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**Insulin degludec/liraglutide
(Addendum to Commission A15-15)¹**

Addendum

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Table of contents

	Page
List of tables	iv
List of figures	v
List of abbreviations	vi
1 Background	1
2 Assessment of the DUAL V study	2
2.1 Study design	2
2.2 Relevance of the study for the research question	3
2.3 Results tables	7
3 References	10

List of tables

	Page
Table 1: Results (dichotomous outcomes) – RCT, direct comparison: insulin degludec/liraglutide + metformin vs. insulin glargine + metformin	8
Table 2: Results (continuous outcomes) – RCT, direct comparison: insulin degludec/liraglutide + metformin vs. insulin glargine + metformin	9

List of figures

	Page
Figure 1: Time course of HbA1c levels in the DUAL V study (full analysis set, last observation carried forward [LOCF])	5
Figure 2: Time course of symptomatic hypoglycaemic events (PG < 56 mg/dL) in the DUAL V study	6

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	haemoglobin A1c
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LOCF	last observation carried forward
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
OAD	oral antidiabetic
PG	plasma glucose
SD	standard deviation
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
U	units

1 Background

On 8 September 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A15-15 (*Insulin degludec/liraglutide – Benefit assessment according to §35a SGB V* [1]).

The present addendum refers to research question A2 of the dossier assessment: the assessment of the added benefit of the fixed combination of insulin degludec/liraglutide in combination with oral antidiabetics (OADs) in comparison with the appropriate comparator therapy (ACT) in adult patients with type 2 diabetes mellitus when OADs combined with basal insulin do not provide adequate glycaemic control. For this research question, the company had presented results of the study NN9068-3952 (DUAL V, hereinafter referred to as study “DUAL V”) in its dossier [2]. Based on the information provided in the dossier, the study was assessed as unsuitable for answering the present research question. This is justified by the fact that the patients in the comparator group received no meaningful escalation of their treatment, which resulted in an unfair comparison in the DUAL V study [1].

In the written commenting procedure and in the oral hearing it was argued, particularly by the company, that the intensification of the ongoing therapeutic strategy used in the comparator arm of the study constituted an adequate implementation of the ACT for the present research question [3].

Under consideration of the arguments on intensified therapy in the comparator arm of the DUAL V study put forward in the written commenting procedure and in the oral hearing, the G-BA commissioned IQWiG to assess the data on the DUAL V study submitted by the company.

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 of the DUAL V study

In accordance with the commission, the DUAL V study is assessed in the following sections. Tables presenting the study characteristics and the characteristics of the interventions and the study population can be found in Appendix A of dossier assessment A15-15 [1].

2.1 Study design

The DUAL V study was a randomized, active-controlled, open-label, multicentre study. Adult patients with type 2 diabetes mellitus and inadequate glycaemic control ($7.0\% \leq$ haemoglobin A1c [HbA1c] $\leq 10\%$) despite treatment with insulin glargine + metformin (basal insulin + OAD) were included. According to the inclusion criteria of the study, treatment had been ongoing for at least 90 days before screening. Insulin glargine had to be at a stable daily dose of 20 to 50 units (U) for the last 56 days before screening ($\pm 10\%$ individual fluctuation), the metformin dose had to be stable for at least 90 days (≥ 1500 mg or maximum tolerated dose).

A total of 557 patients were randomized, 278 of these patients to the insulin degludec/liraglutide arm, and 279 patients to the insulin glargine arm. The study included a screening phase of 2 weeks. The treatment phase was 26 weeks. Patient-relevant outcomes of the study were morbidity, health-related quality of life and adverse events including hypoglycaemia.

Interventions

After randomization, the patients in the study received either the fixed combination of insulin degludec/liraglutide or continued their ongoing treatment with insulin glargine. Both interventions were administered once daily subcutaneously. The starting dose of insulin degludec/liraglutide was 16 dose steps, which corresponds to the recommended starting dose when changing from basal insulin therapy [4]. In the control arm, treatment with insulin glargine was continued at the dose administered before the start of the study. In both study arms, the dose was titrated twice weekly on the basis of the fasting plasma glucose to a target level of 4.0 to 5.0 mmol/L (72 to 90 mg/dL). No maximum dose was specified for insulin glargine, whereas the insulin dose of insulin degludec/liraglutide was limited to 50 dose steps (equivalent to 50 U insulin degludec and 1.8 mg liraglutide) according to the Summary of Product Characteristics (SPC). Patients in both study arms continued their previous treatment with the OAD metformin with the same dosage and frequency as before the start of the study.

Characteristics of the study populations

The characteristics of the study populations such as age, weight and body mass index were largely comparable between the 2 study arms (see Table 16 in [1]). About half of the patients in the study arms were women and half were men. The patients' mean disease duration with type 2 diabetes mellitus was approximately 11 years. The mean baseline HbA1c value was about 8.3% in both study arms. The proportion of patients who discontinued the study was about twice as high in the insulin degludec/liraglutide arm (10.1%) than in the insulin glargine arm (5.0%).

2.2 Relevance of the study for the research question

In dossier assessment A15-15, the DUAL V study was assessed as unsuitable for deriving an added benefit of insulin degludec/liraglutide in comparison with the ACT.

The reasons for this were that the DUAL V study investigated the research question of the approval (efficacy: escalation with insulin degludec/liraglutide versus continuation of inadequate treatment), but not the research question of the benefit assessment (added benefit: escalation with insulin degludec/liraglutide versus escalation with the ACT). Whereas the patients in the intervention arm of the DUAL V study received an intensification of their therapy by the additional administration of liraglutide (in addition to basal insulin and metformin), the therapeutic strategy in the comparator arm remained unchanged. Treatment with basal insulin (insulin glargine) + metformin was continued; the dose of basal insulin, on the basis of the fasting plasma glucose levels, was titrated analogously to the intervention arm. Continuation of the ongoing therapeutic strategy in the comparator arm is not meaningful in the present situation, however, and resulted in an unfair comparison because this therapeutic strategy had already been obviously inadequate before [1].

However, main arguments in the written comments and in the oral hearing were that

- IQWiG explicitly recognized increasing the insulin dose as appropriate specification of the ACT in the assessment of the drug combination sitagliptin/metformin [3]
- while treatment of the included patients was inadequate under their ongoing therapy, not all treatment options had been exhausted [3]
- more complex forms of treatment such as intensified insulin therapy (ICT) are not suitable for all patients [3,5]

The arguments presented are examined in greater detail below.

Consistent handling of insulin studies in the benefit assessment

The company's reasoning that increasing the insulin dose had already been recognized in an earlier dossier assessment was not followed. In contrast to the company's presentation, dossier assessment A13-03 on sitagliptin/metformin described that different insulin treatment regimens may be medically reasonable to optimize treatment for the individual patient. Besides insulin dose increase, conventional insulin treatment and ICT were given as examples here [6]. In fact, only studies in which the patients had the possibility to optimize their treatment on an individual basis (including switching treatment type and regimen) were included in the corresponding research question of benefit assessment A13-03. In the DUAL V study, however, only one of several possible options, i.e. dose increase of insulin glargine, was available to the patients in the control arm.

Adequate treatment optimization depends on the individual situation of the patients

In order to be able to derive conclusions on the added benefit from the DUAL V study, insulin dose increase would have to be the treatment optimization of choice for all patients in the study. The company argued that while treatment of the included patients was inadequate under their ongoing therapy, not all treatment options had been exhausted. This cannot be inferred from the inclusion criteria of the study or from the available information on patient characteristics, however. Instead it can be assumed on the basis of the inclusion criteria (basal insulin for at least 90 days, at a stable dose for at least 56 days) that very different patients were included in the study, who had already experienced different extents of adjustment of their basal insulin treatment. It can therefore be assumed that the treatment needs of these patients differed considerably, and it can be expected that patients who at most benefit for a short period of time from further dose increase were included to a relevant extent. Besides, a therapeutic decision would always also depend on the individual treatment goals of a patient [7].

Delineation of patient groups

Alternatively, conclusions on the added benefit could be derived from the DUAL V study if it was possible to delineate groups of patients for whom insulin dose increase would be the treatment optimization of choice. Based on the available information, however, no patient group can be delineated for whom, based on their pretreatment and treatment needs, treatment adjustment with insulin dose increase within the ongoing treatment with basal insulin can be assumed to be a meaningful comparison with an intervention with insulin degludec/liraglutide. Particularly information on the duration of their previous basal insulin treatment and adjustments already conducted would be required to delineate such a patient group. According to the company in the oral hearing, this information is not available for the DUAL V study. Furthermore, additional information on the individual needs and treatment goals of the patients would also be required here to be able to estimate whether a dose increase constitutes a meaningful treatment escalation for the respective patients in the existing therapeutic strategy.

Treatment goals of the DUAL V study require change in strategy

The company also argued that more complex forms of treatment such as ICT are not suitable for all patients. This argument also does not justify suitability of the DUAL V study for the present assessment. It is comprehensible that ICT with several administrations of prandial insulin at mealtimes in addition to basal insulin means more effort for the patients so that it is not an option for certain patients, e.g. older ones. It should still be noted that ICT is not the only alternative insulin strategy to basal insulin. Conventional treatment with mixed insulin, for example, is notably less complex than ICT, for example. This option was also not available in the study, however.

In addition, the design of the DUAL V study was not aimed at offering a therapeutic alternative for patients for whom a therapeutic strategy such as the ICT is not an option. It can

be assumed that these patients only want to achieve moderate improvements in their glycaemic control with simple therapeutic interventions. The treatment goals specified in the DUAL V study were too strict for this purpose: In both study arms, the dose was titrated twice weekly on the basis of the fasting plasma glucose to a target level of 4.0 to 5.0 mmol/L (71 to 90 mg/dL). This value is considerably lower than the orientation values (5.6 to 6.9 mmol/L or 100 to 125 mg/dL) stated by the National Care Guideline (NVL) for the treatment of type 2 diabetes, which aim to achieve an HbA1c target range between 6.5% and 7.5% recommended by the guideline [7]. Even though individual patients in the present study might initially benefit from further adjustment of their ongoing basal insulin treatment, it is questionable whether the titration goal aimed for in the study can be achieved with the ongoing therapeutic strategy. A fair comparison in this study situation with the specified treatment goals would require allowing the patients in the comparator arm to change the therapeutic strategy.

High doses of insulin increase the risk of hypoglycaemia

The fact that the continuation of the ongoing strategy in the comparator arm with dose increase of the basal insulin as only possibility to optimize treatment is subject to clear restrictions can also be seen in the courses of HbA1c values and hypoglycaemic events during the DUAL V study. The following Figure 1 shows the change in HbA1c in the course of the DUAL V study.

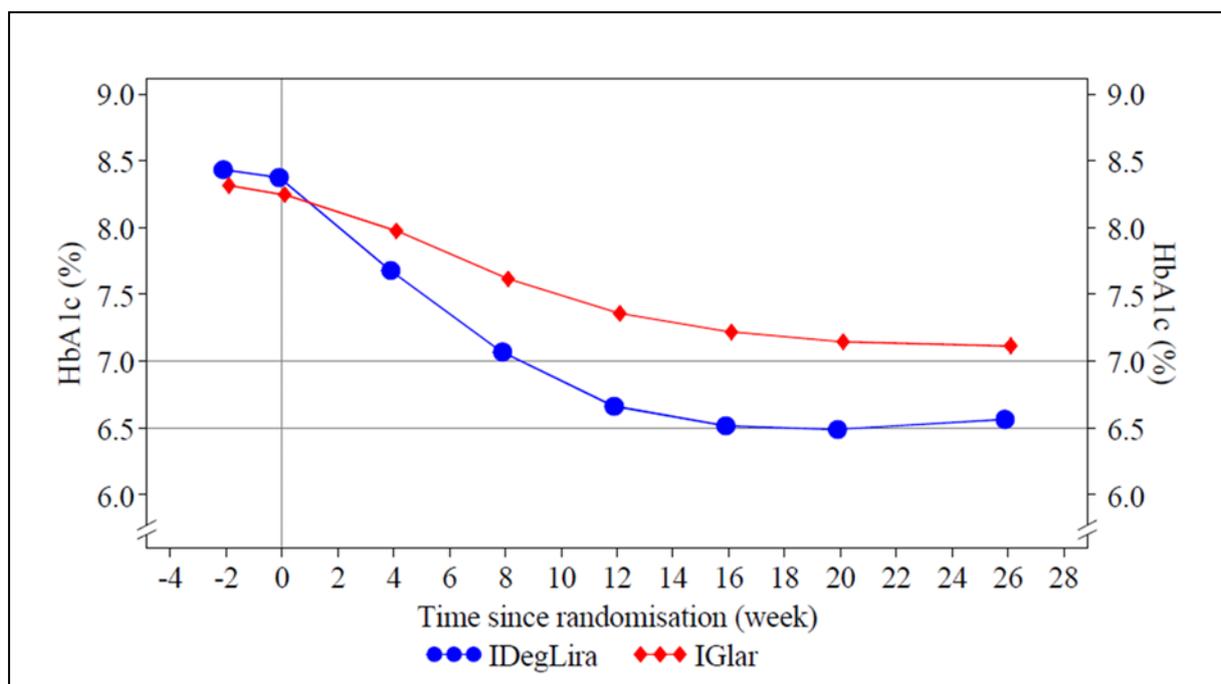


Figure 1: Time course of HbA1c levels in the DUAL V study (full analysis set, last observation carried forward [LOCF])

Decrease in HbA1c levels was shown in both study arms. This was considerably more pronounced in the insulin degludec/liraglutide arm with an observed mean decrease by

1.81 percentage points (standard deviation [SD]: 1.08) than in the insulin glargine arm (mean decrease by 1.13 percentage points, SD: 0.98).

Notable decrease in HbA1c is therefore achieved also in the comparator arm. Besides a possible study effect, this may have been caused also by titration to the low target level of the study (fasting plasma glucose 4.0 to 5.0 mmol/L; 71 to 90 mg/dL), which led to corresponding dose increases in the comparator arm. The mean insulin doses in the 2 study arms were 31 (SD: 10) and 32 U (SD: 10) before the start. In the insulin degludec/liraglutide arm, the starting dose was 16 U for all patients, which was in compliance with the approval. In the comparator group, in contrast, titration of the insulin dose was maintained on the basis of the dose used at the start of the study. By the end of the study (week 26), the mean insulin dose in the comparator arm had more than doubled (mean value: 66 U, SD: 30). In the intervention arm, it was considerably lower (mean value: 41 U [SD: 10]) and the values showed considerably lower variability. At the same time, the time course of hypoglycaemic events (symptomatic, plasma glucose [PG] < 56 mg/dL) in Figure 2 shows that, particularly in the further course of the study (with increased insulin dose in the comparator arm), hypoglycaemic events increased considerably.

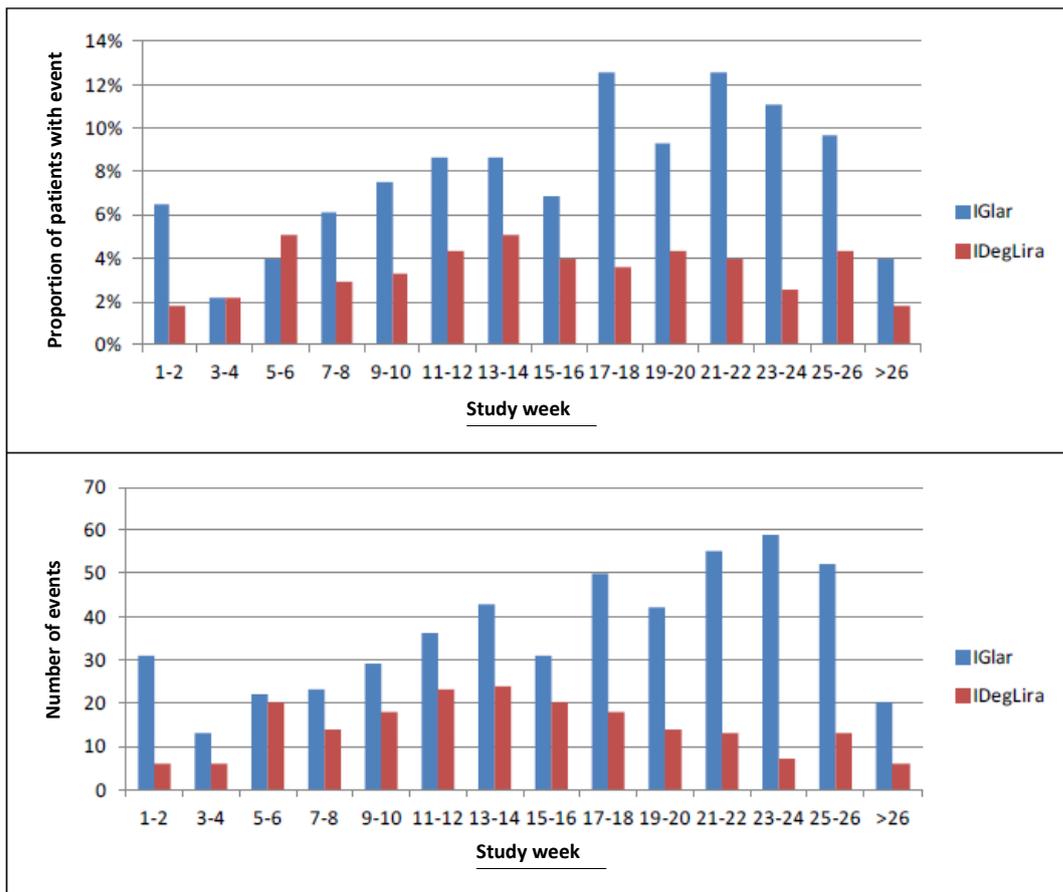


Figure 2: Time course of symptomatic hypoglycaemic events (PG < 56 mg/dL) in the DUAL V study

When interpreting the considerable difference in hypoglycaemic events at the start of the study, it should also be considered that the insulin dose was markedly reduced in the intervention group at the start of the study when changing to the starting dose of 16 U.

Even though considerably fewer hypoglycaemic events were shown for the intervention group, with better glycaemic control at the same time, no meaningful interpretation of the results of the study is possible.

Summary: The DUAL V study cannot be interpreted due to the unfair comparison

Due to the unfair comparison – change of therapeutic strategy in the intervention arm, continuation of the ongoing therapy in the comparator arm (irrespective of the patients' needs) – the extent to which the observed effects were caused by this remains unclear. The impossibility to change therapeutic strategy in the comparator arm is to be assessed as so severe that it can raise doubts about the entire observed effects. Hence the DUAL V study is unsuitable for the assessment of the added benefit of insulin degludec/liraglutide in comparison with the ACT in the present research question.

2.3 Results tables

The results of the DUAL V study are presented in the following tables (Table 1 and Table 2).

Table 1: Results (dichotomous outcomes) – RCT, direct comparison: insulin degludec/liraglutide + metformin vs. insulin glargine + metformin

Study Outcome category Outcome	Insulin degludec/liraglutide ^a		Insulin glargine ^a		Insulin degludec/liraglutide ^a vs. insulin glargine ^a RR [95% CI]; p-value
	N	Patients with event n (%)	N	Patients with event n (%)	
DUAL V					
Mortality					
All-cause mortality	278	0 (0)	279	1 (0.4)	0.33 [0.01; 8.18]; 0.530 ^b
Morbidity					
Symptomatic hypoglycaemia (plasma glucose < 56 mg/dL) ^c	278	59 (21.2)	279	112 (40.1)	0.53 ^d [0.40; 0.69]; < 0.001 ^e
Severe hypoglycaemia	278	0 (0)	279	1 (0.4)	1.00 [1.00; 1.01]; 0.530 ^e
<i>Additional: symptomatic nocturnal hypoglycaemia (plasma glucose < 56 mg/dL)^c</i>	278	14 (5.0)	279	58 (20.8)	0.24 [0.14; 0.42]; < 0.001 ^e
Cardiovascular morbidity (MACE) ^f	278	1 (0.4)	279	1 (0.4) ^b	1.00 [0.06; 15.97]; > 0.999 ^b
Nonfatal myocardial infarction	278	0 (0)	279	0 (0)	NC
Nonfatal stroke	278	1 (0.4)	279	0 (0)	3.01 [0.12; 73.59]; 0.370 ^b
Cardiovascular death	278	0 (0)	279	1 (0.4) ^b	0.33 [0.01; 8.18]; 0.530 ^b
Adverse events					
AEs	278	160 (57.6)	279	141 (50.5)	
SAEs	278	5 (1.8)	279	9 (3.2)	0.56 [0.19; 1.64]; 0.299 ^b
Discontinuation due to AEs	278	7 (2.5)	279	1 (0.4)	7.03 [0.87; 56.72]; 0.034 ^g
<p>a: Each in combination with metformin.</p> <p>b: Institute's calculation.</p> <p>c: Hypoglycaemic events that are only based on the patient's narration of the symptoms without confirmed decreased blood glucose measurement are not sufficiently valid. Non-symptomatic deviations in blood glucose lack the aspect of patient relevance. Only the operationalization of hypoglycaemia that considers both criteria is therefore presented here.</p> <p>d: RR estimated from regression model with region as fixed effect.</p> <p>e: Institute's calculation, unconditional exact test (CSZ method according to [8]).</p> <p>f: Includes the following events: nonfatal myocardial infarction, nonfatal stroke and cardiovascular death.</p> <p>g: Institute's calculation, asymptotic. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.</p> <p>AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; MACE: major adverse cardiovascular events; N: number of analysed patients; n: number of patients with event; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus</p>					

Table 2: Results (continuous outcomes) – RCT, direct comparison: insulin degludec/liraglutide + metformin vs. insulin glargine + metformin

Study Outcome category Outcome	Insulin degludec/liraglutide ^a			Insulin glargine ^a			Insulin degludec/ liraglutide ^a vs. insulin glargine ^a MD ^c [95% CI]; p-value
	N ^b	Baseline values mean (SD)	Change at end of study mean ^c (SE)	N ^b	Baseline values mean (SD)	Change at end of study mean ^c (SE)	
DUAL V							
Health-related quality of life							
SF-36 ^d							
Physical sum score	278	47.4 (9.0)	1.5 (0.4)	277	47.7 (8.4)	-0.5 (0.4)	1.9 [0.8; 3.1]; < 0.001 Hedges' g 0.30 [0.13; 0.47] ^e
Mental sum score	278	46.7 (11.4)	1.3 (0.5)	277	48.1 (9.9)	1.3 (0.5)	-0.1 [-1.5; 1.3]; 0.928
Supplementary outcomes							
Body weight (kg)	278	88.3 (17.5)	-1.39 (0.20)	279	87.3 (15.8)	1.81 (0.20)	-3.20 [-3.77; -2.64]; < 0.001
<p>a: Each in combination with metformin.</p> <p>b: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.</p> <p>c: Unless stated otherwise, LOCF analysis of FAS population; adjusted mean change from start of study, ANCOVA with treatment and region as fixed effects and value at start of the study as covariate.</p> <p>d: A higher value indicates better health status.</p> <p>e: Hedges' g, Institute's calculation. The confidence interval includes the irrelevance threshold of 0.2 [9]. It can therefore not be inferred that the effect is relevant.</p> <p>ANCOVA: analysis of covariance; CI: confidence interval; FAS: full analysis set; LOCF: last observation carried forward; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36: Short Form (36) Health Survey; vs.: versus</p>							

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