

# Biphasic Insulin Aspart 30: Premix Analogue for Initiating Insulin Therapy in Type 2 Diabetes



Malcolm Natrass

## Abstract

Intensive therapy to achieve glycemic target has become the standard of care in management of patients with type 2 diabetes mellitus (DM). This approach has been predicted to reduce the occurrence of long term diabetic complication and can be achieved only with early and aggressive use of insulin. The most acceptable choice will be a regimen which mimics physiologic pattern of insulin secretion from healthy pancreatic  $\beta$ -cells. This can be fulfilled by using a premix insulin regimen. However, considerable variability has been found in onset and duration of action, as well as peak insulin levels, with premixed human insulin. Therefore, premixed insulin analogues have been developed to more closely mimic physiological endogenous insulin secretion and meet the needs of patients. BIAsp 30 is a new premix analogue containing 30 % insulin aspart (rapid acting component) and 70% protaminated insulin aspart (intermediate acting component). It has been shown to have better post prandial and overall glycemic control than premix human insulin (BHI 30), lispro Mix 25 or neutral protamine Hagedorn (NPH) & insulin glargine in several randomised control trials. Moreover, compared with BHI 30, the reduction in mean daily blood glucose with BIAsp 30 is achieved with fewer hypoglycaemic events. Significant proportion of patients have achieved glycosylated hemoglobin target of <7%, even with once daily start in combinations with OADs. Thus it has proved to be a better choice for insulin initiation in type 2 diabetic patients. Also, therapy with BIAsp 30 can be intensified to twice and thrice daily in patients not achieving the targeted glycemic control. Its unique pharmacokinetic profile offers patients flexibility with regard to injection time, as efficacy is maintained even if injection is delayed 15 minutes after the start of a meal. Also availability of NovoMix 30 in FlexPen<sup>®</sup>, its precise and discreet delivery device, make its administration simple, easy and more acceptable to the patients.

Key words: type 2 diabetes, insulin analogue, premixed human insulin, biphasic insulin aspart, post prandial glycemia, hypoglycemia

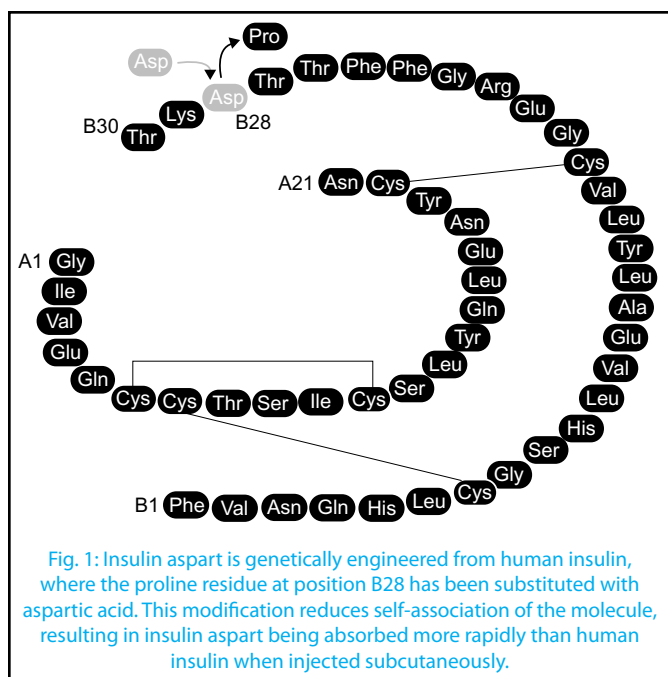
## Introduction

The last two decades have seen an explosive increase in the number of people with diabetes globally due to changes in lifestyle and genetic predisposition.<sup>1,2</sup> Patients with diabetes mellitus have an impaired capacity to regulate blood glucose. In type 1 diabetes, autoimmune destruction of pancreatic beta cells results in a diminished and rapidly absent ability to produce insulin. With type 2 diabetes, the disease is progressive, typically starting with peripheral insulin resistance. In the early disease state, the first phase of the prandial insulin response is lost, resulting in hyperglycaemia. A compensatory mechanism may be initiated in the form of increased insulin production during the second stage of the prandial insulin response. This hyperinsulinaemia, however, serves only to exacerbate insulin resistance. The inability of beta cells to maintain this over-production of insulin results in a reduced prandial insulin response and subsequent postprandial hyperglycaemia,<sup>3,4</sup> a pre-diabetic state called impaired glucose tolerance (IGT). Many of these patients will develop clinical diabetes, in which fasting blood glucose becomes chronically raised, and postprandial glucose (PPG) becomes elevated to as much as three-times normal values.<sup>5</sup>

The percentage of glycated haemoglobin type A<sub>1c</sub> (% HbA<sub>1c</sub>) represents a 2–3 month average of overall blood glucose control, which is a reflection of both fasting and prandial blood glucose. There is growing evidence that hyperglycaemia is associated with microvascular & macrovascular complications,<sup>6–8</sup> and tight glycaemic control has been shown in type 1 and type 2 diabetes to significantly reduce the risk of microvascular complications, including neuropathy, nephropathy and retinopathy.<sup>9,10</sup> The recommended HbA<sub>1c</sub> goals are <7% (American Diabetes Association [ADA]) and <6.5% (American College of Endocrinologists [ACE] and International Diabetes Federation [IDF]). ACE also recommends that fasting and postprandial blood glucose should not exceed 110 mg/dl (6.1 mmol/l) and 140 mg/dl (7.8 mmol/l), respectively. Thus, aggressive therapy is becoming the standard of care to prevent long-term complications of DM.

Insulin is the therapy of choice for both type 1 and 2 diabetes mellitus. However, many treatment options exist for patients with type 2 DM, including dietary changes, physical activity, oral antidiabetic drugs (OADs) and the new injectable medications (eg, pramlintide, exenatide). UKPDS 57 has shown that majority of patients with type II diabetes mellitus also eventually require insulin<sup>11</sup>.

Initiating insulin is a challenge for both the patients and physicians. A wide array of insulin regimens along with fear of



injection and hypoglycaemia always require good counselling for the patients before putting them up on insulin therapy. Basal bolus therapy with multiple daily injections or an insulin pump is the most physiological approach to insulin replacement therapy. However, regimen complexity, patient preference, and other practical factors may dictate the treatment option chosen. Often, simplicity and convenience must be balanced against metabolic control. Premixed insulin is always an acceptable option as it provides both basal and prandial coverage in one injection.

With the advent of insulin analogues i.e. newer designer insulins, the convenience and acceptability has increased to a great extent. They have a more predictable onset and duration of action than human insulin formulations. Premix insulin analogue preparations are composed of a single type of insulin that is modified to have dual-action PK profiles (a short-acting peak and a longer basal release) and are biphasic rather than truly premixed.

The aim of this review is to consider the evidence for the premix analogue insulin, biphasic insulin aspart 30 (BIAsp 30, NovoMix® 30, Novo Nordisk), as a viable treatment option when initiating insulin in patients with type 2 diabetes.

## Insulin Therapy and Importance of Post Prandial Glucose Control

Insulin injections are the standard treatment for type 1 diabetes, and often need to be initiated in the later stages of type 2 diabetes. During the early stages of type 2 diabetes, the first-line treatment comprises altered diet and exercise, although oral antidiabetic drugs (OADs) are usually soon required to stimulate pancreatic insulin secretion (e.g. sulfonylureas), increase insulin sensitivity of peripheral tissues (e.g. metformin) or both.<sup>12</sup> Even with maximal doses, oral monotherapy cannot maintain glycaemic control indefinitely, because of continued deterioration of beta-cell function.<sup>13</sup> Although oral combination therapy may benefit some people, insulin treatment is eventually required to control fasting and postprandial blood glucose.

The relative contributions of fasting and postprandial blood glucose to HbA<sub>1c</sub> and the associated risks have been much

studied and debated. A recent study recruited 290 patients with type 2 diabetes and assessed the relative contribution of fasting and postprandial glucose to overall diurnal hyperglycaemia.<sup>14</sup> They found that in poorly controlled patients (>10.2% HbA<sub>1c</sub>), postprandial glucose accounted for only 30% of the hyperglycaemia, but this proportion increased rapidly with decreasing % HbA<sub>1c</sub>. Thus, in patients with HbA<sub>1c</sub> <7.2%, postprandial glucose accounted for 70% of the hyperglycaemia, with fasting glucose contributing only 30%.<sup>14</sup> The risk of complications associated with hyperglycaemia can be reduced, not only by tight overall control of blood glucose, but transient postprandial peaks of hyperglycaemia also need to be addressed specifically.

The role of postprandial BG as an independent contributor to diabetes complications and the need to target it for prevention of cardiovascular events are a matter of intense debate.

In Diabetes Intervention Study (DIS), plasma glucose after breakfast, but not fasting plasma glucose, has been found to predict myocardial infarction and mortality in newly diagnosed type 2 diabetic patients<sup>15</sup>. The DECODE Study Group, by analyzing both fasting and postchallenge glucose concentrations from 14 prospective European cohorts also found the strong correlation between cardiovascular mortality and post prandial glycemia<sup>16</sup>. Also Cavalot et al 2006, in 529 type 2 diabetic patients concluded that postprandial, but not fasting, blood glucose is an independent risk factor for cardiovascular events in type 2 diabetes, with a stronger predictive power in women than in men, suggesting that more attention should be paid to postprandial hyperglycemia, particularly in women<sup>17</sup>. Thus, there is ample evidence which demands a better PPG control along with FPG, making premix insulin a desirable alternative regimen for targeted glycemic control.

## Development of Insulin Analogue: A New Era of Insulin Therapy

To mimic the 'normal' prandial release of insulin and control blood glucose excursions, short-acting insulin injected subcutaneously must be absorbed quickly. Human insulin, however, forms hexamers at the high concentrations at which it is injected. Little absorption of hexamers can occur, and absorption through capillary walls must await dilution and disassociation into monomers or dimers.<sup>18</sup> Although patients are told to inject half-an-hour before eating, peak plasma concentrations of human insulin occur after approximately 2 hours.<sup>19</sup> The postprandial insulin profile is therefore less than optimal and does not mimic that of 'normal' physiology. Moreover, patient compliance with insulin injection is often poor. A study of patients with type 2 diabetes found only 63% of insulin doses were taken as prescribed,<sup>20</sup> and 62% of type 1 patients injected human insulin 15 minutes, or less, before a meal.<sup>21</sup>

In recent years, analogues of human insulin have been developed by introducing small changes to the amino acid sequence that alter the kinetic profile of the insulin, while retaining its metabolic actions.<sup>22</sup> One of these analogues, insulin aspart, has aspartic acid inserted at position B28 in place of the usual proline (Fig 1). This substitution reduces the self-association property of the molecule, such that the insulin aspart hexamer dissociates more readily than that of human insulin, enabling more rapid absorption from a subcutaneous depot.<sup>23,24</sup> The pharmacokinetics of insulin aspart are thus altered relative to soluble human insulin, such that plasma insulin aspart

Table 1: Summary of comparative pharmacological studies of BIAsp 30 with other insulins

Insulin comparison	Number and type of patients	Duration of treatment	Outcome	Reference
BIAsp 30 vs. BHI 30	24 healthy individuals	Single injection on 2 days (with crossover)	BIAsp 30 resulted in earlier onset and greater metabolic effect in first 4 h post injection compared with BHI 30 ( $p < 0.0001$ ) in 24 h euglycaemic clamp	25
BIAsp 30 vs. BHI 30	24 healthy individuals	Single injection on 2 days (with crossover) 4–10 days apart	BIAsp 30 was absorbed faster, and reached a greater maximum plasma insulin concentration ( $\sim 1.8$ times higher, $AUC_{0-90 \text{ min}}$ ) twice as quickly, compared with BHI 30 (all $p < 0.0001$ )	26
BIAsp 30 vs. BHI 30	50 patients with type 1 diabetes, taking human insulin for $\geq 12$ months	Single injection on 3 days (three-way crossover [two injection times for BHI]), 5–21 days apart	BIAsp 30 gave a superior 4 h postprandial insulin profile and reached a higher maximum plasma concentration more quickly than BHI 30	27
BIAsp 30 vs. BHI 30 vs. Mix25	61 patients with insulin-treated type 2 diabetes	Single injection on 3 days (three-way crossover) at least 5 days apart	BIAsp 30 gave reduced 5 h postprandial serum glucose compared with both BHI 30 and Mix25	28
BIAsp 30 BID vs. IGlarg OD	12 patients with type 2 diabetes	2 days (with crossover), 4–10 days apart	Plasma insulin and glucose infusion rate profiles were 28 and 34% larger, respectively, with BIAsp 30 compared with IGlarg during a 24 h isoglycaemic clamp	29

BIAsp 30, Biphasic insulin aspart 30/ 70; BHI 30, Biphasic human insulin 30/ 70; Mix25, Biphasic insulin lispro Mix25; IGlarg, Insulin glargine; BID, twice-daily; OD, once-daily

concentrations rise significantly more quickly and reach greater maximum concentrations.<sup>19</sup>

The development of insulin aspart has been followed by the addition of a novel pre-mix analogue insulin: dual-release or 'biphasic' insulin aspart (BIAsp 30, NovoMix® 30, Novo Nordisk). This combines rapid-acting soluble insulin aspart (30%), which addresses prandial insulin needs, with protamine-crystallised insulin aspart (70%), which has a delayed action of intermediate duration, for between meal and nocturnal insulin requirements.

## Better Pharmacokinetic and Pharmacodynamic Profile of BIAsp30

When combined with protamine-crystallised insulin aspart in BIAsp 30, insulin aspart retains its pharmacological profiles.<sup>25</sup> This has been demonstrated in several studies comparing the pharmacokinetic and pharmacodynamic properties of BIAsp 30 with those of biphasic human insulin (BHI 30, consisting of 30% soluble human insulin and 70% neutral protamine Hagedorn), intermediate-acting insulin and other insulin analogues (Table 1).

BIAsp 30 is absorbed more quickly into the circulation than BHI 30, achieving a greater maximum plasma concentration more rapidly.<sup>25-27</sup> In all the studies the time to peak insulin concentration was significantly faster (30–50%;  $p < 0.0001$ ) with BIAsp 30 as compared to BHI 30. Also, peak insulin concentration was 50 to 70 % higher in the BIAsp 30 group. Compared with BHI 30, treatment with BIAsp 30 necessitated a 37% increase in the glucose infusion rate during a euglycaemic clamp procedure (Fig 2) over the first 4 hours ( $p < 0.0001$ )<sup>25</sup>. Similar findings were observed when BIAsp 30 was compared with biphasic insulin lispro (Mix25): the maximum serum insulin concentration was 12% higher for BIAsp 30.<sup>28</sup> This three-way crossover study, has shown the 5 h post-meal glucose excursion for BIAsp 30 to be 17% lower than with BHI 30 ( $p < 0.001$ ) and 10% lower than with Mix25 ( $p < 0.05$ ).<sup>28</sup>

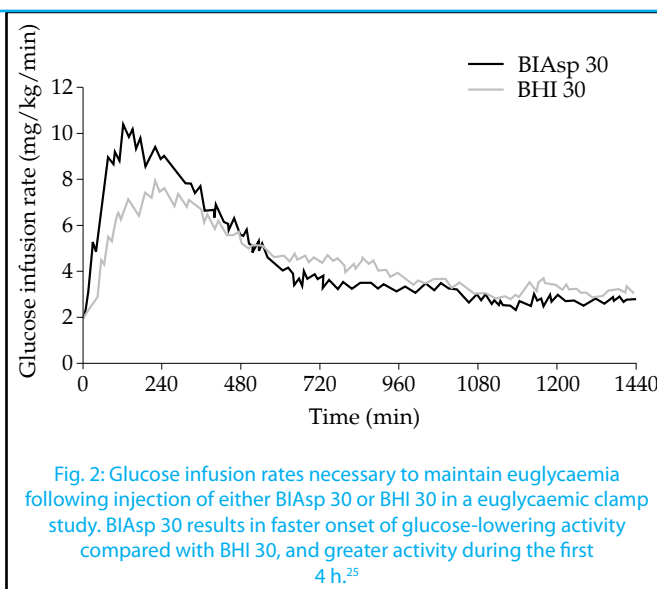


Fig. 2: Glucose infusion rates necessary to maintain euglycaemia following injection of either BIAsp 30 or BHI 30 in a euglycaemic clamp study. BIAsp 30 results in faster onset of glucose-lowering activity compared with BHI 30, and greater activity during the first 4 h.<sup>25</sup>

A 24 h euglycaemic clamp crossover study, comparing equal total daily doses of BIAsp 30 and insulin glargine (IGlarg, a basal insulin analogue; 0.5 U/kg once for IGlarg and 0.25 U/kg twice for BIAsp 30) has shown that the overall plasma insulin ( $AUC_{0-24 \text{ h}}$ ) in patients injected with BIAsp 30 was 28% higher than in patients given insulin glargine (4.5 nmol/l per h and 3.5 nmol/l per h, respectively;  $p < 0.01$ ). Moreover, the two injections of BIAsp 30 (12 h apart) produced a 34% greater overall ( $AUC_{0-24 \text{ h}}$ ) glucose infusion rate than one injection of IGlarg ( $p < 0.01$ ) despite the total daily doses being the same.<sup>29</sup>

Earlier and lower maximum serum glucose concentrations have been found for BIAsp 30 compared with BHI 30, both in single injection<sup>27,28</sup> and longer-term studies.<sup>30</sup>

Table 2 : Summary of comparative efficacy studies of BIAsp 30 with other insulins

Insulin comparison	Number and type of patients	Duration of treatment	Outcome	Reference
BIAsp 30 BID vs. BHI 30 BID	13 patients with type 2 diabetes taking twice-daily BHI 30 for $\geq 6$ months	4 weeks (crossover after 2 weeks)	Mean postprandial blood glucose was lower with BIAsp 30 ( $p=0.02$ ). Specifically, they were lower for BIAsp 30 after breakfast and dinner (both $p<0.05$ ) but greater after lunch ( $p<0.05$ )	30
BIAsp 30 BID vs. BHI 30 BID	294 patients with either type 1 or type 2 diabetes, already using twice-daily insulin	12 weeks	Mean postprandial glucose increment was lower in BIAsp 30 compared with BHI 30 ( $p<0.02$ ); HbA <sub>1c</sub> values for the two groups were similar after 12 weeks	31,34
BIAsp 30 BID vs. NPH BID	403 patients with type 2 diabetes on various treatments	16 weeks	Mean prandial blood glucose was lower with BIAsp 30 ( $p<0.0001$ ) and greater after lunch ( $p=0.003$ ). In patients coming from NPH monotherapy, BIAsp 30 reduced HbA <sub>1c</sub> significantly more than NPH	32
BIAsp 30 TID vs. BIAsp 30 BID + metformin vs. OADs	308 type 2 patients poorly controlled on OADs	16 weeks	Both BIAsp groups reduced mean plasma glucose (both $p<0.001$ vs. OADs) and HbA <sub>1c</sub> (both $p<0.001$ ) significantly more than OAD therapy.	36
BIAsp 30 BID + OADs vs. IGLarg OD + OADs	209 patients with type 2 diabetes on OADs	28 weeks	BIAsp 30 gave significantly lower HbA <sub>1c</sub> figures ( $p<0.01$ ) compared with IGLarg	33

BIAsp 30, Biphasic insulin aspart 30/ 70; BHI 30, Biphasic human insulin 30/ 70; NPH, Neutral protamine Hagedorn insulin; IGLarg, Insulin glargine; OADs, oral antidiabetic drugs; OD, once-daily; BID, twice-daily; TID, thrice-daily; HbA<sub>1c</sub>, glycated haemoglobin type A<sub>1c</sub>

## BIAsp 30 Provides more Effective Blood Glucose Control than other Insulin Regimens

In long-term efficacy trials ranging from 16 weeks to 4 years, a twice-daily regimen of BIAsp 30 has been shown to provide greater postprandial glycaemic control than twice-daily NPH or BHI 30,<sup>30-32</sup> or once-daily IGLarg (Table 2).<sup>33</sup> In a randomised double blind trial by Christiansen et al<sup>32</sup> comparing 403 patients with type II diabetes, insufficiently controlled on OADs or NPH insulin, mean prandial glucose in patients previously treated with NPH monotherapy was 1.05 mmol/l lower for the BIAsp 30 group, compared with those on NPH ( $p<0.0001$ ). These patients (coming from NPH monotherapy) also achieved a greater reduction in HbA<sub>1c</sub> when treated with twice-daily BIAsp 30, than when given twice-daily NPH (-0.78% vs -0.58%, respectively;  $p=0.03$ ).

Boehm et al compared postprandial and overall glycaemic control in a population of patients with type I or type II diabetes ( $n=294$ ) treated with BIAsp 30 or human insulin 30 in a randomised, open label parallel group study. The study was initially planned for 12 weeks then serially extended for one, two and four years.<sup>31,34</sup> The HbA<sub>1c</sub>-lowering effect of BIAsp 30 is equal to that of BHI 30 (twice-daily in patients with type 1 or type 2 diabetes) but treatment with BIAsp 30 resulted in a more favourable degree of postprandial blood glucose control than BHI 30. After completion of 3 month trial, the study patients with type 2 diabetes ( $n=125$ ) were allowed to continue treatment in an open – label fashion for an additional 21 months. There was no significant difference in HbA<sub>1c</sub> values between the two treatment groups but increment in body weight was only 0.5 kg in patients treated with BIAsp 30 as compared to 2 kg in BHI 30 ( $p=0.07$ ).<sup>34</sup>

Raskin et al.<sup>33</sup> compared twice-daily BIAsp 30 with once-daily IGLarg in insulin-naïve patients with type 2 diabetes who were poorly controlled on OADs (only continuation with pioglitazone was allowed during the treatment phase). At the 28-week

endpoint, the BIAsp 30 group had a lower mean HbA<sub>1c</sub> value than the IGLarg group ( $6.91\% \pm 1.17$  vs.  $7.41\% \pm 1.24$ ;  $p<0.01$ ) and 66% of patients using BIAsp 30 reached the target HbA<sub>1c</sub> of  $<7\%$  (from  $\sim 9.8\%$  at the start of the study) compared with 40% of patients on IGLarg ( $p<0.001$ ).

The first insulin treatment for patients with type 2 diabetes is often a basal insulin in a once- or twice-daily regimen, initially in combination with an OAD. In a recent study, a once-daily regimen of BIAsp 30, when titrated to fasting plasma glucose targets, enabled 41% of patients with type 2 diabetes to achieve HbA<sub>1c</sub>  $<7.0\%$ . The patients were either insulin-naïve or previously treated with insulin glargine or NPH.<sup>35</sup> Furthermore, for patients who do not reach HbA<sub>1c</sub> targets on once- or twice-daily BIAsp 30, intensification to thrice-daily administration has been shown to be effective<sup>35,36</sup>.

In this 48-week, open-label trial of 100 type 2 patients poorly controlled on OADs (with or without once-daily basal insulin), all patients were started on once-daily BIAsp 30 before dinner (phase 1). The starting dose of 12U was titrated according to an algorithm, based on FPG levels. After 16 weeks of therapy, those patients that had not attained an HbA<sub>1c</sub>  $\leq 6.5\%$  had their dosing frequency increased to twice-daily (phase 2). This was then increased to thrice-daily (phase 3) after 32 weeks for patients that had not achieved this target. The cumulative proportions of patients (per protocol population) that achieved HbA<sub>1c</sub>  $\leq 6.5\%$  was 24%, 66% and 77% for once-, twice- and thrice-daily BIAsp 30, respectively<sup>35</sup>. These data show that the variable dosing regimen with BIAsp 30 enables patients to start and stay on premix analogue, allowing treatment intensity to keep pace with disease progression.

Thrice daily regimen with BIAsp 30 has also been compared with basal bolus regimen in both type 1<sup>37</sup> and type 2<sup>38</sup> diabetes. Both studies concluded that a thrice daily meal-time BIAsp 30 regimen is a suitable alternative to an intensified insulin regimen in people with inadequately controlled type 1 & 2 diabetes, and requires fewer daily injections than a basal-bolus therapy without compromising efficacy and safety. In type 1 patients<sup>37</sup> significant

improvement in long term glycaemic control was found, without increasing the risk of hypoglycaemia and there was minimum inter day variation in BIAsp 30 pharmacokinetics.

### Easy Once Daily Start with BIAsp 30:

Frequency of insulin administration affects the compliance with insulin therapy. A physician is in search of an insulin regimen which is simple to start and stay with. Once daily start with a premix insulin is simple and better as it takes care of both prandial and basal insulin requirements. The finding of 41% patients achieving target HbA1c of < 7% with BIAsp 30 in Garber study<sup>35</sup> has been corroborated by many other studies.

Kilo et al<sup>39</sup> evaluated the clinical effectiveness of starting patients on a relatively simple regimen of once-daily injections of either biphasic insulin aspart 70/30 (10 min before dinner), NPH insulin (at 10 p.m.), or biphasic human insulin 70/30 (30 min before dinner) in combination with metformin. HbA1c was decreased by 2.3%, 1.9% and 1.8% from base line after treatment with BIAsp 70/30, NPH insulin or human insulin 70/30 respectively.

Similarly Lund et al<sup>40</sup> at Steno Diabetic Center assessed the effect of once daily BIAsp 70/30 in combination with metformin or repaglinide in 86 non obese type II diabetic patients. Patients switched to 2 or 3 daily injections after 3, 6 or 9 months if target glycaemic goals were not reached. After 3 months the majority (14% of all patients) who reached target HbA1c < 6.5% were treated with once daily BIAsp30 injection compared to only 10% of all patients after 12 months.

Bebakar et al 2007<sup>41</sup>, randomised 192 type 2 diabetic patients in a 2 : 1 ratio either to receive BIAsp30 or OAD only. Subjects randomized to BIAsp30 treatment received BIAsp30 once daily (o.d.) at dinnertime between Week 2 and Week 14, and those not reaching treatment targets were switched to twice daily (b.i.d.) BIAsp30 at Week 14. Significantly greater reductions in HbA1c was found with BIAsp30 (o.d.) vs. OAD-only treatment (1.16 vs. 0.58%;  $p < 0.001$ ), with BIAsp30 (o.d.) and BIAsp30 (b.i.d.) treatments vs. OAD only treatment (1.24 vs. 1.34 vs. 0.67%;  $p < 0.01$ ) over 26 weeks of therapy.

Therefore, it may be appropriate to commence with one injection at dinnertime (or the largest meal) and add additional injections i.e intensify therapy to twice and thrice daily<sup>35-38</sup>, if patient has not achieved the target blood glucose control. This can enable patients to be managed with single premixed insulin analogue throughout the course of their disease.

### BIAsp 30 is Safer Alternative to BHI 30: Low Risk of hypoglycaemia

To reduce the risk of long-term complications of diabetes such as neuropathy, retinopathy and atherosclerosis, blood glucose must be tightly controlled.<sup>7,9,10</sup> However, there has to be a balance between achieving good glycaemic control and avoiding hypoglycaemia.

The frequency of major hypoglycaemic events (those requiring third-party intervention/intravenous glucose) in patients using twice-daily BIAsp 30 is lower than for those using the same regimen of BHI 30, in both short-term and long-term studies.<sup>31,34</sup> In a 12-week trial involving people with type 1 or type 2 diabetes, there were 52% fewer major hypoglycaemic episodes in those using BIAsp 30 compared with those using BHI 30.<sup>31</sup> When this trial was extended for a further 21 months, results showed that only 2.5% of patients with type 2 diabetes experienced one or

more major hypoglycaemic episodes on BIAsp 30, compared with 9% on BHI 30 (averaged by year).<sup>34</sup>

According to the REACH study (Randomised Evaluation of premix insulin Aspart 30 in Controlling Hypoglycaemia in type 2 diabetes), the risk of hypoglycaemia is, in general, greater at night than during the day.<sup>42</sup> From a group of 122 insulin-treated patients with type 2 diabetes, continuous blood glucose monitoring revealed the nocturnal hypoglycaemia (blood glucose <3.5 mmol/l) rate to be more than double that of the day time (8.54% and 3.35%, respectively). Furthermore, in this 32-week crossover study, patients with type 2 diabetes experienced significantly fewer nocturnal hypoglycaemic episodes (same criterion as above) while using BIAsp 30 than when using BHI 30 ( $p=0.02$ ).<sup>43</sup>

Increasing the dosing frequency of BIAsp 30 does not necessarily lead to a greater risk of hypoglycaemia<sup>36</sup>. In a recent study, 308 insulin-naïve type 2 patients poorly controlled on OADs were randomised to BIAsp 30 thrice-daily, BIAsp 30 twice-daily plus metformin, or optimised OAD therapy. Although improvement in glycaemic control for all treatment groups was associated with a slight increase in minor hypoglycaemia (no significant difference between BIAsp 30 twice- or thrice-daily), no major hypoglycaemia was reported in any treatment group during the 16 weeks of the trial<sup>36</sup>. Similarly Garber et al<sup>35</sup> 2006 found that inspite of increament in dasage from once to thrice daily, there were no major nocturnal hypoglycaemic events, and none of the patient withdrew from the study due to any hypoglycaemic event.

### Novomix 30 in Real Life Clinical Practice

A largest clinical experience observational study (PRESENT) with BIAsp 30 was done to provide complementary data to support the clinical trial data already existing on BIAsp 30 treatment in type 2 diabetes. This was a 6-month, prospective, multinational, multiethnic observational study involving 21,977 patients from 13 countries. Significant reductions from baseline were observed in the mean haemoglobin A1c (-1.81%), fasting plasma glucose (-3.74 mmol/l) and postprandial plasma glucose (-5.82 mmol/l) at the end of 6 months. Moreover, 15.3% and 27.7% patients achieved target HbA1c of less than 7% at 3 months and 6 months respectively. Overall, the mean HbA1c at 6 months was lowered in patients regardless of prior treatment i.e -2.15% (OAD), -1.45% (insulin), -1.47% (OAD+insulin) and -2.35% (treatment naïve). The rate of total hypoglycaemia was significantly reduced from 5.4 events per patient-year at baseline to 2.2 events per patientyear at study end<sup>44</sup>.

In a subgroup analysis of patients previously uncontrolled (HbA1c  $\geq 7.0\%$ ) on BHI 30 significant improvement in HbA1c (by  $1.58 \pm 1.69\%$  points), FPG (by  $2.92 \pm 3.71$  mmol/L) and PPPG (by  $4.75 \pm 4.87$  mmol/L) was found. The incidence of hypoglycaemic episodes also decreased from 38.7% at baseline to 20.8% at the end of 6 months. These findings concurred with those from clinical trials, and showed that the use of BIAsp 30 treatment in clinical practice was both effective and safe in patients with type 2 diabetes mellitus who were considered to be poorly controlled on prior diabetes therapy<sup>45</sup>.

**Table 3 : NovoMix® FlexPen® safety and user-friendly design features**

FlexPen® safety features	FlexPen® user-friendly features
Large, easily visible, scale numbers on the dosing dial <sup>48</sup>	Simple, single-step dosing system <sup>51</sup> , from 1–60 units per injection
Audible 'click' when dialling the dose <sup>53</sup>	Easy, dial back, dose correction
Scale returns to zero during injection	Always ready to use, as dial returns to zero during each injection
Impossible to dial a larger dose than remains in the FlexPen®	Discreet, looks non-medical <sup>52,53</sup>

## Meal Time Flexibility Adds to the Convenience of the Patient

The efficacy of BIAsp 30 is optimal when injected immediately before the start of a meal. However, efficacy is not significantly reduced when the injection time is delayed relative to the start of a meal.<sup>46</sup> When administered immediately before a meal, BIAsp 30 produces a lower 5-h postprandial serum glucose profile (AUC<sub>0-5h</sub>) than that of BHI 30 when given either 15 minutes before or immediately before a meal. If the injection of BIAsp 30 is delayed 15 minutes after the start of a meal, the resulting AUC<sub>0-5h</sub> is similar to that of BHI 30 injected either immediately before or 15 minutes before a meal.<sup>47</sup> BIAsp 30 therefore offers the patient a degree of flexibility in terms of injection timing, allowing individual adjustment for meal size and content without significantly affecting efficacy. This may be useful for the elderly, in circumstances where meal size and/or timing are uncertain.<sup>46</sup>

## FlexPen® Design Features Confer Usability

A user-friendly insulin delivery system may improve patient compliance, and consequently improve glycaemic control.<sup>48</sup> It is important, therefore, to ensure that the delivery system is simple, easy to operate and discreet.

Patients generally prefer a pen-type delivery device to the conventional vial and syringe, for improved quality of life.<sup>48–51</sup> BIAsp 30 uses the FlexPen® delivery system, which incorporates a number of features designed to maximise user confidence, such as an audible 'click' when dialling-up the dose. In a comparative handling evaluation by patients and healthcare professionals, 82% of both groups showed a preference for the FlexPen® over both the Humalog® Pen and OptiSet®.<sup>52</sup>

In a recent crossover trial,<sup>53</sup> patients with type 2 diabetes were asked to assess both the FlexPen® and the Humalog® Pen after injecting insulin (BIAsp 30 and biphasic insulin lispro 25, respectively) for 12 weeks. Responses showed the FlexPen® to be superior for ease of use, utility and convenience, and confidence in optimal diabetes management. Moreover, 74% of patients found the FlexPen® easier to use than the Humalog® Pen, with 76% of patients choosing to continue using the FlexPen® after the trial.<sup>53</sup>

The preference for the FlexPen® over the Humalog® Pen and OptiSet® in handling studies,<sup>48,52</sup> by patients of all ages, including those with mild visual and dexterity deficits, is testament to its safety and user-friendly design features (Table 3).

## Conclusion

Insulin analogues are chemically modified to alter their pharmacokinetic profiles, without compromising their metabolic actions. BIAsp 30, a premix insulin analogue is a simple regimen for insulin initiation in patients with type 2 diabetes. It can be started once daily in combination with oral antidiabetics and then can be intensified to twice and thrice daily dosing. Being more physiological, it provides a significantly better postprandial blood glucose and HbA<sub>1c</sub> control compared with BHI 30, biphasic insulin lispro 25, NPH and insulin glargine.

This better glycaemic control has been achieved with significantly less number of hypoglycaemic events (both major and nocturnal) in comparison to other regimens, which have not increased despite intensification with BIAsp 30. Its availability in the patient-friendly FlexPen® and meal time flexibility adds to the convenience of the patient resulting in better compliance to regimen. Given the importance of post prandial glycaemic control along with simplicity of dosing regimen, BIAsp 30 is an obvious choice for initiating insulin therapy and reducing the long term morbidity and mortality in patients with type 2 diabetes.

## References

1. Yoon KH, Lee JH, Kim JW et al. Epidemic obesity and type 2 diabetes in Asia. *Lancet* 2006; 368: 1681–88
2. Wild S, Roglic G, Green A et al. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27(5): 1047-1053.
3. Coates PA, Ollerton RL, Luzio SD, Ismail I, Owens DR. A glimpse of the 'natural history' of established type 2 (non-insulin dependent) diabetes mellitus from the spectrum of metabolic and hormonal responses to a mixed meal at the time of diagnosis. *Diabetes Res Clin Pract* 1994;26:177–87.
4. Home PD. Rapid-acting insulin secretagogues: a clinical need? *Exp Clin Endocrinol Diabetes* 1999;107(Suppl 4):S115–9.
5. Polonsky KS, Given BD, Hirsch LJ, et al. Abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1988;318:1231–9.
6. Balkau B, Shipley M, Jarrett RJ, et al. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. *Diabetes Care* 1998;21:360–7.
7. DECODE study group, on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 1999;354:617–21.
8. DECODE study group, on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality. *Arch Intern Med* 2001; 161:397–404.
9. DCCT (Diabetes Care and Complications Trial) Research group. The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes* 1996;45:1289–98.
10. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–53.
11. Wright A, Burden AC, Paisey RB, et al. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS 57). *Diabetes Care* 2002; 25: 330-6

12. Turner R, Cull C, Holman R, for the United Kingdom Prospective Diabetes Study Group. United Kingdom Prospective Diabetes Study 17: a 9-year update of a randomized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1996; 124(1 pt 2):136-45.
13. Wright A, Felix Burden AC, Paisey RB, Cull CA, Holman RR, for the UK Prospective Diabetes Study Group. Sulfonylurea inadequacy. Efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the UK Prospective Diabetes Study (UKPDS 57). *Diabetes Care* 2002;25:330-6.
14. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care* 2003;26:881-5.
15. Hanefeld M, Fischer S, Julius U, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the diabetes intervention study, 11-year follow-up. *Diabetologia* 1996; 39: 1577-83
16. DECODE study group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 1999; 354: 617-21
17. F. Cavalot, A. Petrelli, M. Postprandial Blood Glucose Is a Stronger Predictor of Cardiovascular Events Than Fasting Blood Glucose in Type 2 Diabetes Mellitus, Particularly in Women: Lessons from the San Luigi Gonzaga Diabetes Study. *Traversa, J Clin Endocrinol Metab* 2006; 91: 813-819,
18. Kang S, Brange J, Burch A, Volund A, Owens DR. Subcutaneous insulin absorption explained by insulin's physicochemical properties. Evidence from absorption studies of soluble human insulin and insulin analogues in humans. *Diabetes Care* 1991;14:942-8.
19. Home PD, Barriocanal L, Lindholm A. Comparative pharmacokinetics of the novel rapid-acting insulin analogue, insulin aspart, in healthy volunteers. *Eur J Clin Pharmacol* 1999;55:199-203.
20. Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004;27:1218-24.
21. Overmann H, Heinemann L. Injection-meal interval: recommendations of diabetologists and how patients handle it. *Diabetes Res Clin Pract* 1999;43:137-42.
22. Brange J, Owens DR, Kang S, Volund A. Monomeric insulins and their experimental and clinical implications. *Diabetes Care* 1990;13:923-54.
23. Brange J, Volund A. Insulin analogs with improved pharmacokinetic profiles. *Adv Drug Deliv Rev* 1999;35:307-35.
24. Bolli GB. Physiological insulin replacement in type 1 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2001;109(Suppl 2):S317-32.
25. Weyer C, Heise T, Heinemann L. Insulin aspart in a 30/70 premixed formulation. Pharmacodynamic properties of a rapid-acting insulin analog in stable mixture. *Diabetes Care* 1997;20:1612-14.
26. Jacobsen LV, Sogaard B, Riis A. Pharmacokinetics and pharmacodynamics of a premixed formulation of soluble and protamine-retarded insulin aspart. *Eur J Clin Pharmacol* 2000;56:399-403.
27. Hermansen K, Vaaler S, Madsbad S, et al. Postprandial glycemic control with biphasic insulin aspart in patients with type 1 diabetes. *Metabolism* 2002;51:896-900.
28. Hermansen K, Colombo M, Storgaard H, et al. Improved postprandial glycemic control with biphasic insulin aspart relative to biphasic insulin lispro and biphasic human insulin in patients with type 2 diabetes. *Diabetes Care* 2002;25:883-8.
29. Luzio S, Dunseath G, Peter R, Pauvaday V, Owens DR. Comparison of the pharmacokinetics and pharmacodynamics of biphasic insulin aspart and insulin glargine in people with type 2 diabetes. *Diabetologia* 2006; 49: 1163-1168.
30. McSorley P, Bell P, Jacobsen L, et al. Twice-daily biphasic insulin aspart 30 vs biphasic human insulin 30: a double-blind crossover study in adults with type 2 diabetes mellitus. *Clinical Ther* 2002;24:530-9.
31. Boehm B, Home P, Behrend C, et al. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in type 1 and type 2 diabetic patients. *Diabet Med* 2002;19:393-9.
32. Christiansen JS, Vaz J, Metelko, et al. Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin, with low risk of hypoglycaemia, in patients with type 2 diabetes. *Diabetes Obes Metab* 2003;5:446-54.
33. Raskin P, Allen E, Hollander P, et al. for the INITIATE Study Group. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care* 2005;28:260-5.
34. Boehm BO, Vaz JA, Brondsted L, et al. Long-term efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. *Eur J Intern Med* 2004; 15: 496-502
35. Garber A, Wahlen J, Wahl T et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (The 1-2-3 study) *Diab Obes Metab* 2005;8:58-66
36. Ushakova O, Sokolovskaya V, Morozova A, Valeeva F, Zanozina O, Sazonova O, Zhdanova E, Starceva M Biphasic insulin aspart 30 (NovoLog® Mix 70/30), a premix analogue, is an effective and well tolerated starter insulin in type 2 diabetes. *Diabetes* 2005;54(Suppl 1):A502
37. Chen JW, Lauritzen T, Bojesen A et al. Multiple mealtime administration of biphasic insulin aspart 30 versus traditional basal-bolus human insulin treatment in patients with type 1 diabetes. *Diabetes, Obesity and Metabolism*. 2006;8: 682-689
38. Ligthelm RJ, Mouritzen U, Lynggaard H et al. Biphasic Insulin Aspart Given Thrice Daily is as Efficacious as a Basal-Bolus Insulin Regimen with Four Daily Injections A Randomised Open-Label Parallel Group Four Months Comparison in Patients with Type 2 Diabetes. *Exp Clin Endocrinol Diabetes* 2006; 114: 511-519
39. Kilo C, Mezitis N, Jain R, et al. Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart 70/30, biphasic human insulin 70/30, or NPH insulin in combination with metformin. *J Diabetes Complications* 2003; 17: 307-13
40. Lund SS, Tarnow L, Pedersen OB et al. Effect of BIAsp30 in combination with oral hypoglycaemic agents on glycaemic control in nonobese patients with type 2 diabetes mellitus. *Diabetes* 2005;56(suppl 1):A126
41. Bebakar WMW, Chow CC, Kadir KA, on behalf of the BIAsp-3021 study group. Adding biphasic insulin aspart 30 once or twice daily is more efficacious than optimizing oral antidiabetic treatment in patients with type 2 diabetes *Diabetes Obes Metab*. 2007 Sep; 9(5): 724-32
42. McDougall A, McNally PG, Fitch M, Nelson G. Insulin treated patients with type 2 diabetes mellitus have higher rates of nocturnal than day time hypoglycaemia: continuous blood glucose monitoring (CBGM) run-in data from the REACH study. *Diabetologia* 2004;47(Suppl 1):A275.
43. McNally P, Fitch M, Nelson G. Patients with type 2 diabetes mellitus have lower rates of nocturnal hypoglycaemia on biphasic insulin aspart (BIAsp 30) than on biphasic human insulin-30 (BHI30): data from the REACH study. *Diabetologia* 2004;47(Suppl 1):A327.
44. Khutsoane D, Sharma SK, Almoustafa M et al. Biphasic insulin aspart 30 treatment improves glycaemic control in patients with type 2 diabetes in a clinical practice setting: experience from the PRESENT study. *Diabetes Obes Meta* 2008;10:212-222.
45. Shestakova M, Sharma SK, Almoustafa M et al. Transferring type 2 diabetes patients with uncontrolled glycaemia from biphasic human insulin to biphasic insulin aspart 30: experiences from the PRESENT study. *Current Medical Research and Opinion* 2007;23(12):3209-3214.

46. Warren ML, Conway MJ, Klaff LJ, Rosenstock J, Allen E. Postprandial versus preprandial dosing of biphasic insulin aspart in elderly type 2 diabetes patients. *Diabetes Res Clin Pract* 2004;66:23–29.
47. Kapitza C, Nosek L, Lindholm A, Leth G, Codony SG, Heise T. Postprandial dosing of the “lowmix” biphasic insulin aspart. *Diabetologia* 2001;44(Suppl 1):A211.
48. Asakura T. Comparison of the dosing accuracy of two insulin injection devices *Journal of Clinical Research* 2005; 8: 33–40
49. Hornquist JO, Wikby A, Anderson P-O, Dufva A-M. Insulin-pen treatment, quality of life and metabolic control: retrospective intra-group evaluations. *Diabetes Res Clin Pract* 1990;10:221–30.
50. Korytkowski M, Bell D, Jacobsen C, Suwannasari R. NovoLog Mix 70/30 delivery: FlexPen vs. vial and syringe. *Diabetologia* 2002;45(Suppl 2):A255.
51. Korytkowski M, Bell D, Jacobsen C, Suwannasari R, for the FlexPen study team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 and type 2 diabetes mellitus. *Clin Ther* 2003;25:2836–48.
52. Lawton S, Berg B. Comparative evaluation of FlexPen™, a new prefilled insulin delivery system, among patients and healthcare professionals. *Diabetes* 2001;50(Suppl 2):A440.
53. Niskanen L, Jensen LE, Raastam J, Nygaard-Pedersen L, Erichsen K, Vora JP. Randomized, multinational, open-label, 2-period, crossover comparison of biphasic insulin aspart 30 and biphasic insulin lispro 25 and pen devices in adult patients with type 2 diabetes mellitus. *Clin Ther* 2004;26:531–9. v