Biphasic Insulin Aspart 30 (BIAsp 30) is Safe and Improves Glycaemic Control in Insulin Naïve Patients with Type 2 Diabetes

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Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by gradual decline in beta-cell function and insulin resistance [1]. The recommendations for initial treatment of T2DM include lifestyle adjustments and oral anti-diabetic medications [2]. The United Kingdom Prospective Diabetes Study (UKPDS) and other studies have shown that intensive glycaemic control in type 2 diabetes significantly reduces the risk of development and/or deterioration of microvascular complications [1,3]. The incidence and progression of microvascular complications correlate with the glycaemic control and lower glycated haemoglobin (HbA1c) levels are associated with the reduction of cardiovascular risks [3]. Both fasting blood glucose (FBG) and post-prandial blood glucose (PPBG) contributes to the level of HbA1c, and current data suggest that postprandial hyperglycaemia is associated with an increased risk of macrovascular disease [4]. Therefore, it seems reasonable to target postprandial hyperglycaemia in addition to FBG levels to achieve maximum benefits [5,6].

Biphasic insulin aspart 30 (BIAsp 30) (NovoMix®30) is an insulin analogue mixture which contains 30% unbound rapid-acting insulin aspart and 70% intermediate-acting protaminated insulin aspart. This premix formulation aims at postprandial hyperglycaemia and also provides basal insulin coverage [7]. In patients with type 2 diabetes inadequately controlled with OADs, insulin therapy is frequently started by adding basal to existing OADs [8]. BIAsp 30 provides both postprandial plasma glucose and fasting plasma glucose control [9]. In a treat-to-target trial, 41% of subjects with type 2 diabetes achieved the target of HbA1c < 7% on once-daily treatment with BIAsp 30 [10]. In addition, more patients could safely achieve the goals for optimal glycaemic control when the number of daily injections of BIAsp30 increased from one to two, and then if not meeting the HbA1c target, from two to three daily injections [11,12].

In Iran, quality of care of patients with type 2 diabetes is poor. It has been reported that only 6.4% of Iranian patients had HbA1c measurements at least once in a year and majority of them had poor glycaemic control according to their most recent HbA1c levels [13].

The aim of the IMPROVE™ study was to evaluate the clinical safety profile and efficacy while using BIAsp 30 (NovoMix 30) under normal clinical practice conditions. Data from a subgroup of insulin naïve patients with type 2 diabetes in Iran are reported. Beneficial information on safety, efficacy and pattern of use of a drug in an extensive patient population can be gained from this observational study.

Patients and Methods

Study design

IMPROVE™ was a 26-week, open-label, non-randomized, multi-centre observational study of patients with type 2 diabetes conducted in 11 countries (Canada, China, Greece, Persian Gulf region countries, India, Iran, Italy, Japan, Poland, Russia and South Korea) [14,15]. BIAsp 30 (100 IU/ml) was prescribed by the physician in routine clinical evaluations. The starting dose and frequency of injection, as well as subsequent dose adjustments were individualised and were at the discretion of the physician. No study-specific investigations were performed except the collection of data at baseline, follow-up visit (approximately 13 weeks after enrolment), and final visit (approximately 26 weeks after enrolment). Study procedures complied with local regulations and practice governing observational studies. Health authority approval and ethics committee approval were achieved. This is a subgroup analysis from the IMPROVE study. Results from the insulin naïve Iranian patients with T2DM are reported in this paper.

Patients

Written informed consent was obtained for all patients before any trial-related activity. The study was performed in accordance with the Declaration of Helsinki [16] and International Conference on Harmonisation Good Clinical Practice [17]. Patients recruited in the IMPROVE study were 18 years and older treated with BIAsp 30 in routine clinical practice. Patients were excluded if they had known or suspected allergy to BIAsp 30. Females who were pregnant, breast-feeding or intending to become pregnant were also excluded. This subgroup included insulin naïve patients with T2DM who were previously treated with oral anti-diabetic medications only in Iran. The majority of these patients (69.2%) were on a combination of Biguanides and Sulphonylureas, while 8.8%, 9.4% of patients were on Biguanides only and Sulphonylureas only, respectively. The dose of insulin was not specifically adjusted for OADs but at the physician's discretion.

Endpoints

The primary endpoint was the incidence of major hypoglycaemic episodes reported as serious adverse drug reactions (SADRs). Major hypoglycaemic episode was defined as an episode with severe central
nervous system symptoms consistent with hypoglycaemia in which the patient was unable to treat himself/herself and had one of blood glucose <50 mg/dl (2.8 mmol/l) or reversal of symptoms after either food intake or glugon or intravenous glucose administration.

The secondary endpoints included the number of minor hypoglycaemic episodes, changes in body weight and body mass index (BMI), HbA1c, FBG, the variability in FBG, PPBG after all main meals and treatment satisfaction as assessed by the Diabetes Medication Satisfaction (DiabMedSat) questionnaire (0 to 100-point scale with higher scores indicating higher quality of life) [18]. Minor hypoglycaemic episode was defined as an episode with symptoms of hypoglycaemia with the confirmation of blood glucose measurement <56 mg/dl (3.1 mmol/l) and which was handled by the patient or any asymptomatic blood glucose measurement <56 mg/dl (3.1 mmol/l).

Statistical analyses

In this predefined subgroup, data were collected at baseline (159 patients), follow-up visit (approximately 13 weeks, 154 patients), and final visit (approximately 26 weeks, 149 patients). The summary of the baseline characteristics and safety data were based on Full Analysis Set (FAS), which consisted of all patients with a baseline visit, had been prescribed BIAsp 30 at least once and did not use BIAsp 30 prior to the start of the study. The analysis of the efficacy outcome variables were based on Efficacy Analysis Set (EAS), which was defined as all patients from FAS who had the final visit, at least one measurement concerning FBG, PPBG, most recent HbA1c, weight or hypoglycaemic episodes at baseline and final visit, with the final visit within 18 to 31 weeks from baseline. FBG and PPBG Variability were defined as the standard deviation of the most recent 3 values obtained by the investigator. The analysis of the quality of life (QoL) data was based on Quality of Life Analysis Set (QLAS, 132 patients), which was defined as all patients from FAS who were treated before the study with either OAD or insulin and who had completed at least one item of the DiabMedSat questionnaire at baseline and final visit.

Statistical comparisons of BIAsp 30 outcome measures at baseline and final visit were performed using Wilcoxon signed rank test for discrete variables (hypoglycaemic episodes) and using paired t-test for continuous variables (HbA1c, mean FBG and FBG variability, mean PPBG and PPBG variability). All testing used two-sided tests with significance level α= 0.05 and PPBG and PPBG variability).

Results

Baseline demographics

Of the 478 patients enrolled in Iran, 159 (33.3%) were previously treated with oral anti-diabetic medications only and 151 of them completed the study. A total of 8 (5.0%) patients discontinued from the study, due to "lost contact" (3.1%) or "other reasons" (1.9%). The demographic characteristics of all patients are summarised in Table 1. The patients had mean age of 54.9±11.1 years, with a slightly lower rate of males to females (48/52 %). Mean BMI was 27.1±4.7 kg/m² and mean diabetes duration was 12.6±7.0 years. Microvascular complications (60%) were more commonly reported than macrovascular complications (34%) by the patients. The majority of the patients (73%) were previously treated with two oral anti-diabetic medications, 9% patients with more than two oral anti-diabetic medications, and 18% patients with one oral anti-diabetic medication.

The most common reason for starting a new therapy was to improve FBG (76%) and for an easy start of insulin therapy (76%) (Table 2). The mean daily dose of BIAsp 30 after entering into the study (baseline) was 18.3 IU (0.26 IU/kg) and increased to 48.4 IU (0.60 IU/kg) at final visit. A majority of patients were injected BIAsp 30 twice daily throughout the study period (56.6% at baseline and 67.5% at final visit) (Table 3). Patients were exposed to BIAsp 30 for approximately 27.3 weeks.

Safety

Hypoglycaemic episodes: Major hypoglycaemic episodes

| Reason(s) for starting a new therapy | Total |
|-------------------------------------|-------|
| Easy Start of Insulin Therapy       | 121   (76.1) |
| Easy Intensification of Insulin Therapy | 22   (13.8) |
| Improve HbA1c                      | 106   (66.7) |
| Improve FBG                        | 121   (76.1) |
| Improve PPBG                       | 113   (71.1) |
| Reduce Risk of Hypoglycaemia       | 27    (17.0) |
| Patient Dissatisfaction with Previous Therapy | 84   (40.3) |
| Side Effects from Previous Therapy | 12    (7.5) |
| Change Due To Insulin Pen          | 29    (18.2) |
| Allow For Mealtime Administration  | 50    (31.4) |

Percentages are based on the number of patients with non-missing values. A patient may have findings in more than one category in Reason(s) for starting a new therapy.
### Table 4: Change from baseline in efficacy parameters.

| Parameter (SD)          | Baseline          | Final visit         | Absolute change |
|-------------------------|-------------------|---------------------|-----------------|
| Mean HbA1c, %Hb         | 9.26 (1.96)       | 7.49 (1.26)         | -1.77 (1.85)    |
| Mean FBG, mg/dL         | 222 (62)          | 138 (35)            | -84 (68)        |
| Mean PPBG, mg/dL        |                   |                     |                 |
| At breakfast            | 306 (81)          | 193 (52)            | -114 (86)       |
| At lunch                | 220 (100)         | 151 (38)            | -75 (97)        |
| At dinner               | 266 (111)         | 165 (52)            | -101 (109)      |
| Body weight, kg         | 73.70 (14.90)     | 76.39 (14.72)       | +2.69 (5.21)    |
| BMI, kg/m²              | 27.24 (4.69)      | 28.30 (4.89)        | +1.08 (1.97)    |

#### Figure 1: Number of hypoglycaemic episodes (episodes/patient years).

- **Major hypoglycaemic episodes**
  - Baseline: 0.15, Week 26: 0.25
  - Major: 0.05 (p < 0.05), Daytime major: 0.25 (p > 0.05), Nocturnal major: 0.15 (p > 0.05)

- **Minor hypoglycaemic episodes**
  - Baseline: 0.344, Week 26: 0.172
  - Major: 0.05 (p < 0.05), Daytime minor: 0.15, Nocturnal minor: 0.05

#### Figure 2: Patient treatment satisfaction among insulin naive patients (Diab-MedSat).

- **Overall score**
  - Baseline: 59.2, Week 26: 75.6 (p < 0.001)
- **Burden**
  - Baseline: 59.2, Week 26: 75.6 (p < 0.001)
- **Relief of symptoms**
  - Baseline: 59.2, Week 26: 75.6 (p < 0.001)
- **Efficacy**
  - Baseline: 59.2, Week 26: 75.6 (p < 0.001)

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Absolute change decreased from 0.344 episodes/patient year at baseline to 0.172 episodes/patient year at final visit, though this decrease was not statistically significant (p > 0.05). From baseline to end of the study, daytime major events were increased by 0.172 episodes per patient year while nocturnal major events were decreased by 0.344 episodes per patient year. Neither of these changes were statistically significant (p > 0.05). Minor hypoglycaemic episodes increased from 7.318 episodes/patient year at baseline to 12.053 episodes/patient year at final visit (p < 0.05). Similar trends were observed for daytime minor episodes (7.060 episodes/patient year at baseline to 9.728 episodes/patient year at final visit) as well as nocturnal minor events (0.258 episodes/patient years at baseline to 2.325 episodes/patient year at final visit) (p < 0.05 for both cases; Figure 1).

**Adverse events:** In the total Iranian cohort (N=478), 22 adverse events (AEs) were reported and the diagnosis included angina unstable, cardiac arrest, familial tremor, hypoglycaemia, diabetic amyotrophy, haemarthrosis, optic nerve infarction, etc. Among all those reported AEs, 14 events were categorized as serious adverse events (SAEs). A total of 5 AEs (2 SAEs) were categorized as probable, 4 AEs (3 SAEs) were reported as possible and 13 AEs (9 SAEs) were considered as unlikely to be associated with the study medication by study investigators. In Iranian patients, 9 adverse drug reactions (ADRs) were reported and there were 5 serious adverse drug reactions (SADRs) among them. A total of 5 ADRs (2 SADRs) were categorized as probable to be related to the study drug, 4 ADRs (3 SADRs) were possible to be due to the study medication. In Iranian insulin naive subgroup (N=159), 8 AEs were reported in 8 patients and there were 5 reports of SAEs in 5 patients. Four ADRs were reported in 4 patients and there were 3 reports of SADRs in 3 patients in Iranian insulin naive subgroup. In the current study, two major hypoglycaemic episodes were reported by two patients as SADRs.

**Body weight**

Compared with baseline, body weight was increased at final visit by 2.69±5.21 kg. Accordingly, BMI was increased at final visit by 1.06±1.97 kg/m² (Table 4).

From baseline to final visit, small increases in body weight were observed in different BMI groups (BMI<25 group: 4.0±5.2kg, 25≤BMI<30 group: 2.0±4.4kg, 30≤BMI<35 group: 2.3±6.2kg, in BMI≥35 group: 2.5±5.9kg).

**Effectiveness**

HbA1c was 9.26±1.69% at baseline and 7.49±1.26% at final visit. There was a mean reduction in HbA1c of 1.77±1.85% from baseline to final visit.

FBG was reduced from baseline to final visit by 84±68 mg/dl. Meanwhile, FBG variability was reduced by 1.06±1.97 mg/dl.

Breakfast PPBG was reduced from baseline to final visit by 114±86 mg/dl. Meanwhile, lunch PPBG was reduced by 75±97 mg/dl and dinner PPBG was reduced by 101±109 mg/dl.

**Patient treatment satisfaction**

The Diabetes Medication Satisfaction questionnaire evaluated relief of burden, relief of symptoms and effectiveness before and after treatment with BIAsp 30. The overall treatment satisfaction was increased from baseline to final visit (on a 100-point scale, baseline vs. final visit: 59.2 point score vs. 75.6 point score). All three domains showed an improvement in scores from baseline to final visit, while the largest improvement was observed in the efficacy domain (baseline vs. final visit).
The improved glycaemic control in the present observational study is consistent with the fact that most physicians decide to initiate treatment with BIAsp 30 in order to improve FBG and for an easy start of insulin therapy. A study effect could also contribute partially to this improvement. Heterogeneity of real-life populations and the absence of a control group in observational studies may limit the conclusions we can draw from them.

There are also limitations with the current study. The lack of randomization and the lack of other treatment arms added confounding factors to the study. In addition, other parameters regarding lipid metabolism and insulin resistance may be informative; however, we did not investigate into detail.

In summary, initiating BIAsp 30 in insulin naïve Iranian patients with type 2 diabetes was safe and effective. Treatment with BIAsp 30 improved glycaemic control and patient treatment satisfaction without an increased risk of major hypoglycaemia. Furthermore, the results in Iranian patients are consistent with the global IMPROVE™ study cohort.

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