A Response to: Letter to the Editor with Regard to the Cost-Effectiveness of an Advanced Hybrid Closed-Loop System in People with Type 1 Diabetes: A Health Economic Analysis in Sweden

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We would like to thank Levrat-Guillen and Ghazi for their interest in our recent analysis relating to the cost-effectiveness of advanced hybrid closed-loop (AHCL) insulin delivery relative to intermittently scanned continuous glucose monitoring (isCGM) in combination with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) in people with type 1 diabetes (T1D) [1]. Levrat-Guillen and Ghazi have expressed concern over several aspects of the analysis. In an attempt to alleviate these concerns, the issues raised are addressed in a point-by-point fashion below.

In the absence of head-to-head comparisons of AHCL versus isCGM, Levrat-Guillen and Ghazi expressed concern over the clinical input data used to inform the analysis. For the isCGM arm, the HbA1c treatment effect was sourced from the real-world FUTURE study published by Charleer et al. [2]. Whilst several other potential data sources were available, the FUTURE study was chosen owing to the robust nature and design of the study (e.g., the study was conducted in specialist diabetes centers, with a large number of patients and long duration of follow-up) and a baseline HbA1c value that closely matched the levels observed in the study published by Collyns et al. [3], which was used to inform the AHCL arm. Levrat-Guillen and Ghazi mentioned three sources specifically (Gilbert et al. [4], Evans et al. [5], and Rose et al. [6]) but these studies were not considered for several reasons. The study published by Gilbert et al. [4] was considered inappropriate as the authors assessed the effectiveness of real-time CGM (rtCGM) rather than isCGM; utilization of this study would therefore require the assumption that isCGM and rtCGM are equivalent and evidence from a recent head-to-head study has suggested that this is not the case [7]. The meta-analysis by Evans et al. [5] reported a mean HbA1c reduction of 0.56% with isCGM; however, this was based on a large number of studies with baseline HbA1c values ranging from 6.79% to 10.28%. Finally, in the German observational study by Rose et al. [6], patients had a mean...
baseline HbA1c of 8.15%, which was higher than that in the AHCL arm.

Levrat-Guillen and Ghazi also highlighted several limitations with regard to the clinical input data used for the AHCL arm, including the short study duration and that HbA1c calculations were based on sensor levels rather than laboratory measurements [3]. However, the 4-week duration of the study was in part mitigated by the crossover design, with each 4-week study period preceded by a 2–4-week run-in period and separated by a 2-week wash-out period. Moreover, the subsequent extrapolation of the short-term clinical data was acknowledged as a limitation in the “Discussion” section of the manuscript, and extrapolation of treatment effects is necessary in any long-term cost-effectiveness analysis. It should also be noted that the treatment effect sourced from the study by Collyns et al. [3] is of a similar magnitude to HbA1c reductions observed in studies using the earlier generation MiniMed 670G device [8–11]. For example, in a 3-month study of the MiniMed 670G system, mean HbA1c decreased from 7.4% to 6.9% in patients with previous CGM use and from 7.5% to 6.8% in patients with no prior CGM use [8]. Additionally, the authors of a recent real-world study on the MiniMed 780G system noted that, in routine clinical practice, the MiniMed 780G system was associated with superior outcomes relative to the MiniMed 670G system [12], suggesting that the 0.5% reduction modeled in the analysis may potentially represent a conservative scenario. The same MiniMed 670G studies also demonstrated a persistence of treatment effect over periods of up to 6 months. Given the evidence for the MiniMed 670G system, as well as the added sophistication of the MiniMed 780G system, it was deemed reasonable to assume a similar persistence of treatment effect with AHCL. The lack of head-to-head trials comparing isCGM with AHCL was also acknowledged in the manuscript. Further, this comparison is the subject of ongoing research [13] and, as Levrat-Guillen and Ghazi suggest, it would be prudent to repeat this analysis once head-to-head data become available.

In the cost-effectiveness analysis, it was assumed that the use of AHCL would reduce the incidence of severe hypoglycemic events to zero. Levrat-Guillen and Ghazi suggested that the evidence base for this assumption is lacking. However, Carlson et al. [14] reported no severe hypoglycemic events with AHCL over a 90-day study period, and data from studies on earlier generation devices, including the MiniMed 670G system, are in line with the assumptions applied in the analysis (e.g., Cordero et al. [8] and Petrovski et al. [15]).

A further concern raised by Levrat-Guillen and Ghazi pertained to assumptions around the utility benefit assumed to be conferred to simulated patients in the AHCL arm owing to a reduction in fear of hypoglycemia (FoH). As noted by Levrat-Guillen and Ghazi, this assumption was based on the findings of the 2013 INTERPRET study by Nørgaard et al. [16]. Whilst this study examined the effectiveness of sensor-augmented pump therapy (SAP) rather than AHCL, it was considered reasonable to assume that, given the additional sophistication of AHCL relative to SAP, this benefit would also apply to AHCL.

No utility benefit relating to reduced FoH was applied to the isCGM arm. While Levrat-Guillen and Ghazi drew attention to the fact that a reduction in FoH was reported by Al Hayek et al. [17] in a study conducted in children with T1D in Saudi Arabia, the data presented were collected using the child rather than the adult version of the Hypoglycemia Fear Survey (HFS) and may therefore be of limited generalizability to adults with long-standing disease. Moreover, in the FUTURE study, which was used to inform the isCGM arm, no significant change in HFS worry score was reported [2]. Similarly, recent data from a 6-month prospective randomized controlled trial that directly compared rtCGM with isCGM reported that FoH (measured using the HFS worry subscale) decreased from 18.8 to 15.4 with rtCGM, but only from 18.7 to 18.0 with isCGM, resulting in a significant between-group difference in favor of rtCGM at 6 months [7]. A point worthy of note with regard to FoH is that isCGM requires engagement from the user, whereas rtCGM devices with alert features will alert the user to hypoglycemia (or predicted imminent hypoglycemia) without engagement from the user.
AHCL goes further by both detecting hypoglycemia and adjusting insulin delivery accordingly. Consequently, it is reasonable to assume that AHCL would confer a greater utility benefit relative to isCGM in terms of reduced FoH, particularly in specific instances such as in patients with an impaired awareness of hypoglycemia, which can be a key risk factor for FoH [18].

Finally, to mitigate the concerns around a lack of sensitivity analyses, a series of additional sensitivity analyses have been performed around the incidence rates and costs of severe hypoglycemic events, as well as the utility benefit associated with reduced FoH (Table 1). As shown in Table 1, and acknowledged in the “Discussion” section of the manuscript, reduced FoH is a key driver of cost-effectiveness.

Table 1 Findings of additional sensitivity analyses

| Analysis | Quality-adjusted life expectancy, QALYs | Total lifetime costs, SEK | ICER, SEK per QALY gained |
|----------|-----------------------------------------|--------------------------|----------------------------|
|          | AHCL isCGM plus MDI or CSII Difference   | AHCL isCGM plus MDI or CSII Difference   |                             |
| Cost of SHE + 20% | 14.25 12.31 1.95 | 3,414,589 2,698,751 715,838 367,756 |
| Cost of SHE − 20% | 14.25 12.31 1.95 | 3,414,589 2,675,612 738,977 379,644 |
| QoL benefit with reduced FoH − 50% | 13.71 12.31 1.40 | 3,414,589 2,687,181 727,408 518,060 |
| SHE rate reduced by 50% | 14.25 12.66 1.60 | 3,414,589 2,620,182 794,407 497,967 |

AHCL advanced hybrid closed-loop, CSII continuous subcutaneous insulin infusion, ICER incremental cost-effectiveness ratio, isCGM intermittently scanned continuous glucose monitoring, MDI multiple daily injections, QALY quality-adjusted life year, SHE severe hypoglycemic event

*Refers to a 50% reduction in the incidence of SHEs in the isCGM arm

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Declarations

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Compliance with Ethics Guidelines This article is based on previously conducted studies and does not contain any new studies with human
participants or animals performed by any of the authors.

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