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ORIGINAL ARTICLE

Projected long-term outcomes in patients with type 1 diabetes treated with fast-acting insulin aspart vs conventional insulin aspart in the UK setting

David Russell-Jones MD[1] | Simon R. Heller MD[2] | Sarah Buchs MSc[3] |
Anna Sandberg MSc[3] | William J. Valentine PhD[4] | Barnaby Hunt MSc[4]

[1]Department of Diabetes and Endocrinology, Royal Surrey County Hospital, Guildford, UK

[2]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK

[3]Novo Nordisk A/S, Søborg, Denmark

[4]Ossian Health Economics and Communications, Basel, Switzerland

Correspondence
Barnaby Hunt, Ossian Health Economics and Communications GmbH, Bäumleingasse 20, 4051 Basel, Switzerland.
Email: hunt@ossianconsulting.com

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Aim: To assess the impact of faster aspart vs insulin aspart on long-term clinical outcomes and costs for patients with type 1 diabetes mellitus (T1DM) in the UK setting.

Methods: The QuintilesIMS CORE Diabetes Model was used to project clinical outcomes and costs over patient lifetimes in a cohort with data on baseline characteristics from the "onset 1" trial. Treatment effects were taken from the 26-week main phase of the onset 1 trial, with costs and utilities based on literature review. Future costs and clinical benefits were discounted at 3.5% annually.

Results: Projections indicated that faster aspart was associated with improved discounted quality-adjusted life expectancy (by 0.13 quality-adjusted life-years) vs insulin aspart. Improved clinical outcomes resulted from fewer diabetes-related complications and a delayed time to their onset with faster aspart. Faster aspart was found to be associated with reduced costs vs insulin aspart (cost savings of £1715), resulting from diabetes-related complications avoided and reduced treatment costs.

Conclusions: Faster aspart was associated with improved clinical outcomes and cost savings vs insulin aspart for patients with T1DM in the UK setting.

KEYWORDS

cost-effectiveness, insulin therapy, type 1 diabetes

1 | INTRODUCTION

It has been estimated that there are 370 000 adults and 26 500 children living with type 1 diabetes mellitus (T1DM) in the UK.[1,2] Patients with T1DM are at a higher risk of chronic complications and mortality than people without diabetes of the same age.[3] In 2010/2011, the direct costs attributable to T1DM in the UK were approximately £1 bn.[4] In addition, it is estimated that 830 000 sick days are taken per year as a result of T1DM, leading to indirect costs of approximately £0.9 bn. Projections suggest that, if no changes are made to treatment patterns, direct and indirect costs will increase to £1.8 and £2.4 bn, respectively, by 2035/2036.[4]

Long-term studies in patients with T1DM, such as the Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study,

suggest that improving glycaemic control can reduce the incidence of diabetes-related complications, lowering the clinical and economic burden of the disease.[5,6] In the UK in 2015, however, only 29.9% of patients with T1DM were achieving the glycaemic control target of glycated haemoglobin (HbA1c) < 7.5%.[7] This target has recently been lowered to 6.5% by the National Institute for Health and Care Excellence (NICE), and whilst no data have been published on the proportion of patients achieving the revised target, it is likely to be lower than for the previous guidance.[1]

Fast-acting insulin aspart (faster aspart) is conventional insulin aspart (insulin aspart) in a new formulation for the treatment of diabetes requiring insulin. Faster aspart has been developed to have a faster onset of action which more closely matches physiological secretion of endogenous insulin.[8] When compared with insulin aspart, faster aspart has a twice faster onset of appearance in

the bloodstream, a twice higher insulin exposure within the first 30 minutes and a 74% greater glucose-lowering effect in the first 30 minutes after administration.[9]

"Onset 1" was a 26-week multicentre, multinational, double-blind trial in patients with T1DM in which faster aspart was compared with insulin aspart, both in combination with insulin detemir in a basal-bolus insulin regimen.[10] The trial also included a 26-week open-label faster aspart post-meal dosing arm (also in combination with insulin detemir). The initial 26-week trial period was followed by an additional 26-week treatment period to assess long-term safety and efficacy. Compared with insulin aspart, mealtime faster aspart was associated with a significantly greater reduction in the primary endpoint of the trial, HbA1c at 26 weeks. Faster aspart administered post-meal did not compromise glycaemic control compared with insulin aspart administered at mealtime. Faster aspart compared with insulin aspart, both administered at mealtime, was also associated with statistically significant improvements in 1- and 2-hour postprandial glucose (PPG) increments. No statistically significant differences in changes in body weight or rates of hypoglycaemic events were observed, and the safety profiles of faster aspart and insulin aspart were similar.

Economic evaluation of new healthcare interventions plays a key role in ensuring efficient allocation of limited healthcare resources within the National Health Service (NHS), with the aim of maximizing healthcare gains across the population of the UK. In the UK, faster aspart and insulin aspart are associated with the same acquisition cost. The aim of the present study, therefore, was to assess the impact of basal-bolus insulin therapy with mealtime faster aspart plus insulin detemir vs mealtime insulin aspart plus insulin detemir on long-term clinical outcomes and costs in patients with T1DM, from a healthcare payer perspective in the UK setting.[11]

2 | MATERIALS AND METHODS

2.1 | Model description

The analysis was performed using the QuintilesIMS CORE Diabetes Model.[12] This model is a validated, non-product-specific diabetes policy analysis tool and is based on a series of interdependent submodels that simulate the complications of diabetes. The model uses data from a range of published long-term clinical and epidemiological studies to make predictions of outcomes, including the Diabetes Control and Complications Trial (DCCT), the UK Prospective Diabetes Study (UKPDS), the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the US Renal Disease Study (USRDS) and many others.[12] Long-term outcomes projected by the model have been validated against real-life data in 2004 and more recently in 2014.[13,14] Version 9.0 of the QuintilesIMS CORE Diabetes Model was used in the present analysis, as this model update includes risk equations specific to T1DM based on data from the EDIC study, and the Pittsburgh Epidemiology of Diabetes Complications Study, and includes the option to use a diminishing disutility for non-severe hypoglycaemic events.[15]

Outcomes were projected over patient lifetimes (up to 70 years) to capture all relevant long-term complications and associated costs and assess their impact on life expectancy and quality-adjusted life expectancy, consistent with good practice guidance for economic evaluation of interventions for diabetes.[16] Future clinical benefits and costs were discounted at 3.5% annually, based on health economic guidance for the UK setting.[17]

2.2 | Simulated cohort and treatment effects

The baseline cohort characteristics applied in the analysis were based on all patients included in the onset 1 study.[10] The mean (standard deviation [s.d.]) age was 44.4 (13.9) years, with mean duration of diabetes of 19.9 (12.3) years, and mean HbA1c of 7.6 (0.7)%. The proportion of patients using tobacco products was based on the trial data, but the number of cigarettes smoked per day was assumed to be the same as the general UK population and was based on country-specific data, as was alcohol consumption.[18,19]

Treatment effects applied in the faster aspart and insulin aspart arms (both in combination with insulin detemir) were taken from the 26-week main phase of the trial, in line with the primary endpoint, with data from mealtime insulin administration used (Table 1). Modelled data were used to account for any differences in the baseline cohort characteristics between the treatment arms.[10]

After application of the treatment effects in the first year of the analysis, HbA1c was assumed to remain constant over time. There are currently no published progression equations for HbA1c in patients with T1DM, and data from long-term studies such as DCCT and EDIC suggest that HbA1c does not increase as patients age.[6] Unlike type 2 diabetes mellitus (T2DM), T1DM is not a progressive disease and it is unlikely that substantial changes in HbA1c over time would be observed. Patients were assumed to receive faster aspart plus insulin detemir or insulin aspart plus insulin detemir for the duration of their lifetimes, with no treatment switching applied.

TABLE 1 Treatment effects applied in the first year of the analysis

	Faster aspart Mean (s.d.)	Insulin aspart Mean (s.d.)
HbA1c, %	−0.32 (0.56)*	−0.17 (0.56)
Systolic blood pressure, mm Hg	−1.47 (11.70)	−1.15 (11.70)
Diastolic blood pressure, mm Hg	−0.40 (9.40)	+0.40 (8.90)
Total cholesterol, mg/dL	+0.01 (0.65)	+0.02 (0.65)
HDL cholesterol, mg/dL	+0.01 (0.25)	−0.01 (0.25)
LDL cholesterol, mg/dL	−0.01 (0.53)	0.00 (0.53)
Triglycerides, mg/dL	+0.01 (0.62)	+0.07 (0.62)
Body mass index, kg/m²	+0.23 (0.99)	+0.19 (0.99)
Severe hypoglycaemia event rate (events per 100 patient years)	25	27
Non-severe hypoglycaemia event rate (events per 100 patient years)	5849	5811
Percentage of severe hypoglycaemic events that were nocturnal (%)	24.0	37.0
Percentage of non-severe hypoglycaemic events that were nocturnal (%)	12.0	13.0

Abbreviations: HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*P < .05.

2.3 | Costs and utilities

Costs were accounted from a healthcare payer perspective (NHS) in 2015 pounds sterling (£). Diabetes medication resource use was based on the onset 1 trial, with modelled doses taken from the 26-week main phase of the trial. At the end of the trial, patients in the faster aspart arm received mean daily doses of 30.60 and 30.44 IU basal and bolus insulin, respectively, compared with 31.24 and 33.06 IU per day in the insulin aspart arm. Costs of medications and consumables (needles and self-monitoring of blood glucose test strips and lancets) were taken from the Monthly Index of Medical Specialities.[11]

Costs of treating diabetes-related complications were identified through literature review, with costs inflated to 2015 values using the Hospital and Community Health Services price index where necessary.[20–30] Over time, patients develop complications that influence their overall health-related quality of life and therefore utilities, reflecting the patients quality of life, were applied in the year of the complication and in subsequent years based on published sources.[12,31–33] Whilst utilities specific to T1DM have been published, no full set of utilities for all complications included in the QuintilesIMS CORE Diabetes Model have been published using a single method. There is significant evidence that utility estimates vary depending on the methods used, therefore, the majority of utilities were based on patients with T2DM or the general population, with consistency in the methodology used to elicit the values. Application of utilities for patients with T2DM in patients with T1DM is a common approach in cost-effectiveness analyses of interventions for T1DM.[34–37] For disutilities applied after non-severe hypoglycaemic events, a diminishing disutility approach as described by Lauridsen et al.[38] was used. This approach was chosen as there is evidence that the marginal impact of non-severe hypoglycaemia on quality of life falls as the frequency of hypoglycaemic events increases.

2.4 | Sensitivity analyses

Sensitivity analyses were conducted to evaluate the key drivers of outcomes and to assess the effect of changes in modelling assumptions on the projected outcomes. The influence of time horizon on the outcomes projected by the model was investigated by running analyses over 10, 20 and 30 years. It should be noted that a time horizon of 70 years was required for all modelled patients to have died, and therefore shorter time horizons do not capture all complications and costs. To examine the effect of discounting on outcomes, simulations were performed with (symmetric) discount rates of 0% and 6%. A total of five simulations were run to assess the key drivers of clinical benefit associated with faster aspart. In the faster aspart arm, changes in HbA1c, blood pressure, serum lipids, body mass index and hypoglycaemic events were set to the value in the insulin aspart arm in turn. A further analysis with only the statistically significant difference in HbA1c applied in the faster aspart arm, with all other parameters equal to the insulin aspart arm, was conducted.

To evaluate the impact of alternative assumptions around long-term parameter progression on projected outcomes, 5 sensitivity analyses were conducted. In the base case analysis, the difference in

HbA1c between the treatment arms was assumed to persist for the entire simulation, with sensitivity analyses conducted with the difference abolished after 1, 5 and 10 years. A further analysis was conducted with the HbA1c difference abolished linearly over 10 years (ie, the difference between the treatment arms disappeared gradually). A final analysis was conducted with HbA1c difference between the treatment arms maintained for the duration of patient lifetimes, but an increase of 0.045% per year was applied in both arms, based on data from the DCCT.[5] This analysis reflects that patients with T1DM may develop some characteristics of T2DM due to weight gain and family history. In contrast to T1DM, T2DM is a progressive disease, with insulin resistance increasing and β-cell function declining over time.

The effect of over- or underestimating the direct cost of treating diabetes-related complications was investigated in 2 scenarios, by increasing and decreasing costs of complications by 20%. The base case analysis was conducted using a diminishing disutility approach for non-severe hypoglycaemic events, and a sensitivity analysis was conducted using a static disutility approach with disutilities applied based on T1DM-specific data from Evans et al.[32,38] The impact of hypoglycaemia disutilities was further explored in an analysis with no disutility applied after severe and non-severe events.

Version 9.0 of the QuintilesIMS Core Diabetes Model incorporates a number of risk equations to predict cardiovascular mortality and varying of the risk equations applied can be used to address structural uncertainty. The base case analysis used risk equations derived from the EDIC study, with risk equations based on data from the Pittsburgh Epidemiology of Diabetes Complications Study applied in a sensitivity analysis.[39] In a further sensitivity analysis to examine structural uncertainty, a combined mortality risk equation was applied.[40]

Reflecting the primary endpoint of onset 1, the 26-week data were applied in the base case analysis. The 52-week data, including the additional 26-week treatment period, were used in a sensitivity analysis with equivalent assumptions. An analysis was also conducted with the 26-week data applied in the first year of the analysis, and then treatment effects were applied to bring parameters to the values seen at 52 weeks in the second year of the analysis (the QuintilesIMS CORE Diabetes Model uses an annual cycle, and therefore it was not possible to apply changes at 6 months). Probabilistic sensitivity analysis was performed using a second-order Monte Carlo approach with sampling of baseline cohort characteristics, treatment effects, costs and utilities.

3 | RESULTS

3.1 | Base case analysis

In the base case analysis, long-term projections showed that faster aspart was associated with improved discounted life expectancy (by 0.11 years) and discounted quality-adjusted life expectancy (by 0.13 quality-adjusted life-years [QALYs]) vs insulin aspart in patients with T1DM (Table 2). Improved clinical outcomes resulted from a reduced incidence of diabetes-related complications over patient lifetimes (Figure 1A). In addition to a reduced incidence of

TABLE 2 Results of the base case analysis

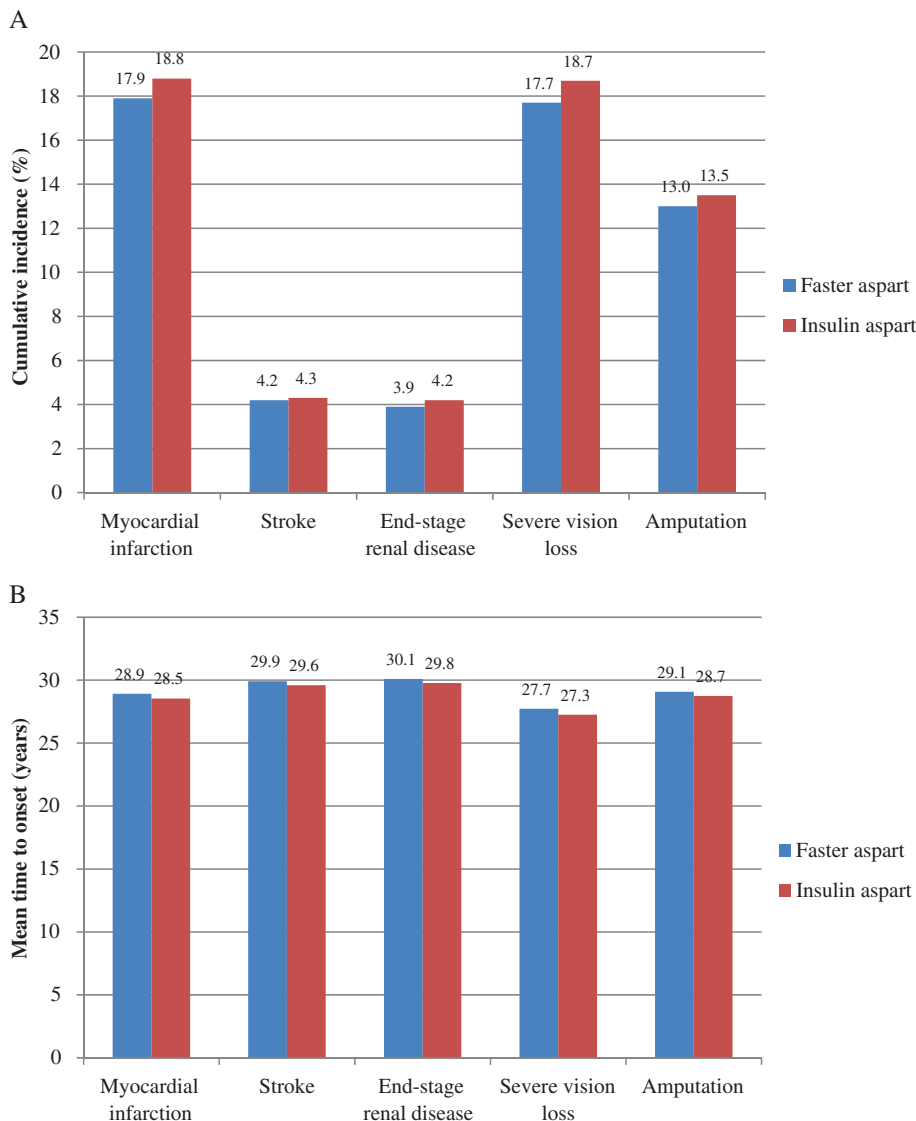|	Faster aspart Mean (s.d.)	Insulin aspart Mean (s.d.)	Difference
Discounted life expectancy, years	17.38 (0.16)	17.27 (0.19)	+0.11
Discounted quality-adjusted life expectancy, QALYs	11.54 (0.12)	11.40 (0.14)	+0.13
Discounted direct costs, £	50 004 (1363)	51 719 (1261)	−1715
ICER (life expectancy)		Faster aspart dominant	
ICER (quality-adjusted life expectancy)		Faster aspart dominant	

Abbreviation: ICER, incremental cost-effectiveness ratio.

Costs are in 2015 pounds sterling (£).

complications, faster aspart was associated with a delayed time to onset of complications (Figure 1B), with mean time free of all complications increased by ~6 months and mean time to onset of myocardial infarction, stroke, end-stage renal disease, severe vision loss and amputation all delayed by 4 to 6 months.

Evaluation of direct costs suggested that the mean cost per patient receiving faster aspart was £1715 lower than in the insulin aspart arm over a patient lifetime (Figure 2A). Faster aspart was associated with cost savings as a result of avoided diabetes-related complications, most notably as a result of avoided ulcer and neuropathy complications, and avoided ophthalmic complications, where mean per-patient savings of £516 and £225, respectively, were identified. Faster aspart was associated with cost savings after 1 year for the majority of complications, but cost savings as a result of avoided renal complications were only apparent after 15 years (Figure 2B). Cost savings as a result of all complications avoided increased over patient lifetimes, before plateauing 40 years into the analysis. Faster aspart was also associated with reduced treatment costs, driven by the lower doses of basal and bolus insulins, with mean cost savings of £478 per patient. Estimation of long-term clinical outcomes indicated that both life expectancy and quality-adjusted life expectancy were improved with faster aspart treatment

FIGURE 1 Cumulative incidence and mean time to onset of diabetes-related complications over patient lifetimes.
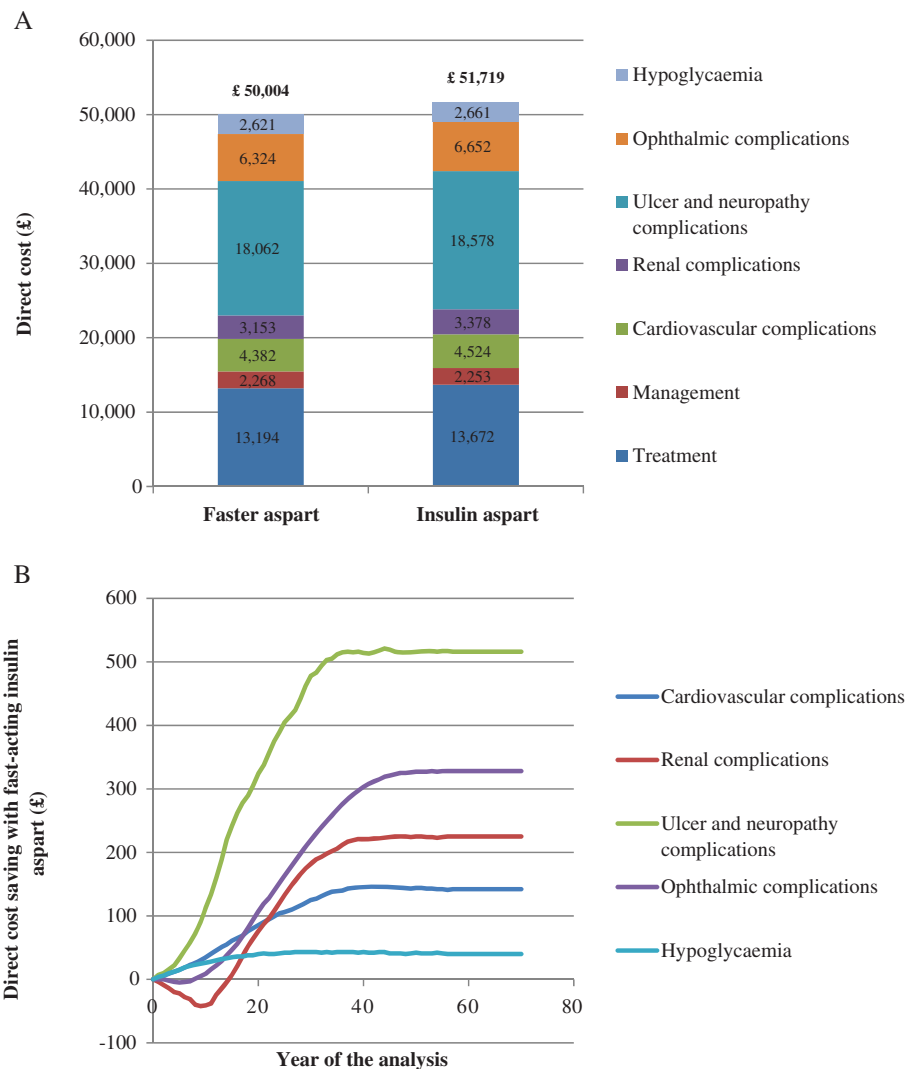
FIGURE 2 Direct costs over patient lifetimes with faster aspart and insulin aspart and cost savings with faster aspart as a result of avoided diabetes-related complications. £, 2015 pounds sterling

3.2 | Sensitivity analyses

Faster aspart was associated with improved clinical outcomes and reduced costs from a healthcare payer perspective vs insulin aspart in all sensitivity analyses conducted (Table 3). Variation in the time horizon had the greatest impact on the results. Over shorter time horizons, faster aspart was associated with smaller clinical benefits and smaller cost savings than in the base case analysis. This was due to the improvements in physiological markers (predominantly HbA1c) associated with faster aspart resulting in a reduced risk of diabetes-related complications over the long term. Changing the discount rates also highlighted the long-term benefits of improved glycaemic control with faster aspart, with clinical benefits and cost savings increased when discount rates of 0% were applied.

Abolishing each of the changes in physiological variables associated with faster aspart identified that the improvement in HbA1c compared with insulin aspart was the key driver of improved clinical outcomes and cost savings. When this difference between the treatment arms was abolished the clinical benefit with faster aspart fell to 0.05 QALYs. The analyses with alternative HbA1c progression approaches reflect the uncertainty around long-term changes in HbA1c and that patients with T1DM may develop some characteristics of T2DM, with faster aspart remaining associated with improved outcomes and reduced costs compared with insulin aspart in all analyses conducted.

Using the static approach to disutilities applied after non-severe hypoglycaemic events resulted in reduced quality-adjusted life expectancy in both arms relative to the base case, with the benefit associated with faster aspart falling to 0.12 QALYs. Similarly, when no hypoglycaemia disutilities were applied, the quality-adjusted life expectancy benefit with faster aspart was 0.12 QALYs. Probabilistic sensitivity analysis showed similar mean results to those of the base case, but increased measures of variance around the mean outcomes. Assuming a willingness-to-pay threshold of £20 000 per QALY gained, the analysis indicated that there was an 87.0% probability that faster aspart would be cost-effective vs insulin aspart.

4 | DISCUSSION

Based on clinical effectiveness data from the onset 1 trial, the present analysis projected that basal-bolus insulin therapy with faster aspart plus insulin detemir was likely to improve clinical outcomes vs basal-bolus insulin therapy with insulin aspart plus insulin detemir for patients with T1DM in the UK setting. The key driver of

TABLE 3 Results of the sensitivity analyses

| Analysis | Discounted quality-adjusted life expectancy, QALYs | | | Discounted direct costs, £ | | | ICER |
	Faster aspart	Insulin aspart	Difference	Faster aspart	Insulin aspart	Difference	£ per QALY gained
Base case	11.54	11.40	+0.13	50 004	51 719	−1715	Faster aspart dominant
30-year time horizon	10.60	10.50	+0.10	41 423	42 974	−1551	Faster aspart dominant
20-year time horizon	8.85	8.79	+0.06	30 468	31 606	−1138	Faster aspart dominant
10-year time horizon	5.55	5.53	+0.02	15 506	15 971	−464	Faster aspart dominant
0% discount rates	19.72	19.40	+0.32	101 998	105 422	−3424	Faster aspart dominant
6% discount rates	8.59	8.51	+0.08	33 511	34 645	−1134	Faster aspart dominant
HbA1c difference abolished	11.45	11.40	+0.05	51 150	51 719	−570	Faster aspart dominant
Blood pressure difference abolished	11.54	11.40	+0.13	50 027	51 719	−1693	Faster aspart dominant
Lipid difference abolished	11.51	11.40	+0.11	49 967	51 719	−1753	Faster aspart dominant
Body mass index difference abolished	11.53	11.40	+0.13	50 023	51 719	−1696	Faster aspart dominant
Hypoglycaemia difference abolished	11.49	11.40	+0.09	50 015	51 719	−1704	Faster aspart dominant
Statistically significant differences only	11.50	11.40	+0.10	50 165	51 719	−1554	Faster aspart dominant
HbA1c benefit abolished after 1 year	11.45	11.40	+0.05	51 061	51 719	−658	Faster aspart dominant
HbA1c benefit abolished after 5 years	11.46	11.40	+0.06	50 564	51 719	−1155	Faster aspart dominant
HbA1c benefit abolished after 10 years	11.49	11.40	+0.09	50 453	51 719	−1267	Faster aspart dominant
HbA1c benefit abolished linearly over 10 years	11.48	11.40	+0.07	50 973	51 719	−746	Faster aspart dominant
HbA1c increasing over time in both arms	11.22	11.07	+0.14	54 121	56 003	−1882	Faster aspart dominant
Cost of complications +20%	11.54	11.40	+0.13	56 847	58 813	−1966	Faster aspart dominant
Cost of complications −20%	11.54	11.40	+0.13	42 713	44 183	−1470	Faster aspart dominant
Static hypoglycaemia disutility	7.95	7.83	+0.12	50 004	51 719	−1715	Faster aspart dominant
No hypoglycaemia disutility	12.80	12.68	+0.12	50 004	51 719	−1715	Faster aspart dominant
Pittsburgh cardiovascular risk equations	10.79	10.69	+0.10	48 130	49 755	−1625	Faster aspart dominant
Combined mortality based on Western Australia data	12.12	12.00	+0.11	60 104	62 511	−2406	Faster aspart dominant
52-week data	11.47	11.35	+0.12	51 760	53 676	−1916	Faster aspart dominant
25 and 52-week data	11.51	11.37	+0.14	51 483	53 256	−1773	Faster aspart dominant
Probabilistic sensitivity analysis	11.12	11.00	+0.13	49 692	51 448	−1756	Faster aspart dominant

Abbreviations: HbA1c, glycated haemoglobin; ICER, incremental cost-effectiveness ratio.

Costs are in 2015 pounds sterling (£).

improved clinical outcomes was a greater improvement in HbA1c, resulting in a reduced incidence and increased time to onset of diabetes-related complications. This led to improvements in both duration and quality of life in the faster aspart arm. The improvements in glycaemic control associated with faster aspart in onset 1 were achieved with a similar risk of hypoglycaemic events to that associated with insulin aspart treatment, as opposed to previous observations where improvements in glycaemic control have been compromised by an association with an increase in hypoglycaemic events.[5,6] Projected over patient lifetimes, faster aspart was associated with cost savings as a result of diabetes-related complications avoided, which were apparent from the first year of the analysis and increased over time. Faster aspart was also associated with cost savings resulting from lower doses of both basal and bolus insulins, as the two formulations are associated with the same acquisition cost. Faster aspart was considered cost- and life-saving vs insulin aspart as part of a basal-bolus insulin regimen for treatment of T1DM in the UK setting.

While the improvement in HbA1c with faster aspart compared with insulin aspart may be relatively modest (0.15%), maintaining this difference over the long term may substantially reduce the risk of developing diabetes-related complications. This reduces both mortality and morbidity associated with T1DM. For healthcare payers, this improved patient management may also result in significant cost savings as a result of avoidance of costly treatment of complications.

The present modelling analysis does not take into account changes in PPG control, as this variable cannot be captured in the QuintilesIMS CORE Diabetes Model. In the onset 1 study, faster aspart was associated with statistically significant improvements in PPG increments compared with insulin aspart.[10] It has been suggested that lower PPG may be associated with a reduced risk of diabetes-related complications, with guidance from the International Diabetes Federation stating that post-meal hyperglycaemia is independently associated with macrovascular disease, ophthalmic disease and cancer.[41] A 2012 review found that higher PPG was associated with increased all-cause and cardiovascular mortality, increased incidence of major cardiovascular events, and progression of diabetic retinopathy.[42] However, the impact of reduced PPG may to some extent be indirectly included in the present analysis, as HbA1c was used as the measure of glycaemic control. Some studies have

suggested that PPG makes a significant contribution to HbA1c in patients who are relatively well controlled, although other studies have been more cautious and have suggested that fasting plasma glucose is a better indicator of HbA1c, particularly in patients with a very high HbA1c concentration.[43,44]

In addition to improving glycaemic control, the rapid onset of action of faster aspart and the faster appearance in the bloodstream may provide patients with T1DM with increased flexibility around timing of doses.[8,9] Currently, mealtime insulins must be injected pre-prandially, and this may result in hypoglycaemia if the meal is delayed or not consumed. Faster aspart represents a mealtime insulin with the option of post-meal dosing when needed, without compromising glycaemic control compared with insulin aspart.[10] This opportunity for post-meal dosing, when required, may improve convenience, and furthermore, flexibility in the timing of insulin dosing has been shown to be associated with improved quality of life in patients with diabetes, beyond the impact on hypoglycaemic events.[45,46] The present analysis did not capture the utility of flexible insulin dosing, as data were used from the arms of the trial in which mealtime dosing was specified, but this impact on quality of life may be seen in real-world clinical practice, and remains an area of interest for future research.

A limitation of the present analysis, common to a number of health economic analyses and particularly those for diabetes interventions, was the reliance on relatively short-term clinical trial data to make long-term projections. However, in the absence of long-term trial data, modelled projections represent a valuable source of information for healthcare decision-makers aiming to allocate resources efficiently to maximize healthcare across the population. Furthermore, projecting outcomes over patient lifetimes is recommended in guidelines for economic evaluation of interventions for patients with diabetes. The present analysis aimed to minimize the impact of this by using a model of diabetes based on published long-term epidemiological studies that has been extensively published and validated.[13,14]

A further limitation may be the clinical data used to inform the analysis. The study was based on a randomized controlled trial (onset 1), and therefore there is an assumption that the effects observed in the trial would be transferable to clinical practice in the UK setting. Registry data provide evidence of the impact of interventions in the real world, but it was not possible to use registry data in the present analysis, as, at the time the analysis was conducted, faster aspart was not available in the UK. As faster aspart becomes more widely used, data from registries such as the Clinical Practice Research Datalink could be used to conduct equivalent long-term analyses. Additionally, data from registries would allow the clinical effects to be assessed in a larger patient cohort and over a longer duration than was possible in the onset 1 trial. Nevertheless, the onset 1 trial represents the best data source currently available to inform the present analysis.

Faster aspart has been shown to have a greater glucose-lowering effect within the first 30 minutes after injection compared with insulin aspart because of its faster appearance within the bloodstream, and the onset 1 trial found that this resulted in improved glycaemic control in patients with T1DM. Long-term projections, as part of the present analysis, suggested that treatment with faster aspart plus insulin detemir was likely to improve long-term clinical outcomes for patients with T1DM at a reduced cost from a UK healthcare payer perspective vs insulin aspart plus insulin detemir.

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Conflict of interests

B. H. and W. J. V. are employees of Ossian Health Economics and Communications. Ossian received funding from Novo Nordisk A/S to perform the present analysis. S. B. was an employee of Novo Nordisk when this research was conducted. A. S. is an employee of Novo Nordisk A/S. D. R.-J. has received research funding, advisory panel fees and lecture panel honoraria from Astra Zenica, Boehringer Ingelheim, Cellnovo, Lilly, Novartis, Novo Nordisk, and Sanofi. S. R. H. has received personal fees from Sanofi Aventis, Eli Lilly, Takeda, Novo Nordisk and Astra Zeneca for serving on Speaker panels, and is an employee of the University of Sheffield, which has received remuneration from Eli Lilly, Boeringher Ingelheim, Novo Nordisk, and Takeda for consultancy.

Author contributions

The study was designed by all authors and was conducted by B. H. All authors contributed to analysis of the results. B. H. drafted the manuscript and D. R.-J., S. R. H., S. B., A. S. and W. V. critically reviewed the manuscript and revised it for important intellectual content. All authors approved the final manuscript and agree to be accountable for all aspects of the work.

REFERENCES

1. National Institute for Health and Care Excellence. NG17: Type 1 diabetes in adults: diagnosis and management. 2015. Available at: http://www.nice.org.uk/guidance/ng17. Accessed November 1, 2016.
2. National Institute for Health and Care Excellence. NG18: Diabetes (type 1 and type 2) in children and young people: diagnosis and management. 2015. Available at: http://www.nice.org.uk/guidance/ng18. Accessed November 1, 2016.
3. National Diabetes Audit 2011–2012. Report 2: Complications and Mortality. 2013. Available at: http://www.hscic.gov.uk/catalogue/PUB12738/nati-diab-audi-11-12-mort-comp-rep.pdf. Accessed November 1, 2016.
4. Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of type 1 and type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med.* 2012;29(7):855–862.
5. The DCCT Research Group, Nathan DM, Genuth S, Lachin J, et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329:977–986.
6. Nathan DM, Bayless M, Cleary P, et al; DCCT/EDIC Research Group. Diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: advances and contributions. *Diabetes.* 2013;62(12):3976–3986.
7. Health and Social Care Information Centre. National Diabetes Audit 2013-2014 and 2014-2015. Report 1: Care processes and treatment targets. 2016. Available at: http://content.digital.nhs.uk/catalogue/PUB19900/nati-diab-rep1-audi-2013-15.pdf. Accessed November 1, 2016.
8. Heise T, Hövelmann U, Brøndsted L, Adrian CL, Nosek L, Haahr H. Faster-acting insulin aspart: earlier onset of appearance and greater

early pharmacokinetic and pharmacodynamic effects than insulin aspart. *Diabetes Obes Metab*. 2015;17(7):682–688.

9. Heise T, Pieber TR, Thomas Danne T, Erichsen L, Pakseresht A, Haahr H. Faster onset and greater early exposure and glucose-lowering effect with faster-acting insulin aspart vs. insulin aspart: a pooled analysis in subjects with type 1 diabetes. Presented at: The American Diabetes Association 76th Scientific Sessions; June 10–14, 2016. New Orleans, Louisiana.

10. Russell-Jones D, Bode BW, de Block C, et al. Fast-acting insulin aspart improves glycemic control in basal-bolus treatment for type 1 diabetes: results of a 26-week multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (Onset 1). *Diabetes Care*. 2017 pii:;dc161771 https://doi.org/10.2337/dc16-1771. [Epub ahead of print].

11. Monthly Index of Medical Specialities. 2016. Available at: http://www.mims.co.uk/. Accessed November 1, 2016.

12. Palmer AJ, Roze S, Valentine WJ, et al. The CORE diabetes model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Curr Med Res Opin*. 2004;20-(suppl 1):5–26.

13. Palmer AJ, Roze S, Valentine W, et al. Validation of the CORE diabetes model against epidemiological and clinical studies. *Curr Med Res Opin*. 2004;20(suppl 1):27–40.

14. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE diabetes model. *Value Health*. 2014;17(6):714–724.

15. IMS Health. IMS CORE Diabetes Model user group forum. November 8, 2015.

16. American Diabetes Association Consensus Panel. Guidelines for computer modeling of diabetes and its complications. *Diabetes Care*. 2004;27(9):2262–2265.

17. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. 2014. Available at: https://www.nice.org.uk/process/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869. Accessed November 1, 2016.

18. Health and Social Care Information Centre. Statistics on smoking: England, 2015. Available at: http://www.hscic.gov.uk/catalogue/PUB17526/stat-smok-eng-2015-rep.pdf. Accessed November 1, 2016.

19. Health and Social Care Information Centre. Statistics on alcohol: England, 2015. Available at: http://www.hscic.gov.uk/catalogue/PUB17712/alc-eng-2015-rep.pdf. Accessed November 1, 2016.

20. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2015. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2015/. Accessed November 1, 2016.

21. National institute for Health and Care Excellence. Clinical Guideline 48. MI: secondary prevention (CG48). Appendix B. 2007. Available at: http://www.nice.org.uk/CG48. Accessed November 1, 2016.

22. Dyer MT, Goldsmith KA, Khan SN, et al. Clinical and cost-effectiveness analysis of an open label, single-centre, randomised trial of spinal cord stimulation (SCS) versus percutaneous myocardial laser revascularisation (PMR) in patients with refractory angina pectoris: the SPiRiT trial. *Trials*. 2008;9:40.

23. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. *CMAJ*. 2009;180(4):400–407.

24. National Institute for Health and Care Excellence. Technology Appraisal 94: Statins for the prevention of cardiovascular events, Appendix B. 2006. Available at: http://www.nice.org.uk/guidance/TA94. Accessed November 1, 2016.

25. Youman P, Wilson K, Harraf F, Kalra L. The economic burden of stroke in the United Kingdom. *Pharmacoeconomics*. 2003;21(suppl 1):43–50.

26. Department of Health. NHS reference costs 2014-15. 2015. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2014-to-2015. Accessed November 1, 2016.

27. National Institute for Health and Care Excellence. Chronic kidney disease (CG73). Appendix 2. 2008. Available at: http://www.nice.org.uk/nicemedia/live/12069/42116/42116.pdf. Accessed November 1, 2016.

28. Clarke P, Gray A, Legood R, Briggs A, Holman R. The impact of diabetes-related complications on healthcare costs: results from the United Kingdom prospective diabetes study (UKPDS study no. 65). *Diabet Med*. 2003;20(6):442–450.

29. Meads C, Hyde C. What is the cost of blindness? *Br J Ophthalmol*. 2003;87(10):1201–1204.

30. Ghatnekar O, Willis M, Persson U. Cost-effectiveness of treating deep diabetic foot ulcers with Promogran in four European countries. *J Wound Care*. 2002;11(2):70–74.

31. Clarke P, Gray A, Holman R. Estimating utility values for health states of type 2 diabetic patients using the EQ-5D (UKPDS 62). *Med Decis Making*. 2002;22:340–349.

32. 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(1):90.

33. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care*. 2000;38(6):583–637.

34. Roze S, Smith-Palmer J, Valentine WJ, et al. Long-term health economic benefits of sensor-augmented pump therapy vs continuous subcutaneous insulin infusion alone in type 1 diabetes: a UK perspective. *J Med Econ*. 2016;19(3):236–242.

35. Roze S, Saunders R, Brandt AS, de Portu S, Papo NL, Jendle J. Health-economic analysis of real-time continuous glucose monitoring in people with Type 1 diabetes. *Diabet Med*. 2015;32(5):618–626.

36. Pratoomsoot C, Smith HT, Kalsekar A, Boye KS, Arellano J, Valentine WJ. An estimation of the long-term clinical and economic benefits of insulin lispro in Type 1 diabetes in the UK. *Diabet Med*. 2009;26(8):803–814.

37. Wolowacz S, Pearson I, Shannon P, et al. Development and validation of a cost-utility model for Type 1 diabetes mellitus. *Diabet Med*. 2015;32(8):1023–1035.

38. Lauridsen JT, Lønborg J, Gundgaard J, Jensen HH. Diminishing marginal disutility of hypoglycaemic events: results from a time trade-off survey in five countries. *Qual Life Res*. 2014;23(9):2645–2650.

39. Zgibor JC, Ruppert K, Orchard TJ, et al. Development of a coronary heart disease risk prediction model for type 1 diabetes: the Pittsburgh CHD in Type 1 Diabetes Risk Model. *Diabetes Res Clin Pract*. 2010;88(3):314–321.

40. Hayes AJ, Leal J, Kelman CW, Clarke PM. Risk equations to predict life expectancy of people with Type 2 diabetes mellitus following major complications: a study from Western Australia. *Diabet Med*. 2011;28(4):428–435.

41. International Diabetes Federation. 2011 Guideline for management of postmeal glucose in diabetes. 2011. Available at: http://www.idf.org/sites/default/files/postmeal%20glucose%20guidelines.pdf. Accessed November 1, 2016.

42. Mannucci E, Monami M, Lamanna C, Adalsteinsson JE. Post-prandial glucose and diabetic complications: systematic review of observational studies. *Acta Diabetol*. 2012;49(4):307–314.

43. Monami M, Lamanna C, Lambertucci L, et al. Fasting and post-prandial glycemia and their correlation with glycated hemoglobin in Type 2 diabetes. *J Endocrinol Invest*. 2006;29(7):619–624.

44. American Diabetes Association. Postprandial blood glucose. *Diabetes Care*. 2001;24(4):775–778.

45. Evans M, Jensen HH, Bøgelund M, Gundgaard J, Chubb B, Khunti K. Flexible insulin dosing improves health-related quality-of-life (HRQoL): a time trade-off survey. *J Med Econ*. 2013;16(11):1357–1365.

46. Boye KS, Matza LS, Walter KN, Van Brunt K, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *Eur J Health Econ*. 2011;12(3):219–230.