	89.4 (16.9)	-1.3 (0.3)	534	89.5 (17.1)	1.2 (0.3)	-2.5 [-3.1; -2.0]; n.d.
< 1700 mg/day		n.d.	n.d.		n.d.	n.d.	—
≥ 1700 mg/day		n.d.	n.d.		n.d.	n.d.	—
Body weight week 104							
Total population	Not presented in assessment report A13-02[q]						
< 1700 mg/day	Not presented in addendum[q]						
≥ 1700 mg/day	Not presented in addendum[q]						

a: All patients as treated, or, out of this, number of patients with a metformin dose of ≥ 1700 mg/day.
b: Peto OR provided in event numbers ≤ 1% in at least one cell.
c: Fisher's exact test.
d: Unless stated otherwise, the results after 104 weeks are presented.
e: Institute's calculation, meta-analysis with random effects according to DerSimonian and Laird. Missing observations were not considered.
f: Serious cardiac events. MedDRA SOC "cardiac disorders", without deaths.
g: Institute's calculation.
h: Serious cerebral events. MedDRA SOC "nervous system disorders", without deaths.
i: Serious renal events. MedDRA SOC "renal and urinary disorders", without deaths.
j: The sum of patients with one AE or with treatment discontinuation due to AE is greater in the subgroups (metformin dose of < 1700 mg/day vs. ≥ 1700 mg/day) than the respective number of patients with one AE or with treatment discontinuation due to AE in the total population.
k: 2 events are mentioned in the dossier. One patient with pancreatitis and one patient with chronic pancreatitis are cited in the clinical study report. It cannot be reconstructed from this information whether these were 2 different patients.

(continued)

Table 4: Results – RCT, direct comparison: combination sitagliptin/metformin vs. glipizide plus metformin (continuation)

l: Hypoglycaemic events were also recorded here. There were no hypoglycaemias as SAEs in the study P024. 4 patients in the glipizide arm discontinued treatment due to hypoglycaemias. Without these 4 patients, the values of the 2 groups approach each other further.
m: Non-fatal SAEs.
n: Unless stated otherwise, LOCF analysis of the ITT population. Includes all patients according to their randomization who received at least one dose of the study medication and for whom a baseline and at least one further measurement were available or, out of this, number of patients with a metformin dose of ≥ 1700 mg/day.
o: Adjusted for prior treatment and baseline values.
p: Change at end of study and difference of the change at end of study were estimated using an ANCOVA. Missing values were imputed using LOCF.
q: Only analysis without replacement of missing values available. The data are not presented because the proportion of the patients who were not considered in the analysis was > 30% and the difference of the proportions of patients who were not considered was more than 15 percentage points between the treatment arms.

ΔLSM: difference calculated with the least squares method; AE: adverse event; ANCOVA: analysis of covariance; CI: confidence interval; HbA1c: glycosylated haemoglobin A1c; ITT: intention to treat; LOCF: last observation carried forward; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with event; n.d.: no data; OR: odds ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SD: standard deviation; SOC: System Organ Class according to MedDRA; vs.: versus

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

The company provided no subgroup analyses for the characteristic "metformin dose" for the outcomes "cardiac morbidity", "cerebral morbidity", "renal impairment" and "pancreatitis". Since only few events occurred in the total population, an effect modification could not have been assessed for the outcomes "renal impairment" and "pancreatitis". It remained unclear for cardiac and cerebral morbidity whether an effect modification was present. However, these outcomes did not lead to a derivation of an added benefit of sitagliptin for the total population either, because the result in the total population was not statistically significant.

Neither indications nor proof of an interaction were shown for the outcomes "symptomatic hypoglycaemias (blood glucose ≤ 50 mg/dl)" and "severe hypoglycaemias" ($p \geq 0.2$). The company did not provide data on the courses of HbA1c values or the HbA1c values at the start or end of the study in the subpopulations. Since there were no relevant differences between subpopulations and total population in the remaining outcomes, however, this did not raise fundamental doubts about the interpretation of the results on hypoglycaemias in the subpopulations.

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. Overall, it seems possible to use the analyses of the total population of the study P024 presented in the dossier assessment A13-02 also for the assessment of the fixed combination sitagliptin/metformin versus glipizide plus metformin.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Sitagliptin/Metformin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-03 [online]. 27 June 2013 [accessed: 28 August 2013]. (IQWiG-Berichte; Volume 176). URL: https://www.iqwig.de/download/A13-03_Sitagliptin-Metformin_Nutzenbewertung-35a-SGB-V.pdf.

2. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Sitagliptin: Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A13-02 [online]. 27 June 2013 [accessed: 28 August 2013]. (IQWiG-Berichte; Volume 175). URL: https://www.iqwig.de/download/A13-02_Sitagliptin_Nutzenbewertung-35a-SGB-V.pdf.

3. Institute for Quality and Efficiency in Health Care. General methods: version 4.0 [online]. 23 September 2011 [accessed: 28 August 2013]. URL: https://www.iqwig.de/download/General_Methods_4-0.pdf.

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

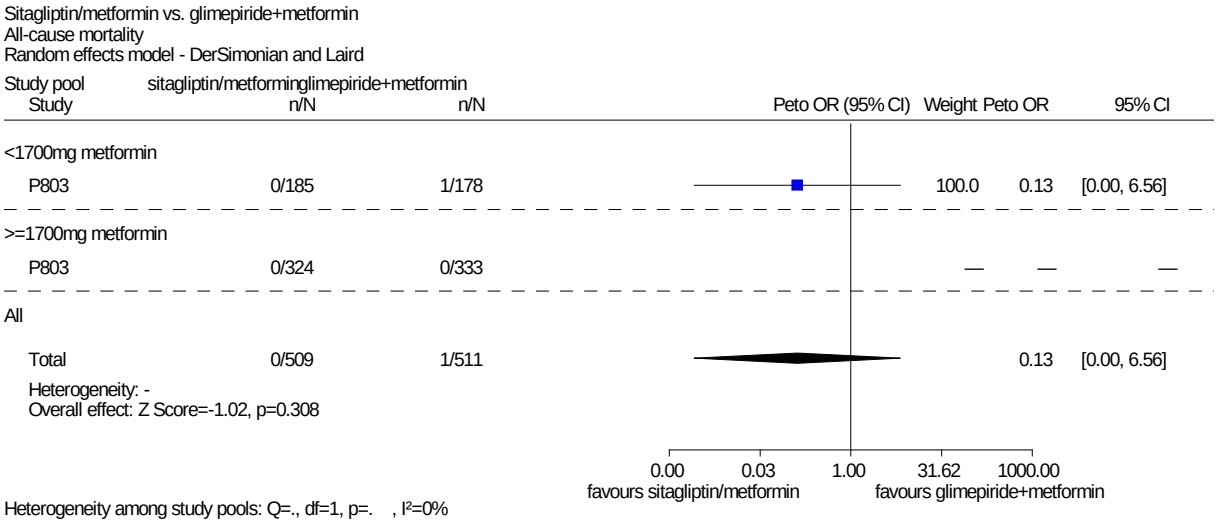

Figure 1: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) all-cause mortality – RCT, direct comparison: sitagliptin/metformin versus glimepiride plus metformin

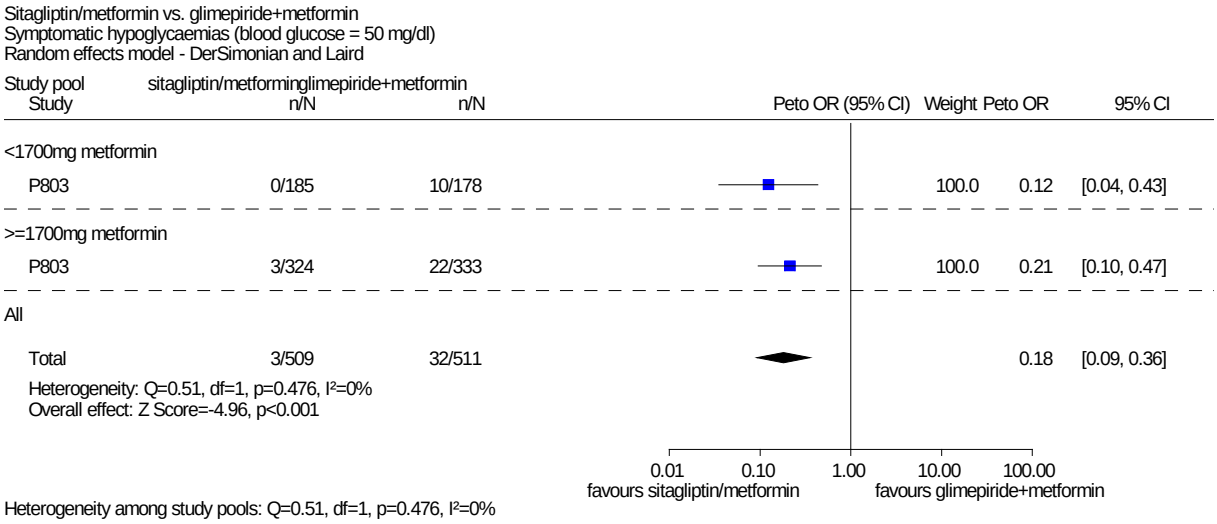

Figure 2: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) confirmed hypoglycaemias (blood glucose ≤ 50 mg/dl) – RCT, direct comparison: sitagliptin/metformin versus glimepiride plus metformin

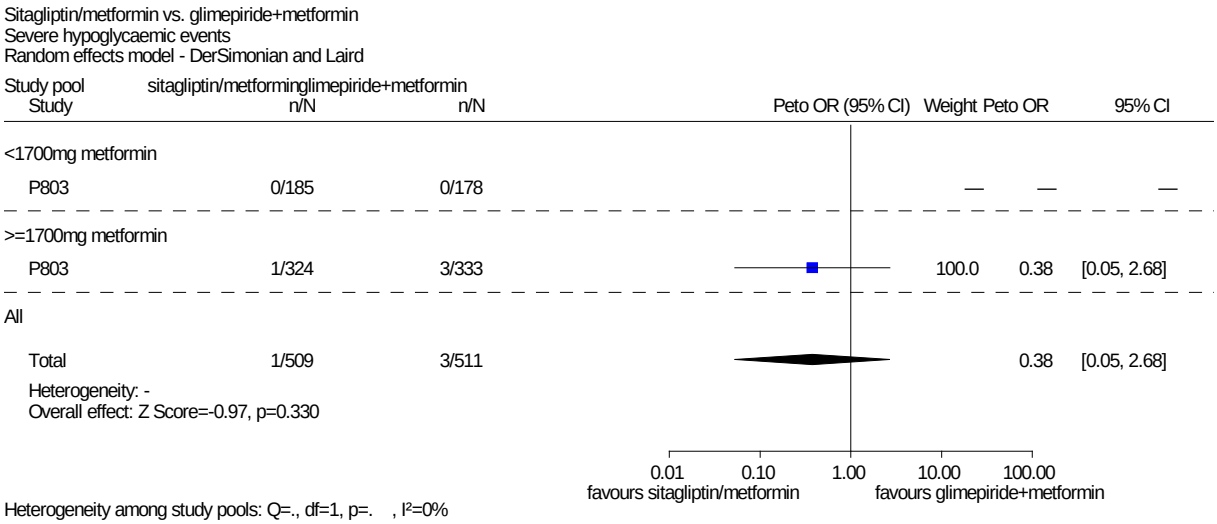

Figure 3: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) severe hypoglycaemias – RCT, direct comparison: sitagliptin/metformin versus glimepiride plus metformin

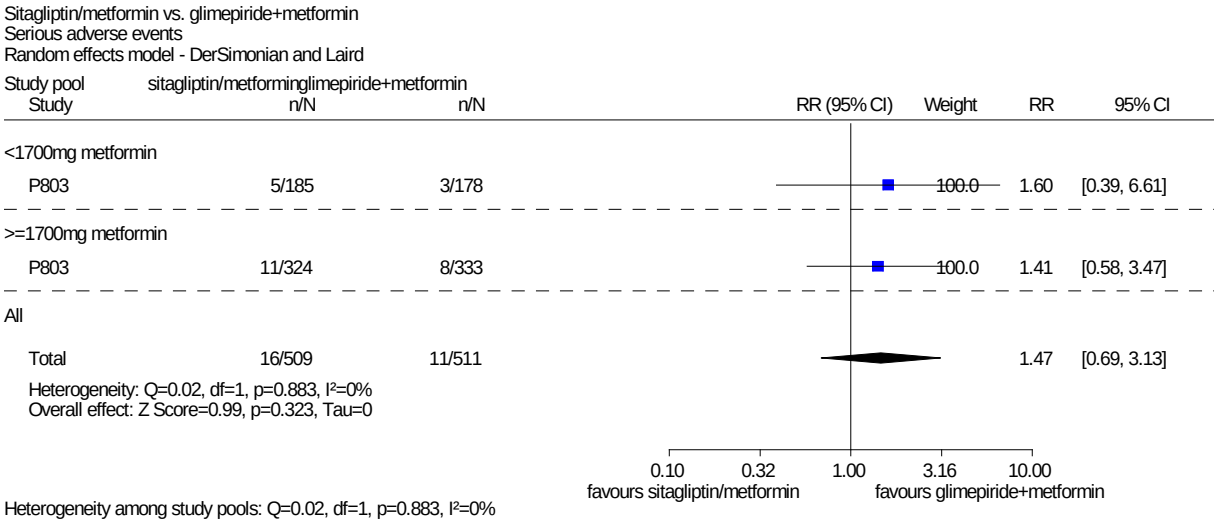

Figure 4: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) overall rate of serious adverse events – RCT, direct comparison: sitagliptin/metformin versus glimepiride plus metformin

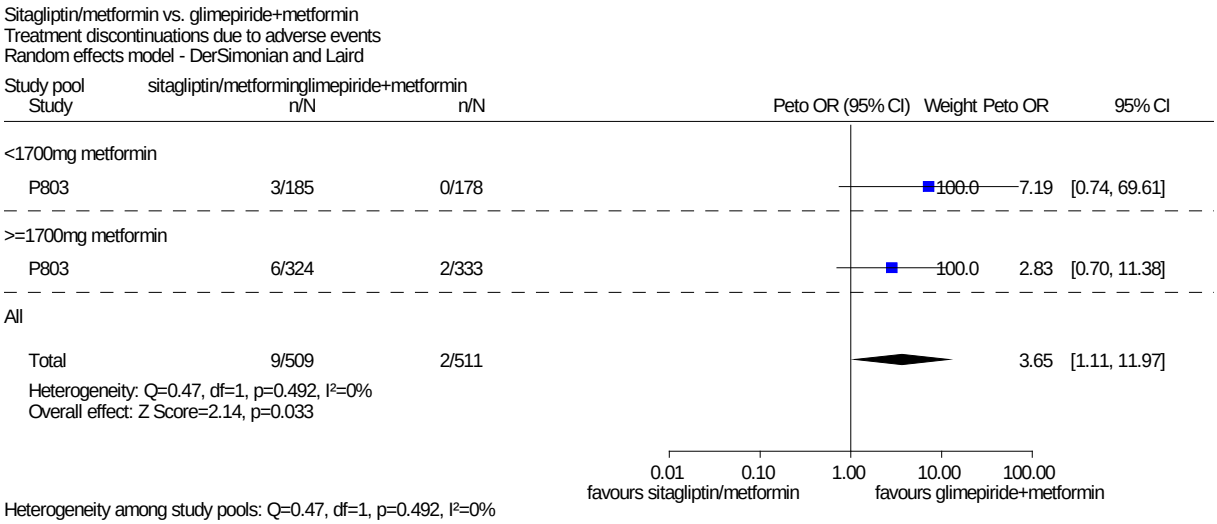

Figure 5: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) treatment discontinuations due to adverse events – RCT, direct comparison: sitagliptin/metformin versus glimepiride plus metformin

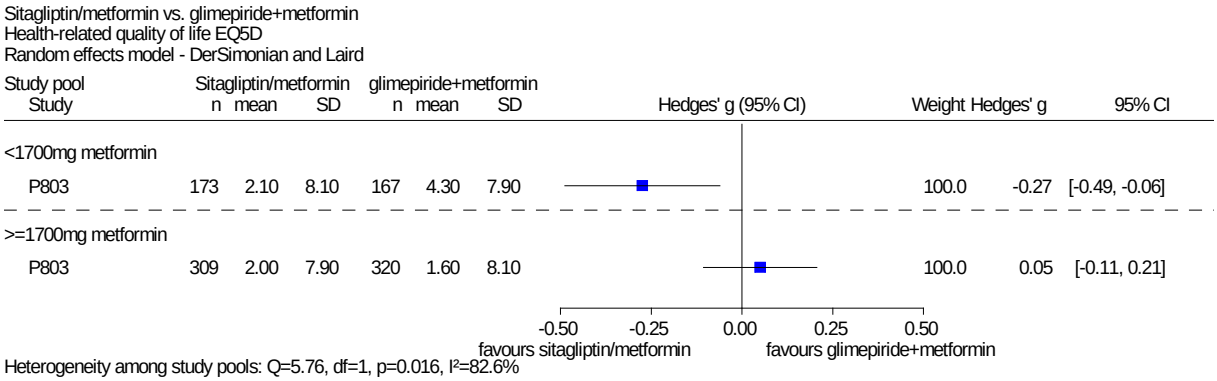

Figure 6: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) health-related quality of life – RCT, direct comparison: sitagliptin/metformin versus glimepiride plus metformin

Appendix B – Forest plots of the subgroup analyses for the characteristic "metformin dose", sitagliptin/metformin versus glipizide plus metformin

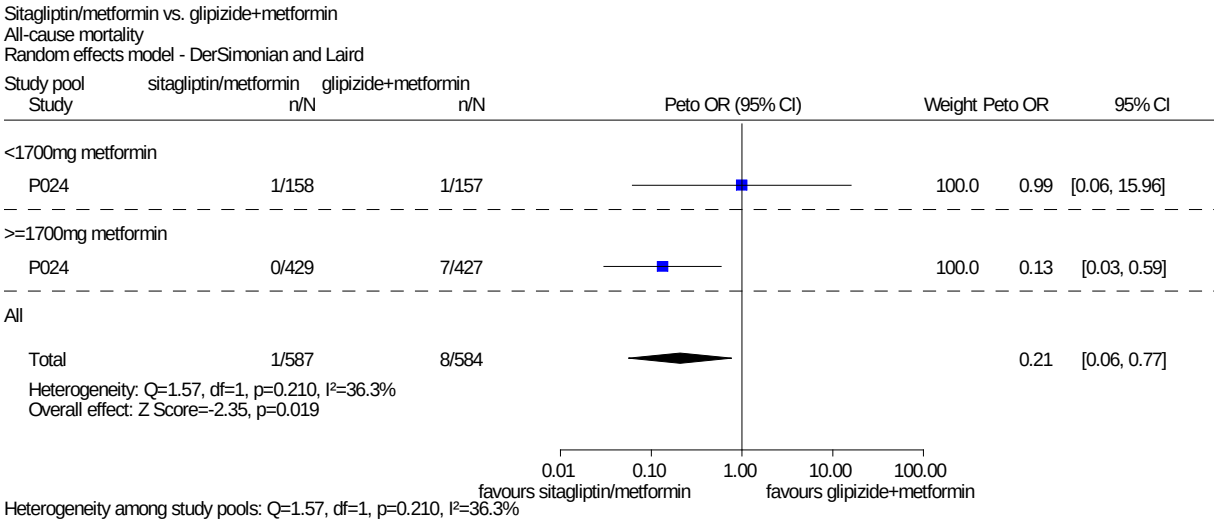

Figure 7: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) all-cause mortality – RCT, direct comparison: sitagliptin/metformin versus glipizide plus metformin

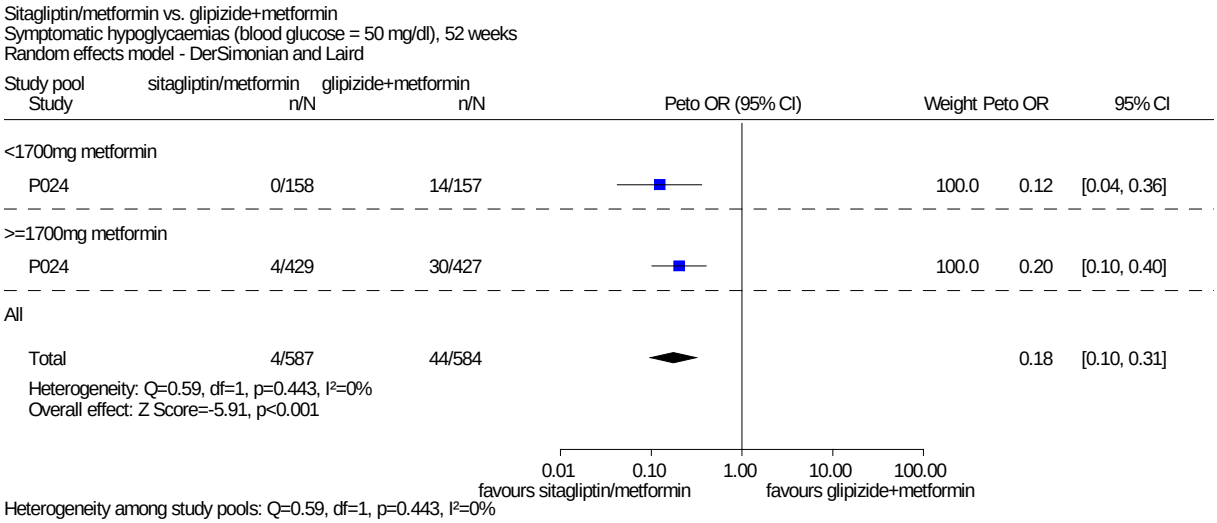

Figure 8: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) confirmed hypoglycaemias (blood glucose ≤ 50 mg/dl) week 0 to 52 – RCT, direct comparison: sitagliptin/metformin versus glipizide plus metformin

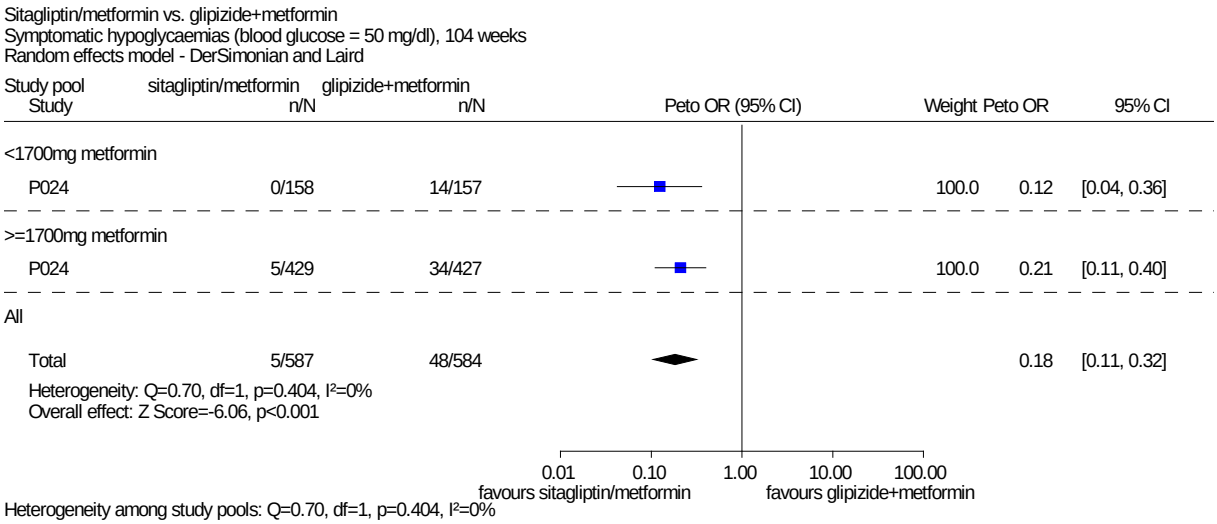

Figure 9: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) confirmed hypoglycaemias (blood glucose ≤ 50 mg/dl) week 0 to 104 – RCT, direct comparison: sitagliptin/metformin versus glipizide plus metformin

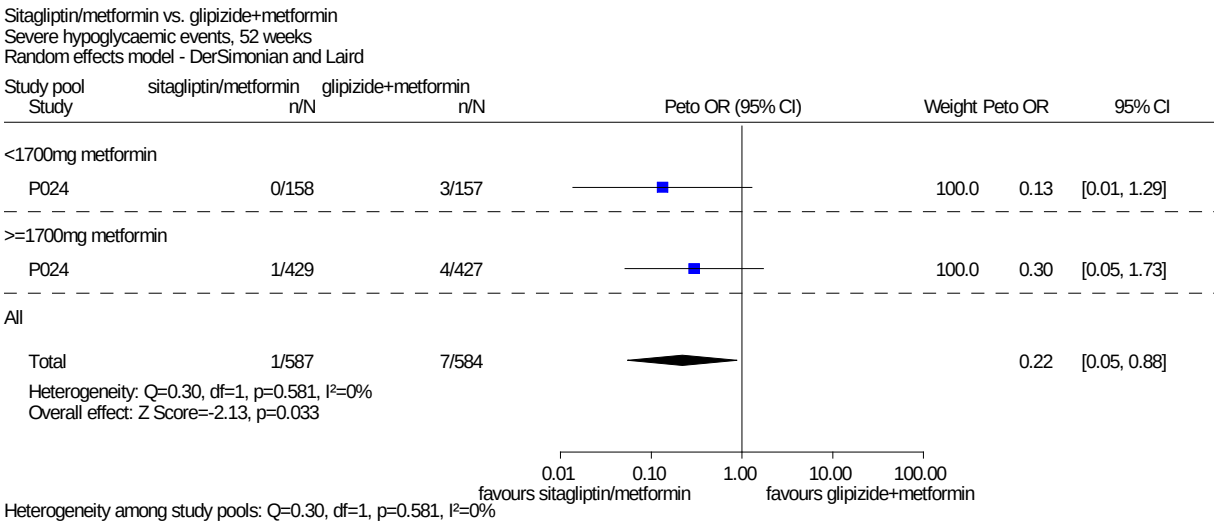

Figure 10: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) severe hypoglycaemias week 0 to 52 – RCT, direct comparison: sitagliptin/metformin versus glipizide plus metformin

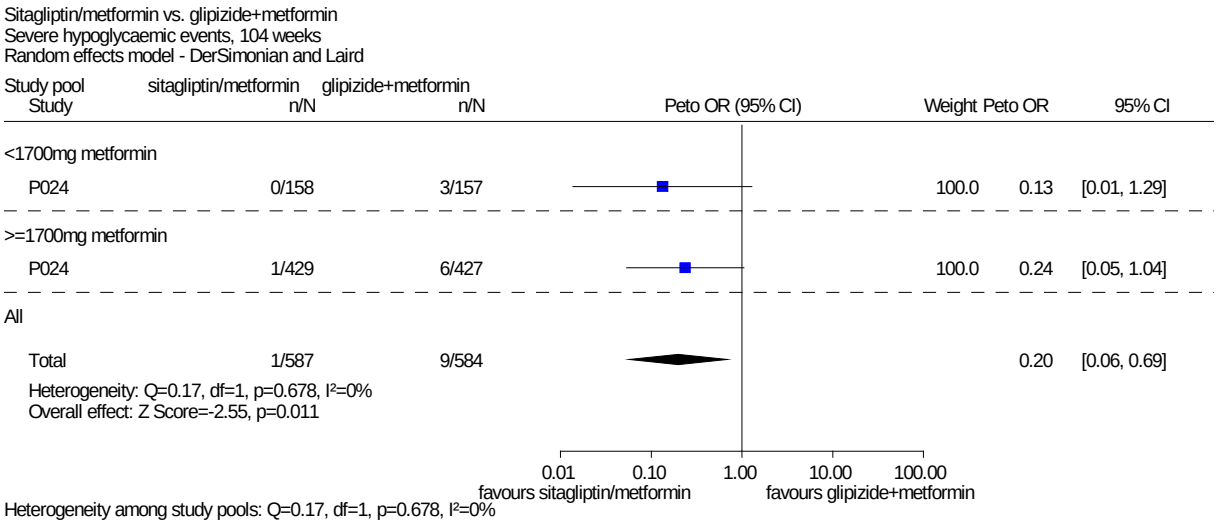

Figure 11: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) severe hypoglycaemias week 0 to 104 – RCT, direct comparison: sitagliptin/metformin versus glipizide plus metformin

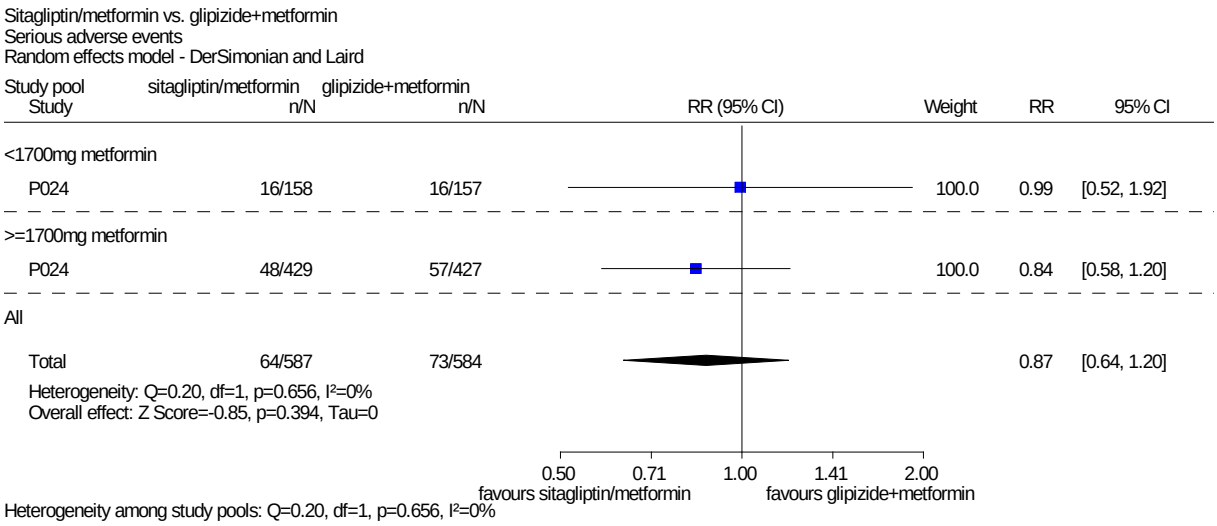

Figure 12: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) overall rate of serious adverse events – RCT, direct comparison: sitagliptin/metformin versus glipizide plus metformin

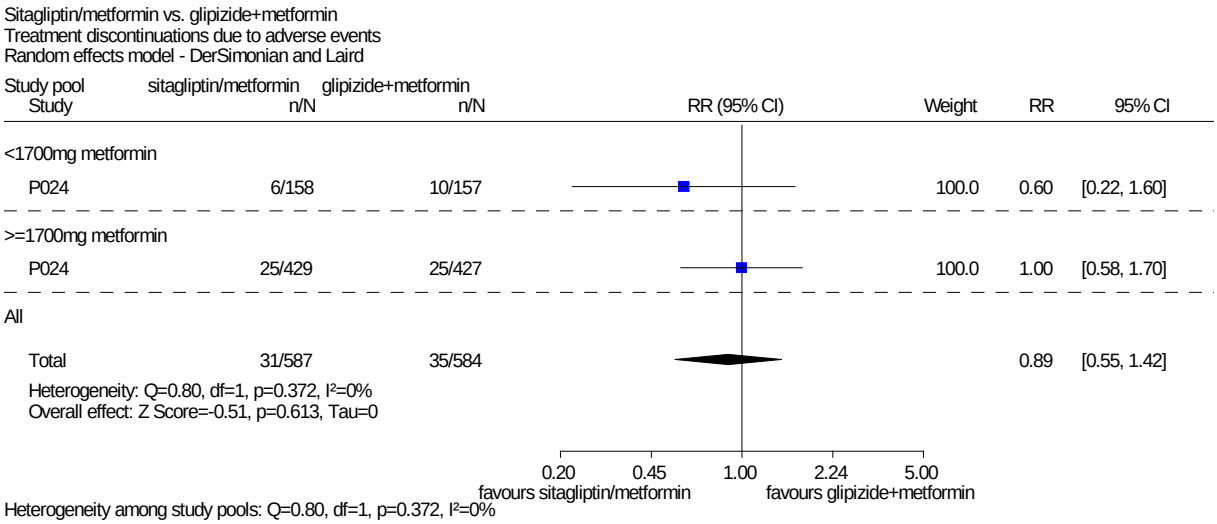

Figure 13: Subgroup analysis (metformin dose < 1700 mg/day versus ≥ 1700 mg/day) treatment discontinuations due to adverse events – RCT, direct comparison: sitagliptin/metformin versus glipizide plus metformin