IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A12-11

Linagliptin –

Renewed benefit assessment according to § 35a Paragraph 5b Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Linagliptin – Erneute Nutzenbewertung gemäß § 35a Absatz 5b SGB V" [Version 1.0; Status: 29.11.2012]). 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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Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICH	International Conference on Harmonisation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
OR	odds ratio
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Paragraph 5b Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to undertake the renewed benefit assessment of the drug linagliptin. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 03.09.2012.

Research question

The aim of this report is to assess the added benefit of linagliptin

- in monotherapy in comparison with sulfonylureas (glimepiride, glibenclamide),
- in dual therapy with metformin in comparison with sulfonylureas (glimepiride, glibenclamide) plus metformin and
- in triple therapy with metformin and a sulfonylurea in comparison with metformin plus human insulin

in each case as appropriate comparator therapy (ACT) in patients with type 2 diabetes mellitus.

The assessment was undertaken with respect to patient-relevant outcomes.

Results

Monotherapy

No study on the direct comparison of linagliptin monotherapy with the ACT was presented and a search conducted by the company for studies with sulfonylureas produced no studies that would be suitable for an indirect comparison either. No conclusions could be drawn regarding the added benefit of linagliptin over the ACT from the placebo-controlled Study 1218.50 (first phase of the study) named by the company for monotherapy. Thus overall no studies were submitted that were suitable for the assessment of added benefit of monotherapy with linagliptin.

Dual therapy

One potentially relevant direct comparative study for dual therapy (comparison linagliptin plus metformin vs. glimepiride plus metformin, Study 1218.20) was identified. This is also the only study that the company used for assessing the added benefit of linagliptin in dual therapy. However, because of the design of Study 1218.20, a comparison was not carried out solely between linagliptin and glimepiride, as would have been necessary for the added benefit assessment. Instead, two different treatment strategies were compared (one strategy without a specific target level for blood glucose versus another strategy where treatment was

directed at such a target level), for each of which different drugs were used (linagliptin or glimepiride). It is therefore not certain that the effects observed in the study are attributable to the respective drugs used. They might also be solely due to the different treatment strategies.

The results of Study 1218.20 themselves support this assumption. From the time course of the change in HbA1c, it is clear that under the treatment with glimepiride directed at a target blood-glucose level, HbA1c fell rapidly during the titration phase (first 12 weeks of the study) to the aspired near-normal value. The lowest HbA1c value was reached after about 16 weeks. An initial reduction in HbA1c was also observed in the linagliptin group, but this was far less pronounced than in the glimepiride group. The difference between the treatment groups was greatest after approx. 16 weeks. By the end of the study, the difference between the two treatment groups had narrowed somewhat, but was still statistically significant (test for difference). The differences in the reduction in HbA1c were also obvious from the responder analyses of HbA1c contained in the submitted documents. For patients with a baseline HbA1c of 6.5 % or more at the start of the study, the chance (measured by the odds ratio (OR)) of having an HbA1c less than 6.5 % at the end of the study was 0.69 times lower with linagliptin than with glimepiride. This difference is statistically significant (linagliptin group: 10.9 % of patients; glimepiride group: 14.7 % of patients; OR 95 % confidence interval (CI): 0.69 [0.50; 0.95], p = 0.024). This similarly applies to a reduction in HbA1c of at least 0.5 percentage points at Week 104 (linagliptin group: 26.2 % of patients; glimepiride group: 33.5 % of patients; OR 95 % CI: 0.70 [0.56; 0.88], p = 0.002).

As expected, the time course of occurrence of hypoglycaemic episodes corresponded with the described course of blood glucose reduction. Episodes of hypoglycaemia of higher severity occurred for the first time especially in the first 16 weeks of the study and were considerably more common under glimepiride. After this phase, first-time hypoglycaemic episodes were only observed as isolated cases up to Week 52 and no such episodes occurred in the second half of the study at all.

The time course of the occurrence of serious cerebral events (operationalized as such events of the outcome “cerebrovascular disorders” that were classified as a serious adverse event (SAE)) also corresponded with the course of blood glucose reduction. The difference between the treatment groups is due solely to the first period of the study up to Week 16. Thereafter, only isolated events occurred in both treatment groups without any tendency in favour of one or the other group.

In summary, it was shown that the time course of occurrence of important outcomes of Study 1218.20 (“hypoglycaemia of higher severity” and “cerebral events”) corresponded with the blood glucose reduction. The substantial differences in blood glucose reduction between the treatment groups were apparently induced by the unilateral specification of a target blood-glucose level for glimepiride. The results of Study 1218.20 cannot therefore be used to assess the added benefit of linagliptin compared to glimepiride.

Triple therapy

No study of triple therapy with linagliptin in a direct comparison with the ACT was presented. The company stated that no indirect comparison was undertaken, because in its view, this is not possible for methodological reasons. No conclusions can be drawn regarding the added benefit of linagliptin compared to the ACT from the placebo-controlled Study 1218.18 named by the company for triple therapy. Thus overall no studies were submitted that were suitable for assessing the added benefit of a triple therapy with linagliptin.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[3]

The company presented no relevant studies for assessing the added benefit of linagliptin in monotherapy, dual therapy or triple therapy in comparison with the ACT specified by the G-BA.

Overall there is no proof of an added benefit of linagliptin. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

The decision regarding added benefit is made by the G-BA.

2.2 Research question

The benefit assessment of linagliptin was performed for the following therapeutic indication: "treatment of type 2 diabetes mellitus to improve glycaemic control in adults" [3].

Linagliptin is approved for monotherapy, dual and triple combination therapies in adults [3]. More details can be found in Table 2.

Table 2: Conditions of approval of linagliptin as mono- and combination therapy

Monotherapy Linagliptin	For patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment
Dual therapy Linagliptin + metformin	When diet and exercise plus metformin alone do not provide adequate glycaemic control
Triple therapy Linagliptin + metformin + sulfonylurea	When diet and exercise plus dual therapy with metformin and sulfonylureas do not provide adequate glycaemic control

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or data not interpretable)., (see [1]). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

In its dossier the company specified sulfonylureas (glibenclamide or glimepiride) as ACT for monotherapy and dual therapy, and human insulin plus metformin for triple therapy. The ACT thus corresponds with that specified by the G-BA. Table 3 summarizes the ACTs for the three treatment situations.

Table 3: Overview of the ACT for linagliptin

	ACT specified by the G-BA and the company
Monotherapy Linagliptin	Sulfonylurea[a]
Dual therapy Linagliptin + metformin	Sulfonylurea[a] + metformin
Triple therapy Linagliptin + metformin + sulfonylurea	Human insulin + metformin
a: glimepiride, glibenclamide	

The assessment was undertaken with respect to patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1 and in Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

- Studies of linagliptin completed by the company up to 10.07.2012 (study list of the company).
- Results of a bibliographical literature search and a search in trial registries for studies of linagliptin (last search 09.07.2012 in bibliographical databases and 09.07.2012 in trial registries, searches by the company)
- Results of a bibliographical literature search and a search in trial registries for studies of the ACT "sulfonylurea" (last search 10.07.2012 in bibliographical databases and 10.07.2012 in trial registries, company searches)

The Institute conducted a separate search in trial registries for studies of linagliptin to check the company's search results. This search covered the period up to 14.09.2012. The check produced no deviations from the study pool presented in the company's dossier.

Further information about the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included in the assessment

Monotherapy

No study on the direct comparison of linagliptin monotherapy with the ACT was presented. A search conducted by the company for studies with sulfonylureas did not produce any studies that would be suitable for an indirect comparison either. No conclusions could be drawn regarding the added benefit of linagliptin over the ACT from the placebo-controlled Study 1218.50 (first phase of the study) named by the company for monotherapy. Thus overall no studies were submitted that were suitable for the assessment of added benefit of monotherapy with linagliptin.

Dual therapy

One potentially relevant direct comparative study for dual therapy (comparison linagliptin plus metformin versus glimepiride plus metformin, Study 1218.20) was identified. This is also the only study that the company used for assessing the added benefit of linagliptin in dual therapy. However, because of the design of Study 1218.20, a comparison was not carried out solely between linagliptin and glimepiride, as would have been necessary for the added benefit assessment. Instead, two different treatment strategies were compared (one strategy without a specific target level for blood glucose versus another strategy where treatment was directed at such a target level), for each of which different drugs were used (linagliptin or glimepiride). Therefore, the results of Study 1218.20 cannot be interpreted for the research question of this benefit assessment. Further comments about this can be found in the following Section 2.3.2.

In summary, there is therefore no study that would be suitable for assessing the added benefit of a dual therapy with linagliptin.

Triple therapy

No study of triple therapy with linagliptin in a direct comparison with the ACT was presented. The company stated that no indirect comparison was undertaken, because in its view, this is not possible for methodological reasons. No conclusions can be drawn regarding the added benefit of linagliptin compared to the ACT from the placebo-controlled Study 1218.18 named by the company for triple therapy. Thus overall no studies were submitted that were suitable for assessing the added benefit of a triple therapy with linagliptin.

Further information about the results of information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 and 4.3.2.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.1 of the full dossier assessment.

2.3.2 Study characteristics

Study 1218.20, which was used by the company to assess the added benefit of a dual therapy with linagliptin, is described in more detail below. In this context, also by reference to

individual results of the study, it is explained why Study 1218.20 is not suitable for assessing the added benefit.

Table 4 gives an overview of the design of Study 1218.20. The interventions used in the study are described in Table 5 and the characteristics of the Study 1218.20 patients are shown in Table 6.

Table 4: Characteristics of the study –RCT, direct comparison of the treatment regime linagliptin vs. treatment regimen glimepiride (Study 1218.20, dual combination with metformin)

Study	Study design	Population	Interventions (number of randomized patients)	Duration of study	Location and period of study	Primary outcome; secondary outcomes[a]
1218.20	RCT double-blind, parallel multicentre	Adults with type 2 diabetes mellitus, pretreated with metformin as monotherapy or in combination with another oral antidiabetic. Metformin daily dose ≥ 1500 mg or less, provided this was the maximum tolerated dose	Treatment regime with linagliptin (N = 776) Treatment regime with glimepiride (N = 775) Of which approval population[b]: Treatment regime with linagliptin (n = 545) Treatment regime with glimepiride (n = 548)	Wash-out: 6 weeks Run-in: 2 weeks Treatment: 104 weeks Follow-up: 1 week	16 countries in Africa, Asia, Europe, USA Treatment period: 02/2008–12/2010	Primary: change im HbA1c from start of study to Week 52 and Week 104 Secondary: Hypoglycaemic episodes, health-related quality of life (EQ-5D), adverse events

a: Primary outcomes contain information without consideration of the relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Relevant population for the assessment: patients who had been previously treated with metformin monotherapy.
N: Number of randomized and treated patients, n: relevant subpopulation, RCT: randomized controlled trial, vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison of treatment regime linagliptin vs. treatment regime glimepiride (Study 1218.20, dual combination with metformin)

Study	Intervention	Comparison	Concomitant medication
1218.20	Linagliptin 5 mg oral once daily Placebo for glimepiride Target blood glucose level: none	Glimepiride 1, 2, 3, or 4 mg once daily Placebo for linagliptin Target blood glucose level: the glimepiride dose was up-titrated in the first 12 weeks of treatment at 4-week intervals, provided the fasting blood glucose levels were above 110 mg/dl (self-measurement by patient)s	Metformin ≥ 1500 mg daily[a]
a: With a daily dose < 1500 mg, the investigator had to confirm this as the maximum tolerated dose. The dose used by patients was not to be altered during the course of the study. RCT: randomized controlled trial, vs.: versus			

Study 1218.20 was a randomized, active-controlled and double-blind approval study sponsored by the company. It was conducted in adult patients with type 2 diabetes mellitus in whom no adequate glycaemic control had been achieved despite treatment with metformin. Patients were enrolled who had either been previously treated with metformin monotherapy or with metformin combined with one or more oral antidiabetics. Since about 30 % of the patients had been treated with 2 or more oral antidiabetics, only approx. 70 % of the study population were treated in accordance with the approval (previous treatment with metformin alone [3]: 1093 of 1551 patients).

The treatment groups did not differ substantially in terms of age, sex, duration of disease, previous treatment, baseline HbA1c or ethnicity. The average age of patients was approx. 60 years. About 40 % of patients were female. The great majority of patients enrolled in the study were of Caucasian origin. Over half of the patients had suffered from type 2 diabetes mellitus for more than 5 years, and the disease had been diagnosed less than 1 year previously in fewer than 10 % of patients. The mean baseline HbA1c (long-term marker for average blood glucose level) in both groups was 7.7 %.

Table 6: Characteristics of the study population – RCT, direct comparison of treatment regime linagliptin vs. treatment regime glimepiride (Study 1218.20, dual combination with metformin)

Group	Treatment regime linagliptin (+ metformin)	Treatment regime glimepiride (+ metformin)
N	776	775
Age [years]		
mean (SD)	59.8 (9.4)	59.8 (9.4)
Sex f /m [%]	40.5 / 59.5	39.2 / 60.8
Duration of disease, n (%)[a, b]		
< 1 year	50 (6.5)	58 (7.7)
> 1 to 5 years	316 (41.4)	291 (38.5)
> 5 years	398 (52.1)	406 (53.8)
Baseline HbA1c [%][b]		
mean (SD)	7.7 (0.9)	7.7 (0.9)
Number of previous OAD, n (%)[b]		
1	535 (70.0)	534[c] (70.7)
2	228 (29.8)	220 (29.1)
3	1 (0.1)	1 (0.1)
Daily metformin dose, n (%)[b, d]		
< 1500 mg	58 (7.6)	44 (5.8)
≥ 1500 mg	706 (92.4)	711 (94.2)
Ethnic group[e]		
Caucasian	660 (85.1)	659 (85.0)
Asian	94 (12.1)	96 (12.4)
Black / African American	20 (2.6)	18 (2.3)
Hispanic / Latino	21 (2.7)	19 (2.5)

a: Time since diabetes diagnosis.
b: Based on the FAS population of 764 patients in the linagliptin group and 755 patients in the glimepiride group. FAS population is defined as all randomized patients with a least one dose of the study medication, with a valid baseline HbA1c and one HbA1c measurement in the treatment phase.
c: Number of patients comes from the submitted documents. Discrepancy with information in Module 4 of the dossiers, where 543 (70.7) patients are quoted.
d: At enrolment into the study.
e: Groups were non-disjunctive so their proportions in the total population can add up to more than 100 %.
FAS: full analysis set, f: female, m: male, N: number of randomized and treated patients, OAD: oral antidiabetics, RCT: randomized controlled trial, SD: standard deviation, vs.: versus

The study comprised a 6-week wash-out phase for patients who had been previously treated with one or more other oral antidiabetics in addition to metformin, a 2-week run-in phase with placebo, a treatment period of 104 weeks and a follow-up phase of 1 week. Patients received the study medication as follows: linagliptin 5 mg oral once daily or glimepiride 1, 2, 3 or 4 mg oral once daily, in each case with placebo administration of the other drug. The daily glimepiride dose was titrated at intervals of 4 weeks in the first 12 weeks of the treatment

phase provided that the fasting blood glucose levels were above 110 mg/dl (self-measurement by patient). In addition, metformin was to be continued in both treatment groups as basal therapy just as before the start of the study and with an unchanged dose.

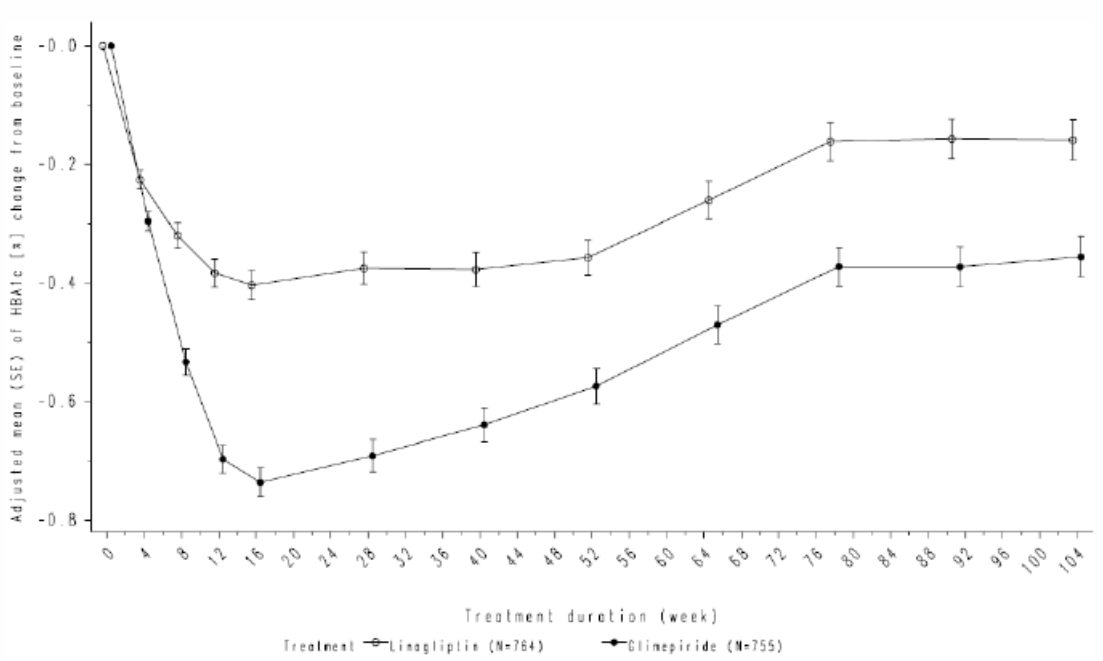
Due to the fact that target blood glucose levels in the first phase of the study were specified only for glimepiride but not for linagliptin, Study 1218.20 does not constitute a comparison just of the two drugs, but rather a comparison of two combined interventions (treatment strategy plus drug). Thus it is not certain that the effects observed in the study are attributable to the respective drugs used. They could also solely be due to the different treatment strategies.

The results of Study 1218.20 themselves support this assumption. Figure 1 shows the change in HbA1c (adjusted means) during the 104-week treatment phase of the study in the total study population; Figure 2 shows the course of absolute mean HbA1c. No corresponding data for the entire course of the study for the subpopulation treated in accordance with the approval were available.

Consideration of the time course of the change in HbA1c showed that under the targeted treatment with glimepiride, HbA1c fell rapidly during the titration phase (first 12 weeks of the study) to the aspired near-normal value. The lowest HbAc1 value was reached after about 16 weeks.

An initial reduction in HbA1c was also seen in the linagliptin group, but was far less pronounced than in the glimepiride group. The difference between the treatment groups was greatest after approx. 16 weeks. By the end of the study, the difference between the two treatment groups had narrowed somewhat, but was still statistically significant (test for difference).

The differences in the reduction in HbA1c were also obvious from the responder analyses of HbA1c contained in the submitted documents. For patients with a baseline HbA1c of 6.5 % or more, the chance (as measured by the OR) at the end of the study of having an HbA1c of less than 6.5 % was 0.69 times smaller than with glimepiride. This difference is statistically significant (linagliptin group 10.9 % of patients, glimepiride group: 14.7 % of patients; OR 95 % CI: 0.69 [0.50; 0.95], p = 0.024). This similarly applies to a reduction in HbA1c of at least 0.5 percentage points at Week 104 (linagliptin group 26.2 % of patients; glimepiride group: 33.5 % of patients; OR 95 % CI: 0.70 [0.56; 0.88], p = 0.002).



Adjusted mean HbA1c from baseline, treatment, pretreatment with oral antidiabetics, random error.

Figure 1: Time course of adjusted mean HbA1c during Study 1218.20 (full analysis set, last observation carried forward, LOCF), data source: study report

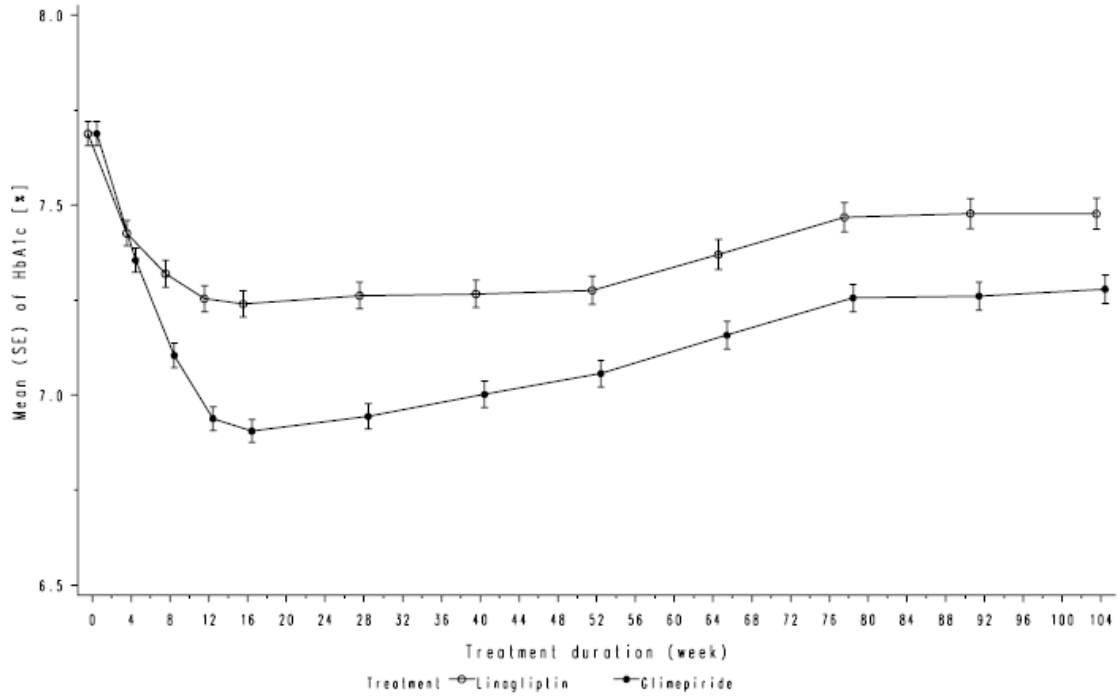
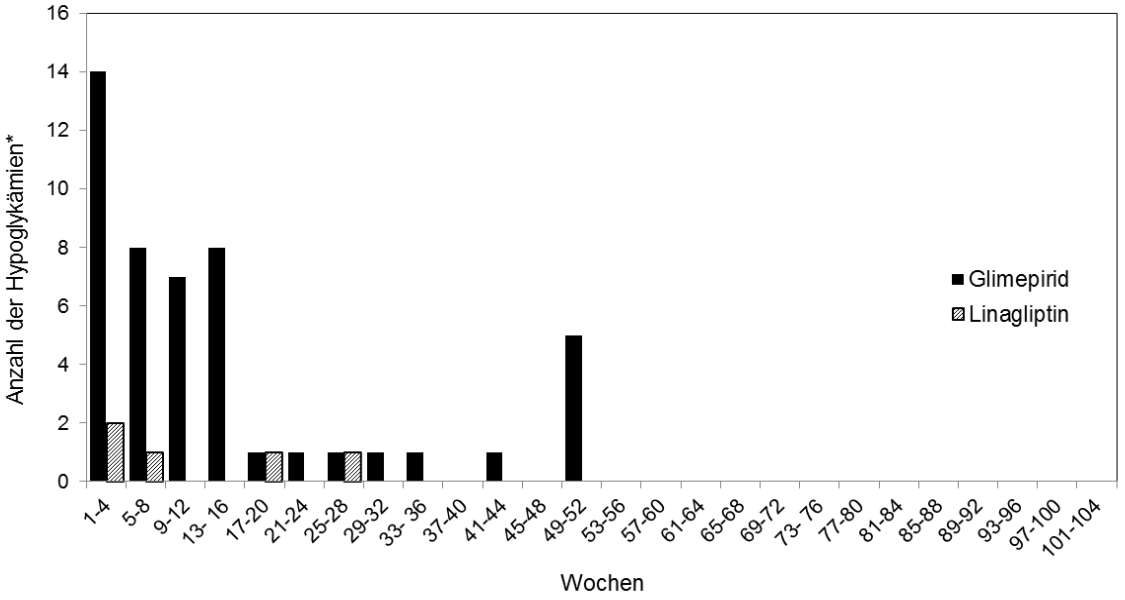


Figure 2: Time course of mean HbA1c during Study 1218.20 (full analysis set, LOCF), data source: study report

As expected, the time course of occurrence of hypoglycaemic episodes corresponded with the described course of blood glucose reduction. This is shown in Figure 3.



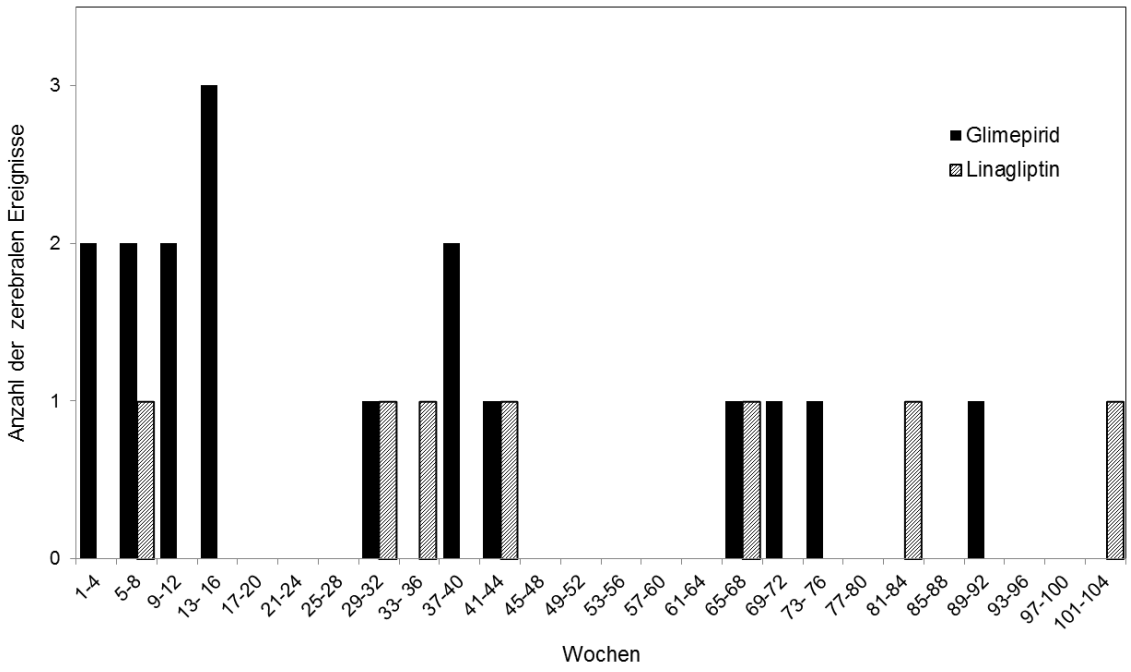
[Number of hypoglycaemic episodes / Weeks. Glimepirid = Glimepiride]

Hypoglycaemic episodes classified as SAE or as "other significant AE" according to ICH E3 (AE that are defined as non-serious and not significant, that led to withdrawal or dose reduction or to institution of significant concomitant therapy or represented marked haematological or other laboratory abnormalities)

Figure 3: Number of classified hypoglycaemic episodes during the course of Study 1218.20

This evaluation presented covers hypoglycaemic events for which individual patient data at the time of the event were presented in the dossier. These were episodes of hypoglycaemia of higher severity, namely those that were classified as serious adverse event (SAE) or as "other significant adverse event (AE)" according to ICH E3 (Guideline E3 of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH). The latter are hypoglycaemias that were defined as those not-serious and non-significant AEs which led to discontinuation of dose reduction of the study drug, led to significant concomitant therapy, or were marked haematological or other laboratory abnormalities. First-occurrence events per patient are shown. Figure 3 shows that hypoglycaemias as defined above occurred especially in the first 16 weeks of the study and were considerably more common under glimepiride. After this phase, hypoglycaemic episodes occurring for the first time were only observed as isolated cases up to Week 52 and no such episodes occurred in the second half of the study at all.

The time course of occurrence of serious cerebral events also corresponded with the course of blood glucose reduction. This is shown in Figure 4.



[Number of cerebral events / Weeks. Glimepirid = Glimepiride]

Data were taken from the available documents on SAE. Cerebral events of the outcome "cerebrovascular disorders" classified as SAE were analysed (standardized MedDRA [Medical Dictionary for Regulatory Activities] query, SMQ).

Figure 4: Number of serious cerebral events during the course of Study 1218.20

The observed difference between the treatment groups is due solely to the first study period up to Week 16. Thereafter, only isolated events occurred in both treatment groups without any tendency in favour of one or the other group.

In summary, it was shown that the time course of occurrence of important outcomes of Study 1218.20 ("hypoglycaemia of higher severity" and "cerebral events") corresponded with the blood glucose reduction. The substantial differences in blood glucose reduction between the treatment groups were apparently induced by the unilateral specification of a target blood-glucose level for glimepiride. The results of Study 1218.20 cannot therefore be used to assess the added benefit of linagliptin compared to glimepiride.

The results of Study 1218.20 for the group of patients treated in accordance with the approval are shown additionally below.

Table 7 summarizes the results of Study 1218.20. Where necessary, the data from the company's dossier are supplemented by the Institute's calculations.

In the case of event numbers of ≤ 1 % (in at least 1 cell), the Peto OR instead of the relative risk was calculated as effect measure and used for the assessment. If the number of events is low, the odds ratio (OR) provides a good approximation of the relative risk.

Table 7: Results on the comparison of the treatment regime linagliptin vs. treatment regime glimepiride (Study 1218.20, dual combination with metformin)

Outcome category outcome	Treatment regime linagliptin (+ metformin)		Treatment regime glimepiride (+ metformin)		Treatment regime linagliptin vs. treatment regime glimepiride
	N	Patients with events n (%)	N	Patients with events n (%)	RR / Peto-OR[a] [95 % CI] p-value
Mortality					
Overall mortality	545	3 (0.6)	548	2 (0.4)	1.50 [0.26; 8.70] 0.686[b]
Cardiac morbidity					
Non-fatal MI[c]	545	5 (0.9)	548	8 (1.5)	0.63 [0.21; 1.88] 0.579[b]
Angina pectoris[d]	545	11 (2.0)	548	8 (1.5)	1.38 [0.56; 3.41] 0.499[b, e]
SMQ "Ischaemic heart disease"[f]	545	28 (5.1)	548	39 (7.1)	0.72 [0.45; 1.16] 0.207[b, e]
Cerebral morbidity					
TIA[c]	545	1 (0.2)	548	4 (0.7)	0.30 [0.05; 1.75] 0.374[b]
Non-fatal stroke[c]	545	2 (0.4)	548	6 (1.1)	0.37 [0.09; 1.48] 0.287[b]
SMQ "Cerebro-vascular disorders"	545	8 (1.5)	548	10 (1.8)	0.80 [0.32; 2.02] 0.813[b]
Health-related quality of life					
EQ-5D (VAS)	No data available for the subpopulation treated in accordance with the approval				

(continued on next page)

Table 7: Results on the comparison of the treatment regime linagliptin vs. treatment regime glimepiride (Study 1218.20, dual combination with metformin) (continued)

Outcome category outcome	Treatment regime linagliptin (+ metformin)			Treatment regime glimepiride (+ metformin)			Treatment regime linagliptin vs. treatment regime glimepiride
	N	Patients with events n (%)		N	Patients with events n (%)		RR / Peto-OR[a] [95 % CI] p-value
Adverse events							
Hypoglycaemias							
Serious/severe hypoglycaemia	545	1 (0.2)		548	8 (1.5)		0.21 [0.06; 0.78] 0.038[b]
Non-serious symptomatic hypoglycaemia (blood glucose ≥ 54 and ≤ 70 mg/dl)	545	14 (2.6)		548	137 (25.0)		0.10 [0.06; 0.18] < 0.001[b]
Non-serious symptomatic hypoglycaemia (blood glucose < 54 mg/dl)	545	2 (0.4)		548	69 (12.6)		0.13 [0.08; 0.22][g] < 0.001[b]
Additionally shown: HbA1c change	N[h]	Values at baseline mean (SD)	Change at study end mean (SD)	N[h]	Values at baseline mean (SD)	Change at study end mean MW (SD)	Effect [CI] p-value
	535	n. k.	-0.29[i] (0. 93[j])	534	n. k.	-0.48[i] (0.92[j])	0.18 [0.08; 0.28][j] < 0.001
Pancreatitis	No data available for the subpopulation treated in accordance with the approval						
Renal events (SMQ "Acute renal failure")[k]	545	1 (0.2)		548	5 (0.9)		0.26 [0.05; 1.31] 0.217[b]
Overall rate of AEs	545	467 (85.7)		548	497 (90.7)		0.94 [0.90; 0.99] 0.011[b]
Overall rate of SAEs	545	90 (16.5)		548	115 (21.0)		0.79 [0.61; 1.01] 0.063[b]
Treatment discontinuations due to AE	545	42 (7.7)		548	65 (11.9)		0.65 [0.45; 0.94] 0.025[b]
Additional outcome							
Body weight	N[l]	Values at baseline mean (SD)	Change at study end mean (SD)	N[l]	Values at baseline mean (SD)	Change at study end mean (SD)	Effect [CI] p-value
	515	n. k.	-1.11[m] (4.08[j])	510	n. k.	1.62[m] (4.06[j])	-2.73 [-3.24; -2.22][j] < 0.001

(continued on next page)

Table 7: Results on the comparison of the treatment regime linagliptin vs. treatment regime glimepiride (Study 1218.20, dual combination with metformin) (continued)

a. Peto-OR (Institute's calculation) provided if number of events ≤ 1 % in at least one cell.
b: Institute's calculation, Fisher's exact test.
c: CEC-adjusted outcome.
d: Institute's calculation, stable and unstable angina pectoris, a double counting of a patient is possible in the glimepiride group.
e: The double counting problem was investigated by sensitivity analyses, which produced no changes in the conclusions to be derived.
f: Institute's calculation. Quoted data may contain double countings of patients (maximum 1 patient in the linagliptin group, maximum 2 patients in the glimepiride group).
g: Due to the very large effect, the RR was calculated as part of a sensitivity analysis (0.03 [0.01; 0.12]).
h: Number of patients in the FAS population previously treated with only one OAD. FAS population is defined as all randomized patients with at least one dose of the study drug with one valid baseline HbA1c measurement and one HbA1c measurement in the treatment phase.
i: Adjusted mean (SD) according to baseline and treatment HbA1c. LOCF evaluation of the ITT population.
j: Institute's calculation.
k: MedDRA SMQ "Acute renal failure".
l: Number of patients in the FAS population previously treated with only one OAD, for whom a baseline weight measurement and another during the treatment phase were available.
m: Adjusted mean (SD) according to baseline HbA1c and body weight and treatment. LOCF evaluation of the ITT population.

AE: adverse event, CEC: Clinical Event Committee, CI: confidence interval, FAS: Full analysis set, ITT: intention-to-treat, MI: myocardial infarction, N: number of analysed patients, n: number of patients with event, n. k.: not known, OAD: oral antidiabetic, OR: Odds Ratio, RCT: randomized controlled trial, RR: relative risk, SMQ: Standardised MedDRA Query, SAE: serious adverse event, TIA: transitory ischaemic attack, vs.: versus.

The documents available for the subpopulation of Study 1218.20 treated in accordance with the approval contained only results for the categories mortality, morbidity and adverse events (with the exception of the outcome "pancreatitis"). These are based on the subgroup analyses carried out by the company for the total population for the factor "previous treatment with oral antidiabetics". The company presented no corresponding evaluation in Module 4 of the dossier for the outcome "health-related quality of life".

Further information about study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and 4.3.2.1.2 as well as in Appendix 4-G of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results concerning added benefit

The company's study pool contained no study that was suitable for assessing the added benefit of linagliptin (in monotherapy, dual therapy or triple therapy) in comparison with the ACT of the G-BA and of the company.

Since no relevant study for the benefit assessment was submitted, there is no proof of an added benefit of linagliptin compared to the ACT specified by the G-BA and the company.

This result deviates from that of the company, who, on the basis of the placebo-controlled study, derived an indication of a non-quantifiable added benefit of linagliptin over the ACT.

Likewise the company also derived a non-quantifiable added benefit for the triple therapy from a placebo-controlled study. For dual therapy, on the basis of the direct comparative Study 1218.20, the company derived an indication of a considerable added benefit.

Further information about the choice of outcome, risk of bias at outcome level and outcome results can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of added benefit

The company presented no relevant studies for the assessment of the added benefit of linagliptin in monotherapy, dual or triple therapy over the ACT specified by the G-BA. Further details can be found in Section 2.4 of this assessment.

Overall, there is no proof of an added benefit of linagliptin. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

The decision regarding added benefit is made by the G-BA.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment

2.6 List of included studies

Only one direct comparative study (1218.20) was submitted for the dual therapy with linagliptin. For the above-mentioned reasons this study is not suitable to assess an added benefit. The sources named in the dossier by the company (Module 4) are presented as supplementary information.

Boehringer Ingelheim. A randomised, double-blind, active-controlled parallel group efficacy and safety study of linagliptin (5 mg, administered orally once daily) compared to glimepiride (1 to 4 mg once daily) over two years, in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy: study 1218.20; clinical trial report (revision no. 2) [unpublished]. 2012.

Boehringer Ingelheim Pharma. A randomised, double-blind, active-controlled parallel group efficacy and safety study of BI 1356 (5.0 mg, administered orally once daily) compared to glimepiride (1 to 4 mg once daily) over two years, in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy [online]. In: International Clinical Trials Registry Platform. 19.03.2012 [accessed 20.11.2012]. URL: http://apps.who.int/trialsearch/Trial.aspx?TrialID=EUCTR2007-004585-40-DE.

Boehringer Ingelheim. A randomised, double-blind, active-controlled parallel group efficacy and safety study of BI 1356 (5,0 mg, administered orally once daily) compared to glimepiride (1 to 4 mg once daily) over two years, in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy: study 1218.20; clinical trial protocol [unpublished]. 2007.

Boehringer Ingelheim. Post-hoc analyses for trial no.1218.20 [unpublished].

Gallwitz B, Rosenstock J, Rauch T, Bhattacharya S, Patel S, Von Eynatten M et al. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet 2012; 380(9840): 475-483.

References for English extract

Please see full dossier assessment for full reference list.

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