Author’s response to reviews

Title: Cost-effectiveness of insulin degludec versus insulin glargine U100 in adults with type 1 and type 2 diabetes mellitus in Bulgaria

Authors:
Monika Russel-Szymczyk (zmns@novonordisk.com; bmoore@dresources.com)
Vasil Valov (vasv@novonordisk.com)
Alexandra Savova (alex_savova@mail.bg)
Manoela Manova (manoela_manova@yahoo.com)

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Author’s response to reviews:

Dear Editor in Chief, dear reviewers,

On behalf of my co-authors, please find below the point-by-point response to the reviewers’ comments. We thank the reviewers for their valuable input and perspective.

Yukihiro Fujita (Reviewer 1):
The reviewer thanks for this opportunity to review the article 'Cost-effectiveness of insulin degludec versus insulin glargine U100 in adults with type 1 and type 2 diabetes mellitus in Bulgaria ' submitted to BMC Endocrine Disorders .

The topic is important and practical in real world health care for insulin therapy. However the reviewer has some concerns in the current article for publication.

1) This study is the comparison of costs and effectiveness between two insulin analogues. If these comparisons are performed by 'employees of one company', the study should be carefully conducted in randomized head to head, double-blind trial, especially when hypoglycaemic events are determined. Otherwise bias can not be eliminated.
Response: Although the present study was funded by Novo Nordisk, A. Savova and M. Manova are independent researchers at the Faculty of Pharmacy, Medical University Sofia, Bulgaria, with no competing interests. Similarly, the meta-analysis of hypoglycaemia and insulin dose was conducted by independent researchers, in collaboration with Novo Nordisk. All clinical data were derived from randomised, active-controlled trials. Double-blinding was not used, as this would have doubled the number of injections for trial participants. Head-to-head trials vs biosimilar glargine U100 are not yet
available, as biosimilar glargine U100 is relatively new to the market. We currently acknowledge this limitation of the analysis in the discussion section, lines 337ff, page 17.

2) The authors described there are more hypoglycaemic events in Bulgaria in discussion, but they used data of hypoglycaemia from multinational Phase3b trials. In contrast, Insulin doses were taken from daily insulin doses used in clinical practice in Bulgaria. The reviewer believes that the authors should use data of hypoglycaemia collected in Bulgaria. If not, the reviewer feels no consistency in the results.

Response: Using the lower, multinational estimates for hypoglycaemic events in the model was a conservative assumption, as higher event rates will make degludec more cost-effective. Although the insulin dose is derived from clinical data, i.e. clinical practice in Bulgaria, it is solely used to calculate the treatment costs in the model, based on the dose ratio between degludec and glargineU100 derived from a meta-analysis of insulin dose (1), which indicated that, to achieve the same clinical results, a slightly lower dose of degludec (compared with glargineU100) can be used. We suggest clarifying this in the publication. Please see the Methods section, line 141, page 7.

3) Degludec is allowed, but the biosimilar in not allowed to inject anytime in a day. In HRQoL, the authors gave 'Flexibility Utility gain' as 0.006 to Degludec. The authors gave advantage to Degludec based on only one study performed otherwhere. (Boye et al. [40]). If the authors intended to give the gain, they must cite multiple studies to justify the value of the gain.

Response: Although the utility value for the base case is derived from a single study, the assumed utility gain of 0.006 can be considered a conservative estimate. Data from a large time trade-off study reported utility gains of 0.016 and 0.013 associated with flexible dosing of basal insulin and vs basal-bolus insulin, respectively (2). The latter value was used in the sensitivity analysis. The data are discussed in lines 334-336 of the discussion, and the results are presented in the supplementary material, last row of Table S1. Furthermore, the utility benefit was also reduced to zero in the sensitivity analyses. The results, presented in Table S1, show that, although the ICER increased from 4,499 BGN (base case) to 7,281 BGN (no utility benefit associated with flexibility), it remained highly cost-effective with regard to the assumed threshold of 39,619 BGN.

Yasutaka Maeda (Reviewer 2): This nation-wide investigation in Bulgaria compared the cost-effectiveness of basal insulin using a preestablished national database. The study design was well conducted to elucidate whether insulin degludec or insulin glargine-U100 was superior in the reduction of hypoglycemia-related economic burden. It is the important suggestion that the cheaper insulin is not always the better choice in a broad aspect. However, the author should describe the manuscript in compliance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement. It would be appreciated if the CHEERS check list is provided in the Supplementary Materials. Therefore, the work will be suitable for publication in "BMC Endocrine Disorders" if the authors properly address the following concerns.

Major concern:
1) Although an approval by the ethical committee is not necessary, the study reporting about healthcare economy is still required to be fair enough to avoid any misguided conclusion. The authors should observe the CHEERS statement and fill up the check list given at the following URL (https://nam01.safelinks.protection.outlook.com/?url=http%3A%2F%2Fwww.ispor.org%2Ftaskforces%2FEconomicPubGuidelines.asp&amp;data=02%7C01%7Cbmoore%40teamdrg.com%7Cf4d0bd5ad14149ed3add08d74af5e5dd%7C5d6495b15cd44a4fa6dd1f5f3bf58831%7C0%7C637060292305541532&amp;sdata=CnxiSpaGEd22%2BXgT3iO377DjBn3bpik0SxOXsjggX8%3D&amp;reserved=0). Then, the list should be included in the Supplementary Materials.

Response: We have completed the CHEERS list, and it is available for inclusion in the supplementary
materials. We would like to point out that both page numbers and line numbers will have changed once the manuscript is type set.

2) The economic burden related to the insulin treatment is not dependent only on hyperglycemia. Unfortunately, it remains controversial whether the difference of insulin analogues affects the incidence of cancers, cardiovascular diseases and other complications. At least, it would be better to mention it in the limitation.

Response: In clinical trials, the safety profiles of the different insulins were similar, except for the incidence of hypoglycaemia. Furthermore, the cardiovascular outcomes trial DEVOTE (3) showed that insulin degludec was non-inferior to insulin glargine in terms of MACE. We have added a statement around these data in the discussion section, page 17, lines 348-351

Minor concern:
1) The authors assumed that the biosimilar glargine U100 has the same efficacy to Lantus. I agree that it is true as far as in bioactivity, but they are actually not completely equal in clinical use because of the difference of device or vender supports. Please just mention it in the limitation.

Response: The devices used for Glargine U100 and Lantus are highly similar and we would not expect there to be any clinical difference caused by the device.

Yours faithfully,

Monika Russel-Szymczyk
Novo Nordisk Sp. z o.o,
Ul. Krakowiaków 46
PL 02-255 Warsaw
Poland
zmns@novonordisk.com

References