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Biphasic insulin aspart 30 in the treatment of elderly patients with type 2 diabetes: a subgroup analysis of the PRESENT Korea NovoMix® study

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Aims: To evaluate the efficacy, safety and treatment satisfaction with biphasic insulin aspart 30 (BIAsp30) in elderly patients with type 2 diabetes.

Methods: The Physicians' Routine Evaluation of Safety and Efficacy of NovoMix® 30 Therapy Korea study was a 6-month, prospective, observational study. No study-specific interventions were involved except the collection of data. All patients with type 2 diabetes not adequately controlled on their previous therapy, and who were prescribed BIAsp30 as monotherapy, or in combination with oral hypoglycaemic agents, were eligible for the study. This subgroup analysis was based on the outcomes in patients $\geq$65 years (n = 1720).

Results: BIAsp30 treatment was associated with significant mean reductions in haemoglobin A1c, fasting plasma glucose and post-prandial plasma glucose levels of 1.2 $\pm$ 1.6%, 2.3 $\pm$ 3.5 mmol/l and 4.8 $\pm$ 5.3 mmol/l at 6 months ($p < 0.0001$ for all), from baseline levels of 9.1 $\pm$ 1.7%, 10.7 $\pm$ 3.4 mmol/l and 16.7 $\pm$ 5.0 mmol/l, respectively. The rate of hypoglycaemia declined from 3.02 to 1.31 episodes per patient year, between baseline and study end. The proportion of patients reporting adverse drug reactions was low (0.3 and 0.1% at 3 and 6 months, respectively). Body weight gain was mild at <0.1 kg at 3 months, and 0.3 kg at 6 months. As compared to the previous treatment, >80% of patients were rated as being either 'very satisfied' or 'satisfied' with BIAsp30 treatment.

Conclusions: In this subanalysis of Korean elderly patients with type 2 diabetes inadequately controlled on their previous therapies, treatment with BIAsp30 offered improvements in glycaemic control and was well tolerated. Body weight gain was minimal with BIAsp30, and treatment satisfaction among these patients appeared to be high.

Keywords: insulin therapy, elderly diabetes, hypoglycemia
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Introduction

The use of insulin in elderly patients with type 2 diabetes poses a particular challenge to clinicians. The benefits of tight glycaemic control in reducing the risks of micro- and macrovascular complications in patients with type 2 diabetes is well established [1,2]. However, tight glycaemic control is also known to be associated with a higher frequency of hypoglycaemic episodes, and in elderly patients, this can have deleterious clinical consequences. Hence, managing the elderly patients with insulin is akin to walking a fine line (or as Niskanen

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puts it, 'a double-edged sword') [3] between achieving a reasonable level of control of hyperglycaemia for the patient on the one hand, and on the other hand, steadfastly avoiding hypoglycaemia.

Recent clinical studies involving insulin treatment have a tendency of not being performed in older people [4], and this observation may mirror clinical practice, where there is a reluctance to prescribe insulin in the elderly patient. This reluctance is also reflected in consensus guidelines; the guidelines by the American Geriatric Society (in conjunction with the American Diabetes Association) [5], as well as the guidelines of the Asian-Pacific Type 2 Diabetes Policy Group [6], for instance, are notably silent about the role of insulin in the management of the elderly patient, and not to mention, the role of the newer insulin analogues in these patients. Indeed, published clinical experience to date regarding the use of insulin analogues in the elderly patient appears limited to only a handful of small studies and subgroup analyses [7–11].

The Physicians' Routine Evaluation of Safety & Efficacy of NovoMix 30 Therapy (PRESENT) Korea study was a large-scale, prospective, open-labelled, uncontrolled, observational study conducted across 174 centres in South Korea to evaluate efficacy, safety and treatment satisfaction with biphasic insulin aspart 30 (BIAsp30, NovoMix 30; manufactured by Novo Nordisk A/S) in Korean clinical practice. The objective of this subgroup analysis was to investigate whether the efficacy, safety and treatment satisfaction benefits of prescribing BIAsp30 to patients with type 2 diabetes not adequately controlled on their previous therapy were observed in the subgroup of elderly patients, that is, those aged 65 years and older.

Methods

Study Design

Male or female patients with type 2 diabetes, who were judged by their treating physicians to be inadequately controlled on their previous therapy, were enrolled into the study and prescribed with BIAsp30 as monotherapy, or in combination with oral hypoglycaemic agents (OHAs). The dosing adjustments were made at the physician's discretion, reflecting routine clinical practice. All patients used the prefilled FlexPen® insulin pen device (manufactured by Novo Nordisk A/S) to administer their BIAsp30.

The physicians that participated in this study were asked to document details of the patient's history, treatments prescribed, blood glucose measurements, adverse drug reactions (ADRs) and hypoglycaemic episodes on data collection forms. 'Minor' hypoglycaemia was defined as an episode in which the patient was able to self-treat, and conversely, 'major' was defined as an episode in which the patient required the assistance of another person.

Physicians were asked to assess their own as well as patients' satisfaction with BIAsp30 treatment. The questions asked were 'In comparison with the patient's previous treatment, how satisfied is your patient with BIAsp30' and 'In comparison with the patient's previous treatment, how satisfied are you (the physician) with BIAsp30'. The reasons for starting BIAsp30 treatment, or for stopping treatment were also assessed. Serious ADRs were to be reported by the participating physicians on separate forms, which were faxed to the pharmacovigilance department of the manufacturer within 24 hours.

Data were collected at baseline and at 3 and 6 months of therapy. No study-specific interventions were involved except the collection of data.

Statistical Analysis

All enrolled patients having baseline data were included in the safety analysis set, which was used for the analyses of efficacy, safety and treatment satisfaction. Subgroup analyses were performed on the subset of Korean patients in the safety analysis set who were aged 65 years and older ($\geq$65 years). For reference, analyses performed on the subset of patients aged below 65 years ($<$65 years) are also presented here.

Descriptive statistics (s.d.) were used to summarize patient baseline characteristics, diabetes therapy and safety outcomes. Paired *t*-test was used to assess changes in glycated haemoglobin A1c (HbA_{1c}), fasting plasma glucose (FPG) and post-prandial plasma glucose (PPPG) levels from baseline. Differences were considered significant at the $p < 0.05$ level. All statistics were calculated with SAS® version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Patients

A total of 5831 patients were enrolled into the PRESENT Korea study, of which 5828 were included in the safety analysis set. Of the patients included in the safety analysis set, 4106 (70%) were $<$65 years, 1720 (30%) were $\geq$65 years, and information on age was missing for the remaining two patients. The demographic and other baseline characteristics of patients $\geq$65 years, as well as those $<$65 years, is shown in table 1. The mean age of patients in

Table 1 Demography and baseline characteristics of patients

	<65 years	≥65 years
n	4106	1720
Age (years)	50.9 ± 10.6	71.6 ± 6.0
Gender (female/male) (%)	47.3/52.7	59.9/40.1
BMI (kg/m^2)	24.1 ± 3.1	24.3 ± 2.9
Duration of diabetes (years)	8.5 ± 6.2	12.4 ± 7.9
Previous treatment (%)		
Insulin only	31.8	35.3
OHA only	28.7	28.2
Insulin + OHA	27.2	27.4
Diet only	12.2	9.0
Unknown/Incomplete information	0.1	0.2

OHA, oral hypoglycaemic agents. Values represent mean ± s.d. unless otherwise noted.

the ≥65 years subgroup was 71.6 years, and their mean duration of diabetes was 12.4 years. There was a preponderance of females to males in this subset of patients.

Glycaemic Control and Insulin Dose

Treatment with BIAsp30 was associated with significant improvements in glycaemic control among patients <65 years, as well as those ≥65 years (figure 1). Among patients ≥65 years, significant baseline reductions in HbA_{1c} of 0.8 ± 1.3% and 1.2 ± 1.6% were observed at 3 months and 6 months of treatment ($p < 0.0001$ for both). The proportion of patients ≥65 years having an HbA_{1c} of <7.0% increased from 7.3% at baseline to 13.3% at 3 months and 23.8% at 6 months. Treatment with BIAsp30 was also associated with significant baseline reductions in FPG of 1.6 ± 3.2 mmol/l at 3 months and 2.3 ± 3.5 mmol/l at 6 months ($p < 0.0001$ for both), as well as reductions in PPPG of 3.6 ± 4.9 mmol/l at 3 months and 4.8 ± 5.3 mmol/l at 6 months ($p < 0.0001$ for both).

Among patients ≥65 years, the mean total BIAsp30 dose was 31.8 U (0.52 U/kg) at baseline, and 33.1 U (0.55 U/kg) and 34.6 U (0.57 U/kg) at 3 months and 6 months, respectively. Throughout the study, the highest proportion of patients ≥65 years were treated with twice-daily administration of BIAsp30 at breakfast and dinnertime (57.7, 61.5 and 64.4% of patients at baseline, 3 months and 6 months, respectively), followed by once-daily administration at breakfast (41.7, 37.9 and 35.2% of patients at baseline, 3 months and 6 months, respectively). The proportion of patients receiving thrice-daily BIAsp30 administration (i.e. at breakfast, lunchtime and dinnertime) was low (0.3, 0.4 and 0.3% of patients at baseline, 3 months and 6 months, respectively).

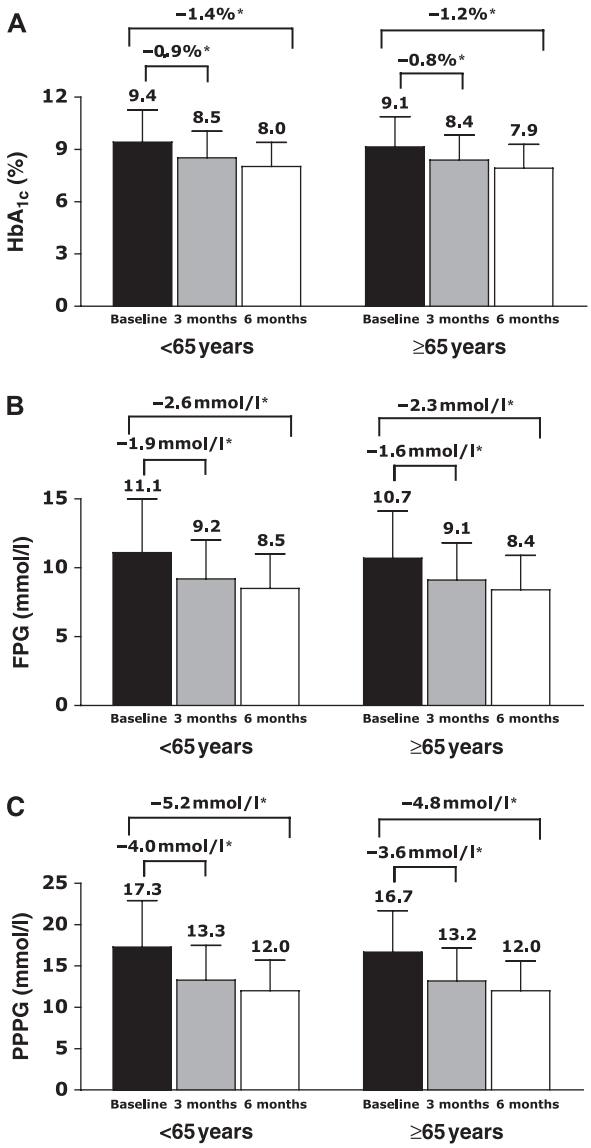

Fig. 1 (A) Mean haemoglobin A1c (HbA_{1c}), (B) fasting plasma glucose (FPG) and (C) post-prandial plasma glucose (PPPG) at baseline, and at 3 months and 6 months of biphasic insulin aspart 30 therapy. *$p < 0.0001$ versus baseline.

Hypoglycaemia and ADRs

The proportion of patients ≥65 years reporting hypoglycaemic episodes declined from 23.3% at baseline to 17.2% at 3 months and 15.0% at 6 months (table 2). The majority of hypoglycaemic episodes reported at 3 months and at 6 months were minor in nature and only 0.2% (1 in 664) of episodes reported at 3 months, and 0.5% (2 in 424) at 6 months were major hypoglycaemic episodes. In addition, hypoglycaemic episodes

Table 2 Hypoglycaemic episodes by severity and time of episode

	<65 years		≥65 years	
	n (%)	*E*	n (%)	*E*
Overall				
Baseline	864 (21.0)	3061	400 (23.3)	1322
3 months	631 (15.8)	1588	288 (17.2)	664
6 months	480 (12.4)	978	242 (15.0)	424
Severity				
Baseline				
Major	25 (0.6)	55	17 (1.0)	28
Minor	861 (21.0)	3006	396 (23.0)	1294
3 Months				
Major	2 (0.1)	3	1 (0.1)	1
Minor	631 (15.8)	1585	287 (17.1)	663
6 Months				
Major	2 (0.1)	4	2 (0.1)	4
Minor	478 (12.4)	974	242 (15.0)	422
Timing of Episode				
Baseline				
Daytime	709 (17.3)	2016	331 (19.2)	913
Nocturnal	454 (11.1)	1045	178 (10.3)	409
3 Months				
Daytime	556 (14.0)	1239	247 (14.7)	540
Nocturnal	191 (4.8)	349	84 (5.0)	124
6 Months				
Daytime	405 (10.5)	787	191 (11.8)	307
Nocturnal	123 (3.2)	191	75 (4.6)	117

n, number of subjects with hypoglycaemic episodes; %, percentage of subjects exposed in the given period having hypoglycaemic episodes; *E*, absolute number of hypoglycaemic episodes.

tended to occur during the day, with 18.7% (124 in 664) of episodes reported at 3 months, and 27.6% (117 in 424) at 6 months occurring during the night. Overall, treatment with BIAsp30 was associated with a decline in the rate of hypoglycaemic episodes among patients ≥65 years, from 3.02 episodes per patient year at baseline, to 1.31 episodes per patient year at the end of the study. Consistent with this trend, the rate of major hypoglycaemic episodes also declined from 0.07 episodes per patient year at baseline to <0.01 episodes per patient year at the end of the study, with BIAsp30 treatment.

Few patients in the <65 years subgroup, as well as the ≥65 years subgroup, reported ADRs. Among patients in the ≥65 years subgroup, a total of 36 ADRs were reported by five patients (0.3%) at 3 months, while one patient (0.1%) reported a single ADR at 6 months. All ADRs were non-serious in nature, and the most frequently reported ADRs among patients ≥65 years were oedema (43.2% of all events reported throughout the study), lipodystrophy (18.9%), followed by symptoms of general hypersensitivity (13.5%). As for the <65 years subgroup, 47 ADRs were reported by seven patients (0.2%) at 3 months, and one patient (<0.1%) at 6 months reported a single ADR. As in the ≥65 years subgroup, all ADRs in the <65 years subgroup were non-serious in nature, and the most frequently reported ADRs were oedema, followed by lipodystrophy.

Body Weight

The mean body weight of patients ≥65 years was 61.9 kg at baseline, and 61.9 kg and 62.2 kg at 3 months and 6 months, respectively. Treatment with BIAsp30 was associated with baseline increases in body weight of <0.1 kg at 3 months and 0.3 kg at 6 months.

Treatment Satisfaction

Patients' satisfaction to BIAsp30 therapy was assessed by their treating physicians, through an unvalidated, close-ended questionnaire (figure 2). The majority (>80%) of patients were perceived as being either 'very satisfied' or 'satisfied' with BIAsp30 over previous treatment, as assessed at 6 months of treatment. The treating physicians were asked to rate how satisfied they were with BIAsp30 over their patient's previous treatment, and the majority of responses (>80%) were also either 'very satisfied' or 'satisfied' at 6 months of treatment.

Discussion

South Korea is now considered to have one of the most rapidly ageing populations in the world. The percentage of people living in Korea aged 65 years and older was 2.9% in 1960, and has since risen to 7.2% in 2000 [12]. In 2030, this figure is projected to reach 24.1%. The prevalence of type 2 diabetes increases dramatically with age [13], and as the number of elderly people increases in Korea, so will the prevalence of type 2 diabetes likewise be expected to increase. The ageing Korean population and its attendant health problems like diabetes will pose a considerable burden to the health-care system. The availability of more published studies involving disease management in the elderly would therefore be useful, given the current dearth of such information.

A recent study by Noh *et al.* [14] shows that a considerable percentage of elderly patients with type 2 diabetes receive inadequate management of hyperglycaemia with fewer than two in five patients having good glycaemic control ($HbA_{1c} < 7.0\%$). It is therefore encouraging to find from our study that it is possible for elderly Korean patients inadequately controlled on their previous therapy to achieve significant reductions in HbA_{1c}

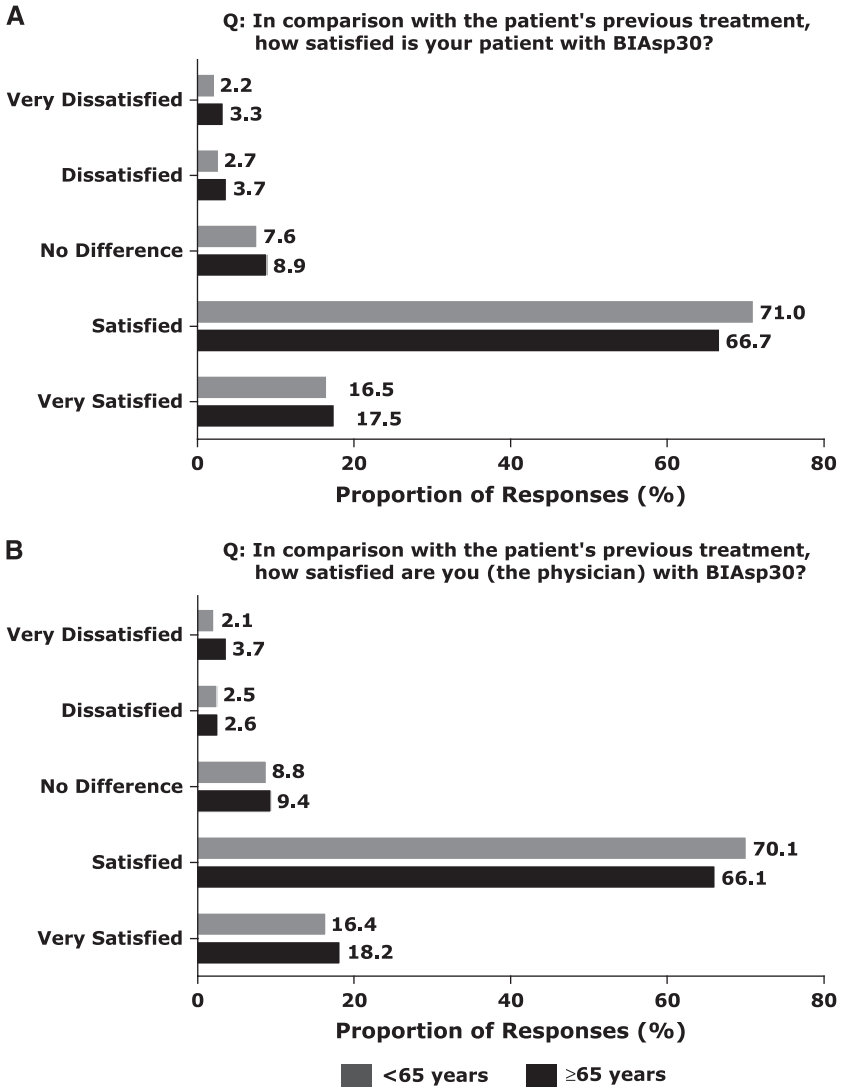

Fig. 2 Treatment satisfaction (A; patients, B; physician), as assessed by the physician at 6 months of biphasic insulin aspart 30 therapy.

of approximately 1.2% at 6 months of treatment with BIAsp30 under clinical practice conditions. In our study, although treatment with BIAsp30 was associated with an increase in the proportion of patients achieving target HbA_{1c} levels (from 7.3% at baseline to 13.3% at 3 months and 23.8% at 6 months), clearly target HbA_{1c} levels was still not achieved in a large majority of patients at the end of the study. The 1-2-3 study has shown that by increasing the dose and frequency of BIAsp30 administration in a stepwise manner, it is possible to increase the percentage of patients achieving a target HbA_{1c} of $<7.0\%$, from 41% with once-daily BIAsp30, to 70% with twice-daily BIAsp30, and 77% thrice-daily BIAsp30 [15]. Similarly, by continuing to increase the dose of BIAsp30 gradually over an extended period of time, we believe it would have been possible to enable a greater proportion of elderly patients in our study to reach glycaemic targets, and at the same, avoid treatment-induced hypoglycaemia.

Unquestionably, the most deleterious effect of insulin therapy is hypoglycaemia. In elderly patients who live alone, as well as those who do not have easy access to medical assistance, the issue of hypoglycaemia would be of graver concern (especially, major hypoglycaemia, because by definition, the patient is unable to self-treat). The Noh *et al.* [14] study showed that in Korea, 5.5% of elderly patients with type 2 diabetes are admitted to hospital because of major hypoglycaemia. Encouragingly,

our study not only found fewer episodes of major hypoglycaemia following treatment with BIAsp30, it also reported fewer overall hypoglycaemic episodes, in spite of the glycaemic improvement achieved. In our study, more than three in five elderly patients were already on some form of insulin therapy at baseline. One possible reason for the reduced hypoglycaemia was that the short acting component of BIAsp30 better mimics the physiological response to meals [16] compared with regular human insulin treatments. Indeed, previous studies have shown BIAsp30 to be associated with a reduced risk of major hypoglycaemia compared with biphasic human insulin in non-elderly patients [17,18].

Apart from an increased risk of hypoglycaemia, another negative aspect of therapy with human insulin is body weight gain. The increase in body weight is often of concern for clinicians, as it may prevent the attainment of glycaemic targets and limit the success of treatment [19]. In the UK Prospective Diabetes Study, patients assigned to insulin treatment gained, on average, 4 kg more body weight than those assigned to conventional (diet) therapy, at 10 years [1]. In a separate study of elderly patients in the Netherlands, a mean body weight increase of 4 kg was observed after 6 months of treatment with Neutral Protamine Hagedorn insulin [20]. As compared with these studies, body weight gain among elderly patients was minimal in our study, at 0.3 kg at 6 months.

In our study, we sought to examine patient and physician satisfaction with BIAsp30 treatment through an unvalidated questionnaire that was completed by the physician. The results suggest an improvement in treatment satisfaction with BIAsp30 therapy over the patients' previous insulin treatment among the majority of patients and physicians. Contrary to popular opinion, it has been shown that the initiation of insulin in elderly patients with type 2 diabetes inadequately controlled on OHAs does not lead to deterioration of patient treatment satisfaction, but on the other hand, may improve it [21,22]. For patients in our study who were already on some form of insulin therapy at baseline, and in whom improvements in treatment satisfaction were observed, one reason for the improved treatment satisfaction may perhaps be attributed to the prefilled FlexPen insulin pen device that the patients were using to administer their BIAsp30 during the study. The device has been shown in a previous study (where over half of the patients enrolled were aged 60 years and above) to improve quality of life and treatment satisfaction over other insulin delivery devices [23]. Previously, it has also been shown that prefilled insulin pens are highly accepted among elderly patients [24] and that elderly patients find prefilled insulin pens to be more acceptable than conventional insulin syringes [25].

Overall, BIAsp30 appears to be well tolerated in elderly Korean patients with type 2 diabetes, and the proportion of patients reporting ADRs, as well as the proportion of patients discontinuing treatment because of ADRs, was low. The overall efficacy and safety profile of BIAsp30 in elderly patients appears comparable with the non-elderly subpopulation, and we did not find any evidence that the elderly population merits more attention when prescribed with BIAsp30. The trends in treatment satisfaction also appear comparable between the elderly and non-elderly subpopulations.

Study Limitations

This was an observational study and patients were not selected based on any strict inclusion or exclusion criterion. Hence, a small percentage of patients with baseline $HbA_{1c} < 7\%$ were enrolled as they may have been considered by their physicians to have poor glycaemic control. Improvements in glycaemic control can potentially be because of study effects, although this effect should be minimized in an observational study compared with randomized clinical trials, as patients in an observational study are less likely to make an extra effort to control their condition. Information on hypoglycaemic episodes and adverse drug reactions were based on patient recollection, which may result underreporting.

Conclusions

In conclusion, this study demonstrated that for Korean elderly patients with type 2 diabetes who are inadequately controlled on their previous therapy, treatment with BIAsp30 offers improvements in glycaemic control and is well tolerated. Body weight gain was minimal with BIAsp30, and treatment satisfaction among these patients appears to be high. A well-designed, randomized control study is needed to confirm our results.

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