CMRO

Current Medical Research & Opinion Vol. 26, No. 6, 2010, 1399–1412

0300-7995
doi:10.1185/03007991003689381

Article 5387/469460

Review

Systematic review of the cost-effectiveness of biphasic insulin aspart 30 in type 2 diabetes

William J. Valentine
Richard F. Pollock
Ossian Health Economics and Communications, Basel, Switzerland

Juliette Plun-Favreau
Novo Nordisk Health Care AG, Zürich, Switzerland

Jeremy White
Novo Nordisk International Operations, Zürich, Switzerland

Address for correspondence:
Dr. William J. Valentine, Ossian Health Economics and Communications GmbH, Oberwilerstrasse 20, Basel 4054, Switzerland.
Tel.: +41 61 271 6214;
valentine@ossianconsulting.com

Key words:
Biphasic insulin aspart 30 – Cost–benefit analysis – Cost-effectiveness – Diabetes mellitus

Accepted: 9 February 2010; published online: 13 April 2010
Citation: Curr Med Res Opin 2010; 26:1399–412

Abstract

Objectives:
To review the cost-effectiveness of biphasic insulin aspart (BIAsp 30) compared to other insulin regimens in the treatment of type 2 diabetes based on published literature.

Methods:
The electronic databases MEDLINE, EMBASE, the Cochrane Library and EconLit and a selection of congress/meeting databases were systematically searched using combinations of search terms designed to identify publications describing cost-effectiveness analyses of BIAsp 30 in patients with type 2 diabetes. Searches were limited to studies in humans, and published in the English language between January 1999 and July 2009. All records were screened for inclusion in the review.

Results:
Seven published cost-effectiveness analyses and ten abstracts were identified. One was a health technology assessment from the UK, which evaluated cost-effectiveness using the UKPDS Outcomes Model and meta-analysis of published clinical trials and concluded that premixed insulin analogs were unlikely to be cost-effective versus insulin glargine or biphasic human insulin. In all other studies the cost-effectiveness of BIAsp 30 versus other insulin regimens was assessed using the validated CORE Diabetes Model and outcomes from either the INITIATE randomized controlled trial, or the PRESENT or IMPROVE observational studies. However, notable limitations include the fact that all cost-effectiveness analyses to date have been performed using a single model and that a number of these are based on data from observational studies rather than randomized controlled trials. Nevertheless, long-term clinical and economic outcomes were reported for several countries: UK, US, Sweden, Saudi Arabia, Poland, South Africa, South Korea and China. BIAsp 30 was associated with improvements in quality-adjusted life expectancy in all countries. Estimates of direct costs varied according to country and comparator, but incremental cost-effectiveness ratios for the US and UK were USD 46 533 and GBP 6951 per quality-adjusted life year gained for BIAsp 30 versus insulin glargine.

Conclusions:
Although cost-effectiveness data on BIAsp 30 are scarce the majority of the analyses identified in this review suggest that BIAsp 30 is likely to be cost-effective compared to insulin glargine and biphasic human insulin across a wide range of settings, and under certain circumstances would be a dominant treatment option.

Introduction

A critical component of effective management in type 2 diabetes is achieving adequate control of blood glucose levels. However, this is a challenging goal, partly due to the chronic and progressive nature of the disease, but also to the availability of new drugs and therapeutic classes[1]. With increasing demands being placed on limited healthcare resources the availability of newer treatment options is dependent on economic, as well as efficacy and safety, considerations.

In the US in 2007, there were an estimated 36 million patient visits for treated diabetes, leading to an estimated financial burden in 2007 of $174 billion[2]. Treatment of diabetes-related complications including retinopathy, neuropathy and cardiovascular disease accounts for the majority of diabetes-related costs[3]. Pharmacotherapy to control glucose levels contributed approximately 10% of the cost, of which approximately 8.7% was associated with insulin (i.e. <1% of the total cost)[2]. However, the total cost of insulin analogs in the US increased from $0.5 billion in 2001 to $3.9 billion in 2007[1]. Retrospective analyses of administrative claims data suggest that for patients switching to insulin, despite an immediate increase in treatment cost compared to oral medications, the overall cost after 1 year may be lower (depending on regimen)[4,5]. This is largely attributed to reduced diabetes-related complication costs resulting from improved disease control.

Nevertheless, use of insulin and other newer therapies has increased in recent years with the increased cost of insulin prescriptions in particular prompting calls for cost-effectiveness analyses to demonstrate that these higher treatment costs translate into long-term improvements in outcomes[1]. As a growing number of countries now request health economic data to support decision-making procedures, the demonstration of cost-effectiveness has become central to achieving reimbursement in many countries.

Biphasic insulin aspart 30 (BIAsp 30) is a pre-mixed insulin analog comprising 30% rapid-acting soluble component and 70% long-acting protaminated component to control post-prandial and basal glucose levels, respectively. Randomized controlled trials have demonstrated the safety and efficacy of BIAsp 30 compared with other insulins (including insulin glargine, human insulin, biphasic insulin lispro, and premixed human insulin)[6–10]. Moreover, observational studies have confirmed and extended such findings and yielded safety and efficacy information in 'real world' patient groups which are more clinically and racially diverse[11,12]. The aim of this review was to evaluate, based on the identification of previously published analyses, the cost-effectiveness of BIAsp 30 compared with other insulin regimens in the treatment of type 2 diabetes.

Literature review

A literature search was conducted to identify published articles and conference abstracts describing cost-effectiveness analyses of biphasic insulin aspart versus other insulins including but not restricted to human insulin, insulin glargine or insulin lispro. No exclusion criterion was applied to exclude any other comparator treatments. Comparisons between insulin administration devices were excluded from the review. The electronic databases MEDLINE, EMBASE and Cochrane Library were searched using the MeSH terms 'diabetes mellitus' AND 'insulin' AND 'cost-benefit analysis' or 'QALY' or 'cost-effectiveness' or 'economic' AND 'English', for articles published through to August 2009. The database EconLit was also searched using the terms 'type 1 diabetes' and 'type 2 diabetes.' All searches were performed on 27 July, 2009 and were limited to studies specific to humans, published in the English language and between January 1999 – August 2009. Abstracts were reviewed independently by two reviewers and disputes relating to inclusion/exclusion of articles were resolved by consensus. In addition to the basic searches, relevant publications were identified by hand searching of references within articles, and searching congress/meeting abstract archives for the years 2006–2009 from the American Diabetes Association (ADA), International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the European Association for the Study of Diabetes (EASD), and the Society for Medical Decision Making (SMDM). As no searchable databases of the International Diabetes Federation (IDF), Health Technology Assessment International (HTAi) or International Health Economics Associated (iHEA) congresses were found, the proceedings of these meetings did not form part of our literature review. Congress/meeting searches were limited to 2006–2009 based on the assumption that studies presented at congresses/meetings pre-2006 would have been subsequently published in full manuscript form.

In total, more than 500 articles were captured with the electronic database search, and after reviewing all abstracts, 13 full text articles were extracted, of which six were identified as relevant to the specific topic 'cost-effectiveness of BIAsp 30 versus other insulins' (one health technology assessment and five published manuscripts) (Tables 1 and 3). Comparator treatments were insulin glargine, biphasic human insulin and basal human insulin. Although a randomized controlled trial comparing BIAsp 30 versus the biphasic lispro analog (Mix25) has been published, no corresponding cost-effectiveness analysis was identified as part of the review[13]. Main reasons for rejecting articles were: not concerned with BIAsp 30, non-English language, and not an economic study. Searches of congress archives using the search term 'biphasic insulin' and 'NovoMix' identified 167 abstracts of which 14 were judged to be relevant. A quality assessment of all articles identified in the literature review was performed by two of the authors using the checklist published by Drummond and Jefferson (1996)[14].

As all identified articles and abstracts described country-specific cost-effectiveness studies, reporting outcomes in local currency, outcomes have been listed in original monetary units. However, to gain an overview of between country variance, we also converted main outcomes to United States dollar (USD) 2008 values as

Table 1. Cost-effectiveness evaluation methods in BIAsp 30 versus insulin glargine studies in type 2 diabetes.

Study	Patient group	Country setting	Clinical data source	Time horizon (years)	Change in HbA1c (%)*	Publication type
NICE HTA[18]	UK typical	UK	Meta-analysis	40	−0.43	Health technology assessment
Goodall *et al.*[19]	Insulin naïve	Sweden	INITIATE[10]	35	−0.43	Peer-reviewed manuscript
Ray *et al.*[20]	Insulin naïve	US	INITIATE[10]	35	−0.43	Peer-reviewed manuscript
Valentine *et al.*[21]	Insulin naïve	UK	INITIATE[10]	35	−0.43	Peer-reviewed manuscript
Palmer *et al.*[39] ADA-2543-PO (2005)	Insulin naïve	US	CC/INITIATE	Patient lifetime	−0.43	Poster presentation
Ray *et al.*[40] ADA-2411-PO (2006)	Insulin naïve	Sweden	CC/INITIATE	35	−0.43	Poster presentation
Valentine *et al.*[41] ADA-2376-PO (2006)	Insulin naïve	US	CC/INITIATE	35	−0.43	Poster presentation

*Change for BIAsp 30 compared to comparator.
CC = complete cohort; HbA1c = glycated hemoglobin; INITIATE = Initiate Insulin by Aggressive Titration and Education clinical trial.

follows: In a first step, general consumer price index ratios (from www.economywatch.com) were applied to convert reported costs to 2008 values. These were then converted to USD 2008 values using historical mid-year exchange rates obtained from Money Exchange (www.x-rates.com) on August 27, 2009. Exchange rates for converting to USD 2008 values were as follows: Chinese Yuan (CNY) 0.14414; Saudi Arabian Riyals (SAR) 0.26667; Swedish Kroner (SEK) 0.166764; British pounds sterling (GBP) 1.9759; Euro (EUR) 1.5527; Polish Zloty (PLN) 0.3421; South Korean Won (KRW) 0.00097 and South African Rand (SAR) 0.1471.

Summary of clinical data used as the basis for published cost-effectiveness studies

On review of the health technology assessment (HTA) from the National Institute for Health and Clinical Excellence (NICE) in the UK, six published manuscripts and ten congress abstracts describing cost-effectiveness analysis of BIAsp 30 in type 2 diabetes, it was recognized that, with the exception of the HTA, all studies evaluated cost-effectiveness based on long-term projections using the validated CORE Diabetes Model. In the HTA, the UK Prospective Diabetes Study (UKPDS) Outcomes Model was used to make long-term projections based on meta-analysis data. A random effects meta-analysis of three trials was used for the comparison of premixed insulin with glargine, of which two studies compared insulin lispro mix 75/25 with glargine and one trial compared BIAsp 30 with glargine[15,10]. The meta-analysis showed a weighted mean difference in change from baseline in HbA1c of −0.43% [95% CI −0.46, −0.40] in favor of premixed insulin. No differences in hypoglycemia rates, blood pressure, BMI or serum lipid levels were modeled. For the comparison of premixed insulin with human insulin, a meta-analysis of six trials was performed, five of which compared BIAsp 30 with human insulin and one compared insulin lispro mix 50 with human insulin. For the modeling analysis, a weighted mean difference in HbA1c change of −0.02% [95% CI −0.14, −0.10] benefitting premixed insulin was applied.

In the published analyses using the CORE Diabetes Model, long-term projections with the model were based on short-term outcomes from one of three published clinical studies of BIAsp 30. These were the INITIATE (Initiate Insulin by Aggressive Titration and Education) trial, the PRESENT (Physicians' Routine Evaluation of Safety and Efficacy of NovoMix30 Therapy) study and the IMPROVE™ study. Each of these studies evaluated treatment of type 2 diabetes patients with BIAsp 30; however, only INITIATE was a randomized controlled trial.

INITIATE was a 28-week, open-label, parallel-group, treat-to-target, randomized controlled trial designed to compare BIAsp 30 with insulin glargine in 25 centers in the US[10]. At baseline, 233 insulin naïve patients were randomized to treatment with BIAsp 30 before breakfast and evening meals or to treatment with insulin glargine administered at bedtime using a vial and syringe. Mean patient age was 52 years, HbA1c 9.8% and BMI approximately 31 kg/m^2 at baseline. At study end (209 completers), treatment with BIAsp 30 significantly ($p<0.01$) reduced HbA1c compared to insulin glargine, mean (SD) change −2.79 (0.11)% versus −2.36 (0.11)% respectively, and HbA1c reduction was greatest for those with baseline HbA1c >8.5%. A greater percentage of subjects treated with BIAsp 30 achieved target HbA1c values <7.0% (approximately 66% versus 40%) and ≤6.5% (approximately 42% versus 28%) than reported in the insulin glargine group.

IMPROVE was a 26-week observational study conducted in eleven countries/regions (Canada, China, Greece, Gulf Region, India, Iran, Italy, Japan, Poland, Russia and South Korea) with data currently available for eight (data from the Gulf Region, Iran and South Korea are pending)[11]. The aim of the study was to assess the safety and efficacy of BIAsp 30 treatment in patients with type 2 diabetes in routine practice. Patients were eligible for the study if their treating physician believed

insulin was required and had decided to initiate treatment with BIAsp 30. In total 52 419 patients were included in the study, and although considerable between country variation was noted, in general all patients had poor glycemic control and a high prevalence of diabetes-related complications. At baseline, mean (SD) patient age was 55 (12) years, HbA1c 9.3 (1.9)% and BMI 26.3 (4.8) kg/m^2. Although not designed as a treat-to-target study, when switched to BIAsp 30 most patients (98%) were set a target HbA1c by their treating physician. At study end the mean (SD) changes in HbA1c were −3.1 (2.1)%, −2.1 (1.7)% and −2.0 (1.8)% ($p<0.0001$ for all) respectively for patients treated at baseline with no pharmaceutical therapy, oral agents only and insulin with or without oral agents. The proportion of patients achieving an HbA1c target <7.0% was 53% overall, and ranged between 44% and 67% depending on therapy at baseline. Major hypoglycemia decreased in all groups, whilst the incidence of minor hypoglycemia increased in the insulin-naïve group.

PRESENT was a 24-week, multinational, multiethnic observational study involving 21 977 patients with type 2 diabetes from 13 countries (India, Iraq, Jordan, Kuwait, Lebanon, Qatar, Romania, Russia, Saudi Arabia, South Africa, South Korea, Turkey and the United Arab Emirates)[12]. The aim of the study was to assess the safety and efficacy of BIAsp 30 in routine clinical practice. Only patients inadequately controlled on their current therapy and prescribed BIAsp 30, either as a monotherapy or in combination with OADs, were included. At baseline, approximately 48% of all patients included in the study were switched from insulin based treatment regimens, in the majority of cases from human insulin[12,16]. Overall for the entire cohort, mean (SD) age was 55 (12) years, mean HbA1c 9.5 (1.9)% and BMI 27.1 (5.1) kg/m^2. After 24-weeks the mean (SD) change in HbA1c was a reduction of 1.81 (1.84)% ($p<0.001$ versus baseline), and approximately 28% of patients achieved a target HbA1c of <7.0%. Rates of all hypoglycemic events decreased in all groups previously treated with insulin compared to baseline; however, an increase in minor hypoglycemia occurred in treatment-naïve patients.

Cost-effectiveness analyses of BIAsp 30 versus insulin glargine

Insulin glargine is a long-acting insulin analog, providing basal coverage of insulin requirements. In contrast, BIAsp 30 comprises both short- and long-acting components providing both basal and post-prandial (after-meal) blood glucose control. A recent review of randomized controlled trials published to February 2008, concluded that premixed insulins are better at decreasing HbA1c and post-prandial glucose levels but less effective at decreasing fasting glucose levels compared to long-acting insulins[17]. A non-significant tendency for more hypoglycemia (unspecified severity) and statistically significant greater weight gain was noted with premixed insulins compared to long-acting insulin analogs.

In total, one HTA, three articles and three conference abstracts investigating the cost-effectiveness of BIAsp 30 compared to use of insulin glargine in type 2 diabetes were identified (Table 1 and Table 2)[18–21]. Assessment of study quality using the Drummond and Jefferson checklist indicated that the HTA and three published papers scored highly (scores ≥26 out of 35), with the conference abstracts (and corresponding posters) scoring lower most likely due to word count limitations (scores 15 out of 35). In the HTA, the UKPDS Outcomes Model was used to make long-term projections of costs and clinical outcomes

Table 2. Long-term health economic outcomes and study quality for BIAsp 30 versus insulin glargine in type 2 diabetes.

Study	Country Setting	Study quality assessment	BIAsp 30 versus insulin glargine		
			Difference in direct costs (2008 USD values)	Difference in QALE (QALYs)	ICER/outcome (2008 USD value)
NICE HTA[18]	UK	31/35	GBP 1566 (USD 3207)	0.045	GBP 34 800 per QALY gained (USD 71 258 per QALY gained)
Goodall *et al.*[19]	Sweden	26/35	SEK −10 367 (USD −1816)	0.21	BIAsp 30 dominant
Ray *et al.*[20]	US	30/35	USD 8824 (USD 10 559)	0.19	USD 46 533 per QALY gained (USD 55 682 per QALY gained)
Valentine *et al.*[21]	UK	27/35	GBP 1319 (USD 2764)	0.19	GBP 6951 per QALY gained (USD 14 566 per QALY gained)
Palmer *et al.*[39] ADA-2543-PO (2005)	US	15/35	NR	0.15	USD 39 000 per QALY gained (USD 46 688 per QALY gained)
Ray *et al.*[40] ADA-2411-PO (2006)	Sweden	15/35	SEK −23 368 (USD −4602)	0.21	BIAsp 30 dominant
Valentine *et al.*[41] ADA-2376-PO (2006)	US	15/35	NR	0.17	USD 30 265 per QALY gained (USD 33 354 per QALY gained)

GBP = British pounds sterling; ICER = incremental cost effectiveness ratio; QALE = quality-adjusted life expectancy; QALYs = quality-adjusted life years; SEK = Swedish Kroner; USD = US Dollar; NR = not reported.

associated with treatment and estimate cost-effectiveness. The UKPDS Outcomes Model was developed based on patient level data from the UKPDS and an article providing a full description of the model has been published[22]. In short, the UKPDS Outcomes Model is a probabilistic discrete-time model that uses an integrated set of parametric proportional hazard models to predict absolute risk of first occurrence of seven major diabetes-related complications (ischemic heart disease, myocardial infarction [fatal and nonfatal], heart failure, stroke, blindness, renal failure, and amputation). These predictions are based on patient characteristics (such as age and sex) and risk factors that vary with time (such as HbA1c level and systolic blood pressure).

The three published studies used the CORE Diabetes Model to project long-term outcomes that can be expected based on patient characteristics and short-term efficacy and safety data for BIAsp 30 versus insulin glargine as reported from INITIATE[10]. The model is based on data from a variety of published clinical and epidemiological studies. Its structure has been published[23] and the reliability of model outcomes has been validated against real-life clinical and epidemiological data in 66 separate analyses[24]. The structure is based on a series of sub-models that simulate the major complications of diabetes (angina, myocardial infarction, heart failure, stroke, peripheral vascular disease, neuropathy, foot ulcer and amputation, renal disease and eye disease) and, like the UKPDS Outcomes Model, it makes predictions based on patient characteristics and risk factors varying over time. Although identical modeling approaches were used in the CORE Diabetes Model analyses, the country perspectives of these cost-effectiveness analyses differed and this was reflected in the use of country-specific data for costs, non-diabetes mortality, end stage renal disease (ESRD) treatment modalities and discount rates applied to future clinical and economic outcomes, thus providing detailed analyses specifically relevant to the US, UK and Swedish healthcare systems. The conference abstracts identified in the search were based on the same analyses published in the peer reviewed literature and therefore are not discussed further in the current review.

In the NICE HTA, the cost-effectiveness of premixed insulin (based on meta-analysis of data from studies of insulin lispro 75/25 and BIAsp 30) versus insulin glargine was based on a cohort of patients representative of the type 2 diabetes population in the UK. Premixed insulin treatment was associated with an improvement in HbA1c of 0.43% versus insulin glargine (no other treatment effects were captured in the analysis). Long-term projections (time horizon 40 years) with the UKPDS Outcomes Model indicated that premixed insulin was associated with improvements in quality-adjusted life expectancy (0.045 quality-adjusted life years [QALYs]) versus insulin glargine. Direct medical costs were estimated from a healthcare payer perspective and indicated that premixed insulin was more expensive than insulin glargine over patients' lifetimes (GBP 23 033 versus 21 467, difference 1566), leading to an incremental cost-effectiveness ratio (ICER) of approximately GBP 34 800 per QALY gained (calculated) for premixed insulin versus insulin glargine. Higher costs on premixed insulin were driven by higher estimates of self-monitoring of blood glucose costs and improved survival, despite lower insulin costs and complication costs in comparison with the glargine regimen.

The cost-effectiveness analysis of BIAsp 30 versus insulin glargine in the UK setting by Valentine *et al.* generated a simulation cohort based on baseline characteristics and risk factors corresponding to the INITIATE trial cohort, supplemented where necessary with data specific for type 2 diabetes patients in the UK[21]. Treatment effects were also taken from INITIATE, and included an improvement in HbA1c by −0.43% for BIAsp 30 versus insulin glargine (comparable to the value used in the NICE HTA). However, although the decrease in HbA1c was significantly larger in the BIAsp 30 group versus insulin glargine in the INITIATE trial it should be noted that the BIAsp 30 group had a significantly higher rate of minor hypoglycemic events (3.4 [6.6] versus 0.7 [2.0] episodes per patient year; $p < 0.05$), significantly greater weight gain (5.4 [4.8] kg versus 3.5 [4.5] kg; $p < 0.01$) and a significantly higher insulin dose versus those patients treated with insulin glargine (78.5 [39.5] versus 51.3 [26.7] units per day). Over a 35-year time horizon, and assuming an HbA1c creep of 0.15% annually in line with estimates from the UKPDS, it was estimated that BIAsp 30 would improve discounted life expectancy by 0.19 ± 0.20 years (12.07 ± 0.16 versus 11.88 ± 0.16 years) and quality-adjusted life expectancy by 0.19 ± 0.14 (8.46 ± 0.11 versus 8.27 ± 0.11) QALYs (Table 2). Estimation of direct medical costs demonstrated that BIAsp 30 therapy was more expensive than insulin glargine by approximately GBP 1319 per patient. This was due to higher pharmacy costs in the BIAsp 30 arm of approximately GBP 2296 per patient, which was in part driven by improved life expectancy with BIAsp 30 versus glargine. However, these additional costs were partially offset by the reduced cost of complications, in particular nephropathy complications where a mean cost saving of GBP 569 per patient was observed, with BIAsp 30 versus glargine therapy over patients' lifetimes. Evaluations of an ICER produced a value of GBP 6951 per QALY gained, which would be considered cost-effective in the UK (assuming a theoretical willingness to pay of GBP 20–30 000 per QALY gained). Valentine *et al.* also showed via sensitivity analyses that a key driver of these outcomes was change from baseline in HbA1c, and when no difference between treatments was assumed insulin glargine was dominant to BIAsp 30.

Applying a similar modeling approach to that employed by Valentine *et al.* (making long-term projections based on short-term data from the INTIATE trial), publications from Ray *et al.* and Goodall *et al.* described cost-effectiveness analyses in the US and Swedish settings, respectively. These analyses indicated that BIAsp 30 represents a cost-effective (US) or dominant (Sweden) treatment compared to insulin glargine[19,20]. In the Swedish analysis, treatment effects from INITIATE were modeled in a cohort based on INITIATE but receiving country specific management (in terms of concomitant medications and screening). Treatment with BIAsp 30 was associated with increased life expectancy by 0.21 years (13.10 ± 0.15 versus 12.89 ± 0.16 years) and increased quality adjusted life expectancy by 0.21 QALYs (9.16 ± 0.11 versus 8.96 ± 0.11 QALYs) when compared with insulin glargine over a 35-year time horizon (Table 2). Direct medical costs over patients' lifetimes were reduced with BIAsp 30 by SEK 10 367 compared to treatment with insulin glargine. This difference was accounted for by the reduced incidence and hence cost of diabetes-related complications including nephropathy, cardiovascular disease, diabetic foot and retinopathy. Treatment with BIAsp 30 was projected to be associated with both improved life expectancy and cost savings, thus representing a dominant therapy option compared with insulin glargine in the Swedish setting from a healthcare payer perspective. Sensitivity analyses demonstrated that the projected outcomes were sensitive to the length of time that the between-treatment group difference in HbA1c efficacy was assumed to endure. However, even assuming that the difference lasted for only 1 year, BIAsp 30 was cost-effective versus glargine with an ICER of SEK 7102 per QALY gained.

In the US setting, the analysis of Ray *et al.* showed that treatment with BIAsp 30 was associated with an increase in life expectancy of 0.19 years (13.47 ± 0.17 versus 13.29 ± 0.16 years) and an increase in quality-adjusted life expectancy of 0.19 QALYs (9.40 ± 0.12 versus 9.21 ± 0.12 QALYs) when compared with insulin glargine over a 35-year time horizon (Table 2). Lifetime direct medical costs increased with BIAsp 30 by USD 8824 (USD 107 393 versus 98 569) compared to treatment with insulin glargine, resulting in an ICER of USD 46 533 per QALY gained. In line with observations from INITIATE that patients with baseline HbA1c ≥8.5% experienced a greater improvement in glucose levels (reductions of 3.15% and 2.95% for BIAsp 30 and insulin glargine respectively), a subgroup analysis was performed to assess cost-effectiveness in patients with worse baseline control (HbA1c 10.2%). Total lifetime costs were then USD 8908 more with BIAsp 30 compared to insulin glargine, leading to an ICER of USD 34 916 per QALY gained. Sensitivity analyses demonstrated that change in HbA1c was a key driver of outcomes, and insulin glargine was a dominant treatment option when no between-treatment difference in HbA1c was assumed. In the base case analysis it was assumed that between-treatment differences endured. When it was assumed that after 2 years the HbA1c levels were equivalent in the BIAsp 30 and glargine treatment groups, BIAsp 30 was projected to improve quality adjusted life expectancy by 0.11 QALYs with an ICER of USD 91 316 per QALY gained. Further sensitivity analyses also showed that a higher baseline age diminished costs and benefits in both treatment arms.

Cost-effectiveness analyses of BIAsp 30 versus biphasic human insulin

Premixed or biphasic insulins provide both post-prandial and basal insulin requirements in a single injection. Because these insulin formulations achieve glucose control with fewer injections compared with basal/bolus regimens they are more convenient and more readily accepted by patients[25]. Available as premixed human insulin (biphasic human insulin consists of a short-acting and an intermediate-acting insulin in standard proportions) or as biphasic analog insulin (such as BIAsp 30 consisting of a mixture of 30% soluble and 70% protaminated versions of analog insulin) the decision to initiate analog preparations is often related to the more physiological profile of analog mixtures. A number of randomized and observational studies have demonstrated the safety and efficacy of BIAsp 30 compared with biphasic human insulin[8,26–28]. Published systematic reviews of randomized controlled trials comparing biphasic human insulin and biphasic analog insulins found the two treatments to be equivalent with respect to reducing HbA1c and fasting glucose levels, with a similar incidence of hypoglycemia, but found that biphasic analogs were more effective in terms of reducing post-prandial glucose levels[17,29].

The literature search of publication databases identified only one HTA and three published manuscripts on the cost-effectiveness of BIAsp 30 versus human premixed insulin (Table 3)[18,30,33,34]. However, the search of conference proceedings identified seven posters (and corresponding abstracts) that compared use of BIAsp 30 to human premixed insulin using cohort and cost data specific to the country setting of interest (Table 3). The cost-effectiveness analyses identified were based on outcomes reported from either the PRESENT or IMPROVE observational studies. Where these observational studies were used to evaluate the cost-effectiveness of BIAsp 30, it was assumed that the effects on risk factors (e.g. HbA1c and body weight) and hypoglycemia rates of switching to BIAsp 30 would be applied, and in some cases, maintained over the long term. However, no direct comparator was included in these studies and as such it should be noted

Table 3. Cost-effectiveness evaluation methods of BIAsp 30 versus human insulin in type 2 diabetes.

Study	Comparator	Patient group	Country setting	Clinical data source	Time Horizon (years)	Change in HbA1c (%)*	Publication type
NICE HTA[18]	Biphasic human insulin	UK typical Inadequate control with comparator	UK	Meta-analysis	40	−0.02	Health technology assessment
Palmer *et al.*[30]			China	PRESENT[12,27]	30	−1.82	Peer-reviewed manuscript
Lynch *et al.*[42] -ISPOR PDB27 (2007)			China	SC/PRESENT	Patient lifetime	−1.82	Poster presentation
Aristides *et al.*[43] ISPOR PDB23 (2007)			Poland	CC/PRESENT	Patient lifetime	−1.66	Poster presentation
Tucker *et al.*[44] ISPOR PDB30 (2007)			Spain	CC/PRESENT	Patient lifetime	−1.66	Poster presentation
White *et al.*[45] ISPOR-PD35 (2008)		Insulin naïve	China	SC/IMPROVE	Patient lifetime	NR	Poster presentation
Aagren *et al.*[46] -DB1 (2009)			US	SC/IMPROVE	35	−0.58	Poster presentation
Ali *et al.*[33]	Human premix insulin	Inadequate control with comparator	Saudi Arabia	PRESENT[12,27]	40	−2.31	Peer-reviewed manuscript
Ali *et al.*[47] ISPOR-PDB3 (2008)			Saudi Arabia	SC/PRESENT	40	−2.31	Poster presentation
White *et al.*[48] ISPOR-PDB25 (2008)			South Africa	SC/PRESENT	30	−1.46	Poster presentation
Lee *et al.*[34]			South Korea	SC/PRESENT	30	−0.82	Poster presentation

*Change for BIAsp 30 compared to comparator.
CC = complete cohort; HbA1c = glycated hemoglobin; INITIATE = Initiate Insulin by Aggressive Titration and Education clinical trial; ISPOR = International Society For Pharmacoeconomics and Outcomes Research; PRESENT = Physician's Routine Evaluation of Safety and Efficacy of NovoMix 30 Therapy observational study; SC = country specific sub-cohort.

that the comparison is therefore that of BIAsp 30 against patients who continue to be poorly controlled, rather than treated with another treatment regimen with comparable efficacy. Evaluation of study quality showed that the both the HTA and the published manuscripts scored highly (31 out of 35 for the HTA and 25,28 and 30 out of 35 for the published manuscripts) and the posters scored between 15 and 17 out of 35.

In the NICE HTA published in 2008, the comparison of premixed analog insulin with human insulin was based on a meta-analysis of six trials[18]. Five out of the six trials used biphasic human insulin in the control arm (the sixth used neutral protamine Hagedorn (NPH) insulin), and of these, four studies had BIAsp 30 as the active treatment whereas one used insulin lispro mix 50. The UKPDS Outcomes Model was used to project clinical and cost outcomes over 40 years for a population representative of type 2 diabetes patients in the UK. The only treatment effects captured were a slight benefit in HbA1c associated with premixed analog insulin treatment (−0.02%). All other treatment parameters were assumed to be the same in both treatment arms. Quality-adjusted life expectancy was marginally higher (0.004 QALYs) in the premixed analog insulin arm, but direct medical costs were projected to be approximately GBP 3505 higher than on human insulin (driven mainly by higher pharmacy costs). An ICER was not reported for premixed insulin versus human insulin (but based on these figures it would have been in excess of GBP 850 000 per QALY gained for premixed analog versus human insulin due to the very small effectiveness benefit projected in the modeling analysis).

In a cost-effectiveness analysis of switching patients from biphasic human insulin to BIAsp 30 in the Chinese setting, Palmer *et al.* were able to optimize the relevance of their analysis by taking advantage of the availability of cohort characteristics and treatment effect data from the relevant Chinese subgroup ($n = 2289$) of patients in PRESENT[30]. In addition, clinical cost data were derived from a survey of physicians in Beijing and Chengdu to ensure validity of cost estimates. The CORE Diabetes Model was used to project long-term outcomes, based on the treatment effects associated with switching to BIAsp 30 from biphasic human insulin: mean change in HbA1c −1.82%, mean change in BMI −0.22 kg/m^2, reduction in minor hypoglycemia from 1337 to 446 events per 100 patient years and in major hypoglycemia from 239 to 30 events per 100 patient years. Projected over a 30-year time horizon, switching to BIAsp 30 was associated with an improvement in life expectancy by 0.38 years (9.91 ± 0.18 versus 9.53 ± 0.1 years) and in quality-adjusted life expectancy by 0.91 QALYs (6.32 ± 0.12 versus 5.41 ± 0.11 QALYs). Total lifetime costs increased moderately by approximately CNY 1751 when switching to BIAsp 30 compared with remaining on biphasic human insulin CNY 203 126 versus CNY 201 376 respectively.

When these projections were used to estimate cost-effectiveness, switching to BIAsp 30 was highly cost-effective with an ICER of CNY 1926 per QALY gained compared with remaining on biphasic human insulin. It is noteworthy that the costs of biphasic human insulin are relatively high in China (being generally only 20–30% lower than analog insulin) in comparison with other countries, and this may well be a factor in the low ICER in this analysis (relative to other settings). Sensitivity analysis showed that outcomes were most sensitive to changes in treatment effects. Assuming no improvement in HbA1c resulted in an ICER of CNY 22 681 per QALY gained, whilst assuming no between-treatment differences in incidence of hypoglycemia resulted in an ICER of CNY 15 995 per QALY gained. Outcomes were also moderately affected by 20% increases or decreases in all complication and management costs, with the former resulting in BIAsp 30 being dominant and the latter associated with an ICER of CNY 5377 per QALY gained compared with human biphasic insulin.

As discussed by the authors, a potential limitation of the cost-effectiveness analysis presented is that the CORE Diabetes Model uses risk equations derived from predominately white Caucasian cohorts. However, China-specific non-diabetes-related mortality and ESRD data were incorporated into the analysis, and the model has been previously validated and applied to various ethnicities including Asian[24,31]. The authors also provide limited details of attempts to include a correction factor for the reduced incidence of myocardial infarction observed among persons of Asian descent (approximately one third of that in white populations)[32], and note that this had the effect of increasing life expectancy in both treatment groups compared with the base case. The consequence of this being that patients receiving biphasic human insulin would experience more hypoglycemia events (as they were alive for longer) and this would, in turn, improve the cost-effectiveness of BIAsp 30. Another limitation of this analysis, and those analyses based on the PRESENT observational study is that it is based on a study designed to switch patients from sub-optimal therapy with human insulin to a BIAsp 30 regimen. As a result, the cost-effectiveness profile could be regarded as a comparison of BIAsp 30 with sub-optimal human insulin and has the potential to overestimate the cost-effectiveness of BIAsp 30 versus human insulin in the clinical practice setting.

In a cost-effectiveness analysis of switching from HI to BIAsp 30 in Saudi Arabia, Ali *et al.* based clinical efficacy and safety data on the Saudi subgroup of PRESENT patients ($n = 598$) who, compared to the 3414 multi-ethnic patients noted above, were considerably younger (46.5 versus 56.8 years) and heavier (BMI 29.8 versus 26.4 kg/m^2), but had comparable diabetes duration (11.3 versus 10.9 years) and baseline HbA1c (9.4% versus 9.3%)[33]. The BIAsp 30 associated improvement in HbA1c was greater in the Saudi Arabian subgroup (−2.31%) compared to all PRESENT patients (−1.42%) switching from HI, and this together with reductions in minor hypoglycemia (206 versus 1435 events per 100 patient years), major hypoglycemia (0 versus 145 events per 100 patient years) and a moderate reduction in BMI (0.34 kg/m^2) when switching from human insulin to BIAsp 30 were modeled in the cost-effectiveness analysis.

When projected over a 40-year time horizon switching to BIAsp 30 improved life expectancy by 0.62 years and quality-adjusted life expectancy by 0.96 QALYs compared to continuing with HI treatment. Whilst treatment with BIAsp 30 was associated with a reduced incidence of most diabetes-related complications, the projected 39% reduction in incidence of ESRD was particularly notable. In terms of lifetime costs, BIAsp 30 treatment was cost saving, reducing direct medical costs by SAR 53 879 per patient. This was a consequence of reduced costs for complications, including a saving of SAR 57 151 for hypoglycemic events, which offset the increased cost of treatment with BIAsp 30 compared to HI. In a series of sensitivity analyses it was shown that projected outcomes were sensitive to changes in treatment effect (HbA1c and hypoglycemia), and to changes in time horizon. However, with the exception of changes to the rate of hypoglycemia, BIAsp 30 remained cost saving (dominant) in all scenarios including increasing the cost of complications generally by 20% and assuming no improvement in HbA1c. However, assuming no BIAsp 30 associated difference in hypoglycemia incidence relative to baseline increased costs with BIAsp 30 by SAR 5845. This resulted in an ICER of SAR 14 363 per QALY gained for switching to BIAsp 30 from human insulin.

Lee *et al.* (2009) published a similar analysis adapted to the South Korean setting[34]. Long-term costs and clinical outcomes were projected using the CORE Diabetes Model based on the South Korean sub-group from the PRESENT study ($n = 1321$), which showed that switching to BIAsp 30 was associated with improvements in HbA1c, hypoglycemic event rates, and BMI versus human premix insulin. Direct medical costs were accounted in 2007 South Korean Won (KRW). Projections were made over a time horizon of 30 years and future costs and clinical benefits were discounted at 5% per annum.

Switching to BIAsp 30 was projected to improve life expectancy by 0.15 ± 0.18 years and quality-adjusted life expectancy by 0.30 ± 0.12 QALYs versus remaining on human insulin. Benefits in life expectancy and quality-adjusted life expectancy were driven by a reduced incidence of diabetes-related complications in the BIAsp 30 arm. Estimation of lifetime direct costs indicated that treatment with BIAsp 30 was likely to be slightly more expensive than that with human insulin (KRW 12 214 835 versus 10 437 982, difference 1 776 855).

Table 4. Long-term health economic outcomes for BIAsp 30 versus human insulin in type 2 diabetes.

Study	Country setting	Study quality assessment	BIAsp 30 versus human insulin		
			Difference in direct costs (2008 USD values)	Difference in QALE (QALYs)	ICER/outcome
NICE HTA[18]	UK	31/35	GBP 3505 (USD 7177)	0.004 QALYs	NR
Palmer *et al.*[30]	China	30/35	CNY 497 (USD 76)	0.91	CNY 1926 per QALY gained (USD 295 per QALY gained)
Lynch *et al.*[42] ISPOR PDB27 (2007)	China	16/35	CNY 7485 (USD 1197)	1.02	BIAsp 30 dominant
Aristides *et al.*[43] ISPOR PDB23 (2007)	Poland	16/35	PLN 7790 (USD 2871)	0.28	BIAsp 30 dominant
Tucker *et al.*[44] ISPOR PDB30 (2007)	Spain	15/35	EUR −8339 (USD 16 601)	1.03	BIAsp 30 dominant
White *et al.*[45] ISPOR-PD35 (2008)	China	17/35	CNY 2386 (USD 364)	0.55	CNY 4315 per QALY gained (USD 658 per QALY gained)
Aagren *et al.*[46] DB1 (2009)	US	21/35	USD 4936 (USD 4936)	0.276	USD 17 859 per QALY gained (USD 17 859 per QALY gained)
Ali *et al.*[33]	Saudi Arabia	28/35	SAR −53 879 (USD 15 786)	0.96	BIAsp 30 dominant
Ali *et al.*[47] ISPOR-PDB3 (2008)	Saudi Arabia	16/35	SAR −53 879 (USD 15 786)	0.97	BIAsp 30 dominant
White *et al.*[48] ISPOR-PDB25 (2008)	South Africa	18/35	ZAR −33 601 (USD 4941)	0.39	BIAsp 30 dominant
Lee *et al.*[34]	South Korea	25/35	KRW 1.8 million (USD 1829)	0.30	NR

CNY = Chinese Yuan; EUR = Euros; GBP = British Pounds Sterling; ICER = incremental cost-effectiveness ratio; KRW = South Korean Won; PLN = Polish Zloty; QALE = quality-adjusted life expectancy; QALYs = quality-adjusted life years; SAR = Saudi Arabian Riyal; USD = US Dollar; ZAR = South African Rand; NR = Not reported.

Higher pharmacy costs in the BIAsp 30 arm were partially offset by the reduced cost of treating diabetes-related complications. This led to an ICER of approximately KRW 5 915 198 per QALY gained for BIAsp 30 versus human insulin. Acceptability curve analysis (based on 1000 runs of cohorts of 1000 patients through the model) indicated that, assuming a willingness-to-pay threshold of KRW 25 million per QALY gained (less than gross domestic product per capita on a purchasing power parity basis), there is a 97.5% chance that switching to BIAsp 30 will be cost-effective compared with remaining on human premix insulin. Sensitivity analysis showed that the findings were most sensitive to variations in improvements in hypoglycemia and HbA1c associated with BIAsp 30 treatment.

In addition to the published articles, the literature search identified eight conference abstracts describing cost-effectiveness analyses of switching to BIAsp 30 from biphasic human insulin in the US, Polish, (two) Chinese, Spanish, South Korean, Saudi Arabian and South African settings (Table 3). All of the abstracts identified projected long-term outcomes based on use of the CORE Diabetes Model, and in six of these clinical treatment effects were taken from the PRESENT study (Spain, China, Poland, South Korea, South Africa and Saudi Arabia) with the remaining utilizing clinical data from IMPROVE (US and China). In Spain, China and Poland, switching to BIAsp 30 was associated with improvements in quality-adjusted life expectancy of 1.03, 0.28 and 1.02 QALYs respectively compared with remaining on biphasic human insulin. Switching to BIAsp 30 also reduced direct medical costs compared to biphasic human insulin by EUR 8339 in Spain, CNY 7485 in China and PLN 33 601 in Poland. Therefore, as shown in Table 4, for Spain, China and Poland, switching to BIAsp 30 represented a dominant treatment option (cost and life saving) for patients failing to achieve adequate control with biphasic human insulin based on treatment effects from PRESENT. One abstract corresponded to the publication of Ali *et al.* (described above), one described the Lee *et al.* analysis in South Korea (described above) and the remaining abstract was based on an analysis in the South African setting, and again on use of the CORE Diabetes Model and to project outcomes from PRESENT. In the South African setting, patient characteristics and treatment effects, including a reduction in HbA1c of 1.46%, were based on a sub-cohort of 208 South African patients enrolled in the PRESENT study. Locally derived costs (from the perspective of private healthcare insurers) were captured in the analysis. Projected over a 30-year time horizon, switching to BIAsp 30 after failure with HI was both cost- (reduction of ZAR 33 601) and life-saving (difference 0.39 QALY), and therefore represented a dominant treatment option. In the US analyses based on outcomes from the Canadian subgroup of IMPROVE patients, quality-adjusted life expectancy improved by 0.276 QALYs and direct costs increased by USD 4936. The ICER for switching to BIAsp 30 was USD 17 859 per QALY gained compared to biphasic human insulin in the US setting. Similarly, in the Chinese cost-effectiveness analysis based on outcomes from IMPROVE, treatment with BIAsp 30 was

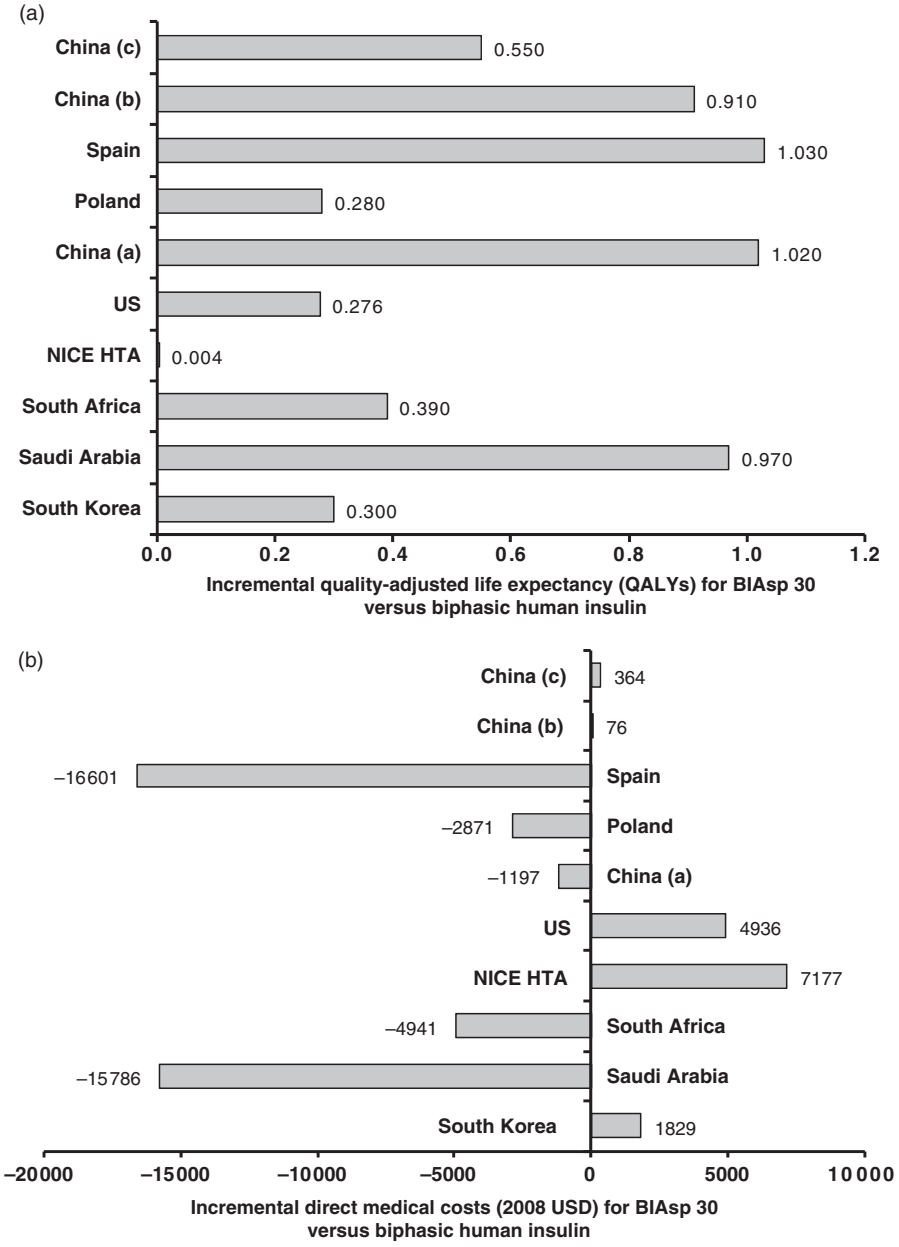

Figure 1. Change in quality-adjusted life expectancy and direct costs (converted to 2008 USD values) for BIAsp 30 versus biphasic human insulin in various country settings.

more costly (increase by CNY 2386) but also associated with improved quality-adjusted life expectancy (by 0.55 QALYs) resulting in an ICER of CNY 4315 per QALY gained. Therefore whilst in all settings investigated treatment with BIAsp 30 was associated with improved quality-adjusted life expectancy, the impact on direct costs varied considerably (Figure 1). Differences in projected outcomes reflect between country differences in the observed treatment efficacy and baseline characteristics of patients as observed in IMPROVE and PRESENT, as well as differences in healthcare costs and practices in the different settings.

Discussion

A single HTA and six peer-reviewed publications were identified and included in the current review of the cost-effectiveness of BIAsp 30 versus other insulins in type 2 diabetes. The HTA was based on meta-analysis of published trial data and, of the published studies, three were based on outcomes from the INITIATE trial of BIAsp 30 versus insulin glargine, and three were based on sub-analyses from the observational PRESENT study of switching patients to BIAsp 30 in routine clinical practice. In brief, the HTA indicated that, although improving

outcomes, premixed analog insulin is unlikely to be cost-effective either versus insulin glargine or biphasic human insulin. In contrast, the published analyses showed that use of BIAsp 30 would be cost-effective versus insulin glargine for insulin naïve patients in the US and UK settings (respective ICERs USD 46 533 and GBP 6951 per QALY gained), and would be a dominant treatment option in Sweden. Similarly, based on data collected in Saudi Arabia and South Korea as part of PRESENT, switching to BIAsp 30 after failing to adequately control glucose levels with human insulin would be a dominant or highly cost-effective treatment option. In addition, it was shown that switching to BIAsp 30 after failure to achieve control with biphasic human insulin would be cost-effective in China assuming a willingness to pay threshold of approximately CNY 100 000, as the estimated ICER was CNY 1926 per QALY gained. In addition to published articles, a number of abstracts were identified that indicated outcomes that can be expected for BIAsp 30 versus insulin glargine or biphasic human insulin, in a variety of country-specific settings. From the abstracts reviewed it was noted that in general terms, and mindful that it is difficult to assess the robustness of this type of publication, BIAsp 30 is likely to be a cost-effective or a dominant treatment option compared with biphasic human insulin in a number of countries in which BIAsp 30 is available. As was shown for the full publications, it is anticipated that these outcomes would be sensitive to the modeled changes in HbA1c and hypoglycemia event rates. Whilst we acknowledge that until full accounts of the abstracts are published it is difficult to fully evaluate these cost-effectiveness studies, they do provide preliminary indications of cost-effectiveness for BIAsp 30 versus other insulins, and in many cases are based on treatment-associated outcomes, costs, and clinical and demographic data obtained directly from the country setting of interest as increasingly requested by decision makers[35].

The difference in outcomes between the UK HTA and the published papers is interesting. Although the potential influence of publication bias cannot be precluded as a factor, it is important to note some key differences in the methodologies applied. Both the UKPDS Outcomes Model (used in the HTA) and the CORE Diabetes Model (used in the published analyses) are widely published and generally well accepted model of diabetes. However, whilst the models share some similarities, in particular the calculation of risk of first cardiovascular events and the evolution of risk factors (such as HbA1c) over time, there are some notable differences which stem from the origins of the respective models. The CORE Diabetes Model was developed as an independent policy analysis tool by a team at the Center for Outcomes Research, Basel, Switzerland and as such uses a range of heterogeneous data sources to make long-term projections of clinical and cost outcomes. It covers a broad range of complications and is very adaptable (in terms of using different approaches or capturing new data). The UKPDS Outcomes Model was built by a team at the University of Oxford with a view to making long-term projections of clinical and cost outcomes based on a single dataset (UKPDS). Whilst this makes the model statistically robust, the main limitations of the model are linked to that dataset, namely only modeling first events and only modeling a select list of seven complications (hypoglycemia, neuropathy, early stages of retinopathy or renal disease, peripheral vascular disease (PVD), foot ulcer and other minor complications are not adequately captured). The limited scope of the input data used in the NICE HTA (HbA1c differences only) compared with the range of effects (e.g. HbA1c, hypoglycemia rates, BMI) used in the published evaluations, and the limited scope of complications modeled in the HTA, are likely to be a key factor in explaining why the cost-effectiveness profile of BIAsp 30 was more positive in the published evaluations than in the HTA. It is also notable that the treatment effects applied in the HTA were based on meta-analysis and those in the published evaluations were not. Using meta-analysis has the obvious advantage of being statistically more robust; however, there is uncertainty as to its applicability in terms of the target population (given that the findings of the meta-analysis in terms of HbA1c change were applied to a completely distinct cohort based on UK-specific data). Moreover, the meta-analysis appeared to be limited to only HbA1c change for the HTA and could potentially have missed some important treatment effects for the cost-effectiveness analysis.

In this paper we reviewed three cost-effectiveness analyses based on BIAsp 30-associated treatment effects observed in the INITIATE trial conducted in the US, the analyses differed only in terms of the country setting. Despite use of country specific data for diabetes management, non-diabetes related mortality and use of country specific rates for discounting of clinical and cost outcomes, the estimated quality-adjusted life expectancy for BIAsp 30 versus insulin glargine was very similar across countries with improvements of 0.19, 0.21 and 0.19 QALY in the UK, Swedish and US settings respectively. However, as a consequence of major differences in the direct cost of healthcare in those settings the estimated ICERs for BIAsp 30 varied considerably, ranging from USD 46 533 per QALY gained in the US to being a dominant treatment option compared to insulin glargine in Sweden. To gain an appreciation of the impact of country setting on outcomes we converted reported incremental costs to a common currency, year 2008 US$ values. It is evident from the approximated ICER values that cost-effectiveness analyses are not transferable between countries. This is illustrated graphically in Figure 1 where incremental quality-adjusted life expectancy and incremental costs

for BIAsp 30 versus human biphasic insulin based on studies identified in the current review are depicted. Nevertheless, it was found that based on commonly accepted willingness to pay thresholds, BIAsp 30 would represent a cost-effective treatment option in all settings investigated in the country-specific analyses identified in the current review, with the possible exception of the UK, given the findings of the NICE HTA discussed above[36].

The question of transferability of economic evaluations across jurisdictions has become an important consideration for decision makers, and as highlighted in this review differences in healthcare costs clearly can have a major impact on cost-effectiveness. In fact, as noted by Drummond *et al.*, there are many reasons why the cost-effectiveness of a given therapy might vary between countries and it is reasonable for national guidelines to request that analyses be relevant to the local context[35]. Whilst multinational trials offer the benefit of rapid patient recruitment and large sample size, it is disputed whether this translates into being 'generalizable' across countries[37]. Conducting rigorous randomized controlled trials in a number of countries would be both logistically and financially prohibitive, therefore cost-effectiveness analyses based on outcomes from large, well-run observational studies such as PRESENT and IMPROVE are likely to represent an important component of the decision making process, complementing analyses based on randomized controlled trials. In the case of BIAsp 30 therapy for patients with type 2 diabetes the amount of suitable data available from randomized controlled trials and observational studies is considerable. As use of BIAsp 30 in type 2 diabetes gains support from clinical experts and patients alike, it is hoped that more detailed accounts of country-specific cost-effectiveness analyses will be published in the future[38].

The dataset identified by this review is not without its limitations. All of the long-term cost-effectiveness analyses published on BIAsp 30 to date have been performed using the CORE Diabetes Model. Whilst the model is adaptable and therefore suited to this type of evaluation, it would have been helpful to have results from other diabetes models and other research groups for purposes of comparison. In addition, the influence of publication bias cannot be ruled out on the dataset identified here as all of the published studies were supported by industry funding. The approach of making long-term projections of clinical and cost outcomes based on short-term trial results is associated with an inherent element of uncertainty. However, in the absence of long-term clinical or epidemiological follow-up data, modeling is a valuable tool that provides us with estimates of long-term clinical and cost outcomes to inform decision making. To succeed in this role, models must be transparent and validated against published clinical and epidemiological data. Both the CORE Diabetes Model and UKPDS Outcomes Model, which have been described in detail in a previous peer-reviewed publication, validated against published data sources and used in reimbursement submissions in several countries, can be considered to meet these criteria.

Additionally, the literature review performed here was limited to those articles published in the English language and as such there may be other cost-effectiveness analyses published in other languages for local journals/country specific meetings that will not have been included in the current review. Furthermore, a potential criticism of the evaluations based on PRESENT and IMPROVE is that they relied on short-term data from an observational study as opposed to a randomized controlled trial to make long-term projections. However, the aim of these cost-effectiveness evaluations was to make an evaluation of the potential value (or otherwise) of treatment with BIAsp 30 versus other insulin regimens in clinical practice. Whilst it can be argued that an observational study provides less-robust data than a randomized controlled trial, it could be countered that observational studies better reflect the real-life situation. The value of randomized controlled trials lies in the ability to establish causal relationships between different regimens and effects. However, these comparisons rely on selected and tightly controlled patient groups. The demonstration of efficacy or effectiveness on a setting where patients are treated under normal clinical conditions is also important, confirming that treatment effects can be achieved in the real-world setting and providing information on likely outcomes in the target population. It could be contended that this type of data may even be more germane to long-term modeling evaluation.

Conclusions

In conclusion, although small in number, published analyses evaluating treatment with BIAsp 30 versus other insulin based regimens show that BIAsp 30 regimens are likely to represent cost-effective treatment options for many type 2 diabetes patients failing to achieve adequate control with current therapies. In contrast, the one HTA that has been published to date concluded that premixed analog insulin is unlikely to be cost-effective in comparison with insulin glargine and biphasic human insulin. Key drivers of cost-effectiveness in the analyses published to date were magnitude of HbA1c change, duration of HbA1c change and reduction of hypoglycemia. A number of clinical studies have provided evidence in terms of HbA1c and hypoglycemia benefits of BIAsp 30 versus other insulins. Long-term follow up studies designed to ascertain the duration of effect in patients with type 2 diabetes would help inform future modeling analysis. It is reassuring to note, however, that even assuming short duration of HbA1c benefit with BIAsp 30 (e.g. 1 year) the analyses published to date support the conclusion of cost-effectiveness.

Published studies have also highlighted the necessity of conducting country-specific evaluations of cost-effectiveness, and this is likely to remain an important avenue of future research.

Transparency

Declaration of funding
This review was supported by a grant from Novo Nordisk A/S, Copenhagen, Denmark.

Declaration of financial/other relationships
J.P.F. and J.W. are current employees of Novo Nordisk. R.P. and W.V. are current employees of Ossian Health Economics and Communications, which has received consulting fees from Novo Nordisk A/S.

The CMRO peer reviewers 1 and 2 have received honoraria for their review work on this manuscript. Both have disclosed that they have no relevant financial relationships.

Acknowledgments
The authors would like to acknowledge and thank Dr Katrina Erny-Albrecht for editorial assistance in the preparation of this manuscript.

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