15 Years of Experience with Biphasic Insulin Aspart 30 in Type 2 Diabetes

Andreas Liebl1 • Viswanathan Mohan2 • Wenying Yang3 • Krzysztof Strojek4 • Sultan Linjawi5

Abstract Since clinical experience with biphasic insulin aspart 30 (BIAsp 30) in type 2 diabetes mellitus (T2DM) was reviewed in 2012 after 10 years of use worldwide, additional studies have been published that highlight new aspects, including use in real-world populations. Evidence from 35 new studies confirms and builds upon previous work indicating that BIAsp 30 continues to have pharmacodynamic and clinical advantages over biphasic human insulin (BHI 30), including in real-world practice with unselected populations of patients. BIAsp 30 has also been shown to be safe and efficacious as an add-on to dipeptidyl peptidase-4 (DPP-4) inhibitors. Intensification with BIAsp 30 is a safe and effective way to improve glycemic control, and titration performed by patients can achieve results that are at least comparable to those when being guided by healthcare providers. Stepwise intensification using BIAsp 30 is comparable to intensification using a basal–bolus regimen, and twice-daily BIAsp 30 provides similar glycemic control to a basal-plus regimen. Data from large observational studies, in particular, have identified patient-related characteristics that are associated with improved clinical responses, suggesting that earlier initiation and intensification of therapy is warranted. Finally, new health-economic analyses continue to confirm that BIAsp 30 is cost effective versus other therapies such as BHI 30, neutral protamine Hagedorn (NPH), or insulin glargine in both insulin-naïve and insulin-experienced patients. After 15 years of clinical use worldwide, analysis of more recent 5-year data indicates that BIAsp 30 remains a safe, effective, and simple-to-use insulin for initiation and intensification by diabetes specialists and primary care physicians in a variety of patients with T2DM.

Key Points

- Evidence from new studies including unselected populations of patients with type 2 diabetes mellitus (T2DM) confirms that BIAsp 30 has advantages over regular human insulin.
- Patients with T2DM can safely and effectively titrate BIAsp 30 to improve glycemic control.
- BIAsp 30 is cost effective versus other insulin therapies in both insulin-naïve and insulin-experienced patients.
1 Introduction

Biphasic insulin aspart 30 (BIAsp 30) was launched internationally in 2002, with the primary advantage of offering the possibility of effectively controlling both postprandial and fasting blood glucose levels with a single, convenient drug while also having the pharmacokinetic (PK) and pharmacodynamic (PD) advantages of an analog-based insulin formulation for people with type 2 diabetes mellitus (T2DM). In 2012, after 10 years of use of BIAsp 30 in millions of patients worldwide, a review co-written by two of the present authors (Liebl, Mohan) described its discovery, structure, PK, and PD and summarized clinical efficacy and safety data, primarily from randomized trials [1]. That review concluded that BIAsp 30 administered once daily (OD) or twice daily (BID) was appropriate for insulin initiation and was a good option for patients wishing to switch from biphasic human insulin (BHI 30). Studies also demonstrated that intensification could be safely achieved by increasing the number of injections up to three times daily (TID). Finally, health-economic analyses also demonstrated that BIAsp 30 was cost effective or dominant versus BHI 30 or insulin glargine (IGlar) in several different healthcare settings.

Since publication of the 10-year review, new studies have been published describing further patient experience with initiation of insulin therapy using BIAsp 30, intensification of therapy, including stepwise, patient-directed titration of BIAsp 30 up to TID, BIAsp 30 as an add-on to dipeptidyl peptidase-4 (DPP-4) inhibitors, and, most recently, evaluation of a new co-formulation of insulin aspart (IAsp) + insulin degludec using BIAsp 30 as the comparator insulin. Much of this new work also includes non-European/non-US populations and describes experience with BIAsp 30 in regular clinical practice from large, multinational, observational studies. This review describes that additional evidence and puts it into context with previous work.

2 Literature Search

We searched PubMed using the following medical subject heading (MeSH) terms: ("insulin aspart, insulin aspart protamine drug combination 30:70" [supplementary concept] OR "insulin aspart, insulin aspart protamine drug combination 30:70"[all fields] OR "biasp 30" [all fields]) AND ("2011/01/01"[PDAT]: "2016/11/01"[PDAT]). 1 January 2011 was chosen to ensure overlap with the search dates for the 10-year review so that no studies would be missed. A total of 66 records were retrieved, with 18 eliminated from this review because they were review articles (n = 7), covered in the previous 10-year review (n = 6), published in a non-English language (n = 2), case reports (n = 2), or not applicable (n = 1). We eliminated 17 papers because they were country-specific substudy reports from the Achiieve observational parent study. Further investigation revealed four additional papers, for a total of 35 relevant papers.

3 Pharmacokinetics and Pharmacodynamics of Biphasic Insulin Aspart 30 (BIAsp 30)

As reviewed previously [1], the PK profile of BIAsp 30 more closely mimics normal physiologically prandial insulin secretion than either BHI 30 or IGlar. With an earlier onset of action, BIAsp 30 can be dosed immediately before or after a meal, providing greater convenience and flexibility for patients than BHI 30, which requires a considerable and variable interval between injection and eating. Its ability to control postprandial glucose means that BIAsp 30 BID also shows a significantly greater glucose-lowering response than IGlar.

Two new studies have used continuous glucose monitoring to more precisely characterize our understanding of the PK/PD of BIAsp 30. One of these trials has directly compared the PK/PD profiles of BIAsp 30 with those of BHI 30. Using a crossover design, subcutaneous tissue glucose (interstitial glucose) was monitored for 48 h in 12 Japanese patients with T2DM who administered either BIAsp 30 or BHI 30 BID [2]. As shown in Fig. 1, mean

![Fig. 1 Average glucose profile during BHI 30 or BIAsp 30 treatment using 48-h continuous glucose monitoring](image-url)

* * *
postprandial glucose was significantly lower with BIAsp 30 than with BHI 30 2–3 h after breakfast, and from 2 through 4 h after dinner. The mean amplitude of glucose excursion (MAGE) was also significantly lower with BIAsp 30 ($p < 0.05$). There were no problems with hypoglycemia with either treatment.

A study from eight centers in China used continuous glucose monitoring to compare glucose fluctuations in patients with T2DM treated with BIAsp 30 TID, continuous subcutaneous insulin infusion (CSII) with IAsp, or IGlar (U100)-based basal–bolus therapy (four injections daily) [3]. This randomized, parallel-group trial enrolled 116 newly diagnosed patients and 127 patients with longstanding diabetes. All had glycated hemoglobin (HbA1c) 9.0–12.0%. Patients randomized to BIAsp 30 administered their insulin before each of the three main meals, whereas those randomized to basal–bolus therapy administered IAsp at each of the three main meals and IGlar at bedtime. The more complicated basal–bolus regimen provided better glucose control with lesser fluctuation in glucose than BIAsp 30 TID in patients with longstanding diabetes. As might be expected, CSII was associated with less fluctuation in glucose than either of the multiple daily injection (MDI) regimens. There was no difference in MAGE between the MDI regimens for newly diagnosed patients, but those with longstanding diabetes experienced more improvement from baseline in MAGE with CSII or basal–bolus therapy administered IAsp at each of the three main meals and IGlar at bedtime.

The more complicated basal–bolus regimen provided better glucose control with lesser fluctuation in glucose than BIAsp 30 TID in patients with longstanding diabetes. As might be expected, CSII was associated with less fluctuation in glucose than either of the multiple daily injection (MDI) regimens. There was no difference in MAGE between the MDI regimens for newly diagnosed patients, but those with longstanding diabetes experienced more improvement from baseline in MAGE with CSII or basal–bolus therapy administered IAsp at each of the three main meals and IGlar at bedtime. BIAsp 30 appeared to achieve comparable decreases from baseline in glucose fluctuations for both newly diagnosed patients and those with longstanding diabetes. No episodes of serious hypoglycemia were recorded in any of the groups, but the time spent in conditions of hypoglycemia (defined as sensor glucose values <3.9 mmol/l) was significantly reduced ($p < 0.01$) after each treatment in patients with newly diagnosed T2DM as well as in those with longstanding T2DM. Furthermore, in the latter group, patients assigned to CSII and glargine basal–bolus therapy spent significantly less time under conditions of hypoglycemia than those using BIAsp 30 TID.

### 4 Initiating Insulin Therapy with BIAsp 30

Progressive deterioration of β-cell function in T2DM means most patients will eventually need to add insulin therapy when they are not achieving satisfactory glycemic control with oral antidiabetic drugs (OADs) in conjunction with dietary and lifestyle adjustments. Insulin-naïve patients may be fearful of injections and worry about the practical burden of therapy [4], but a formulation such as BIAsp 30 can address these concerns by minimizing the number of injections.

#### 4.1 Results of Randomized Controlled Trials

Previous data from randomized trials have shown that BIAsp 30 offers equivalent or better glycemic control than various combinations of OADs, BHI 30, OD IGlar or neutral protamine Hagedorn (NPH) insulin, although weight gain may be somewhat higher with BIAsp 30 than with IGlar [1]. BIAsp 30 offers the advantage of convenience and a lower risk of hypoglycemia compared with a basal–bolus regimen for insulin-naïve patients.

A meta-analysis of five previously published randomized controlled trials (RCTs) involving 1758 patients followed for 24–28 weeks confirmed that BIAsp 30 reduced HbA1c to a greater extent than IGlar (weighted mean difference [WMD] $-0.21$; 95% confidence interval [CI] $-0.35$ to $-0.08$) (Fig. 2) [5]. This analysis also reported that, in two trials, patients using BIAsp 30 had slightly higher weight gain; in one trial, no difference (WMD in gain $1.16$ kg; 95% CI $-0.41$ to 2.74); and in four trials, no increased risk of severe hypoglycemic events (odds ratio [OR] 0.88; 95% CI 0.31–2.53). An analysis of three of the five trials indicated that patients using BIAsp 30 had a greater chance of experiencing at least one adverse event (AE) (60 vs. 53%, OR 1.32; 95% CI 1.02–1.71). Analysis of two trials indicated that the odds of a serious AE were not significantly different (3 vs. 4% of patients, OR 0.92; 95% 0.41–2.07). A similar analysis of data from three of these trials also confirmed a significantly lower prandial glucose increment with BIAsp 30 than with IGlar (WMD $-0.82$ mmol/l; 95% CI $-1.11$ to $-0.52$).

In a randomized, parallel-group, 24-week, treat-to-target trial (EasyMix study), 521 insulin-naïve Japanese and Chinese patients with T2DM that was poorly controlled with OADs were randomized (1:1) to either BIAsp 30 or IGlar U100, each taken OD [6]. OADs were standardized to gliclazide 4 mg/day and metformin 1500 or 2500 mg/day before randomization. Doses of both insulins were titrated to a pre-breakfast fasting plasma glucose (FPG) target of 5.0–6.1 mmol/l using self-measured plasma glucose (SMPG), based on the average of values from three consecutive days prior to visit or contact by phone. Mean HbA1c decreased in both treatment groups at 24 weeks (BIAsp 30: $8.17 \pm 0.88$ to $7.39 \pm 0.83$%; IGlar: $8.14 \pm 0.86$ to $7.49 \pm 0.93$%; treatment difference: $-0.12$% [95% CI $(-0.25$–$-0.02$)] indicating non-inferiority. Approximately 30% of patients in each group achieved HbA1c <7.0%, and there was no significant change in body weight, either from baseline or between groups at end of treatment. The rate of treatment-emergent hypoglycemic episodes was 6.45 episodes/patient-year for BIAsp 30 and 5.28 episodes/patient-year for IGlar, using the American Diabetes Association (ADA) classification. Analysis of a responder subgroup suggested that it might have been possible to adopt a more
aggressive titration schedule for BIAsp 30 without compromising safety, thereby bringing more patients to target.

4.2 Results of Observational Studies

A large body of observational studies, mostly in real-world clinical settings, has provided further evidence for the safety and efficacy of initiating therapy with BIAsp 30 in both insulin-naive and insulin-experienced patients. The efficacy and safety of BIAsp 30 were studied in 1154 insulin-naive patients with T2DM (aged 20–95 years) who initiated therapy in 203 primary care practices in Sweden [7]. HbA1c and FPG improved from 8.8 ± 1.6 to 7.2 ± 1.0% and from 11.7 ± 3.7 to 7.9 ± 1.9 mmol/l, respectively, after 6 months; \( p < 0.001 \) for both (89% completed). Importantly, at 6 months, 49% of patients were at or below an HbA1c target of 7.0%, compared with only 6% of patients prior to starting BIAsp 30. There were only two major hypoglycemic events, and the rate of total events was 4.1 per patient-year, an increase of 0.5 events per patient-year prior to using insulin. Nocturnal events increased from 0.1 to 0.9 events per patient-year. Body weight increased by a mean of 1.5 kg (95% CI 1.2–1.8); \( p < 0.001 \). Most (73%) patients used BIAsp 30 BID, 24% used it only OD, and 3% used it TID.

A similar study was conducted in 496 patients, about half \( (n = 197) \) of whom were insulin-naive, at 81 centers in Finland [8]. HbA1c decreased by −1.4% compared with baseline \( (p < 0.0001) \) among insulin-naive patients and by −1.1% among prior insulin users. Consistent with the Swedish study, half (51%) of insulin-naive patients achieved HbA1c <7% after 26 weeks of treatment, compared with only 10% at baseline. As expected, improvement in the proportion of patients achieving HbA1c <7% was somewhat less marked among prior insulin users (30% at 26 weeks vs. 10% at baseline). The rate of minor hypoglycemic events increased for insulin-naive patients (0.66 to 6.45 events/patient-year; \( p < 0.0001 \)) and for prior insulin users (5.11 to 8.58 events/patient-year; \( p < 0.05 \)). Minor nocturnal events increased in insulin-naive patients but remained low at 26 weeks (0.07–1.25 events/patient-year; \( p < 0.05 \)). There was no significant increase for prior insulin users. Body weight also increased slightly (1.0 kg for insulin-naive patients and 1.3 kg for prior insulin users). At the end of the study, most patients (75.1%) used BIAsp 30 BID, with 8.8% using it only OD and 16.1% TID.

In a shorter study (16 weeks) of 60 insulin-naive patients (55 completed) at six centers in Korea, HbA1c improved from 9.2 to 8.2% \( (p < 0.001) \) [9]. However, only 22% \( (n = 12) \) achieved HbA1c <7.0%. There were 3.4 episodes

---

**Fig. 2** Meta-analysis showing weighted mean difference in glycated hemoglobin (HbA1c) for BIAsp 30 versus IGlar across five randomized controlled trials [5]. BIAsp 30 biphasic insulin aspart 30, BID twice daily, CI confidence interval, IGlar insulin glargine, OD once daily, WMD weighted mean difference. Republished from Rys et al. [5] with permission of John Wiley and Sons Inc.
of minor hypoglycemia per patient-year. Only one episode of severe hypoglycemia was reported. A lack of improvement in post-lunch glycemic control in these comparatively more insulin-deficient Asian patients, and discontinuation of prior OADs, may explain the relatively low number of patients achieving optimal control with BIAsp 30 observed in this study. In addition, whether all patients complied with recommended dose titration was uncertain; therefore, insulin dosing may have been lower than desired.

The safety of BIAsp 30 during the critical period immediately after initiating therapy was evaluated in 2223 patients with T2DM, who were observed for up to 6 days in a hospital setting in Poland. Half (50.2%) of patients were initiating insulin therapy [10]. Only 20 severe hypoglycemic events (i.e. requiring assistance of a third party) were identified overall, with most (13/20) occurring in the first 2 days of treatment. Minor episodes were also uncommon, and more or less evenly divided across the observation period.

IMPROVE was a large (n = 51,430), multinational (11 countries), 26-week, observational study conducted to evaluate safety and efficacy in routine clinical practice in patients initiating insulin therapy or switching from basal insulin or BHI 30 to BIAsp 30 OD, BID, or TID as needed [11]. A subanalysis from the IMPROVE study was conducted to assess predictors of reaching a composite end-point of HbA1c < 7.0% without hypoglycemia 6 months after initiating therapy [12]. Data from 28,696 patients were included in evaluation of this composite endpoint. Lower HbA1c at baseline and shorter duration of diabetes significantly predicted achieving the composite endpoint for all patients (all p < 0.0001). Decreasing body mass index (BMI) was an additional significant predictor for all patients (insulin-naıve and BHI 30, both p < 0.0001; basal insulin, p = 0.0471). A lack of hypoglycemia at baseline was a significant predictor for insulin-naıve patients and patients switching from BHI 30 (both p < 0.0001). Finally, for insulin-naıve patients, being aged > 65 years was also a significant predictor (p < 0.0001). Taken together, these results suggested it is advisable to initiate or optimize treatment as soon as there is evidence that desired glycemic targets are not being reached with current therapies.

Results from the A1chieve observational study have demonstrated that patients with T2DM in real-life practice currently using BHI 30 may benefit from switching to BIAsp 30. The A1chieve study was a large (n > 60,000), multinational, prospective, non-interventional study in which patients starting treatment with BIAsp 30, IAsp, or insulin detemir (IDet) in routine clinical care were followed for 24 weeks [13, 14]. Among the 6323 patients switching from BHI 30 ± OADs to BIAsp 30 ± OADs, there was a significant reduction in HbA1c (1.7%; p < 0.001) as well as decreases in major (from 0.69 to 0.03 events/patient-year) and minor (from 5.31 to 2.04 events/patient-year) hypoglycemic events [15]. Mean overall body weight increased by 0.1 kg, although this varied across countries. Results from 1024 patients switching from basal–bolus regimens to BIAsp 30 were also consistent with these findings [16].

Another observational study in Belgium and Luxembourg followed 592 patients at 12 and 26 weeks after switching from BHI 30 to BIAsp 30, BIAsp 50, or BIAsp 70 [17]. About two-thirds of patients took BIAsp 30 and one-third BIAsp 50, with few patients using BIAsp 70. Overall, HbA1c improved from baseline; at the same time, the incidence of hypoglycemia did not change during the period of observation. However, outcomes were not reported separately for patients using BIAsp 30.

4.3 Combination with Newer Therapies

Drugs of the incretin class represent a newer group of glucose-lowering drugs that have gained in popularity since the introduction of BIAsp 30. However, evidence about their safety and efficacy when combined with BIAsp 30 is scarce. One new randomized, multinational, parallel-group trial has compared strategies for initiating insulin therapy in patients with T2DM poorly controlled with sitagliptin + metformin (Sit2Mix) [18]. In that open-label, 24-week trial, 582 insulin-naıve patients were randomly assigned to either BIAsp 30 OD added to sitagliptin, BIAsp 30 BID added to sitagliptin, or BIAsp 30 BID without sitagliptin. All groups continued to use metformin. After 24 weeks, the reduction in HbA1c was significantly greater in the group administering BIAsp 30 with sitagliptin than in the group using BIAsp 30 OD with sitagliptin (treatment difference: −0.36% [95% CI −0.54 to −0.17]; p < 0.001) as well as versus BIAsp 30 BID without sitagliptin (treatment difference: 0.24% [95% CI 0.06–0.43]; p < 0.01). The proportions of people reaching HbA1c <7% were 59.8, 46.5, and 49.7% for BIAsp 30 BID, BIAsp 30 OD + sitagliptin, and BIAsp 30 BID without sitagliptin, respectively. Postprandial plasma glucose (PPG) was also reduced after breakfast for all patients, as well as in individual regions (p < 0.001 for all). The rate of confirmed hypoglycemic events was 2.24 episodes/patient-year with BIAsp 30 BID, 1.50 episodes/patient-year for BIAsp 30 BID + sitagliptin, and 1.17 episodes/patient-year for BIAsp 30 OD + sitagliptin. Overall, each of the regimens was well tolerated, suggesting that several suitable treatment options are available according to the needs of the patient. The combination of BIAsp 30 with the more widely used modern OAD sitagliptin was deemed safe and effective.

The combination of BIAsp 30 with other modern OADs, namely sodium-glucose cotransporter-2 (SGLT-2) inhibitors, seems to be very attractive and is also increasingly
used in daily practice. No published studies have yet investigated this combination scientifically.

5 Intensification of Therapy

Intensification of therapy is necessary when patients who are already using insulin OD are unable to reach desired HbA1c targets. Several new RCTs have demonstrated the advantages of intensification using BIAsp 30 versus a variety of other comparator insulin intensification regimens, such as basal insulin with multiple stepwise prandial injections [19], basal insulin with a single prandial injection [20], basal insulin alone [6] or with either single or multiple prandial injections [21, 22], or a 50:50 premixed insulin [23]. With the introduction of IDegAsp, a new co-formulation of insulin degludec, a basal insulin with an ultra-long duration of action, plus IAsp as the prandial component, several head-to-head studies have been published using BIAsp 30 as the comparator product [24–27].

Glucose control and safety during intensification with BIAsp 30 were shown to be comparable for BIAsp 30 and a basal-plus regimen using IDet with or without IAsp in an open-label, multicenter, parallel-group, randomized, non-inferiority trial of 50 weeks duration in four African countries [19]. A total of 403 insulin-naïve patients with T2DM were allocated (1:1) to either BIAsp 30 1-2-3 intensification or basal-plus intensification with IDet as the basal insulin and IAsp at mealtimes (IDet + IAsp). Initially, patients randomized to IDet + IAsp began with a single injection of IDet OD at bedtime, whereas patients randomized to BIAsp 30 1-2-3 intensified their therapy as follows: at week 14, if indicated, patients using IDet + IAsp added an injection of IAsp at the largest meal in addition to the basal insulin, whereas patients using BIAsp 30 at dinner added an injection at lunchtime; at week 26, if indicated, patients using IDet + IAsp added an injection at the meal preceding the largest meal, and those using BIAsp 30 added a third injection at breakfast; finally, for those patients requiring intensification at week 38, those in the IDet + IAsp group added a third injection of IAsp at the remaining meal, and those in the BIAsp 30 group continued to administer TID while further optimizing doses. In total, 370 (91.8%) patients completed the trial. At week 50, HbA1c levels were similar in the two groups, demonstrating non-inferiority of IDet + IAsp versus BIAsp 30 1-2-3 (treatment difference: 0.1% [95% CI −0.1 to 0.3]), with comparable proportions of patients in each group achieving HbA1c <7.0% (44.9% with BIAsp 30 1-2-3 and 40.3% with IDet + IAsp) and with similar rates of hypoglycemia (9.4 events/patient-year with BIAsp 30 1-2-3 and 9.8 events/patient-year for IDet + IAsp).

The comparability of intensification with BIAsp 30 with a basal insulin (IGlar) plus a single injection of mealtime insulin (insulin glulisine) was demonstrated in a phase IV randomized parallel-group trial conducted in the UK and Australia (LanScape trial) [20]. In that 24-week trial, 335 patients with T2DM and HbA1c 7.5–11% were randomized (1:1) to either BIAsp 30 BID at breakfast and evening meal or to IGLar OD plus a single injection of insulin glulisine at the largest meal (basal-plus regimen). Insulin doses were titrated weekly in both groups up to week 14, and then once every 2 weeks, following a protocol-specified algorithm. The majority of patients (n = 298 [89%]) completed the study. The upper one-sided 97.5% CI met the non-inferiority margin, with a mean difference of 0.21 ± 0.38%. Slightly more patients using BIAsp 30 achieved HbA1c <7.0%, but the difference was not significant (27.9 vs. 20.7%, respectively; p = 0.12). Similarly, the treatment difference in body weight was not significant (0.44 kg [95% CI 0.37–1.12]; p = 0.20), with a gain of roughly 2 kg in each group. The incidence of hypoglycemia was also similar between treatments (18.2 vs. 15.3 events/patient-year, for BIAsp 30 and basal-plus, respectively), estimated rate ratio 0.84 (95% CI 0.64–1.11; p = 0.22). However, the incidence of nocturnal hypoglycemia was higher with the basal-plus regimen (5.7 vs. 3.6 events/patient-year, rate ratio 1.57 [95% CI 1.08–2.29]; p = 0.019).

Another RCT in 588 patients at 99 sites in the USA who had not used insulin for >1 week in the previous 12 months (mean HbA1c 9.4%) investigated intensification with BIAsp 30 BID with IGLar OD and up to one daily injection of insulin glulisine at mealtimes (G+1) compared with IGLar and up to three daily injections of insulin glulisine at mealtimes [21]. After 60 weeks, HbA1c improved in all three groups (7.2 ± 1.37, 7.1 ± 1.68, and 7.0 ± 1.21%, respectively). Adjusted changes from baseline were not significantly different across groups (−2.0 ± 0.12%, −2.3 ± 0.12%, and −2.4 ± 0.12%, respectively; p > 0.05 for both comparisons). However, the proportion of patients with one or more confirmed hypoglycemic events was 40% higher with BIAsp 30 than with either of the IGlar regimens.

Glycemic control with BIAsp 30 was compared with treatment with IGLar and stepwise intensification with insulin glulisine OD or BID in 161 Korean patients with T2DM poorly controlled with basal insulin alone [22]. Adjusted mean change from baseline at 24 weeks indicated that the basal + prandial intensification regimen was non-inferior to BIAsp 30 (estimate treatment difference −0.09% [95% CI −0.35 to 0.16]). During the initial 12-week titration period, the rate of overall hypoglycemia was lower for BIAsp 30 (p = 0.0020); afterwards, the rate

△ Adis
was not significantly different between the two groups ($p = 0.0871$).

In an open-label, single-center, parallel-group trial, 72 insulin-naïve Japanese patients with T2DM that was poorly controlled with OADs ($\text{HbA}_1\text{c} \geq 8.4\%$) were randomized (1:1) to either BIAsp 30 or insulin lispro 50/50 (Mix50) taken before dinner [23]. At 16 ± 2 weeks, an additional injection was added before breakfast if patients had not achieved $\text{HbA}_1\text{c} < 7.4\%$. A similar adjustment was made at 32 ± 2 weeks at lunchtime for patients not at $\text{HbA}_1\text{c} < 7.4\%$. The cumulative proportion of patients who reached $\text{HbA}_1\text{c} = 7.4\%$ with a single injection at dinner was 36.1% for each formulation. When an additional injection was added before breakfast, 62.9% of patients using BIAsp 30 and 52.8% of those using Mix50 achieved that $\text{HbA}_1\text{c}$ target. The addition of a third injection before lunch brought 66.7% of patients using BIAsp 30 and 72.2% of patients using Mix50 to target. These differences were not statistically significant. There were no severe hypoglycemic episodes in either group.

The pivotal comparison studies for BIAsp 30 versus IDegAsp include two 26-week, randomized, multinational, phase IIIa, treat-to-target, non-inferiority trials, one enrolling a more global population of patients [24] and one focusing specifically on Asian patients [25]. The eligible population for both trials was patients with T2DM that was poorly controlled with pre- or self-mixed insulin administered OD or BID, with or without OADs. Both pivotal RCTs demonstrated non-inferiority for IDegAsp versus BIAsp 30 with respect to $\text{HbA}_1\text{c}$ at 26 weeks [24, 25]. In the trial focusing on Asian patients, the incidence of AEs was 69.5% and 73.0% for IDegAsp and BIAsp 30, respectively, with serious events reported in 8.2% and 8.5% of patients, respectively [25]. In the more global population, IDegAsp was superior to BIAsp 30 with respect to FPG (estimated treatment difference [ETD] $= -1.14 \text{mmol/L} [95\% \text{CI} -1.53$ to $-0.76]; p < 0.001$) [24]. In addition, patients using IDegAsp gained slightly less weight than those using BIAsp 30 (1.7 vs. 2.2 kg, ETD $= -0.62 \text{kg} [95\% \text{CI} -1.15$ to $-0.10]$). Furthermore, there were fewer episodes of confirmed, nocturnal confirmed, and severe hypoglycemia with IDegAsp than with BIAsp 30 in the global population [24]. The rates of confirmed and nocturnal confirmed hypoglycemic episodes were 32% (estimated rate ratio 0.68 [95\% CI 0.52–0.89]; $p = 0.0049$) and 73% (estimated rate ratio 0.27 [95\% CI 0.18 to 0.41]; $p < 0.0001$) lower, respectively, with IDegAsp than with BIAsp 30. Severe hypoglycemic events were infrequent (0.09 vs. 0.25 events per person-year for IDegAsp and BIAsp 30, respectively) and not significantly different. The incidence of AEs was 65.6 versus 63.1% for IDegAsp and BIAsp 30, respectively. However, serious AEs were reported in 19/224 (8.5%) randomized patients using IDegAsp versus in 36/223 (16.1%) randomized patients using BIAsp 30. These results were extended and confirmed in a meta-analysis of data from the two trials [26]. Rates of overall confirmed hypoglycemia and nocturnal confirmed hypoglycemia were statistically significantly lower, by 19% and 57%, respectively, for IDegAsp (estimated rate ratio 0.81 [95\% CI 0.67–0.98]; $p = 0.03$; 0.43 [95\% CI 0.31–0.59], $p < 0.0001$). An analysis of the Japanese subgroup of the Pan-Asian trial was also consistent with results from the main trial [28].

Results of a phase II, open-label, three-arm, randomized, controlled, 16-week, treat-to-target trial in five European countries were consistent with the above findings [27]. With respect to hypoglycemia, patients using IDegAsp had a 58% lower rate of confirmed hypoglycemia than those using BIAsp 30 (rate ratio 0.42 [95\% CI 0.23–0.75]). The reported incidence of AEs was 45% and 55%, for IDegAsp and BIAsp 30 respectively. Two serious AEs were reported for BIAsp 30, but neither was deemed by the investigators to be related to trial product. A shorter (6 weeks) and smaller ($n = 66$) RCT in Japan, in patients previously using either basal insulin (except IGlar) or premix insulin BID (except BIAsp 30), focused on the safety aspects of switching unit-for-unit to IDegAsp versus BIAsp 30 [29]. At the end of the trial, there was no significant difference in mean total daily insulin dose (treatment difference IDegAsp–BIAsp 30, $= -1.4 \text{U} [95\% \text{CI} -3.7$ to $0.08]$). There were no episodes of severe hypoglycemia in either group, and the proportion of patients experiencing confirmed non-severe episodes was similar (57.6% for IDegAsp, 59.4% for BIAsp 30). The number of patients experiencing non-severe nocturnal confirmed hypoglycemia was low (1–2 events per patient-year) and similar between groups (rate ratio 0.49 U [95\% CI 0.10–2.38]).

The differences in favor of IDegAsp described above are not unexpected given that BIAsp 30 exhibits an initial insulin peak with a shoulder effect and gradual decline due to the overlapping of the two forms of IAsp (30% soluble and 70% protaminated), whereas IDegAsp has a clearer separation of the prandial and basal components, resulting in a more distinct mealtime peak because it includes only the soluble form of IAsp. In addition, the novel basal component in IDegAsp leads to flatter and more consistent insulin levels for patients. Given the lower cost associated with a newer product. In any case, treatment should be individualized and account for these factors.

The use of injectable incretins (glucagon-like peptide-1 receptor agonists [GLP-1-RAs]) has recently been encouraged by current guidelines, both as early diabetes therapy and as intensification in combination with different insulin therapies. These regimens have been adopted
widely in daily practice, but no studies have been published on the use of BIAsp 30 in combination with or compared with GLP-1-RAs.

6 Patient-Directed Self-Titration

Titration is key to effective intensification of therapy, and the value of SMPG and patient-directed titration of insulin dose has been established for type 1 diabetes mellitus [30, 31]. Studies have demonstrated the effectiveness of patient-driven titration in T2DM using formulations other than BIAsp 30 [32, 33]. Here, we report the results of studies demonstrating the safety and efficacy of patient-directed titration to improve blood glucose control using BIAsp 30.

The efficacy of patient-directed versus physician-directed titration using BIAsp 30 was investigated in a multinational, randomized, parallel-group, non-inferiority trial involving 33 sites in five countries across the globe (SimpleMix) [34]. In that 20-week, open-label trial, patients with T2DM currently being treated with a basal insulin analog (for at least 3 months) and with HbA1c 7.0–10.0% were randomized into either patient-driven or investigator-driven titration groups. Although mean HbA1c declined in both groups after treatment, the decrease was slightly greater in the investigator-driven group than in the patient-driven group (−0.97 vs. −0.72%; treatment difference 0.25% [95% CI 0.04–0.46]). Because the upper limit exceeded the pre-specified non-inferiority margin (0.4%), non-inferiority was not met. In addition, significantly fewer patients in the patient-driven group reached HbA1c targets of <7.0% (28.7 vs. 38.5%; p = 0.032) or ≥6.5% (12.1 vs. 20.7%; p = 0.023), as well as reaching these targets without hypoglycemia (19.5 vs. 28.2%, p = 0.042; and 8.0 vs. 16.1%, p = 0.018, respectively). There were no significant differences in rate of hypoglycemia (rate ratio 0.77 [95% CI 0.54–1.09]); however, subjects in the patient-directed titration group did gain more weight than those in the investigator-driven group (1.6 vs. 0.9 kg, treatment difference 0.72%; treatment difference 0.05% [95% CI −0.54 to 0.08]). Numerically greater proportions of patients achieved HbA1c <7.0% and ≤6.5% with patient-driven titration, but the differences with physician-driven titration were not statistically significant. Similar results were observed when comparing incidence of hypoglycemia between the two groups.

7 BIAsp 30 in Special Populations

A few new studies have examined the efficacy and safety of BIAsp 30 in special populations (i.e. patients not typically included in clinical trials conducted for regulatory purposes). In one pilot study, BIAsp 30 was compared with premixed human insulin in gestational diabetes mellitus (GDM) [38]. A total of 76 women with GDM and mean gestation of ~23 weeks at entry were randomized (1:1) to either BIAsp 30 or premixed human insulin, and maternal efficacy and safety, along with fetal and perinatal outcomes, were assessed. HbA1c was nearly the same between the groups (5.98 and 6.04, for BIAsp 30 and premixed human insulin, respectively; p > 0.05), and no maternal hypoglycemic events or adverse perinatal outcomes were reported. Fewer babies were born with birth weight >90th percentile in the women using BIAsp 30 (6.8 vs. 9.2% for BIAsp 30 and premixed human insulin, respectively), but the proportion with macrosomia was not significantly different (p = 0.819).

The effect of race (White vs. Black/African-American) or ethnicity (Hispanic/Latino vs. non-Hispanic/Latino) on efficacy and safety of BIAsp 30 was explored in a post hoc analysis of the INITIATEplus trial [39]. The parent trial was conducted to compare differences in efficacy and safety according to three different levels of dietary

△ Adis
counseling to which subjects were randomized. Results showed that glycemic control in all groups improved to a similar extent, with HbA1c decreasing by 2.4–2.6% after 24 weeks and decreases in FPG also being similar (141–146 mg/dl). All groups showed comparable increases in mean body weight (2.69–3.19 kg). Hypoglycemia rates varied somewhat and ranged from 0.30 to 0.60 minor events and from 0.03 to 0.08 major events per patient-year. However, the trial was neither designed nor powered to detect statistically significant differences among racial or ethnic groups, and subjects were not stratified according to prior diabetes treatments.

8 Predictors of Response to Therapy

A key advantage of BIAsp 30 over many other diabetes treatments is the targeting of postprandial glucose in addition to fasting glucose levels. However, patient-related factors that influence the degree of postprandial response with BIAsp 30 have not been previously reported. IMPROVE was a prospective, 6-month study of patients initiating therapy with BIAsp 30 in routine clinical practice in eight countries in Europe and Asia. A subanalysis of data from 52,419 patients in the IMPROVE study was conducted to determine whether certain factors could predict a postprandial response [40]. One of the strongest predictors was high PPG at baseline; other predictors included lower BMI, FPG, and HbA1c at baseline, older age, and shorter duration of diabetes (all \( p < 0.0001 \)). However, despite these predictors of a greater response, patients were able to reduce their PPG levels regardless of their baseline characteristics. Another analysis looked at predictors of a composite endpoint of treatment success in the IMPROVE trial (i.e. HbA1c \(<8\%\) without experiencing hypoglycemia), which included 28,696 patients [12]. Those results indicated that patients with lower baseline HbA1c (\(\leq 8\%\)), shorter duration of diabetes (<5 years), and no incidence of either major hypoglycemia within 13 weeks prior to the trial or minor hypoglycemia within 4 weeks prior to the trial were associated with treatment success.

9 Cost Effectiveness

Health-economic analyses take into account the direct and indirect costs of a particular treatment in light of the clinical benefits accrued. Thus, a new drug or procedure may have higher medication costs than a previous/comparator treatment, but in the long term, may be very cost effective because of either increased efficacy or reduced incidence of complications. The first health-economic analyses of BIAsp 30 (reviewed in Liebl et al. [1]) simulated cost effectiveness over a 35-year horizon and were performed using data mostly from the INITIATE trial, a 28-week, randomized, parallel-group study that investigated BIAsp 30 + OADs compared with IGlar + the same OADs. Analyses were done for US, Chinese, Swedish, and UK settings, and BIAsp 30 was shown to be cost effective versus IGlar in the USA and the UK. Other studies also reviewed indicated that BIAsp 30 was cost effective versus BHI 30 in South Korea and the USA and was dominant over BHI 30 in Saudi Arabia.

New studies evaluating cost effectiveness are shown in Table 1. One analysis used data from a subset of patients from India, Indonesia, and Saudi Arabia participating in A1chieve and showed that patients were able to obtain improvements in glycemic control without clinically important problems with hypoglycemia or weight gain and with improvements in quality of life [41]. The economic impact of switching from BHI 30, IGlar, or NPH insulin was projected over a 30-year horizon, and the impact on quality of life was projected over 1 year. BIAsp 30 was projected to be cost effective versus the other treatments over both the short (1 year) and long (30 years) term in insulin-naïve [42] and insulin-experienced patients [43].

The cost effectiveness of BIAsp 30 versus NPH insulin + regular human insulin for insulin-naïve patients with poorly controlled T2DM was estimated in a single-center RCT in Iran [44]. Direct and indirect costs were estimated over 48 weeks of treatment. Although BIAsp 30 was more expensive, treatment with BIAsp 30 was found to be cost saving versus NPH insulin + regular human insulin (the incremental cost-effectiveness ratio [ICER] indicated that BIAsp 30 was dominant). Contributing to the cost effectiveness of BIAsp 30 was a lower rate of hypoglycemic events despite equivalent glycemic control.

One final analysis examined the cost effectiveness in Denmark of IDegAsp using BIAsp 30 as the comparator [45]. As the source data were from treat-to-target trials in which insulin was titrated to achieve similar HbA1c between the groups, a short-term model was deemed more appropriate for evaluating the influence of secondary endpoints such as hypoglycemia, body weight, and insulin dose on cost effectiveness. IDegAsp was determined to be cost effective versus BIAsp 30, mainly due to a reduction in severe hypoglycemia.

10 Quality of Life

In the A1chieve study, health-related quality of life measured with a visual analog scale (VAS) was significantly improved after switching to BIAsp 30 from basal–bolus regimens using either IGlar or NPH insulin as the basal insulin [16]. At 24 weeks, VAS scores for those switching from IGlar to BIAsp 30 increased from 70.6 ± 14.4 to 76.5 ± 12.7 (\( p < 0.001 \)) and
increased from 64.7 ± 17.6 to 76.4 ± 13.3 (p < 0.001) for those switching from NPH insulin, with 0 = worst and 100 = best imaginable health state. Also in the A1chieve study, quality of life improved for patients switching to BIAsp 30 from BHI 30, again using the VAS, from a mean ± standard deviation (SD) of 64.0 ± 16.3 at baseline to 76.5 ± 11.9 at the end of the study [15].

11 Conclusion

Studies published since the prior review have confirmed using continuous glucose monitoring that BIAsp 30 has a more favorable PD effect than BHI 30 [2] and fewer glucose fluctuations than a basal–bolus regimen [3]. Results from the large, prospective, multinational A1chieve study have expanded on results from previously reported RCTs and have shown that patients in real-life clinical practice using BHI 30 can realize clinical benefit from switching to BIAsp 30 [15, 17] as well as improvements in quality of life [15, 16]. Also consistent with previous work are several studies demonstrating that BIAsp 30 is safe and effective when used in insulin-naïve patients in primary care practice [7–9].

BIAsp 30 administered OD or BID with sitagliptin has been shown to have statistically significant advantages over BIAsp 30 alone when initiated in insulin-naïve patients [18]. Thus, BIAsp 30 can be combined safely and effectively with the popular modern OAD sitagliptin [6, 19, 23]. Insulin therapies using BIAsp 30 compare favorably to intensification with an IGlar® insulin glulisine basal-plus regimen [20]. New studies have shown that patient-directed titration is feasible [35, 36], although it might not always be quite as effective as the more complicated and costly physician-driven process [34].

Head-to-head studies of the new co-formulation IDeg-Asp versus BIAsp 30 have demonstrated non-inferiority in glycemic control (HbA1c) versus BIAsp 30 [24, 25], with the main advantage of the new co-formulation in the more global population being a statistically significant reduction in incidence of nocturnal hypoglycemia and a lower total insulin dose [24], as to be expected from the unique PK

### Table 1 Cost effectiveness of biphasic insulin aspart 30

| Health-economic study | Clinical data source | Country setting | Health-economic model, time horizon | Study endpoint summary |
|-----------------------|----------------------|----------------|------------------------------------|------------------------|
| BIAsp 30 in insulin-naïve patients | A1chieve observational study [41] | India, Indonesia, Saudi Arabia, Algeria, Tunisia, Morocco | IMS CORE Diabetes model, 30 years and 1 year | Switching to BIAsp 30 was cost effective in both the long and short term across all country settings |
| Switching to BIAsp 30 from other insulin | A1chieve observational study [41] | India, Indonesia, Saudi Arabia | IMS CORE Diabetes model, 30 years and 1 year | Switching to BIAsp 30 was cost effective in both the long and short term across all country settings |
| Switching to BIAsp 30 from basal–bolus therapy | RCT | Iran | Direct and indirect costs estimated, 48 weeks | Treatment with BIAsp 30 had significantly higher QALYs (p = 0.011). ICER dominant for BIAsp 30 |
| BIAsp 30 vs. IDegAsp | Intensify Premix 1 [24] and Intensify All [25], both RCTs | Denmark | Short-term model, 5 years | Cost effectiveness driven mainly by reduction in severe hypoglycemia |

BHI 30 biphasic human insulin 30, BIAsp 30 biphasic insulin aspart 30, BID twice daily administration, DKK Danish Kroner, ICER incremental cost-effectiveness ratio, IDegAsp co-formulation of insulin degludec + insulin aspart, IGlar insulin glargine, NPH neutral protamine Hagedorn, OAD oral antidiabetic drug, QALY quality-adjusted life-year, RCT randomized controlled trial, T2DM type 2 diabetes mellitus
data of IDeGAsp. A lower risk of overall confirmed hypoglycemia, nocturnal confirmed hypoglycemia, and severe hypoglycemia for IDeGAsp versus BIAsp 30 was also demonstrated in a meta-analysis [26].

Large observational studies have also facilitated new analyses, which have indicated that certain patient-related factors are associated with clinical response to BIAsp 30 (e.g. lower HbA1c at baseline, shorter duration of diabetes, lower BMI, and lack of history of hypoglycemia) [12]. These results reinforce the value of initiating or optimizing treatment sooner rather than later in patients not reaching desired glycemic targets. Finally, new health-economic studies are also in line with previous work and now demonstrate that, projected over a 30-year horizon, BIAsp 30 is cost effective versus BHI 30, NPH insulin, or IGlar (in India, Saudi Arabia, and Indonesia) for both insulin-naïve [42] and insulin-experienced [43] patients.

In summary, after 15 years of clinical use worldwide, including more recent data, BIAsp 30 remains a safe, effective, and simple-to-use insulin for initiation and intensification by diabetes specialists and primary care physicians. It is also safe and effective for different patient groups and in combination with different and some newer OADs. Finally, BIAsp 30 is cost effective and a good choice for early initiation of insulin in T2DM.

Acknowledgements Medical writing and submission support were provided by Gary Patronek and Helen Marshall of Watermeadow Medical, an Ashfield company, part of UDG Healthcare plc, funded by Novo Nordisk. Novo Nordisk also reviewed the manuscript for medical accuracy.

Compliance with Ethical Standards

Conflicts of interest AL has received funding for membership on Novo Nordisk and Eli Lilly advisory boards and/or consulting services and for lectures from Novo Nordisk, Eli Lilly, Sanofi, Boehringer-Ingelheim, AstraZeneca, Roche, and MSD. VM has received research grants and honoraria from Novo Nordisk, Sanofi, MSD, Johnson & Johnson, and Eli Lilly and lecture fees from Novo Nordisk. WY has attended advisory boards and been a speaker for Novo Nordisk. KS has received honoraria for speaking engagements from Eli Lilly, Novo Nordisk, Sanofi-Aventis, Servier, Boehringer-Ingelheim, and Polfa-Tarchomin and has participated in clinical trials for AstraZeneca, PZifer, and A Mengen. SL has received funding for advisory activities from Novo Nordisk and for speaker activities from Novo Nordisk, Novartis Pharma AG, Roche Pharmaceuticals, and AstraZeneca Pharmaceuticals LP.

Open Access This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/), which permits any noncommercial use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Liebl A, Prusty V, Valensi P, Kawamori R, Christiansen JS, Palmer AJ, et al. Ten years of experience with biphasic insulin aspart 30: from drug development to the latest clinical findings. Drugs. 2012;72:1495–520.
2. Ohta A, Suwa T, Sada Y, Kato H, Koganei R, Asai S, et al. Comparison of daily glucose excursion by continuous glucose monitoring between type 2 diabetic patients receiving biphasic insulin aspart 30 or biphasic human insulin 30. J Diabetes Investig. 2011;2:406–11.
3. Li FF, Fu LY, Zhang WL, Su XF, Wu JD, Sun J, et al. Blood glucose fluctuations in type 2 diabetes patients treated with multiple daily injections. J Diabetes Res. 2016;2016:1028945.
4. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. Diabetes Care. 2013;36:3411–7.
5. Rys P, Wojciechowski P, Siejka M, Malecki P, Hak L, Malecki MT. A comparison of biphasic insulin aspart and insulin glargine administered with oral antidiabetic drugs in type 2 diabetes mellitus—a systematic review and meta-analysis. Int J Clin Pract. 2014;68:304–13.
6. Yang W, Xu X, Liu X, Yang G, Seino Y, Seino S, et al. Treatment to target comparison between once daily biphasic insulin aspart 30 and insulin glargine in Chinese and Japanese insulin-naïve subjects with type 2 diabetes. Curr Med Res Opin. 2013;29:1599–608.
7. Berntorp K, Haglund M, Larsen S, Petrucevitch A, Landin-Olsson M; Swedish BIAsp Study Group. Initiation of biphasic insulin aspart 30/70 in subjects with type 2 diabetes mellitus in a largely primary care-based setting in Sweden. Prim Care Diabetes. 2011;5:89–94.
8. Makelä JK, Schmiöser C, Askonen K, Sulkkonen T. Starting or switching to biphasic insulin aspart 30 (BIAsp 30) in type 2 diabetes: a multicenter, observational, primary care study conducted in Finland. Diabetes Res Clin Pract. 2012;95:10–8.
9. Song KH, Kim JM, Noh JH, Park Y, Son HS, Min KW, et al. Efficacy and safety of biphasic insulin aspart 30/70 in type 2 diabetes suboptimally controlled on oral antidiabetic therapy in Korea: a multicenter, open-label, single-arm study. Diabetes Metab J. 2013;37:117–24.
10. Wolnik B, Hak L. Multicenter, open-label, non-randomized, non-interventional observational study of safety of treatment initiation with a biphasic insulin aspart. Expert Opin Drug Saf. 2013;12:137–44.
11. Kawamori R, Valensi P. IMPROVE™ observational study of biphasic insulin aspart 30/70 in patients with type 2 diabetes mellitus. Expert Rev Endocrinol Metab. 2010;5:507–16.
12. Valensi P, Shaban J, Benroubi M, Kawamori R, Borzi V, Shah S, et al. IMPROVE Study Expert Panel. Predictors of achieving HbA1c <7% and no hypoglycemia 6 months after initiation of biphasic insulin aspart 30 in patients with type 2 diabetes in the IMPROVE study. Curr Med Res Opin. 2013;29:601–9.
13. Home P, Naggar NE, Khamseh M, Gonzalez-Galvez G, Shen C, Chakkwar P, et al. An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: The Alchieve study. Diabetes Res Clin Pract. 2011;94:352–63.
14. Shah SN, Litwak L, Haddad J, Chakkwar PN, Hajjaji I. The Alchieve study: a 60 000-person, global, prospective, observational study of basal, meal-time, and biphasic insulin analogs in daily clinical practice. Diabetes Res Clin Pract. 2010;88(Suppl. 1):S11–6.
15. El Naggar NK, Soewondo P, Khamseh ME, Chen JW, Haddad J. Switching from biphasic human insulin 30 to biphasic insulin aspart 30 in type 2 diabetes is associated with improved glycaemic control and a positive safety profile: results from the Alchieve study. Diabetes Res Clin Pract. 2012;98:408–13.

16. Dieuzeide G, Chuang LM, Almaghamsi A, Zilov A, Chen JW, Lavalle-González FJ. Safety and effectiveness of biphasic insulin aspart 30 in people with type 2 diabetes switching from basal-bolus insulin regimens in the Alchieve study. Prim Care Diabetes. 2014;8:111–7.

17. Nobels F, D’Hooge D, Crenlier L. Switching to biphasic insulin aspart 30/50/70 from biphasic human insulin 30/50 in patients with type 2 diabetes in normal clinical practice: observational study results. Curr Med Res Opin. 2012;28:1017–26 (Erratum in: Curr Med Res Opin. 2012;28:1546).

18. Linjawi S, Sothiratnam R, Sari R, Andersen H, Hiort LC, Rao P. The study of once- and twice-daily biphasic insulin aspart 30 (BIAsp 30) with sitagliptin, and twice-daily BIAsp 30 without sitagliptin, in patients with type 2 diabetes uncontrolled on sitagliptin and metformin-The Sti2Mix trial. Prim Care Diabetes. 2015;9:370–6.

19. Malek R, Ajili F, Assaad-Khalil SH, Shinde A, Chen JW, Van der Berg E. Similar glucose control with basal-bolus regimen of insulin detemir plus insulin aspart and thrice-daily biphasic insulin aspart 30 in insulin-naive patients with type 2 diabetes: Results of a 50-week randomized clinical trial of stepwise insulin intensification. Diabetes Metab. 2015;41:223–30.

20. Vora J, Cohen N, Evans M, Hockey A, Speight J, Whately-Smith C. Intensifying insulin regimen after basal insulin optimization in adults with type 2 diabetes: a 24-week, randomized, open-label trial comparing insulin glargine plus insulin glulisine with biphasic insulin aspart (LanScape). Diabetes Obes Metab. 2015;17:1133–41.

21. Riddle MC, Rosenstock J, Vlajnic A, Gao L. Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. Diabetes Obes Metab. 2014;16:396–402.

22. Jin SM, Kim JH, Min KW, Lee JH, Ahn KJ, Park JH, et al. Basal-bolus versus premixed insulin in patients with type 2 diabetes requiring insulin intensification after basal insulin optimization: a 24-week randomized non-inferiority trial. J Diabetes. 2016;8:405–13.

23. Domeki N, Matsunaga M, Monden T, Nakatani Y, Aso Y. A randomized, controlled step-up treatment with premixed insulin lispro 50/50 vs. aspart-70/30 in patients with type 2 diabetes mellitus. Diabetes Ther. 2014;5:403–13.

24. Fulcher GR, Christiansen JS, Bantwal G, Polaszewska-Muzynska M, Mersebach H, Andersen TH, et al. BOOST: Intensify Premix 1 Investigators. Comparison of insulin degludec/insulin aspart and biphasic insulin aspart 30 in uncontrolled, insulin-treated type 2 diabetes: a phase 3a, randomized, treat-to-target trial. Diabetes Care. 2014;37:2084–90.

25. Kaneko S, Chow F, Choi DS, Taneda S, Hirao K, Park Y, et al. BOOST: Intensify All Trial Investigators. Insulin degludec/insulin aspart versus biphasic insulin aspart 30 in Asian patients with type 2 diabetes inadequately controlled on basal or pre-/self-mixed insulin: a 26-week, randomised, treat-to-target trial. Diabetes Res Clin Pract. 2015;107:139–47.

26. Christiansen JS, Niskanen L, Rasmussen S, Johansen T, Fulcher G. Lower rates of hypoglycemia during maintenance treatment with insulin degludec/insulin aspart versus biphasic insulin aspart 30: a combined analysis of two Phase 3a studies in type 2 diabetes. J Diabetes. 2016;8:720–8.

27. Niskanen L, Leiter LA, Franek E, Weng J, Damci T, Muñoz-Torres M, et al. Comparison of a soluble co-formulation of insulin degludec/insulin aspart vs biphasic insulin aspart 30 in type 2 diabetes: a randomised trial. Eur J Endocrinol. 2012;167:287–94 (Erratum in: Eur J Endocrinol. 2012;167:453).

28. Taneda S, Hyllested-Winge J, Gall MA, Kaneko S, Hirao K. Insulin degludec/insulin aspart versus biphasic insulin aspart 30 twice daily in insulin-experienced Japanese subjects with uncontrolled type 2 diabetes: subgroup analysis of a pan-Asian, treat-to-target phase 3 trial. J Diabetes. 2017;9:243–7.

29. Onishi Y, Yamada K, Zacho J, Ekelund I, Iwamoto Y. Insulin degludec/insulin aspart vs biphasic insulin aspart 30 twice daily in Japanese patients with type 2 diabetes: a randomized controlled trial. J Diabetes Invest. 2017;8:210–7.

30. American Diabetes Association. Standards of medical care in diabetes. 2016. http://care.diabetesjournals.org/content/suppl/2015/12/21/39.Supplement_1.DC2/2016-standards-of-care.pdf. Accessed 06 Jul 2017.

31. International Diabetes Federation Clinical Guidelines Task Force. Global guideline for type 2 diabetes. 2012. https://www.idf.org/e-library/guidelines/79-global-guideline-for-type-2-diabetes.html. Accessed 06 Jul 2017.

32. Davies M, Storms F, Shutter S, Bianchi-Biscay M, Gomis R; ATLANTUS Study Group. Improvement of glycemie control in subjects with poorly controlled type 2 diabetes. Comparison of two treatment algorithms using insulin glargine. Diabetes Care. 2005;28:1282–8.

33. Meneghini L, Koenen C, Weng W, Selam JI. The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes. Results of the randomized, controlled PREDICTIVE 303 study. Diabetes Obes Metab. 2007;9:902–13.

34. Gao Y, Luquez C, Lynggaard H, Andersen H, Saboo B. The SimpleMix study with biphasic insulin aspart 30: a randomized controlled trial investigating patient-driven titration versus investigator-driven titration. Curr Med Res Opin. 2014;30:2483–92.

35. Yang W, Zhu L, Meng B, Liu Y, Wang W, Ye S, et al. Subject-driven titration of biphasic insulin aspart 30 twice daily is non-inferior to investigator-driven titration in Chinese patients with type 2 diabetes inadequately controlled with premixed human insulin: a randomized, open-label, parallel-group, multicenter trial. J Diabetes Invest. 2016;7:85–93.

36. Narita T, Goto T, Suganuma Y, Hosoba M, Morii T, Sato T, et al. Efficacy and safety of patient-directed titration of once-daily pre-dinner premixed biphasic insulin aspart 70/30 injection in Japanese type 2 diabetic patients with oral antidiabetic drug failure: STEP-AKITA study. J Diabetes Invest. 2011;2:63–70.

37. Chraibi A, Al-Herz S, Nguyen BD, Soeatmadji DW, Shinde A, Lakshminikarabam B, et al. An RCT investigating patient-driven versus physician-driven titration of BIAsp 30 in patients with type 2 diabetes uncontrolled using NPH insulin. Diabetes Ther. 2017;8:767–80. Erratum in: Diabetes Ther. 2017;8:781–2.

38. Balaji V, Balaji MS, Alexander C, Srinivasan A, Suganthi SR, Thiagarajah A, et al. Premixed insulin aspart 30 (BIAsp 30) versus premixed human insulin 30 (BHI 30) in gestational diabetes mellitus: a randomized open-label controlled study. Gynecol Endocrinol. 2012;28:529–32.

39. Tripepe BS, Shepherd MD, Couller FC, Bhargava A, Brett J, Chu PL, et al. Efficacy and safety of biphasic insulin aspart 70/30 in type 2 diabetes patients of different race or ethnicity (INITIAteplus trial). Curr Med Res Opin. 2012;28:1203–11.

40. Borzi V, Benroubi M, Gumprecht J, Kawamori R, Ligthelm R, Shaban J, et al. IMPROVE TM Study Expert Panel. Predictors of postprandial blood glucose response to biphasic insulin analogue therapy. Prim Care Diab. 2013;7:63–7.

41. Shah S, Zilov A, Malek R, Soewondo P, Bech O, Litwak L. Improvements in quality of life associated with insulin analogue...
therapies in people with type 2 diabetes: results from the A1chieve observational study. Diabetes Res Clin Pract. 2011;94:364–70.

42. Shafie AA, Gupta V, Baabbad R, Hammerby E, Home P. An analysis of the short- and long-term cost-effectiveness of starting biphasic insulin aspart 30 in insulin-naïve people with poorly controlled type 2 diabetes. Diabetes Res Clin Pract. 2014;106:319–27.

43. Gupta V, Baabbad R, Hammerby E, Nikolajsen A, Shafie AA. An analysis of the cost-effectiveness of switching from biphasic human insulin 30, insulin glargine, or neutral protamine Hagedorn to biphasic insulin aspart 30 in people with type 2 diabetes. J Med Econ. 2015;18:263–72.

44. Farshchi A, Aghili R, Oskuee M, Rashed M, Noshad S, Kebri-aezadeh A, et al. Biphasic insulin aspart 30 vs. NPH plus regular human insulin in type 2 diabetes patients; a cost-effectiveness study. BMC Endocr Disord. 2016;16:35.

45. Evans M, Gundgaard J, Hansen BB. Cost-effectiveness of insulin degludec/insulin aspart versus biphasic insulin aspart in patients with type 2 diabetes from a Danish health-care perspective. Diabetes Ther. 2016;7:809–23.