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The value of fast-acting insulin aspart compared with insulin aspart for patients with diabetes mellitus treated with bolus insulin from a UK health care system perspective

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Abstract

Background: Fast-acting insulin aspart is a new formulation of the rapid-acting insulin analogue insulin aspart and represents an advancement over current rapid-acting insulin analogues in terms of onset of action and postprandial glucose control. The objective of the current analysis was to demonstrate the cost impact of prescribing fast-acting insulin aspart instead of insulin aspart, to highlight the value of fast-acting insulin aspart for the treatment of people with diabetes requiring mealtime insulin.

Methods: A cost-impact analysis was conducted from the perspective of the UK National Health Service (NHS). The analysis excluded patients' out-of-pocket expenses, carers' costs and lost productivity. The time horizon of the analysis was 1 year, and no discounting was therefore applied.

Results: The displacement of insulin aspart with fast-acting insulin aspart is cost neutral for the UK NHS. Fast-acting insulin aspart is at price parity to insulin aspart in terms of the vial and Penfill® cartridge and is available in the FlexTouch® pen at the same price as the insulin aspart FlexPen® (and thus cheaper than the insulin aspart FlexTouch® pen). Patients using the insulin aspart FlexPen® will be upgraded to the FlexTouch® pen device, which is preferred by patients and healthcare professionals, on switching to fast-acting insulin aspart, at no additional cost.

Conclusions: Fast-acting insulin aspart offers additional clinical benefit but at no additional cost when compared with insulin aspart, and thus provides value to the UK NHS.

Keywords: bolus insulin, fast-acting insulin aspart, glycaemic control, postprandial glucose, price parity

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Introduction

Diabetes is one of the biggest health challenges facing the world. The International Diabetes Federation (IDF) estimated that in 2017, approximately 425 million people in the 20–79-year age group worldwide (8.8% of the global population) had diabetes, and projected that this figure would rise to 629 million (9.9% of the global population) by the year 2045.[1]

The clinical goal in the treatment of diabetes is to achieve good glycaemic control. Good glycaemic control with intensive diabetes therapy prevents or delays microvascular complications, and combined with effective blood pressure and lipid-lowering therapies, reduces cardiovascular and all-cause mortality in people with type 1 (T1DM) and type 2 diabetes (T2DM).[2–4] Traditionally,

glycaemic control is assessed by monitoring the levels of glycated haemoglobin (HbA_{1c}), providing an average blood glucose (BG) reading from the previous 2–3 months.[5–7] Despite the importance of HbA_{1c} as an indicator for the development of diabetes-related complications, the metric has some limitations, for example it is a poor marker of glycaemic variability, hypoglycaemia and postprandial glucose (PPG) excursions.[8]

Both fasting plasma glucose (FPG) levels and PPG levels contribute to HbA_{1c} levels, and therefore effective management of both components is essential for optimal glycaemic control.[9] Many patients experience acceptable FPG levels, yet fail to achieve an HbA_{1c} target of $<7\%$.[10] Studies have demonstrated that PPG contributes significantly to overall glycaemic control, with a greater relative effect (up to 70%) observed when patients are nearing HbA_{1c} levels of 7% (53 mmol/mol).[11] Effective management of PPG to avoid postprandial hyperglycaemia (PPH) is an important factor for achieving HbA_{1c} targets, thereby reducing the risk of diabetes-related complications.[12,13]

The use of basal-bolus insulin therapy allows separate coverage of basal and prandial (mealtime) insulin requirements. Bolus (prandial) insulins, which include rapid-acting insulin analogues and short-acting insulins, are usually taken before or with a meal, and act to minimize the rise in PPG that follows eating. Current clinical guidelines recommend the use of a basal-bolus regimen for adults with T1DM and adults with T2DM who do not meet glycaemic targets on basal insulin alone.[14–17]

Over time, rapid-acting insulin analogues have been developed to become increasingly more efficacious, with a reduction in the time to onset and duration of action, however the insulin response still does not match that of a healthy individual.[18] Fast-acting insulin aspart (Fiasp®; Novo Nordisk) is a new formulation of the rapid-acting insulin analogue, insulin aspart (NovoRapid®; NovoNordisk). Fast-acting insulin aspart has been developed to have a faster onset of action and a profile that more closely matches the endogenous physiological insulin profile of healthy individuals without diabetes.[19] In fast-acting insulin aspart, the addition of niacinamide (vitamin B3) results in a faster initial absorption of insulin, leading to an earlier onset of action and greater early glucose-lowering effect compared with insulin aspart. When compared with insulin aspart, fast-acting insulin aspart has: twice faster onset of appearance in the bloodstream; twice higher insulin exposure within the first 30 min; and 74% greater insulin action within the first 30 min.[19,20] With the earlier onset of action, fast-acting insulin aspart aims to approach the physiological insulin secretion in relation to a meal to a greater extent than currently available treatments, resulting in a more effective control of PPG excursions and achieving greater PPG control.

Fast-acting insulin aspart was investigated in four phase III clinical trials as part of the onset programme, involving more than 2100 people with T1DM and T2DM.[21–23] Fast-acting insulin aspart demonstrated an advance in glycaemic control, through improved PPG control in T1DM and T2DM and improved HbA_{1c} control in T1DM, compared with insulin aspart.[21,22] In patients with T1DM post-meal dosing with fast-acting insulin aspart, administered 20 min after the start of eating main meals, was also investigated.[21]

In the onset 1 trial, in patients with T1DM, fast-acting insulin aspart was non-inferior to insulin aspart with regards to HbA_{1c} change from baseline, and the reduction in HbA_{1c} was statistically significantly greater with fast-acting insulin aspart than with insulin aspart (both taken at mealtime). The estimated reduction in HbA_{1c} from baseline was 0.32% for fast-acting insulin aspart and 0.17 % for insulin aspart, giving a treatment difference of −0.15%, despite the non-inferior treat-to-target trial design.[21,24] Mealtime fast-acting insulin aspart provided superior PPG control compared with mealtime insulin aspart based on a 2-hour PPG increment during a standardized liquid meal test, and a statistically significant difference was also demonstrated for a 1-hour PPG increment in favour of mealtime fast-acting insulin aspart.[21] Fast-acting insulin aspart administered post meal was also non-inferior to mealtime insulin aspart regarding HbA_{1c} change from baseline (with no statistically significant difference between the two treatments).[21]

In the onset 2 trial, in patients with T2DM, fast-acting insulin aspart was non-inferior to insulin aspart with regards to change from baseline in $HbA_{1c.}$ The estimated reduction in HbA_{1c} was −1.38% for fast-acting insulin aspart and −1.36% for insulin aspart [estimated treatment difference 0.02% (95% confidence interval, CI: −0.15; 0.10)]. A statistically significant difference was demonstrated for a 1-hour PPG increment after a standardized liquid meal test in favour of fast-acting

insulin aspart compared with insulin aspart (estimated treatment difference −0.59 mmol/l); there was no statistical difference after 2 h.[22]

The overall safety profile for fast-acting insulin aspart is similar to that of insulin aspart. No statistically significant difference was seen in overall rate of severe or BG confirmed hypoglycaemic episodes between fast-acting insulin aspart and insulin aspart in T1DM and T2DM.[21,22]

Fast-acting insulin aspart is also compatible with continuous subcutaneous insulin infusion (CSII) systems and shows similar tolerability to insulin aspart in patients with T1DM.[25] An exploratory crossover trial in T1DM showed that CSII delivery of fast-acting insulin aspart provided a statistically significantly greater glucose-lowering effect than insulin aspart following a standardized liquid meal test. Over the 2-week treatment period, considering all meals together, mean prandial interstitial glucose was lower with fast-acting aspart, with the largest differences occurring at breakfast. The mean reduction in plasma glucose concentration in the first 2 h following the standardized liquid meal was approximately 25% greater with fast-acting insulin aspart than with insulin aspart. Plasma glucose values at 1 h after the meal were also statistically significantly lower with fast-acting insulin aspart than with insulin aspart.[26]

Fast-acting insulin aspart represents an advancement over current rapid-acting insulin analogues in terms of onset of action, and PPG control.[19,21,22] The objective of the current analysis was to demonstrate the cost impact of prescribing fast-acting insulin aspart instead of insulin aspart, and to further explore the value of fast-acting insulin aspart for the treatment of people with diabetes requiring mealtime insulin in the UK.

Methodology

Choice of economic evaluation

In the UK, fast-acting insulin aspart has price parity with insulin aspart (no additional cost), and offers improved efficacy. Therefore, a simple cost-impact analysis (CIA) was conducted to demonstrate cost neutrality.

A CIA is an economic assessment of the net costs (or savings) arising from implementing a new treatment for the purpose of informing budget setting.[27,28] A CIA is used less frequently than traditional cost-effectiveness methodologies such as cost-utility analysis (CUA) or cost-minimization analysis (CMA). A CUA estimates the ratio between the cost of an intervention and its benefits measured in 'utility based' units; the most commonly used unit is the quality-adjusted life year (QALY). CUA is typically used to compare how many additional QALYs are gained at what additional cost, which is termed the incremental cost-effectiveness ratio (ICER). A CMA compares the costs of alternative interventions that have demonstrated equivalent clinical effectiveness, typically, where the new treatment is priced lower than the competitor. In a CMA, value is driven by cost saving, but there is no additional clinical benefit. Thus, neither CUA nor CMA were appropriate in this setting. Although the clinical benefits seen in the trial programme would allow more complex health economic analyses that model the impact on PPG and HbA_{1c}, given the similar prices of the medicines, the more simplistic approach of the CIA was preferred.

Overview of analysis

The CIA was conducted from the perspective of the UK National Health Service (NHS), however, the methodology can be applied to other markets by substituting local prices. The analysis calculated the annual cost per patient associated with treatment with fast-acting insulin aspart *versus* treatment with insulin aspart. The analysis included insulin cost (unit cost of insulin multiplied by daily dose), but excluded patients' out-of-pocket expenses, carers' costs and lost productivity. The time horizon of the analysis was 1 year, and no discounting was therefore applied. A 1-year time horizon was selected because it was assumed that the same cost implications will be seen each year, and therefore the annual cost estimate can be applied year on year.

Cost inputs

The list prices for insulin aspart and fast-acting insulin aspart were taken from MIMS.[29] Insulin aspart is available in vials, Penfill® cartridge, PumpCart® cartridges, FlexPen® pen and FlexTouch® pen. Fast-acting insulin aspart is available in vials, Penfill® cartridge and FlexTouch® pen (Table 1).

For each presentation of insulin aspart and fast-acting insulin aspart, the annual per-patient

Table 1. Pack cost and cost per unit for insulin aspart and fast-acting insulin aspart.

Presentation and strength	Pack size	Number of units	Pack cost§	Cost/unit
Insulin aspart				
Vial 100 units/ml	10 ml	1000	£14.08	£0.0141
Penfill® cartridge 100 units/ml	5 × 3 ml	1500	£28.31	£0.0189
PumpCart® cartridges, 100 units/ml	5 × 1.6 ml	800	£15.10	£0.0189
FlexPen® pen 100 units/ml	5 × 3 ml	1500	£30.60	£0.0204
FlexTouch® pen 100 units/ml	5 × 3 ml	1500	£32.13	£0.0214
Fast-acting insulin aspart				
Vial 100 units/ml	10 ml	1000	£14.08	£0.0141
Penfill® cartridge 100 units/ml	5 × 3 ml	1500	£28.31	£0.0189
FlexTouch® pen 100 units/ml	5 × 3 ml	1500	£30.60	£0.0204

§Source: MIMS January 2018.[29]

treatment cost was calculated as follows: unit cost (pack cost/number of units) × daily dose [defined daily dose (DDD) 40 units] × 365.25 days. For comparison of insulins, the World Health Organization (WHO) recommends using the DDD of 40 units,[30] since insulin dosing is variable and based on individual requirements. The onset 1 and 2 clinical trials in patients with T1DM and T2DM showed there was no difference in daily dose requirement between fast-acting insulin aspart and insulin aspart,[21,22] therefore, it was appropriate to use the WHO DDD for the purpose of this analysis. The actual annual cost will depend on an individual's daily dose of insulin.

It was assumed that other costs of treatment (e.g. use of concomitant medication), healthcare resource use (e.g. needles, self-measured blood glucose (SMBG) test strips/lancets and healthcare professional visits) or other costs resulting from treatment (e.g. long-term outcomes) were equivalent for fast-acting insulin aspart and insulin aspart, and therefore they were not considered in the analysis.

Results

Annual per-patient costs for fast-acting insulin aspart and insulin aspart and the cost impact of switching to fast-acting insulin aspart from insulin aspart in the UK are shown in Table 2.

Fast-acting insulin aspart is at price parity to insulin aspart in terms of the vial and Penfill® cartridge, but is available in the FlexTouch® pen at the same price as insulin aspart FlexPen® (and thus cheaper than insulin aspart FlexTouch® pen). Patients using insulin aspart FlexPen® will be upgraded to the FlexTouch® pen device, which is preferred by patients and healthcare professionals,[31,32] on switching to fast-acting insulin aspart, at no additional cost. Current volume sales split suggests that approximately 45% of patients in the UK prescribed insulin aspart use the FlexPen® and could benefit from the upgrade over time.[33] Any patients switching from insulin aspart FlexTouch® to fast-acting insulin aspart FlexTouch® will save £1.53/pack or £14.91/annum (based on the DDD).

For the purposes of the calculations, it is assumed that patients on insulin aspart vials and Penfill® cartridges transition across to the respective fast-acting insulin aspart vials and Penfill® cartridges. Thus, there is no cost impact associated with switching patients from insulin aspart to fast-acting insulin aspart. However, there are other benefits associated with switching: improved PPG control in T1DM and T2DM and improved HbA_{1c} control in T1DM;[21,22] free upgrade to the patient- and healthcare-professional-preferred pen device[31,32] for patients switching from insulin aspart FlexPen®; and postmeal dosing, when needed.[20]

Table 2. Annual cost per patient for insulin aspart and fast-acting insulin aspart.

Presentation and strength	Cost per year (£)*		Difference in cost per year
	Insulin aspart	Fast-acting insulin aspart	Fast-acting insulin aspart *versus* insulin aspart
Vial 100 units/ml	£205.71	£205.71	£0.00
Penfill® cartridge 100 units/ml	£275.74	£275.74	£0.00
FlexPen® pen 100 units/ml	£298.04	N/A	N/A
FlexTouch® pen 100 units/ml	£312.95	£298.04	–£14.91

*Calculation of annual treatment cost: unit cost (pack cost[29]/number of units) × daily dose (DDD 40 units) × days in year (365.25). Resource use associated with insulin aspart and fast-acting insulin aspart, for example, insulin needles for injection, are assumed to be identical, therefore these costs are not considered. It is assumed that other costs of treatment (e.g. use of concomitant medication) or other costs resulting from treatment (e.g. long-term outcomes) are equivalent in both treatment groups.

Discussion

Value can be demonstrated outside of the common health economic concepts such as CUA, where health utilities derived from quantitative instruments inform the ICER, and CMA, which shows cost reduction. There are occasions when a new medicine may be introduced at price equivalency to the current standard of care, yet provide additional clinical benefit, thus demonstrating value in its simplest form.

Fast-acting insulin aspart is offered with additional clinical benefit, but at no additional cost when compared with insulin aspart. Switching patients from insulin aspart to fast-acting insulin aspart will be budget neutral and may be associated with further economic benefits.

In the onset 1 trial, in patients with T1DM, the observed reduction in HbA_{1c} was statistically significantly greater with mealtime fast-acting insulin aspart than with insulin aspart.[21] The results suggest that the same glycaemic improvements are achieved with fast-acting insulin aspart over insulin aspart in T1DM (0.15% statistically significantly lower HbA_{1c} and 0.7–1.2 mmol/l lower PPG increments), as reported previously with insulin aspart *versus* human insulin (0.15% statistically significantly lower HbA_{1c}[34] and 1.1–1.3 mmol/l lower PPG increments).[35,36] Improved HbA_{1c} control with fast-acting insulin aspart may lead to a delay or reduction in diabetes-related complications, with consequent cost savings.

The impact of fast-acting insulin aspart *versus* insulin aspart on long-term clinical outcomes and costs of complications in patients with T1DM in the UK setting has been assessed using the IMS CORE Diabetes Model.[37] Improved glycaemic control with fast-acting insulin aspart results in reduced cumulative incidence of diabetes-related complications over patient lifetimes. Long-term projections suggest that, in the UK setting, treatment of patients with T1DM with fast-acting insulin aspart is likely to be associated with improved clinical outcomes and reduced costs of treating diabetes-related complications compared with treatment with insulin aspart.[38]

Costs related to hypoglycaemic events were not included in the cost impact model as there were no statistically significant differences in the overall number of treatment emergent severe or BG confirmed hypoglycaemic events between fast-acting insulin aspart and insulin aspart in clinical trials.[22,38] As expected, there was a higher rate of hypoglycaemia in the first 1–2 h after a meal with fast-acting insulin aspart *versus* insulin aspart, which is consistent with the differing clinical pharmacology profiles of the two insulins, where the glucose-lowering effect is earlier with fast-acting insulin aspart.[22,38] Thus, the hypoglycaemia profile is simply shifted and overall, there is no difference in severe or BG-confirmed hypoglycaemia between the two insulins.

In both T1DM and T2DM, fast-acting insulin aspart offers improved PPG control compared with insulin aspart (T1DM, both 1 h and 2 h; T2DM, 1 h).[21,22] Poor control of PPG contributes to poor glycaemic control and is associated with a significant health and economic burden.[11,39–44]

Epidemiological studies have shown an association between PPH and an increased risk of all-cause and cardiovascular-related mortality.[39–42] The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) and the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) studies[40,42] analysed baseline and 2-hour postchallenge glucose data in adults of European and Asian origin and found that 2-hour plasma glucose was a better predictor of cardiovascular disease and all-cause mortality than FPG. There is also accumulating evidence that 1-hour postchallenge glycaemia may be related to an increased risk of cardiovascular disease.[45] There is an association between PPH and oxidative stress,[46–48] carotid intima-media thickening[49] and endothelial dysfunction,[46,50,51] all of which are known markers of cardiovascular disease. Furthermore, PPH is associated with an increased risk of retinopathy[52,53] and certain cancers.[54–56] In addition to the increased risk of morbidity and mortality in people with diabetes, a study has shown that in people with T2DM, poor PPG control is associated with a reduction in cognitive performance and changes in emotional responses, such as reduced mood, increased agitation and anxiety, increased fatigue and lethargy, and a reduced feeling of happiness.[57] There are few health-related quality-of-life (HRQoL) data related to PPG control in patients with diabetes. HRQoL studies in diabetes have primarily considered the long-term complications and hypoglycaemia. PPH is a common occurrence in patients with diabetes and therefore an understanding of the impact of PPG control on a patient's daily life is important. Findings from a time trade-off study suggest that increasing severity in PPH symptoms is perceived as having significant negative consequences for the short-term HRQoL of people with diabetes.[44] Capturing the impact of PPG excursions on HRQoL in a clinical trial setting, however, may be limited by the ability of current instruments to measure this element. Nevertheless, this should not deter the consideration of the impact of improved PPG control on patient quality of life (QoL).

The economic burden of diabetes is well studied, however, there is limited information on the economic costs specific to PPH. A web-based survey investigated the costs of PPH related to diabetes management, use of healthcare resources, and work productivity among 906 adults with T1DM and T2DM taking bolus insulin.[43] From the survey, 62% of respondents experienced PPH in the past week, with an average of 1.7 episodes. Respondents with PPH in the past week measured their BG more frequently than those without PPH, reported greater contact with healthcare professionals related to diabetes in the past year, and were more likely to report medical complications related to diabetes. Working respondents indicated that PPH affected their work productivity.[43] Based on data from the UK respondents, the annual cost associated with PPH due additional blood-glucose testing strips, additional physician visits, and missed work time was estimated to be £720.71 per employed person in the UK.[43]

Many people with diabetes fail to deliver their bolus insulin doses accurately,[58,59] and further improvements in the flexibility of the timing of mealtime insulin administration would be beneficial. Human insulin should be administered 30 min prior to eating and a rapid-acting insulin analogue within 10 min prior to eating,[60–63] however, approximately 40% of patients fail to comply either all or part of the time, and have a higher risk of forgetting to take insulin.[64] Adherence is vital to ensure good glycaemic control; patient preference for flexible dosing indicates this strategy could improve adherence and therefore glycaemic control and health outcomes.[64] It can be difficult for patients to accurately calculate the amount of food they will eat during mealtimes and therefore premeal dosing increases the risk of insulin overdose or underdose, which may lead to hypoglycaemia and hyperglycaemia, respectively. A mealtime insulin that offers good glycaemic control without compromising safety, and can be dosed either before or after meals is viewed as being important.[65] Fast-acting insulin aspart can be administered just before (0–2 min) the start of the meal, with the option to administer within 20 min of starting the meal.[20] Subjects with T1DM in the onset 1 trial who received fast-acting insulin aspart post meal for all meals maintained overall glycaemic control non-inferior to that obtained with mealtime insulin aspart, indicating that flexibility in timing of dose with fast-acting insulin aspart does not lead to worsening of glycaemic control.[21]

Finally, patients using insulin aspart FlexPen® will be upgraded to the FlexTouch® pen on switching to fast-acting insulin aspart, improving the insulin injection experience at no additional

cost. In contrast, upgrading to insulin aspart FlexTouch® from insulin aspart FlexPen® would incur an additional cost. The FlexTouch® pen has a large, easy-to-read scale, an easy-touch button with low ejection force, and an end-of-dose click for patient confidence. The FlexTouch® pen delivers insulin consistently and accurately at minimum, half-minimum, half-maximum, and maximum doses. Compared with other prefilled pens (SoloStar® and KwikPen®), patients and healthcare professionals reported a higher ease of use and a higher preference for the FlexTouch® pen.[31, 66–68]

With a number of pharmaceutical companies developing biosimilar medicines, a biosimilar insulin aspart may become available in the near future. Although it can be anticipated that a biosimilar may be cost saving, there are other important factors to consider. Biosimilar products are similar, but not identical to the original product due to differences in biotechnological manufacturing processes. Small differences can provoke undesirable immune responses, as can the presence of different impurities, or different levels of impurities, which may impact the efficacy and safety profile of the drug.[69] Effectiveness and reliability of biosimilars are key concerns for people with diabetes.[70]

Biosimilars are also often delivered in different devices, which is a key consideration that is often overlooked in regulatory guidance on biosimilars.[71] Devices used for insulin administration are extremely important to both the patient and physician for reasons such as precision of dosing, ease of use, comfort and convenience. Thus, any cost savings achieved with biosimilar insulins may be counterbalanced by potential side effects, or a decline in glycaemic control associated with a change in insulin, or by costs associated with training to use a new device.[72]

Ultimately, the decision to treat a patient with either originator or biosimilar insulin should be made jointly by the treating physician and patient to ensure individual patient medical needs are appropriately considered.[69,73,74]

Conclusion

Fast-acting insulin aspart offers additional clinical benefit but at no additional cost when compared with insulin aspart in the UK, and thus provides value to the NHS.

The CIA has demonstrated that the displacement of insulin aspart with fast-acting insulin aspart will be cost neutral for the UK NHS. Fast-acting insulin aspart improves efficacy by more closely mimicking the physiological response of endogenous insulin in healthy individuals; it offers an advance in glycaemic control through improved PPG control in T1DM and T2DM, and HbA_{1c} control in T1DM compared with insulin aspart.[21,22] Fast-acting insulin aspart provides the option to administer within 20 min of starting the meal, improving insulin requirement accuracy and flexibility without compromising efficacy and safety *versus* insulin aspart dosed 0–2 min before the start of a meal, and is delivered in the patient-preferred FlexTouch® device.

Fast-acting insulin aspart offers improved efficacy at no additional cost, thus supporting the case for its implementation as an additional therapy option for patients with T1DM and T2DM.

In addition to the value to the NHS, fast-acting insulin aspart provides additional benefits to patients which may positively impact their QoL, including improved PPG control, a preferred pen device, and the option of postmeal dosing when required.

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Conflict of interest statement

WP and DA are employees of Novo Nordisk.
CF is an employee of DRG Abacus (sponsored by Novo Nordisk).
LL reports having received speaker honoraria from Minimed Medtronic, Animas, Roche,

Sanofi and Novo Nordisk, and serving on advisory panels for Minimed Medtronic, Animas, Roche and Novo Nordisk.

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