Adv Ther (2009) 26(3):325-335.
DOI 10.1007/s12325-009-0006-9

ORIGINAL RESEARCH

Baseline Characteristics of the Indian Cohort from the IMPROVE™ Study: a Multinational, Observational Study of Biphasic Insulin Aspart 30 Treatment for Type 2 Diabetes

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Received: January 12, 2009 / Published online: February 27, 2009 / Printed: April 8, 2009

ABSTRACT

Introduction: The IMPROVE™ study is an open-label, nonrandomized, observational study aimed at determining the safety and efficacy of biphasic insulin aspart 30 (BIAsp 30) treatment in subjects with type 2 diabetes from 11 countries. Here, we report the baseline data of the Indian cohort. ***Methods:*** All subjects with type 2 diabetes requiring insulin and considered suitable for BIAsp 30 therapy based on their physician's clinical judgment were eligible to enter the study. The data recorded at baseline included demographic characteristics, detailed medical histories, physician-cited reasons for starting BIAsp 30 treatment, and the chosen dosage regimens. ***Results:*** The Indian cohort included 17,995 subjects with diabetes. Poor glycemic control (glycated hemoglobin [HbA_{1c}], 8.7%-9.6%) was observed at baseline in all four geographical zones (North, South, East, and West) and prestudy treatment groups (no therapy, only oral antidiabetic drug [OAD], OAD ± insulin, and OAD ± insulin ± BIAsp 30). Prevalence of both micro- and macrovascular complications was high, also reflecting poor glycemic control. Improving HbA_{1c} and fasting and postprandial blood glucose levels were the most common reasons for starting BIAsp 30 therapy. The subjects were prescribed a mean BIAsp 30 dose of approximately 24 IU, and a twice-daily regimen was employed in almost 80% of subjects. ***Conclusion:*** The baseline results of the IMPROVE study Indian cohort confirm the poor glycemic control and the delayed initiation and/or inadequacy of treatment in

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subjects with type 2 diabetes. These results also highlight the need for timely and appropriately intensive insulin-based therapy.

Keywords: baseline characteristics; biphasic insulin aspart 30; glycemic control; glycated hemoglobin; IMPROVE study; India; type 2 diabetes

INTRODUCTION

Antidiabetic therapy is aimed at normalizing the blood glucose levels of hyperglycemic subjects with diabetes, thereby decreasing the occurrence of associated complications.[1] Type 2 diabetic subjects are prescribed insulin when diet and exercise and/or oral antidiabetic drugs (OADs) are found inadequate for controlling fasting and postprandial hyperglycemia and glycated hemoglobin (HbA_{1c}). Tight blood glucose control decreases the risk of diabetic complications.[2] The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the benefits of improved glycemic control on the incidence and progression of diabetic complications in subjects with type 2 diabetes.[3]

Premixed insulins, eg, biphasic insulin aspart 30 (BIAsp 30; NovoMix® 30; Novo Nordisk, Denmark), can control the changes in blood glucose levels occurring both postprandially and between meals, and are therefore recommended for initiating insulin therapy.[4] Several randomized controlled trials (RCTs) have demonstrated significantly improved glycemic control and absence of major hypoglycemic events in subjects with type 2 diabetes on BIAsp 30 therapy.[5-9] RCTs are considered the "gold standard" for treatment evaluation; however, large, well-designed observational studies are also important since they provide valuable safety and efficacy information derived from routine clinical practice.[10,11]

The IMPROVE™ study and the Physician's Routine Evaluation of Safety and Efficacy of NovoMix* 30 Therapy (PRESENT) study are the two recently conducted observational studies aimed at determining whether the benefits observed in BIAsp 30 randomized clinical trials are duplicated in routine clinical practice. Results of the PRESENT study show that BIAsp 30 treatment is safe and effective in subjects with poorly controlled type 2 diabetes.[12] Baseline results of the multinational IMPROVE study have been published recently.[13] The IMPROVE baseline data reaffirm the global nature of poor glycemic control in type 2 diabetes and echo the concerns that initiation of therapy, particularly insulin, is commonly delayed in clinical practice.

Here, we report the baseline data of the Indian cohort of the IMPROVE study, including the demographic and disease characteristics by geographical and prestudy treatment groups, physician-cited reasons for starting BIAsp 30 treatment, and the BIAsp 30 dosage regimen prescribed at baseline.

METHODS

Study Design

The IMPROVE study is a multicenter, multinational, open-label, nonrandomized, observational study aimed at determining the safety and efficacy of BIAsp 30 treatment in subjects with type 2 diabetes in routine clinical practice. Participants were enrolled from 11 countries: Canada, China, Greece, Saudi Arabia, India, Iran, Italy, Japan, Poland, Russia, and South Korea. Here, we report the baseline data of the Indian study arm that enrolled subjects from North, South, East, and West India. A total of 1144 centers were involved across the four zones. The first subject was enrolled in

April 2007 and the last subject completed the study in December 2007. The study was conducted in accordance with the Declaration of Helsinki; the Drug Controller General of India was notified about the trial and was provided with the clinical trial protocol.

Subjects

All subjects with type 2 diabetes who were considered suitable to receive BIAsp 30 treatment by their physician were eligible to participate. Thus, subjects who were newly diagnosed, receiving only an OAD, and receiving insulin ± OAD were eligible to participate in the study. Exclusion criteria included subjects who were unlikely to comply with protocol requirements (eg, uncooperative attitude or unable to return for final visit), those with hypersensitivity to the study drug or excipient, and pregnant or breastfeeding women or those intending to conceive in the next 12 months. To eliminate selection bias, all centers enrolled the first 10 subjects considered eligible to receive BIAsp 30 treatment; those not meeting the inclusion or exclusion criteria were included in an "exclusion log sheet." All subjects provided written informed consent before participating in any trial-related activity.

Treatment

The study subjects were prescribed commercially available BIAsp 30 (NovoMix 30 Penfill® [100 IU/mL] or NovoMix 30 FlexPen® [100 IU/mL]; Novo Nordisk) on clinical decision of the treating physician. The treating physician determined the starting dose, frequency, and subsequent changes in dose and frequency. Since this was an observational study, there was no comparator arm.

Assessments and Outcome Measures

Each subject visited their respective clinic three times—at week 0 (baseline), week 13 (follow-up visit), and week 26 (final visit). At the baseline visit, the physician determined the subject's eligibility and recorded demographic data (age, gender, height, and weight) and medical history (from subject recall, medical reports, or personal records). The latter comprised type and duration of diabetes, previous and current treatment, diabetic complications (macro- and microvascular), number of hypoglycemic events (minor: over past 4 weeks, daytime and nocturnal; major: over past 13 weeks, daytime and nocturnal, and on omission of meal after injection; over past 26 weeks, after physical exercise of at least 30 minutes), and measures of blood glucose control (most recent HbA_{1c} values; three most recent fasting blood glucose [FBG] values over the last 4 weeks; and three most recent postprandial blood glucose [PPBG] values 2 hours after breakfast, lunch, and dinner over the last 4 weeks). The physicians also recorded the reasons for starting and the dosage of BIAsp 30 and set glycemic targets for HbA_{1c}, FBG, and PPBG after breakfast, lunch, and dinner.

Major hypoglycemic events, reported as serious adverse drug reactions (SADRs), during 26 weeks of BIAsp 30 treatment constituted the primary endpoint. Secondary efficacy and safety endpoints will be reported in future publications. In the present report, baseline demographic and disease characteristics are presented by the geographical groups (North, South, East, and West) and by the four pre-study treatment groups: no therapy, OAD only, OAD ± insulin, and OAD ± insulin ± BIAsp 30. Measures of blood glucose control are presented by geographical groups, while the percentage of subjects with macro- and microvascular compli-

cations is presented by geographical groups as well as by total cohort and prestudy treatment groups. In addition, we present BIAsp 30 dosage prescribed at baseline by geographical groups, the new therapy prescribed at baseline by the prestudy treatment groups, and the physician-stated reasons for starting BIAsp 30 treatment.

Statistical Analysis

The sample size calculation was based on the primary objective of evaluating the incidence of SADRs. For the entire IMPROVE study, a sample size of at least 20,000 was necessary to detect SADRs with a probability of at least 95% and assuming an incidence of at least 0.015%; an additional 6000 subjects were necessary to allow for subject withdrawal and loss to follow-up. Out of the 26,000 subjects constituting the global cohort, 9000 subjects were to be recruited from India.

For this baseline report, descriptive statistics have been used to summarize the data of the full analysis set (subjects receiving at least one dose of study drug and reporting safety information). The results of continuous variables are reported as mean and SD, while those of categorical variables are reported as frequencies and percentages.

As per protocol, only descriptive analysis was required and no further statistical analysis was performed.

RESULTS

Demographic and Disease Characteristics by Geographical Groups

The Indian cohort included 17,995 subjects (full analysis set), including 3031 from the North, 8616 from the South, 1729 from the East, and 4619 from West India. Almost half the subjects were recruited from South India. The Indian cohort constituted more than one-third of the IMPROVE global cohort. Nearly 60% of subjects were male. Across the four geographical regions, the mean ages were in the range of 51.2-53.9 years; mean weights were 65.04-67.77 kg; and mean body mass index was 25.01-25.96 kg/m^2 (Table 1). The overall mean duration of type 2 diabetes was almost 8 years. Poor glycemic control, as evidenced by elevated HbA_{1c}, FBG, and PPBG values, was observed in all four geographical groups at baseline. It was notable that the mean HbA_{1c} values were greater than 9% in all geographical groups (Table 1).

Demographic and Disease Characteristics by Prestudy Treatment Groups

Almost 95% of the enrolled subjects were receiving some form of antidiabetic therapy; 69.5% of subjects were receiving only an OAD (Table 2). The mean age, mean weight, mean body mass index, and mean duration of diabetes were lower in subjects receiving no therapy than in those on some form of antidiabetic therapy; these variables were also lower in subjects receiving only an OAD than in those receiving insulin and/or an OAD. Poor glycemic control was observed in all prestudy treatment groups (HbA_{1c} 8.7%-9.6%) and the entire Indian cohort (HbA_{1c} 9.3%); the group not receiving any pharmacological therapy showed the worst glycemic control (HbA_{1c} 9.6%). Prestudy treatment was missing for 19 subjects.

Diabetic Vascular Complications by Geographical Groups and Prestudy Treatment Groups

Macrovascular complications were present in 20.8%-34.7% of subjects, while micro-

Table 1. Baseline characteristics, diabetic complications, and BIAsp 30 dosage prescribed at baseline by geographical subgroups: IMPROVE India.

Parameter	North *n*=3031	South *n*=8616	East *n*=1729	West *n*=4619
Age, years	51.2 (±9.6)	53.3 (±10.9)	53.9 (±10.6)	53.8 (±10.1)
Male, %	64.1	58.9	61.4	58.0
Weight, kg	67.77 (±9.46)	67.68 (±11.59)	65.04 (±11.11)	67.11 (±11.60)
BMI, kg/m^2	25.47 (±3.09)	25.96 (±4.17)	25.01 (±4.30)	25.71 (±4.35)
Diabetes				
Type 2, %	91.7	97.2	94.8	95.3
Duration, years	8.45 (±4.86)	8.11 (±6.08)	8.06 (±5.64)	7.19 (±5.44)
Blood indices				
HbA_{1c}, %	9.20 (±1.68)	9.31 (±1.63)	9.44 (±1.82)	9.42 (±1.88)
FBG, mmol/L	9.71 (±2.20)	10.63 (±2.99)	11.51 (±3.68)	10.79 (±3.19)
PPBG, mmol/L				
Breakfast	14.24 (±3.28)	15.54 (±3.97)	16.15 (±4.19)	15.78 (±4.10)
Lunch	15.36 (±2.86)	15.86 (±4.25)	16.88 (±4.55)	15.01 (±4.37)
Dinner	–	10.86 (±2.34)	–	13.20 (±2.15)
Diabetic complications				
Macrovascular, %	28.4	22.0	34.7	20.8
Microvascular, %	45.0	45.7	47.3	36.6
Serious adverse drug reactions				
Hypoglycemic events, %	0.3	2.7	2.7	1.1
BIAsp 30 dosage prescribed at baseline				
Dose, IU	24.4 (±10.0)	23.8 (±12.7)	23.8 (±11.2)	24.1 (±11.2)
Twice-daily dosage, %	85.3	71.9	78.5	78.4

All values are represented as mean (SD) unless indicated.
BIAsp 30=biphasic insulin aspart 30; BMI=body mass index; FBG=fasting blood glucose; HbA_{1c}=glycated hemoglobin; PPBG=postprandial blood glucose.

Table 2. Baseline characteristics by prestudy treatment: IMPROVE India.

Characteristics	Total cohort	No therapy	OAD only	Other insulin ± OAD	BIAsp 30 ± other insulin ± OAD
Numbers enrolled	17,995	934	12,500	4437	105
% of total enrolled	–	5.2%	69.5%	24.7%	0.6%
Mean age ± SD, years	53.1±10.5	47.1±11.8	52.5±9.9	56.2±10.9	53.1±9.8
Gender (M/F), %	60/40	62/38	60/40	57/43	66/34
Mean weight ± SD, kg	67.3±11.3	66.1±13.1	67.4±11.0	67.5±11.7	66.3±13.1
Mean BMI ± SD, kg/m^2	25.7±4.1	25.6±4.6	25.7±3.9	25.9±4.4	25.6±4.2
Mean duration* ± SD, years	7.9±5.7	2.2±4.1	7.4±5.0	10.6±6.4	8.5±5.2
Mean HbA_{1c} ± SD, %	9.3±1.7	9.6±2.0	9.3±1.7	9.3±1.7	8.7±1.4

Prestudy treatment was missing for 19 patients.
*Mean duration of type 2 diabetes.
BIAsp 30=biphasic insulin aspart 30; BMI=body mass index; HbA_{1c}=glycated hemoglobin; OAD=oral antidiabetic drug.

vascular complications were identified in 36.6%-47.3% (Table 1). The occurrence of microvascular complications was considerably higher than that of macrovascular complications. The relatively lower rate of diabetic complications in subjects from West India corresponded with their shorter duration of diabetes. Those subjects receiving a greater number of antidiabetic medications had higher rates of complications, reflecting the relationship between complications and worsening glycemic control (Table 3). Interestingly, the rates of peripheral vascular disease, diabetic nephropathy, and peripheral neuropathy were slightly lower in the group receiving BIAsp 30 than in the group receiving an OAD and other insulin but not BIAsp 30 (Table 3).

Reasons for Starting BIAsp 30 Treatment

The three most common physician-cited reasons for starting BIAsp 30 treatment were for improving HbA_{1c} (91.3%), PPBG (87.6%), and FBG (85.5%) levels (Figure 1). This implies that the subjects recruited in the study displayed poor glycemic control at baseline. Over 38% of physicians selected BIAsp 30 treatment for their subjects because it afforded ease of starting insulin therapy. Decreased risk of hypoglycemia, subject dissatisfaction with previous therapy, and ease of intensifying insulin therapy were the other important reasons cited for choosing BIAsp 30.

New BIAsp 30 Therapy Prescribed at Baseline

Before the start of the study, 5.2% of subjects were receiving no therapy; the majority of these subjects were prescribed only BIAsp 30 at baseline (Table 4). Furthermore, 69.5% of subjects were receiving only an OAD before the start of the study; 18.7% of these were prescribed only BIAsp 30 while 50.4% were prescribed an OAD and BIAsp 30 at baseline. Less than 1% of subjects were prescribed an insulin and BIAsp 30 at baseline. The mean BIAsp 30 dose prescribed ranged from 23.8 to 24.4 IU, and the majority of subjects (71.9%-85.3%) required a twice-daily regimen (Table 1).

Table 3. Macrovascular and microvascular complications* by prestudy treatment: IMPROVE India.

		Prestudy treatment groups			
Diabetic complications	Total cohort	No therapy	OAD only	Other insulin ± OAD	BIAsp 30 ± other insulin ± OAD
Macrovascular, %	**24.1**	**10.1**	**21.8**	**33.3**	**33.0**
Peripheral vascular disease, %	8.2	3.9	7.2	11.9	11.7
Coronary heart disease, %	16.7	7.0	15.1	23.0	23.3
Stroke, %	2.4	1.4	1.9	4.0	4.9
Microvascular, %	**43.9**	**23.9**	**39.2**	**60.8**	**63.8**
Retinopathy, %	14.9	4.4	12.5	23.6	26.7
Diabetic nephropathy, %	14.3	10.1	12.9	19.3	19.0
Peripheral neuropathy, %	29.2	14.8	25.9	41.4	34.3
Autonomic neuropathy, %	5.9	4.2	4.9	9.1	9.5

*Patients could have multiple complications.
BIAsp 30=biphasic insulin aspart 30; OAD=oral antidiabetic drug.

Figure 1. Reasons for starting treatment with biphasic insulin aspart 30 (BIAsp 30). The data show the proportion of patients for whom their physicians gave the stated reasons for starting BIAsp 30 at baseline. The physicians were allowed to choose more than one reason. FBG=fasting blood glucose; HbA_{1c}=glycated hemoglobin; PPBG=postprandial blood glucose.

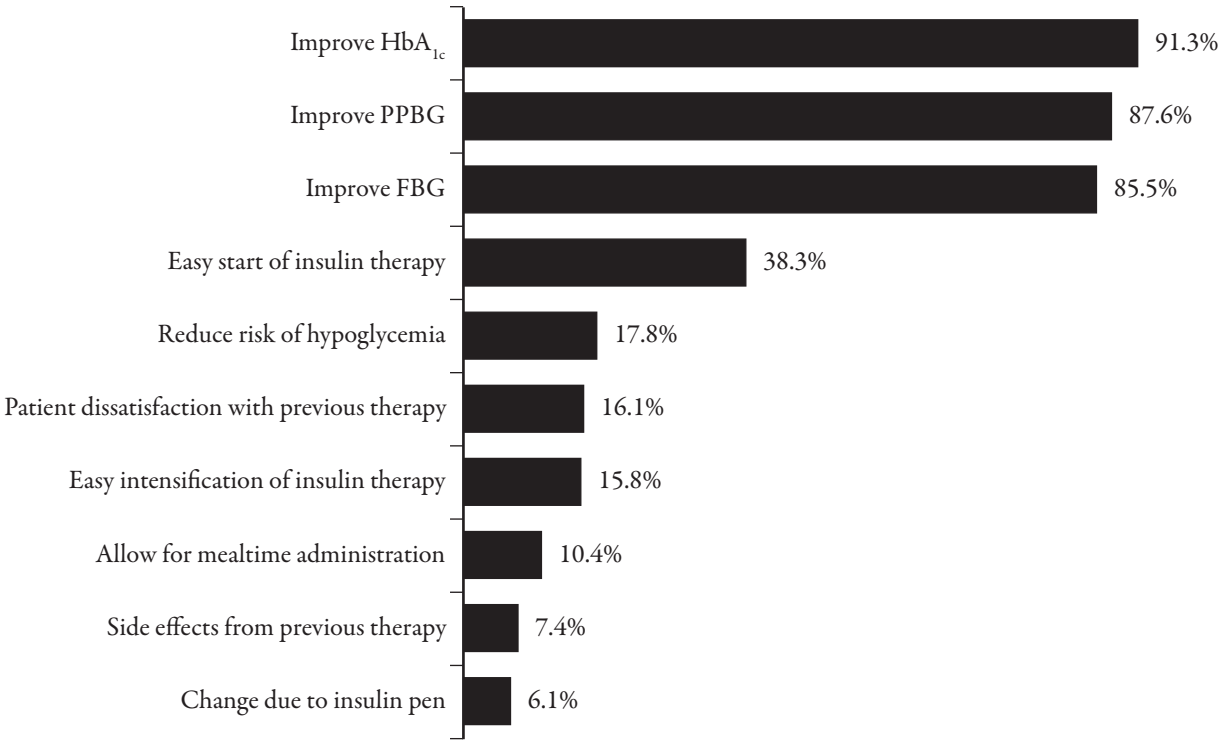

Table 4. New therapy prescribed at baseline: IMPROVE India.

	New therapy prescribed at baseline				
Prestudy treatment groups	**Missing**	**BIAsp 30**	**BIAsp 30 ± OAD**	**BIAsp 30 ± insulin ± OAD**	**Total**
Missing, %	<0.1	<0.1	<0.1	<0.1	<0.1
No therapy, %	<0.1	3.5	1.7	<0.1	5.2
OAD only, %	<0.1	18.7	50.4	0.3	69.5
Other insulin ± OAD, %	<0.1	7.0	16.8	0.9	24.7
BIAsp 30 ± other insulin ± OAD, %	0	<0.1	0.5	<0.1	0.6
Total, %	<0.1	29.2	69.4	1.3	100

BIAsp 30=biphasic insulin aspart 30; OAD=oral antidiabetic drug.

DISCUSSION

The IMPROVE study was a multinational observational study conducted to evaluate the safety and efficacy of BIAsp 30 treatment in subjects with type 2 diabetes under routine clinical conditions. It is hoped that the information gathered from this trial should complement the data available from RCTs and observational studies conducted previously. The present report includes the baseline demographic and disease characteristics of the Indian cohort as well as the dosage regimens and physician-cited reasons for starting BIAsp 30 treatment.

The large Indian cohort constituted more than one-third of the entire global study population.[13] The baseline demographic and disease characteristics of the four geographical groups were largely similar. In their recent position statement, the American Diabetes Association has recommended the following values for measures of glycemic control in adult diabetes subjects: HbA_{1c} <7.0%, FBG <7.2 mmol/L, and PPBG <10.0 mmol/L.[14] The subjects from all four geographical and prestudy treatment groups showed values in far excess of these limits, indicating poor glycemic control across the cohort.

Similar to the IMPROVE study, the PRESENT study was also a multinational, open-label observational study conducted in 2004-2005 to assess the safety, efficacy, and acceptability of BIAsp 30 treatment in subjects with type 2 diabetes.[12] The baseline HbA_{1c}, FBG, and PPBG values of the PRESENT India cohort were 9.2% (SD: 1.5%), 194 (SD: 56.2) mg/dL (10.67 [SD: 3.1] mmol/L), and 285.5 (SD: 76) mg/dL (15.7 [SD: 4.2] mmol/L), respectively; these values are similar to those recorded in the present study. In the Diabcare Asia study conducted in 1998 to examine the relationship between glycemic control and management of diabetes and late complications in subjects from urban India, nearly half the subjects exhibited poor glycemic control.[15] In that study, 53.9% of subjects were receiving only OADs and 22% were on insulin, while 19.8% were receiving a combination of insulin and OADs; the mean HbA_{1c} levels at baseline were 8.9% (2.1%). In contrast, in the IMPROVE India cohort, almost 70% of subjects were receiving only OADs before the study, and the mean HbA_{1c} levels at baseline were 9.3% (1.7%). This suggests that despite oral drug therapy in the majority of subjects, the HbA_{1c} remained suboptimal. Therefore, there is a need to appropriately escalate pre-existing therapies in order to achieve euglycemia in subjects with type 2 diabetes on OADs.

In line with the observation of poor glycemic control, high rates of diabetic vascular complications were reported at baseline in the Indian cohort. This high disease burden is likely to negatively impact the healthcare system in India, particularly in light of the greatest absolute increase in the number of diabetes subjects expected over the next two decades.[16] The Chennai Urban Rural Epidemiology Study (CURES) and the Chennai Urban Population Study (CUPS) reported the first Indian population-based data on diabetic complications. In these studies, diabetic retinopathy was observed in 17.6% of subjects,[17] peripheral neuropathy was encountered in 26.1%,[18] coronary artery disease was observed in 21.4%,[19] and peripheral vascular disease was noted in 6.3% of subjects.[20] In the IMPROVE India cohort, the group receiving insulin ± OADs at baseline showed higher corresponding values than those in the CURES and CUPS studies. While these differences may reflect differences from community-based versus clinic-based cohorts, our results highlight the high

prevalence of complications and the need to screen for them in a real-life setting.

In the IMPROVE India cohort a minor intergroup variation was observed in the rate of macrovascular complications in particular, with slightly higher rates in North and East India than in South and West India. The rates of microvascular complications reported from West India were also relatively lower than those from the other parts of the country. The reasons for these regional variations need to be determined.

Analysis by prestudy treatment groups showed that the group receiving no therapy had the worst glycemic control. Moreover, even the groups receiving some form of antidiabetic treatment showed poor values for all measures of glycemic control when compared with the American Diabetes Association recommended values. This implies that type 2 diabetes subjects should be evaluated systematically to determine the optimal timing of initiation and intensification of antidiabetic treatment. Studies have even shown that short-term intensive insulin treatment at the time of clinical diagnosis may actually facilitate long-term glycemic control.[21] In this cohort almost 70% of subjects receiving only an OAD at baseline had diabetes for a considerable period of time (>7 years) and had poor glycemic control. Subjects who had diabetes for more than 10 years were receiving some form of insulin with/without an OAD. Healthcare providers, because of their concerns related to insulin-induced hypoglycemia and weight gain,[22] might be delaying the initiation or intensification of insulin therapy and thereby not helping in improving the glycemic status of the diabetic population. Improving glycemic control as indicated by HbA_{1c}, FBG, and PPBG levels were the primary reasons for physicians selecting BIAsp 30 treatment for their type 2 diabetes subjects. Easy start of insulin therapy was another key reason for selecting BIAsp 30. Approximately 80% of subjects were put on the twice-daily regimen. This is in agreement with diabetes treatment guidelines[4] and has been shown to be effective in achieving recommended HbA_{1c} levels in 70% of subjects.[22]

While the data generated by the IMPROVE study are impressive and will help in developing a better understanding of issues related to type 2 diabetes, the study has some limitations associated with large observational studies. The vast cultural and socioeconomic diversity of the Indian population and the regional variations in the healthcare systems are bound to impact the study results. A limitation specific to the present study is the recording of medical histories from subject recall, which is likely to result in underestimation of hypoglycemic events at baseline. However, the large number of subjects recruited will prove useful in determining the real-world performance of BIAsp 30 treatment, and the results of well-designed RCTs conducted previously should bolster the evidence collected from the IMPROVE study.

ACKNOWLEDGMENTS

The authors would like to thank all the subjects and investigators for their participation in this study. The authors also accept direct responsibility for this paper but are grateful for the contribution made by Cactus communications Pvt Ltd. (supported by Novo Nordisk) in developing a first draft and in collating comments. The authors would also like to thank the Medical department of Novo Nordisk India for extending support in preparing this manuscript. This study was sponsored by Novo Nordisk. The sponsor support was restricted to the development of protocol, data collection, data analysis, and medical writing. Some

of these data have been previously presented at Annual conference of Research Society for Study of Diabetes in India (2008).

Conflict of Interest

Siddharth Shah is the principal investigator for IMPROVE study in India. A. K. Das and Ajay Kumar have participated in advisory board meetings on IMPROVE study and have given lectures for Novo Nordisk. A. G. Unnikrishnan, Sanjay Kalra, Manash P. Baruah, B. Ganapathi, and R. K. Sahay are expert panel members for the IMPROVE study in India and have no conflicts to disclose.

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