

Health status and hypoglycaemia with insulin degludec versus insulin glargine: a 2-year trial in insulin-naïve patients with type 2 diabetes

Insulin degludec (IDeg) is a new basal insulin with an ultra-long and stable glucose-lowering effect. We compared once-daily IDeg and insulin glargine (IGlar), both in combination with metformin ± dipeptidyl peptidase-4 inhibitors, in a 52-week, open-label, treat-to-target trial in patients with type 2 diabetes followed by a 52-week extension trial in which subjects [$n = 725/1030$ (70.4%)] maintained their initial randomised treatment. Health status was assessed at baseline and 105 weeks using the Short Form-36 (SF-36 v2) questionnaire. SF-36 scores were analysed (ITT population) using ANOVA, with adjustments for covariates. At 105 weeks, the overall physical component score was significantly better with IDeg versus IGlar [treatment contrast (TC): 1.1 (0.1; 2.1)_{95%CI}, $p < 0.05$]. This was largely because of significantly better physical functioning [TC: 1.1 (0.0; 2.3)_{95%CI}, $p < 0.05$] and bodily pain sub-domain scores [TC: 1.5 (0.2; 2.9)_{95%CI}, $p < 0.05$]. Improvements in health status with IDeg compared to IGlar were maintained after 2 years.

Keywords: hypoglycaemia, insulin degludec, patient-reported outcomes, quality of life, SF-36, type 2 diabetes

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Introduction

Diabetes therapies can negatively affect health status/health-related quality of life (HRQoL) because of regimen complexity or rigidity, fear of injections, hypoglycaemia and fear of hypoglycaemia [1,2]. Thus, reducing hypoglycaemia and providing a more predictable treatment regimen might be expected to improve HRQoL. Insulin degludec (IDeg) is a new basal insulin that offers advantages over previous basal insulins. IDeg forms soluble multi-hexamers upon subcutaneous injection, achieving a stable time–action profile, an ultra-long duration of action lasting beyond 42 h, and low within-patient variability [3]. Seven randomised, open-label, controlled, phase 3 trials of 26- or 52-weeks' duration using a treat-to-target non-inferiority design, all confirmed similar glycaemic control for IDeg compared to insulin glargine (IGlar) as expected in treat-to-target trials. However, individual trials, as well as a prospectively planned meta-analysis, showed advantages for IDeg over IGlar with respect to hypoglycaemia [4]. HRQoL, another important treatment outcome, was measured in all of these trials using the SF-36 v2 questionnaire [5] and additional meta-analyses have shown that HRQoL [6], health utility [7] and mental health [8] are improved with IDeg compared to IGlar.

The analysis presented here includes previously unreported data from insulin-naïve patients with type 2 diabetes who were studied for a total of 2 years in a 52-week trial with a 52-week extension; this was the largest of the phase 3 trials in the IDeg clinical development programme [9]. As previously reported [10], at 105 weeks, HbA1c was similar for IDeg and IGlar (estimated treatment difference [ETD] 0.12%-points [-0.01 to 0.25]_{95%CI}, $p = 0.078$). Observed mean reductions in laboratory-measured fasting plasma glucose (FPG) were greater with IDeg (ETD -0.38 mmol/l [-0.70 to -0.06]_{95%CI}, $p = 0.019$). Importantly, these improvements in glycaemic control were accompanied by a lower risk of hypoglycaemia over the entire treatment period. Nocturnal confirmed hypoglycaemia was 43% lower with IDeg than with IGlar (estimated rate ratio [ERR], IDeg/IGlar: 0.57 [0.40; 0.81]_{95%CI}, $p = 0.002$) and rate of severe hypoglycaemia was 69% lower with IDeg (ERR 0.31 [0.11; 0.85]_{95%CI}, $p = 0.023$). Overall confirmed hypoglycaemia (plasma glucose < 3.1 mmol/l or severe) was similar between IDeg and IGlar; estimated rate ratio (IDeg/IGlar): ERR 0.84 [0.68; 1.04]_{95%CI}, $p = 0.115$ [10].

Given that the clinical benefit of reduced hypoglycaemia occurred in conjunction with improved glucose control after 2 years of treatment, improvements in HRQoL might also be expected. In the original 52-week trial, participants treated with IDeg showed improvements in clinical measures and reported greater improvements in 'overall physical' and 'physical functioning' Short Form 36 (SF-36) scores compared with IGlar [9].

The aim of this subanalysis at 105 weeks was to compare IDeg versus IGlar with respect to change in health status from baseline (initiation of basal insulin therapy) in patients with type 2 diabetes, using the SF-36 v2 questionnaire.

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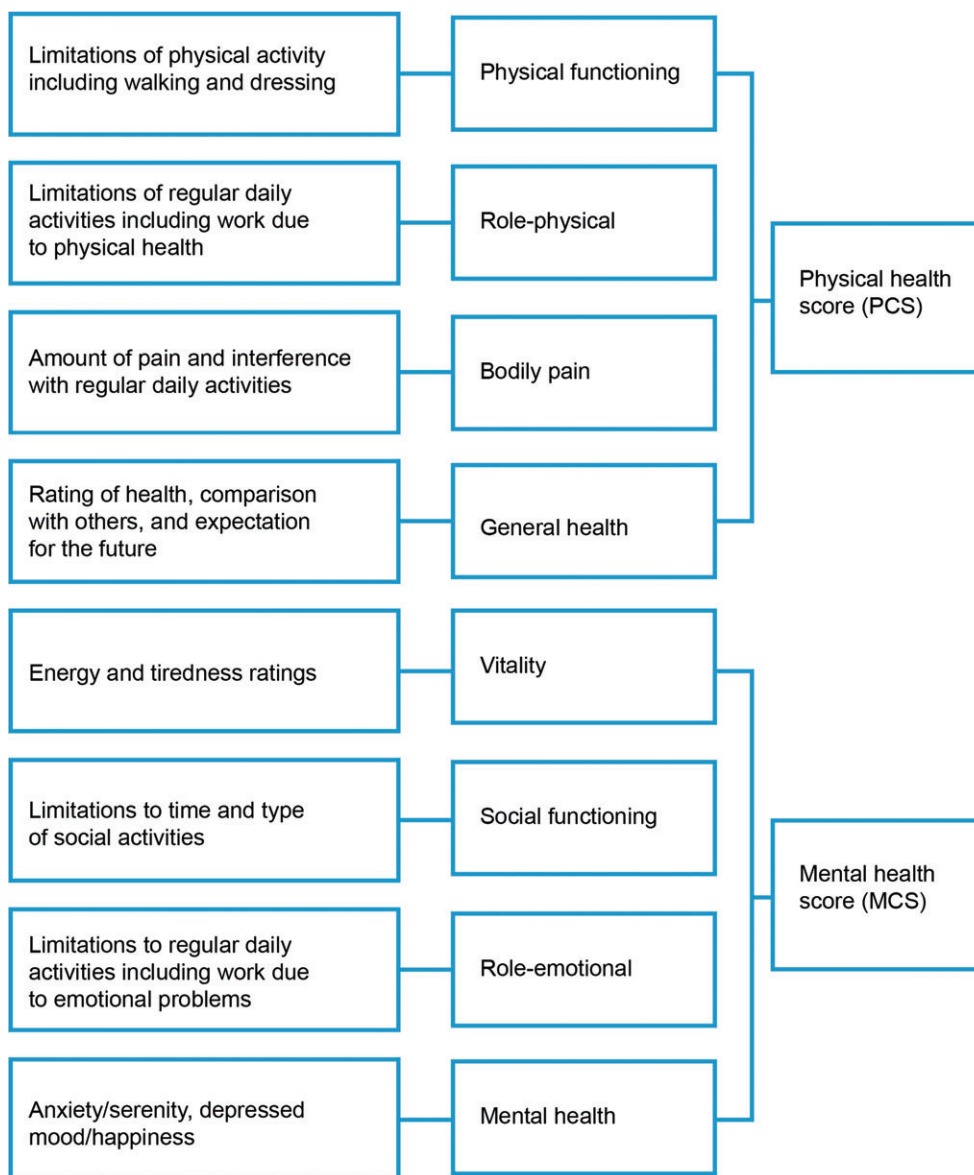


Figure 1. Overview of the Short Form 36 (SF-36 v2) questionnaire.

Methods

Subjects provided informed consent and re-started treatment with IDeg or IGlir at the same dose levels at end-of-treatment in the main trial [9] with optional adjustment at the discretion of the investigator. At the end of the core trial, patients were transferred to neutral protamine Hagedorn insulin for 7 days to allow for insulin antibody evaluation. The insulin dose at the end of the core trial was used as a starting point, and was titrated to a target FPG of 3.9–4.9 mmol/l based upon the mean pre-breakfast self-measured blood glucose for the preceding 2–3 consecutive days.

All assessments for efficacy and safety in this extension trial were as described for the core trial [9]. Health status was measured at baseline (time of randomisation of the core trial), at 52 weeks, and at 105 weeks using the SF-36 v2 questionnaire.

The SF-36 scale is a validated multi-purpose questionnaire that has raw, norm-based scores with a mean (standard deviation) of 50 (10). The SF-36 questions are grouped into eight domains (Figure 1), including a physical component summary (PCS) score and a mental component summary score. The scales are compressed compared to the raw scores. The questionnaire was translated and linguistically validated in all languages relevant to the study. Patients were provided with instructions and given privacy to complete the questionnaires, which were sealed in envelopes and not reviewed by local investigators or study nurses.

Scores from the intent-to-treat population were analysed using ANOVA, with treatment, therapy at screening, sex and region as fixed factors, and age and relevant baseline values as covariates. The long study duration was considered sufficient to ensure that any initial patient reporting bias was minimal.

Table 1. Short Form 36 (SF-36) scores at end-of-trial.

SF-36 component	IDeg OD (n = 773)	IGlar OD (n = 257)	Treatment contrast
			IDeg – IGlar [95% CI]
<i>Physical component score (PCS)</i>	46.3 (0.3)	45.2 (0.5)	1.1 [0.1; 2.1]*
Physical functioning score	45.5 (0.3)	44.4 (0.5)	1.1 [0.0; 2.3]*
Role-physical score	45.8 (0.3)	45.6 (0.5)	0.2 [–1.0; 1.3]
Bodily pain score	48.7 (0.4)	47.1 (0.6)	1.5 [0.2; 2.9]*
General health score	45.7 (0.3)	45.3 (0.5)	0.3 [–0.7; 1.4]
<i>Mental component score (MCS)</i>	48.9 (0.3)	49.2 (0.5)	–0.3 [–1.5; 0.9]
Vitality score	50.3 (0.3)	49.7 (0.5)	0.5 [–0.6; 1.7]
Social functioning score	48.1 (0.3)	48.1 (0.6)	–0.0 [–1.2; 1.2]
Role-emotional score	45.5 (0.4)	45.7 (0.6)	–0.2 [–1.6; 1.2]
Mental health score	48.8 (0.3)	48.7 (0.5)	0.1 [–1.1; 1.3]

CI, confidence interval; IDeg, insulin degludec; IGlar, insulin glargine; OD, once daily.

*Significantly better ($p < 0.05$). Data are estimated mean \pm standard error of the mean, full analysis set. The score and change from baseline in the score at 105 weeks were analysed using an ANCOVA model. Missing values are imputed by last observation carried forward.

Results

As previously reported, 607 (79%) of 773 patients randomised to IDeg and 197 (77%) of 257 randomised to IGlar completed the core trial of 52 weeks [10]. A total of 551 (71%) of those initially randomised to IDeg and 174 (68%) of those initially randomised to IGlar continued into the extension study on the core phase treatment allocation, with 505 (65%) of those continuing on IDeg and 154 (60%) continuing on IGlar completing the entire 104 weeks of treatment. Baseline characteristics have previously been reported, and were well-matched between treatment groups [10].

Health status results for the full analysis set are summarised in Table 1. At 105 weeks, the changes from baseline in overall PCS score, physical functioning score and bodily pain score were statistically significantly ($p < 0.05$) in favour of IDeg compared with IGlar, with ETDs (IDeg/IGlar) of 1.1 [0.1; 2.1]_{95%CI}, 1.1 [0.0; 2.3]_{95%CI} and 1.5 [0.2; 2.9]_{95%CI}, respectively. Other SF-36 domain scores showed no significant differences between groups. When only completers were used, scores tended to further improve in favour of IDeg compared to the full analysis set, but because of the lower number of respondents and loss of statistical power, only the bodily pain domain remained statistically significant.

Discussion

The statistically significant difference in PCS, physical functioning score in favour of IDeg was maintained after 2 years treatment as also reported in the core 52 weeks of the trial [9]. In addition to sustaining the significant difference in PCS and physical functioning, the bodily pain domain also was significantly in favour of IDeg after 2 years. These results are consistent with meta-analysis results of previous studies of IDeg reporting improvements in SF-36 scores [6] and improvements

in health utility versus IGlar [7]. Similarly, earlier studies have reported improvements in various patient-reported outcomes when IGlar was compared against oral therapy or other basal insulins [11].

With respect to the clinical implications of these results, in diabetes, it has been estimated that a 1-point difference on PCS and physical functioning scores, for example, is associated with a 5–9% increase in mortality risk, a 2–4% increased risk of hospitalisation within 6 months and a 7–12% increased risk of being unable to work [12]. Although the SF-36 does not have an established minimal important difference in diabetes, the SF-36 v2 user manual suggests that even small differences in these compressed scores (<1) are relevant in other chronic diseases. For example, having an allergy reduces the SF-36 scores by 0.1–0.8 points [5].

The precise reason for the improvement in SF-36 scores has not been determined. However, as mentioned earlier, IDeg has been shown to have a beneficial effect on hypoglycaemia compared to IGlar [4]. Hypoglycaemic events, both non-severe and severe, are known to be a key marker for reduced HRQoL in diabetes [1]. Also, the SF-36 physical functioning score includes measures of vigorous activity, which may be enhanced if hypoglycaemia is less of a concern. Given that clinical trials exclude people at high risk of hypoglycaemia, the benefit may be even greater in real-world settings.

Although an open-label design could have affected results of this study, the baseline values for SF-36 were collected prior to randomisation, and the long duration of the main trial plus extension study should have allowed any bias associated with initiation of a particular therapy to be minimised. This study emphasises that patient-reported outcomes, which are an important measure of any diabetes treatment, can be improved with IDeg.

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Conflict of Interest

H. W. R. has received grants/research support from Amylin, Eli Lilly, Merck and sanofi-aventis; served as a consultant for

Biodel; served on advisory panels of Amylin Pharmaceuticals, Roche Diagnostics, AstraZeneca, Biodel, Novartis, Novo Nordisk, Janssen, Bristol-Myers Squibb and sanofi-aventis; served on the speaker's bureau for Amylin Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck and Co., and Novo Nordisk. B. C. has served on the advisory panel for Eli Lilly and Company, Genfit, Novo Nordisk and sanofi-aventis and received grants/research support from Novo Nordisk and sanofi-aventis. B. Z. has served on the advisory panel for Eli Lilly and Company, Novo Nordisk, and sanofi-aventis and received research support from Novo Nordisk. Y. H. has received grants/research support from Boehringer Ingelheim, ConjuChem, Daiichi Sankyo, GlaxoSmithKline, Lexicon, Novo Nordisk, Takeda, sanofi-aventis, Xoma, and Tolorex; served as consultant for Amylin Pharmaceuticals, Daiichi-Sankyo, Gilead, Genetech, GlaxoSmithKline, Novo Nordisk, Merck, Xoma, Tolorex, Janssen, Halozyme, Amarin, Liposcience and Santarus; served on speakers bureau for Amylin, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Eli Lilly, GlaxoSmithKline, Novo Nordisk, and Santarus; and is President of the American Association of Clinical Endocrinologists. M. L. W. and A. R. are employees of Novo Nordisk and own stock in the company. C. M. has served on the advisory panel for Novo Nordisk, sanofi-aventis, Merck Sharp and Dohme Ltd., Eli Lilly and Company, Novartis, Bristol-Myers Squibb, AstraZeneca LP, Pfizer, Johnson and Johnson, and Mannkind; has received research support from Novo Nordisk, sanofi-aventis, Merck Sharp and Dohme Ltd., Eli Lilly and Company, and Novartis; and has served on the speakers bureau for Novo Nordisk, sanofi-aventis, Merck Sharp and Dohme, Eli Lilly and Company, and Novartis.

Author declaration

All authors (H. W. R., B. C., B. Z., Y. H., M. L. W., A. R. and C. M.) were involved in critical analysis and interpretation of the data, drafting/critically revising the article and shared in the final responsibility for the content of the manuscript and the decision to submit it for publication.

References

1. Evans M, Khunti K, Mamdani M et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. *Health Qual Life Outcomes* 2013; **11**: 90.
2. Williams SA, Pollack MF, Dibonaventura M. Effects of hypoglycaemia on health-related quality of life, treatment satisfaction and healthcare resource utilization in patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2011; **91**: 363–370.
3. Heise T, Nosek L, Böttcher SG, Hastrup H, Haahr H. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. *Diabetes Obes Metab* 2012; **14**: 944–950.
4. Ratner RE, Gough SC, Mathieu C et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab* 2013; **15**: 175–184.
5. Ware JE, Kosinski M, Bjorner JB, Turner-Bowker DM, Gandek B, Maruish ME. *User's Manual for the SF-36v2 Health Survey*. 2nd edn. QualityMetric Inc: Lincoln, RI, 2007.
6. Freemantle N, Meneghini L, Christensen T, Wolden ML, Jendle J, Ratner R. Insulin degludec improves health-related quality of life (SF-36®) compared with insulin glargine in people with type 2 diabetes starting on basal insulin: a meta-analysis of phase 3a trials. *Diabet Med* 2013; **30**: 226–232.
7. Freemantle N, Evans M, Christensen T, Wolden ML, Bjorner JB. A comparison of health-related quality of life (health utility) between insulin degludec and insulin glargine: a meta-analysis of phase 3 trials. *Diabetes Obes Metab* 2013; **15**: 564–571.
8. Home PD, Meneghini L, Wendisch U et al. Improved health status with insulin degludec compared with insulin glargine in people with type 1 diabetes. *Diabet Med* 2012; **29**: 716–20.
9. Zinman B, Philis-Tsimikas A, Cariou B et al. Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). *Diabetes Care* 2012; **35**: 2464–2471.
10. Rodbard HW, Cariou B, Zinman B et al. Comparison of insulin degludec with insulin glargine in insulin-naive subjects with Type 2 diabetes: a 2-year randomized, treat-to-target trial. *Diabet Med* 2013; **30**: 1298–1304.
11. Bradley C, Gilbride CJ. Improving treatment satisfaction and other patient-reported outcomes in people with type 2 diabetes: the role of once-daily insulin glargine. *Diabetes Obes Metab* 2008; **10**(Suppl. 2): 50–65.
12. Bjorner JB, Lyng Wolden M, Gundgaard J, Miller KA. Benchmarks for interpretation of score differences on the SF-36 health survey for patients with diabetes. *Value Health* 2013; **16**: 993–1000.