ORIGINAL RESEARCH

Safety and Effectiveness of Switching from a Basal-only to Biphasic Insulin Aspart 30 Insulin Regimen

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ABSTRACT

Purpose: This sub-analysis of the A_1chieve study evaluated the safety and effectiveness of changing from a basal-only insulin regimen to biphasic insulin aspart 30.

Methods: A_1chieve was an international, multicenter, prospective, open-label, non-interventional, 24-week study in people with type 2 diabetes mellitus starting/switching to therapy with biphasic insulin aspart 30, insulin detemir, or insulin aspart (alone/in combination) in routine clinical practice. This sub-analysis evaluated the safety and effectiveness of switching from basal insulin with either insulin glargine (GLA group) or insulin neutral protamine Hagedorn (NEU group) to biphasic insulin aspart 30.

Results: A total of 2,818 participants received biphasic insulin aspart 30 (1,395 in the GLA group and 1,423 in the NEU group). After 24 weeks of treatment, there were significant reductions in the proportion of patients with at least one hypoglycemia event: total [baseline vs. 24 weeks: 15.5% vs. 9.7% ($p < 0.001$) and 12.3% vs. 9.9% ($p < 0.05$), in NEU and GLA groups, respectively], major [2.5% vs. 0.08% ($p < 0.001$)

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and 1.2% vs. 0.08% ($p < 0.001$), in NEU and GLA groups, respectively] and nocturnal hypoglycemia [7.2% vs. 3.5% ($p < 0.001$) and 5.4% vs. 3.9% ($p < 0.05$), in NEU and GLA groups, respectively]. After 24 weeks of biphasic insulin aspart 30 there were statistically significant improvements from baseline in glycated hemoglobin, fasting plasma glucose, and post-prandial plasma glucose levels ($p < 0.001$) and in health-related quality of life ($p < 0.001$) in both groups.
Conclusions: Biphasic insulin aspart 30 may benefit patients with poor glycemic control on basal insulin regimens who are seeking to change treatment.

Keywords: A_1chieve; Basal insulin; Biphasic insulin aspart 30; Effectiveness; Type 2 diabetes mellitus

INTRODUCTION

People with type 2 diabetes who fail to attain optimal glycemic control while receiving oral glucose-lowering drugs (OGLDs) are frequently prescribed basal insulin [1]. However, there is a requirement for treatment regimens to be continually assessed, because as disease progresses it may be necessary to intensify treatment to maintain glycemic control within accepted targets [1]. One option for intensifying treatment may be to switch patients from basal insulin to premixed insulin, which contains basal plus rapid-acting insulin in one injection. There are currently few data to describe how effective premixed insulins may be in people with type 2 diabetes who are failing to maintain glycemic control on basal insulin [1]. However, meta-analyses and systematic reviews of published clinical trials indicate that premixed insulin treatment may have benefits over basal

insulin treatment in enabling patients to reach glycemic targets [2, 3].

Interventional studies have demonstrated that targeting raised post-prandial plasma glucose (PPG) hyperglycemia is essential in reducing elevated glycated hemoglobin (HbA_{1c}) to accepted target levels [4]. Indeed, previous studies have demonstrated a strong correlation between elevated PPG levels and the risk of developing diabetes complications [4–7]. In type 2 diabetes, basal insulins such as insulin glargine and neutral protamine Hagedorn (NPH) insulin are effective for basal control of glucose, but do not target PPG fluctuations [8, 9]. Insulin regimens that can reduce PPG fluctuations, such as, biphasic insulin aspart 30, may be beneficial in some clinical situations, such as when basal-only insulin regimens are failing to control blood glucose levels [10].

A_1chieve was an international non-interventional study evaluating the safety and clinical effectiveness of insulin regimens in patients with type 2 diabetes receiving routine clinical care in 28 countries across 4 continents [11]. The full results of the A_1chieve study have been published [11], but it is interesting to look at specific sub-groups of this large observational study to gain information on the potential benefits of specific insulin regimens or switches to new insulin regimens. The purpose of this sub-analysis was to evaluate the safety and effectiveness of switching people with type 2 diabetes from a basal only insulin ± OGLDs regimen to a biphasic insulin aspart 30 ± OGLDs regimen.

METHODS

A_1chieve was a prospective, international, multicenter, open-label, non-interventional, 24-week study in people with type 2 diabetes

in routine clinical practice who were being treated with anti-diabetes medication before starting, or switching to, insulin therapy with biphasic insulin aspart 30 (NovoMix®; Novo Nordisk A/S, Bagsvaerd, Denmark), insulin aspart (NovoRapid®; Novo Nordisk A/S, Bagsvaerd, Denmark), or insulin detemir (Levemir®; Novo Nordisk A/S, Bagsvaerd, Denmark) either in conjunction with or without OGLDs [11]. All study participants signed informed consent forms and were free to withdraw from the study at any time. The study was conducted in accordance with the Declaration of Helsinki of 1964, as revised in 2008 [12], and guidelines for good pharmacoepidemiology practice [13].

Clinic visits were defined as baseline, interim [approximately 12 weeks from baseline (results not reported here)], and a final visit (approximately 24 weeks from baseline).

The primary objective of this sub-analysis was to evaluate the safety profile of switching from a basal-only insulin regimen to insulin therapy with biphasic insulin aspart 30 by measuring the incidence of serious adverse drug reactions (SADRs), including major hypoglycemia events. Other safety assessments included the change in the number of overall, major, or nocturnal hypoglycemia events between baseline and 24 weeks. These were based on patient recall of events within the last 4 weeks before the study visit.

A hypoglycemia event was defined as an event with symptoms of hypoglycemia that resolved with glucagon, oral carbohydrate intake, or intravenous glucose, or any symptomatic or asymptomatic event where plasma glucose was <3.1 mmol/l or <56 mg/dl. Major hypoglycemia events were defined as events with severe central nervous system symptoms consistent with hypoglycemia, in which the patient was unable to self-treat and

had one of the following characteristics: plasma glucose <3.1 mmol/l or <56 mg/dl, or reversal of symptoms after either food intake, glucagon or intravenous glucose administration. Nocturnal hypoglycemia events were defined as individualized symptomatic events consistent with hypoglycemia, which occurred between bedtime after the evening insulin injection and before getting up in the morning; if applicable, events were those that occurred before morning determination of fasting plasma glucose (FPG) and the morning insulin injection.

Secondary endpoints included the change in glycated hemoglobin, FPG levels before breakfast, PPG levels after breakfast, after lunch and after dinner, body weight, systolic blood pressure, and health-related quality of life (HRQoL) between baseline and 24 weeks. HRQoL was self-assessed at baseline and after 24 weeks by the patients using the EuroQol (EQ-5D) a standardized questionnaire for use as a measure of health outcome. The EQ-5D provides a single index value for status of health, and evaluates five domains of patient health/lifestyle (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Patient responses were evaluated on a visual analogue scale (VAS) of 0 (worst imaginable health) to 100 (best imaginable health). The dosage of basal insulin before switching to biphasic insulin aspart 30, the dosage of biphasic insulin aspart 30 at initiation, and the dosage of biphasic insulin aspart 30 administered at subsequent visits were recorded.

Statistical Analysis

This publication reports the results for patients who were receiving basal insulin regimens with insulin glargine (GLA group) or neutral protamine Hagedorn (NPH; NEU group) at pre-study visit and

were switched to biphasic insulin aspart 30 (±OGLDs) in the A_1chieve study. Analysis of each of the safety and effectiveness outcome measures was performed by pre-study basal insulin experience (insulin glargine or NPH insulin).

Analyses were performed on the full analysis set, defined as all patients with a baseline visit and who received at least one dosage of biphasic insulin aspart 30. McNemar's test was used to analyze the proportion of patients reporting at least one hypoglycemia event. The number of SADRs considered to be related to biphasic insulin aspart 30 was also recorded. Changes from baseline in HbA_{1c}, FPG, PPG, systolic blood pressure, body weight, and HRQoL were analyzed using paired t test. All statistical tests were two-tailed, using a 5% significance level, and were conducted by Novo Nordisk A/S using SAS® Version 9.1.3 (SAS® Institute Inc., Cary, NC, USA).

RESULTS

Study Participants

A total of 2,818/66,726 (4.2%) participants were switched to biphasic insulin aspart 30 at baseline: 1,395/66,726 (2.1%; regional range 1.4%–4.2%) in the GLA group and 1,423/66,726 (2.1%; regional range 0.7%–7.7%) in the NEU group. Baseline patient and disease characteristics are shown in Table 1.

Insulin and OGLD Exposure

In the GLA group, the starting mean (SD) total biphasic insulin aspart 30 dose was 0.50 (0.21) U/kg ($n = 1,352$) and at 24 weeks was 0.59 (0.26) U/kg ($n = 1,066$). In the NEU group, the starting total biphasic insulin aspart 30 dose was 0.51 (0.22) U/kg ($n = 1,396$) and at 24 weeks was 0.60 (0.25) U/kg ($n = 1,172$).

In the GLA group, most patients received twice daily biphasic insulin aspart 30 at baseline (86.0%) and after 24 weeks (82.6%). Other injection frequencies at baseline and week 24, respectively, were once daily (9.5% and 7.6%), 3 times daily (4.4% and 9.0%), and more than 3 times daily (0.1% and 0.8%). Similarly, in the NEU group, most patients received twice daily biphasic insulin aspart 30 at baseline (81.9%) and after 24 weeks (75.8%). Other injection frequencies at baseline and week 24, respectively, were once daily (9.0% and 8.7%), 3 times daily (9.0% and 14.3%) and more than 3 times daily (0.1% and 1.3%).

The most frequently prescribed OGLDs were metformin and sulfonylurea. In the GLA group 916 of 1,274 (71.9%) patients were receiving metformin before entering the study and this increased to 768 of 939 (81.8%) after 24 weeks of biphasic insulin aspart 30 treatment. In the NEU group 860 of 1,100 (78.2%) were receiving metformin before entering the study and this increased to 773 of 888 (87.0%) after 24 weeks of biphasic insulin aspart 30 treatment. In the GLA group 794 of 1,274 (62.3%) patients were receiving sulfonylurea before entering the study and this dropped to 307 of 939 (32.7%) after 24 weeks of biphasic insulin aspart 30 treatment. In the NEU group 665 of 1,100 (60.5%) patients were receiving sulfonylurea before entering the study and this dropped to 206 of 888 (23.2%) patients after 24 weeks of biphasic insulin aspart 30 treatment.

Safety Measures

Hypoglycemia
After 24 weeks of receiving biphasic insulin aspart 30, the proportion of participants experiencing hypoglycemia events, major hypoglycemia, and nocturnal hypoglycemia significantly decreased from baseline in the

Table 1 Baseline patient and disease characteristics by pre-study basal insulin group

	GLA group	NEU group
Mean (SD) age (year)[a]	56.2 (12.2)	58.1 (11.3)
Male, n (%)[b]	705 (50.6)	660 (46.4)
Mean (SD) weight (kg)[c]	72.8 (15.8)	74.8 (16.5)
Mean (SD) BMI (kg/m^2)[d]	27.4 (5.4)	28.1 (5.6)
Mean (SD) diabetes duration (year)[e]	10.3 (6.3)	11.4 (6.9)
Mean (SD) pre-switch insulin dose (U/kg)[f]	0.36 (0.19)	0.46 (0.26)

Due to the non-interventional nature of this study, not all baseline data were recorded and some patients were lost to follow-up

GLA insulin glargine group, *NEU* insulin neutral protamine Hagedorn group

[a] $n = 1{,}381$ GLA; $n = 1{,}402$ NEU
[b] $n = 1{,}394$ GLA; $n = 1{,}423$ NEU
[c] $n = 1{,}352$ GLA; $n = 1{,}397$ NEU
[d] $n = 1{,}291$ GLA; $n = 1{,}318$ NEU
[e] $n = 1{,}368$ GLA; $n = 1{,}409$ NEU
[f] $n = 1{,}352$ GLA; $n = 1{,}397$ NEU

NEU and GLA groups ($p < 0.05$; Table 2). There was no indication that the proportion of patients experiencing a hypoglycemia event at baseline and at 24 weeks was higher in those taking sulfonylureas compared with those who were not taking sulfonylureas (Table 2).

SADRs

Two SADRs were recorded that were probably due to biphasic insulin aspart 30: one hypoglycemia unconsciousness event in the GLA group and one hypoglycemia event in the NEU group.

Body Weight

There was a statistically significant ($p < 0.01$) weight gain (0.3 kg) after 24 weeks of biphasic aspart 30 in the GLA group, but no significant weight change in the NEU group (Table 2).

Systolic Blood Pressure

There was a statistically significant ($p < 0.001$) reduction in systolic blood pressure after 24 weeks of biphasic aspart 30 in both the GLA group and NEU group (Table 2).

Effectiveness Measures

Glycemic Measures

After 24 weeks of treatment with biphasic insulin aspart 30, both groups showed statistically significant improvements from baseline in HbA$_{1c}$ (Fig. 1). Specifically there was a mean 1.9% (21 mmol/mol) and 2.0% (22 mmol/mol) improvement in HbA$_{1c}$ in the GLA and NEU group, respectively (Table 3) There were also significant improvements in FPG and PPG (post-breakfast, post-lunch, and post-dinner) levels ($p < 0.001$; Table 3).

At baseline in the NEU group, 4/74 (5.4%), 29/954 (3.0%) and 4/108 (3.7%) individuals who were switched to once-daily, twice-daily, or three or more daily injections of biphasic insulin aspart 30, respectively, had achieved glycemic control targets (HbA$_{1c}$ <7%; <53 mmol/mol). After 24 weeks of biphasic insulin aspart 30, in the NEU group 15/64 (23.4%), 263/851 (30.9%), and 27/93 (29.0%) achieved glycemic control targets, respectively.

At baseline in the GLA group, 10/91 (11.0%), 29/1,041 (2.8%), and 0/55 (0.0%) individuals who were switched to once-daily, twice-daily, or three or more daily injections of biphasic insulin aspart 30, respectively, had reached glycemic control targets. After 24 weeks of biphasic insulin aspart 30 in the GLA group, 17/76 (22.4%), 188/875 (21.5%) and 14/49 (28.6%) individuals achieved glycemic control targets, respectively.

Table 2 Safety outcomes before and after 24 weeks of treatment with biphasic insulin aspart 30

Measurement	GLA group			NEU group		
	% Patients with at least one event (event/person-year)					
	Baseline ($n = 1,395$)	24 weeks ($n = 1,200$)	p	Baseline ($n = 1,423$)	24 weeks ($n = 1,271$)	p
Hypoglycemia (overall)	12.3 (3.10)	9.9 (2.98)	<0.05	15.5 (6.09)	9.7 (2.76)	<0.001
Hypoglycemia (major)	1.2 (0.16)	0.08 (0.01)	<0.001	2.5 (0.62)	0.08 (0.01)	<0.001
Hypoglycemia (nocturnal)	5.4 (1.03)	3.9 (0.88)	<0.05	7.2 (1.97)	3.5 (0.59)	<0.001
Hypoglycemia (overall) sulfonylurea[a]	11.2 (3.06)	5.5 (1.61)		15.3 (5.88)	3.9 (1.07)	
Hypoglycemia (overall) non-sulfonylurea[b]	13.6 (3.16)	11.4 (3.45)		15.7 (6.28)	10.8 (3.09)	
Mean body weight, kg (SD)[c]	73.2 (14.7)	73.5 (14.3)	<0.01	75.4 (16.6)	75.2 (16.4)	0.22
Mean (SD) systolic blood pressure, mmHg[d]	134.0 (18.4)	129.1 (14.7)	<0.001	137.7 (16.8)	129.4 (13.7)	<0.001

Due to the non-interventional nature of this study, some patients were lost to follow-up. p calculated using McNemar's test on incidence of hypoglycemia at baseline vs. 24 weeks

GLA insulin glargine group, *NEU* insulin neutral protamine Hagedorn group

[a] $n = 794$ GLA baseline, $n = 307$ GLA 24 weeks; $n = 665$ NEU baseline, $n = 206$ NEU 24 weeks

[b] $n = 601$ GLA baseline, $n = 893$ GLA 24 weeks; $n = 758$ NEU baseline, $n = 1,065$ NEU 24 weeks

[c] $n = 1,052$ GLA baseline and 24 weeks; $n = 1,167$ NEU baseline and 24 weeks

[d] $n = 1,031$ GLA baseline and 24 weeks; $n = 1,140$ NEU baseline and 24 weeks

HRQoL

There was statistically significant ($p < 0.001$) improvement in VAS scores after 24 weeks in both groups (Table 3). For both groups, there was significant improvement in all five parameters of EQ-5D (no problem performing usual activities, freedom from anxiety/depression; no problem walking; no pain or discomfort and no problems with self-care; $p < 0.001$).

DISCUSSION

This sub-analysis from the A_1chieve study showed that switching to therapy with biphasic insulin aspart 30 (±OGLDs) from basal insulin regimens under routine clinical
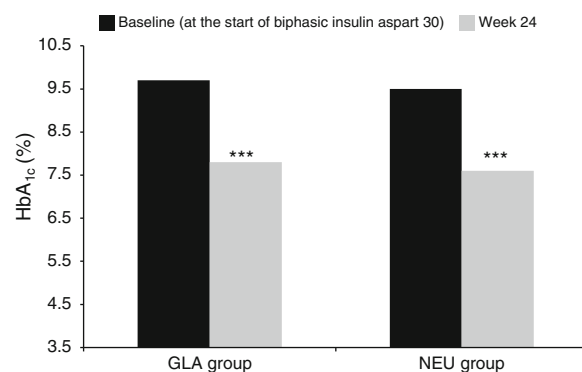

Fig. 1 Mean plasma glycated hemoglobin among patients switching to biphasic insulin aspart 30 from insulin glargine- or neutral protamine Hagedorn-based basal insulin regimens. *GLA* insulin glargine group, HbA_{1c} glycated hemoglobin, *NEU* neutral protamine Hagedorn group. ***$p < 0.001$ vs. baseline $n = 894$ GLA baseline and 24 weeks; $n = 913$ NEU baseline and 24 weeks

Table 3 Change in effectiveness outcomes after 24 weeks of treatment with biphasic insulin aspart 30

	GLA group				NEU group			
	n	Baseline	Change at 24 weeks	*p*	*n*	Baseline	Change at 24 weeks	*p*
HbA$_{1c}$% (SD)	894	9.7 (1.7)	−1.9 (1.7)	<0.001	913	9.5 (1.6)	−2.0 (1.7)	<0.001
HbA$_{1c}$ mmol (SD)		83 (19)	−21 (18)			80 (18)	−21 (18)	
FPG (pre-breakfast) mmol/l (SD)	956	10.4 (3.4)	−2.9 (3.7)	<0.001	1,062	10.7 (3.8)	−3.5 (3.9)	<0.001
PPG (post-breakfast) mmol/l (SD)	710	15.0 (4.2)	−4.6 (4.4)	<0.001	747	14.6 (4.5)	−5.1 (5.0)	<0.001
PPG (post-lunch) mmol/l (SD)	146	13.8 (4.4)	−4.5 (4.5)	<0.001	257	12.5 (3.5)	−3.9 (3.5)	<0.001
PPG (post-dinner) mmol/l (SD)	127	13.1 (3.9)	−4.3 (4.3)	<0.001	246	12.3 (3.5)	−4.0 (3.6)	<0.001
HRQoL, VAS (SD)	923	63.4 (15.8)	+10.3 (17.2)	<0.001	929	63.3 (16.4)	+10.8 (16.0)	<0.001
No problem performing usual activities, %	946	65.8	+14.1	<0.001	952	58.0	+18.4	<0.001
Free from anxiety/depression, %	949	54.9	+12.9	<0.001	956	53.9	+19.5	<0.001
No problems walking, %	949	64.1	+20.3	<0.001	958	59.7	+17.9	<0.001
No pain or discomfort, %	949	49.4	+14.7	<0.001	956	46.9	+14.8	<0.001
No problems with self-care, %	946	73.7	+12.5	<0.001	956	77.2	+11.1	<0.001

Due to the non-interventional nature of this study, not all baseline data were recorded and some patients were lost to follow-up

FPG fasting plasma glucose, *GLA* insulin glargine group, *HbA1c* glycated hemoglobin hemoglobin, *HRQoL* health-related quality of life, *NEU* insulin neutral protamine Hagedorn group, *PPG* post-prandial plasma glucose, *VAS* visual analogue scale

practice led to significant improvements in blood glucose levels (as measured by HbA$_{1c}$, FPG, and PPG) in patients with type 2 diabetes who had poor glycemic control. Switching to biphasic insulin aspart 30 was also well tolerated with only two serious adverse events recorded among the 2,818 participants during the 24 weeks of biphasic insulin aspart 30 treatment.

Importantly in both the NEU and GLA groups, improvement in glycemic control was achieved with a significant reduction in overall, major and nocturnal hypoglycemia during treatment with biphasic insulin aspart 30 (±OGLDs) relative to baseline. Despite the reduction in sulfonylurea use in both groups after 24 weeks compared with baseline, there was no indication that the proportion of patients experiencing hypoglycemia events was higher in those taking sulfonylureas compared with those not taking sulfonylureas. Therefore, the reduction in hypoglycemia events is likely to be due to the optimized treatment with biphasic insulin aspart 30. This finding would be consistent with previous studies that showed significant reductions in hypoglycemia after patients were switched from NPH insulin to biphasic insulin aspart 30 [1, 14]. Others have reported that improved

hyperglycemia and a lower proportion of people experiencing hypoglycemia can be achieved and maintained in patients receiving biphasic insulin aspart 30 who have optimized their insulin dosage [15]. As there was no control arm in the study, it is not possible to determine if the placebo effect due to participation in a clinical trial had any impact on the reduced incidence of hypoglycemia.

Significant improvements in all five parameters of EQ-5D were observed in both groups after 24 weeks of biphasic insulin aspart 30. These findings are similar to those observed for the wider A_1chieve cohort [16], and other studies have found that treatment with biphasic insulin aspart 30 significantly improved HRQoL, improved life-expectancy, and quality-adjusted life expectancy [17–19].

A combination of basal insulin and OGLDs is effective as an initial therapy in people with type 2 diabetes and poor glycemic control [20]. Basal insulins, such as insulin glargine and NPH insulin, do not target PPG fluctuations [8, 9], and, therefore, the efficacy of basal insulin begins to wane in some patients because PPG continues to rise [21]. The significant improvements in HbA_{1c} in this study may be linked to significant improvements in PPG after 24 weeks of biphasic aspart 30 treatment. Previous studies have shown that biphasic insulin aspart 30 may lead to significantly improved PPG control with concomitant significant improvement in HbA_{1c} values compared with basal insulin therapies [14, 22–25]. This is an important distinction because post-prandial hyperglycemia is recognized as being harmful and the International Diabetes Federation recommends the implementation of strategies to lower PPG [26]. The control of PPG plasma levels is now recognized as a fundamental consideration in prevention of endothelial dysfunction leading to the

progression to macrovascular and microvascular complications of diabetes [27, 28]. Furthermore, a joint consensus statement from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) states that mealtime insulin coverage is appropriate for patients receiving basal insulin but who are experiencing significant PPG excursions (>10 mmol/l; >180 mg/dl) [29]. The ADA/EASD consensus also intimates that premixed insulin may be appropriate for patients who eat regularly and who may be in need of a simplified approach to glycemic control beyond basal insulin [29].

Regarding people with type 2 diabetes with poor glycemic control, intensification from basal insulins to biphasic premixed insulin aspart 30 may enable them to reach glycemic targets for longer periods [21]. The glycemic improvements in this analysis occurred in both groups of patients regardless of previous basal insulin regimen.

A statistically significant increase in weight was noted in the GLA group after 24 weeks of insulin aspart 30, which is in line with findings from other studies [30, 31]. However, it is questionable whether a mean 0.3 kg increase in weight after 24 weeks of insulin aspart 30 treatment is clinically important.

A limitation of the study is that it was a sub-analysis of A_1chieve with a reduction in number of participants from over 66,000 in the full study to 2,818 participants in the sub-analysis; this may have led to the risk of type II error or bias in the dataset. Also, observational studies are not randomized and are more susceptible to selection bias. For example, this sub-analysis did not control for concomitant medication or dietary intake, and some outcomes relied on self-reported information, participant recall, or diverse diaries. However, the advantage of this study is the real-world clinical setting, including

actual practice patterns and a broader population than would be included in a randomized controlled trial. Furthermore, despite these limitations, data from this sub-analysis will help to elucidate the safety and effectiveness of biphasic insulin aspart 30 in patients switching from basal insulin regimens.

CONCLUSION

Biphasic insulin aspart 30 can be a well-tolerated and effective treatment in everyday clinical practice for patients with type 2 diabetes who are poorly controlled with basal insulin treatment. Twenty-four weeks of treatment with biphasic insulin aspart 30 led to significant improvements from baseline in HbA_{1c}, FPG, and PPG levels ($p < 0.001$ for all parameters). Risk of major hypoglycemia was reduced in both the GLA and NEU groups and there were significant improvements in all aspects of HRQoL as measured by EQ-5D (no problems performing usual activities, freedom from anxiety and depression, no problems walking, no pain or discomfort and no problems with self-care). Biphasic insulin aspart 30 may benefit patients with poor glycemic control on basal insulin regimens who are seeking to change treatment.

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Compliance with ethics guidelines. All study participants signed informed consent forms and were free to withdraw from the study at any time. The study was conducted in accordance with the Declaration of Helsinki of 1964, as revised in 2008, and guidelines for good pharmacoepidemiology practice.

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