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Scientific Research

Biphasic Insulin Aspart 30 Therapy in Insulin-Naïve and Insulin-Experienced Patients with Type 2 Diabetes: Results from the Jordanian Subgroup of the A$_1$chieve Study

Jihad Haddad[1*], Fares H. Haddad[2], Rashad Nasser[3], Abdel-Ellah Al-Shudifat[1], Firas Abbas Annabi[4], Levent Sandalci[5], Moawia Al-Kilani[6]

[1]Prince Hamzah Hospital, Amman, Jordan
[2]King Hussein Medical Center, Amman, Jordan
[3]Italian Hospital, Amman, Jordan
[4]Islamic Hospital, Amman, Jordan
[5]Novo Nordisk Business Area Near East, Istanbul, Turkey
[6]Jabal Al Zayton Hospital, Zarqa, Jordan
Email: [*]haddad_jihad@yahoo.gr

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Abstract

Objective: To analyse the safety and effectiveness of biphasic insulin aspart 30 (BIAsp 30) in a Jordanian subgroup of the 24-week, non-interventional A1chieve study. Methods: A total of 509 Jordanian patients with type 2 diabetes (392 insulin-naïve and 117 insulin-experienced) starting BIAsp30, alone or in combination with oral glucose-lowering drugs, were included. Safety and effectiveness outcomes were analysed over 24 weeks. Results: Patients had a mean age of 55.8 years, body mass index of 28.8 kg/m^2 and diabetes duration of 9.4 years at baseline. Two serious adverse drug reactions of hypoglycaemia were reported. The proportion of patients who reported major hypoglycaemic events decreased (2.4% at baseline vs. 0.2% at Week 24, p = 0.0039). The proportion of patients reporting overall hypoglycaemia increased marginally (6.3% at baseline vs. 9.9% at Week 24, p = 0.0378), primarily attributed to a rise in minor and nocturnal hypoglycaemia reported in insulin-naïve patients. From baseline to Week 24, the mean ± SD glycated haemoglobin A1c level decreased from 9.8% ± 1.4% to 7.4% ± 0.9% (p < 0.001). Significant reductions after 24 weeks were also noted in the mean fasting plasma glucose, postprandial plasma glucose, lipids,

[*]Corresponding author.

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systolic blood pressure and quality of life (all p < 0.001), while the mean body weight increased by 1.8 ± 6.5 kg (p < 0.001). Conclusion: Overall, BIAsp 30 therapy was well-tolerated and resulted in improved glycaemic control in this Jordanian subgroup over 24 weeks.

Keywords

Biphasic Insulin Aspart 30, Jordan, Type 2 Diabetes, A$_1$chieve, Clinical Practice

1. Introduction

The burgeoning crisis of type 2 diabetes (T2D) has imposed a severe strain on the healthcare resources of developing countries such as Jordan [1]. In 2012, Jordan reported a diabetes prevalence of 8.73% [2]. Data from the national Behavioural Risk Factor Surveillance System in 2004 [3] disclosed an increased prevalence of diabetes risk factors, such as obesity, and a high proportion of participants with undiagnosed diabetes. Also, an analysis involving 917 T2D patients in Jordan revealed that poor glycaemic control was chiefly linked to the long duration of T2D and lack of adherence to recommended self-care behaviours [4]. Indeed, improving T2D awareness and treatment adherence of patients are among the prime goals of T2D management in Jordan.

International treatment guidelines [5] recommend maintaining glycated haemoglobin A_{1c} (HbA_{1c}) levels at <7.0%, fasting plasma glucose (FPG) at <130 mg/dL and postprandial plasma glucose (PPPG) at <180 mg/dL to avoid the risk of incurring long-term diabetic complications. Physicians are further advised to appropriately intensify therapeutic regimens to maintain blood glucose at the recommended levels [5]. However, inadequate monitoring of disease progression and concerns about hypoglycaemia, injections and weight gain may inhibit patients and physicians from following these recommendations. Even so, T2D patients will eventually require supplementation of both basal and prandial insulin owing to the gradual loss of beta-cell function [6]. Premixed insulins, constituting a mixture of rapid-acting insulin with a basal version, were developed to help remedy the endogenous insulin deficit.

Biphasic insulin aspart 30 (BIAsp 30) is a premixed insulin analogue consisting of 70% protaminated insulin aspart (IAsp) and 30% rapid-acting IAsp [7]. The longer-acting protaminated component addresses basal insulin requirements and rapid-acting IAsp addresses the prandial insulin deficit. BIAsp 30 therapy is associated with low incidences of major and nocturnal hypoglycaemia [8] [9] and is known to effectively reduce high blood glucose [10].

Often, healthcare policy design and implementation is hampered by a dearth of local clinical data. Observational studies, such as A$_1$chieve, conducted across 28 countries [11], could provide a key pool of data that can aid in informing local policies and clinical practice guidelines.

The A$_1$chieve study was non-interventional in nature and aimed to gather information on the safety and effectiveness of insulin analogues in routine healthcare in different countries. This Jordanian sub-analysis aimed to document the safety and effectiveness of BIAsp 30 therapy in local practice and also to examine the current status of T2D management in Jordan.

2. Patients and Methods

2.1. Study Design

The A$_1$chieve study was an open-label, 24-week, prospective study of the clinical safety and effectiveness of BIAsp 30 (NovoMix 30®, Novo Nordisk A/S, Denmark), insulin detemir (Levemir®, Novo Nordisk A/S, Denmark) and IAsp (NovoRapid®, Novo Nordisk A/S, Denmark), as monotherapy or in combination with oral glucose-lowering drugs (OGLDs), in the treatment of T2D [11]. Here, the data of Jordanian patients with T2D who started BIAsp 30 therapy (with or without concomitant OGLDs) based on their physicians' decisions was evaluated. The methods and procedures of the A$_1$chieve study have been described in detail elsewhere [11].

2.2. Patient Population

Patients with T2D who started BIAsp 30 therapy within 4 weeks prior to the study were recruited between No-

vember 2009 and December 2010 from 32 centres in Jordan. Pregnant or lactating women as well as those who had the intention of becoming pregnant within the following 6 months were excluded. Patients who had taken any of the Novo Nordisk insulin analogues (BIAsp 30, IDet and IAsp) over 4 weeks prior to the start of the study were excluded as were those with known allergies or hypersensitivity to any of the study drugs or excipients. Appropriate ethical review board approval in Jordan was obtained and patients gave written informed consent for the use of their data at the time of initiation of injectable therapy (baseline).

2.3. Outcomes

The primary outcome was the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events, from baseline to Week 24. Other outcomes included the change in the proportion of patients reporting hypoglycaemic events (overall, major, minor and nocturnal) in the 4 weeks prior to baseline and Week 24, and the change from baseline to Week 24 in HbA_{1c}, FPG, PPPG, lipid profile, systolic blood pressure (SBP), body weight and quality of life (QoL). Only post-lunch PPPG values are presented for this subgroup because of the low number of patients that reported post-breakfast PPPG values (n = 38).

Health-related quality of life (QoL) was assessed at baseline and Week 24 using the EQ-5D questionnaire (comprising a visual analogue scale rated from 0 [worst imaginable health] to 100 [best imaginable health] and five health dimensions). Physicians assessed all parameters at routine clinical visits and recorded the data in standardized case report forms.

2.4. Statistical Analyses

Statistical analyses were performed for the entire subgroup and were also stratified by pre-study insulin exposure, *i.e.*, insulin-naïve and insulin-experienced patients. The changes in HbA_{1c}, FPG, PPPG, SBP, body weight, lipid profile and QoL were analysed using a paired t-test with baseline and Week 24 values. The change from baseline to Week 24 in the proportion of patients reporting at least one hypoglycaemic event was analysed using McNemar's test. For all tests, a significance level of 5% was applied. The analyses were performed using SAS version 9.1.3

3. Results

3.1. General Characteristics

A total of 509 patients (392 insulin-naïve and 117 insulin-experienced) started BIAsp 30 therapy at baseline in Jordan. Demographic and baseline characteristics are presented in **Table 1**. These patients had a mean ± SD age of 55.8 ± 10.9 years and a mean body mass index of 28.8 ± 5.2 kg/m^2. The mean duration of T2D was 9.4 ± 5.1 years in this subgroup.

At pre-study, 59.0% of patients in the entire subgroup were taking 2 OGLDs and 96.7% were on metformin. At baseline, the majority of patients switched to 1 OGLD (78.0%) and continued metformin use (**Table 1**).

3.2. Physicians' Reasons for Starting BIAsp 30 Therapy

A total of 499 patients (98.0%) started BIAsp 30 to improve glycaemic control in the entire subgroup as reported by their physicians. Among insulin-naïve patients, the major reason for starting BIAsp 30 therapy was to improve glycaemic control (99.5%), while among insulin-experienced patients, the major reasons were to improve glycaemic control (93.2%) and to try a new insulin (49.6%).

3.3. Insulin Dose and Frequency of Administration

The mean total insulin dose and frequency of administration is presented in **Table 2**.

The mean insulin dose by weight at pre-study was 0.58 ± 0.26 U/kg in insulin-experienced patients. At baseline, insulin-experienced patients had a mean starting dose of 0.70 ± 0.24 U/kg, which was titrated up to 0.75 ± 0.23 U/kg at Week 24.

Insulin-naïve patients started on 0.49 ± 0.20 U/kg of BIAsp 30 at baseline, which was titrated up to 0.76 ± 0.33 U/kg at Week 24.

Table 1. Baseline demographics and characteristics.

Parameter	All patients	Insulin naïve	Insulin users
N (%)	509 (100)	392 (77)	117 (23)
Gender (male/female)	53.6/46.4	55.6/44.4	47.0/53.0
Age*, years	55.8 (10.9)	55.7 (10.3)	56.0 (12.8)
Body weight*, kg	82.2 (15.9)	81.3 (15.7)	84.8 (16.5)
Body mass index*, kg/m^2	28.8 (5.2)	28.3 (4.9)	30.4 (5.9)
Duration of diabetes*, years	9.4 (5.1)	9.0 (4.8)	10.7 (5.7)
Time to insulin initiation*, years	8.7 (4.9)	9.1 (4.9)	7.6 (4.9)
Duration on OGLDs*, years	8.9 (4.7)	8.9 (4.6)	8.9 (5.0)
Duration on insulin*, years	1.0 (2.6)	0.3 (1.6)†	3.3 (3.7)
HbA_{1c}*, %	9.8 (1.4)	9.9 (1.3)	9.1 (1.4)
	OGLDs, n (%)		
Metformin	338 (98.0)	279 (97.6)	59 (100)
Sulfonylurea	66 (19.1)	62 (21.7)	4 (6.8)
Thiazolidinediones	20 (5.8)	20 (7.0)	0 (0)
One	269 (78.0)	214 (74.8)	55 (93.2)
Two	57 (16.5)	53 (18.5)	4 (6.8)
>Two	19 (5.5)	19 (6.6)	0 (0)

HbA_{1c}: glycated haemoglobin A_{1C}; OGLDs: oral glucose-lowering drugs. *Data are mean (SD). †Some patients were on insulin for a short period in the past, but were not on insulin when they were enrolled into the study.

Table 2. Insulin dose and frequency by pre-study therapy type.

		All patients	Insulin naïve	Insulin users
Daily dose frequency	Pre-study, n	117	0 (0)	117
	Once, n (%)	29 (24.8)	0 (0)	29 (24.8)
	Twice, n (%)	69 (59.0)	0 (0)	69 (59.0)
	Thrice, n (%)	19 (16.2)	0 (0)	19 (16.2)
	Baseline, n	506	390	116
	Once, n (%)	49 (9.7)	47 (12.1)	2 (1.7)
	Twice, n (%)	332 (65.6)	273 (70.0)	59 (50.9)
	Thrice, n (%)	124 (24.5)	70 (17.9)	54 (46.6)
	>thrice, n (%)	1 (0.2)	0 (0)	1 (0.9)
	Week 24, n	463	362	101
	Once, n (%)	30 (6.5)	28 (7.7)	2 (2.0)
	Twice, n (%)	293 (63.3)	241 (66.6)	52 (51.5)
	Thrice, n (%)	135 (29.2)	89 (24.6)	46 (45.5)
	>thrice, n (%)	5 (1.1)	4 (1.1)	1 (1.0)
Insulin dose, U/day	Pre-study*	48.6 (24.0)	0 (0)	48.6 (24.0)
	Baseline*	43.4 (18.3)	39.2 (15.9)	57.2 (19.0)
	Week 24*	60.2 (24.2)	59.7 (25.5)	62.2 (18.7)
Insulin dose, U/kg	Pre-study*	0.58 (0.26)	0 (0)	0.58 (0.26)
	Baseline*	0.54 (0.22)	0.49 (0.20)	0.70 (0.24)
	Week 24*	0.76 (0.31)	0.76 (0.33)	0.75 (0.23)

*Data are mean (SD).

3.4. SADRs and Hypoglycemia

Two SADRs of hypoglycaemia were reported (1 event in an insulin-naïve patient and 1 event in an insulin-experienced patient); both events were considered probably related to BIAsp 30.

The incidence rate of hypoglycaemia and the proportion of patients who reported hypoglycaemic events at baseline and Week 24 are presented in **Table 3**. The incidence rates of overall and major hypoglycaemia appeared to decrease from baseline to Week 24 in insulin-experienced patients, associated with a significant reduction from baseline in the proportion of patients reporting these events at Week 24 (overall hypoglycaemia: 23.1% to 11.8%; major hypoglycaemia: 8.5% to 0%; both $p < 0.05$).

The incidence rate of overall hypoglycaemia was 0.30 events per patient-year at baseline and 2.79 events per patient-year at Week 24 in insulin-naïve patients, corresponding to a statistically significant increase in the proportion of patients that reported overall hypoglycaemia between baseline and Week 24 (1.3% to 9.4%, $p < 0.0001$). The proportion of insulin-naïve patients reporting major hypoglycaemia changed from 0.5% at baseline to 0.3% at Week 24; however, the change was not statistically significant.

3.5. HbA_{1c}, FPG and PPPG

Glycaemic parameters at baseline and Week 24 are presented in **Figure 1**. The mean HbA_{1c} level reduced significantly from 9.8% ± 1.4% at baseline to 7.4% ± 0.9% at Week 24 in the entire subgroup ($p < 0.001$).

At Week 24, 112 patients (25.9%) in the entire subgroup had HbA_{1c} levels < 7.0% compared to 6 patients (1.2%) at baseline. Among insulin-naïve patients, the number of patients with HbA_{1c} < 7.0% changed from 4 patients (1.0%) at baseline to 76 patients (22.4%) at Week 24 and among insulin users, from 2 patients (1.8%) to 36 patients (39.1%).

Statistically significant improvements at Week 24 were also noted in the mean FPG and post-lunch PPPG values in the entire subgroup ($p < 0.001$).

3.6. Body Weight, Systolic Blood Pressure and Blood Lipids

In the entire subgroup, an increase in mean body weight from 81.4 ± 15.0 kg at baseline to 83.1 ± 12.8 kg at Week 24 was observed (mean change: +1.8 kg ± 6.5 kg, $p < 0.001$, **Table 4**). The average SBP decreased from

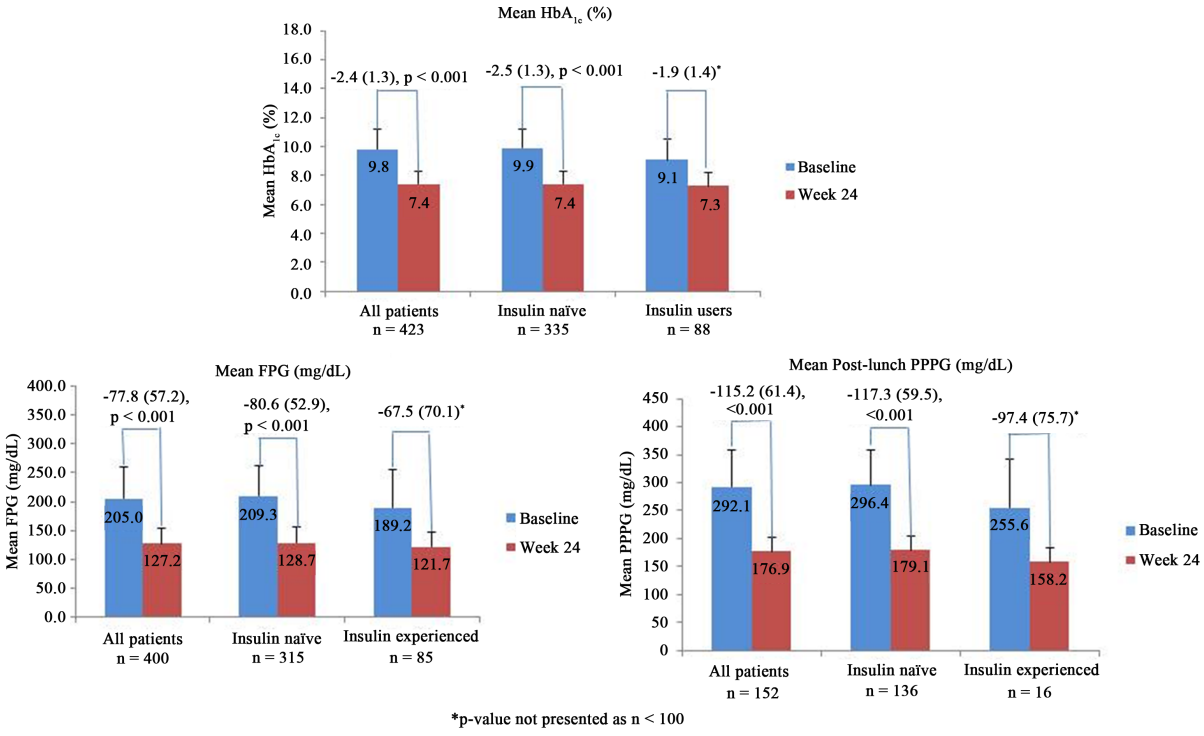

Figure 1. Glycaemic parameters at baseline and Week 24.

Table 3. Hypoglycaemia by pre-study regimen.

Event per patient-year/percent with at least one event		All patients	Insulin naïve	Insulin users
Overall	Baseline	1.92/6.3	0.30/1.3	7.33/23.1
	Week 24	3.02/9.9	2.79/9.4	3.82/11.8
	p	0.0378	<0.0001	0.0285
Major	Baseline	0.41/2.4	0.07/0.5	1.56/8.5
	Week 24	0.03/0.2	0.04/0.3	0.00/0.0
	p	0.0039	0.5637	0.0027
Nocturnal	Baseline	0.79/4.1	0.10/0.8	3.11/15.4
	Week 24	1.01/4.7	0.82/3.6	1.66/8.8
	p	0.6015	0.0075	0.1083
Minor	Baseline	1.51/5.3	0.23/0.8	5.78/20.5
	Week 24	2.99/9.7	2.76/9.1	3.82/11.8
	p	0.0072	<0.0001	0.0833

p-value is from McNemar's test on the paired proportions of patients experiencing hypoglycaemia.

Table 4. Body weight, SBP and blood lipids by pre-study regimen.

		All patients	Insulin naïve	Insulin users
Body weight, kg	n	347	273	74
	Baseline	81.4 (15.0)	80.5 (14.6)	84.7 (16.0)
	Week 24	83.1 (12.8)	82.5 (12.2)	85.6 (14.6)
	Change, p	1.8 (6.5), <0.001	2.0 (6.5), <0.001	0.8 (6.4), 0.268
SBP, mmHg	n	418	329	89
	Baseline	137.9 (16.8)	137.3 (16.3)	139.9 (18.6)
	Week 24	131.7 (12.0)	131.8 (11.9)	131.3 (12.3)
	Change, p	−6.1 (16.1), <0.001	−5.5 (16.1), <0.001	−8.6 (16.0), <0.001
Total cholesterol, mmol/L	n	216	170	46
	Baseline	5.5 (1.1)	5.6 (1.1)	5.2 (1.0)
	Week 24	4.9 (0.7)	4.9 (0.6)	4.8 (0.7)
	Change, p	−0.6 (1.0), <0.001	−0.7 (1.1), <0.001	−0.4 (0.9), 0.009
Triglycerides, mmol/L	n	208	163	45
	Baseline	2.8 (1.1)	3.0 (1.1)	2.2 (1.0)
	Week 24	2.2 (0.8)	2.2 (0.8)	2.0 (0.7)
	Change, p	−0.6 (1.2), <0.001	−0.7 (1.2), <0.001	−0.2 (1.1), 0.149
HDL cholesterol, mmol/L	n	210	164	46
	Baseline	1.0 (0.3)	1.0 (0.3)	1.0 (0.3)
	Week 24	1.0 (0.2)	1.0 (0.2)	1.0 (0.3)
	Change, p	0.0 (0.2), 0.065	0.0 (0.2), 0.037	0.0 (0.3), 0.87
LDL cholesterol, mmol/L	n	215	168	47
	Baseline	3.2 (0.9)	3.2 (0.9)	3.2 (0.9)
	Week 24	2.7 (0.6)	2.7 (0.6)	2.7 (0.8)
	Change, p	−0.5 (0.9), <0.001	−0.5 (0.8), <0.001	−0.5 (0.9), <0.001

HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure. Baseline, Week 24 and change values are mean (SD).

137.9 ± 16.8 mmHg at baseline to 131.7 ± 12.0 mmHg at Week 24 (mean change: −6.1 ± 16.1 mmHg, $p < 0.001$, **Table 4**).

No statistically significant change was noted in the mean HDL cholesterol levels, while the mean total cholesterol, triglyceride and LDL cholesterol levels were lower at Week 24 compared to baseline in the entire subgroup ($p < 0.001$, **Table 4**).

3.7. Quality of Life

The mean QoL increased from 62.1 ± 14.2 points at baseline to 72.3 ± 9.5 points at Week 24 (mean change: +10.2 ± 14.7 points, $p < 0.001$).

4. Discussion

This sub-analysis showed that BIAsp 30 therapy was well-tolerated in Jordanian patients with T2D and was associated with significant reductions of hyperglycaemia in both insulin-naïve and insulin-experienced patients over 24 weeks. Poor glycaemic control was apparent in the entire subgroup at baseline (mean HbA_{1c}, 9.8%; FPG, 205.0 mg/dL; PPPG, 292.1 mg/dL). Even patients previously treated with other insulins for approximately 3 years had average HbA_{1c} levels of 9.1% at baseline. These results are consistent with baseline findings from the overall A_1chieve cohort that also revealed high levels of blood glucose (mean HbA_{1c}, 9.5%) [11].

The incidence of major hypoglycaemia reduced from baseline to Week 24 in the entire Jordanian subgroup, with significantly fewer patients reporting major hypoglycaemic events after 24 weeks of BIAsp 30 therapy. The increased incidence of overall hypoglycaemia noted in the entire subgroup was primarily caused by an increase in the proportion of insulin-naïve patients reporting minor and nocturnal hypoglycaemic events. The proportion of insulin-naïve patients that reported minor hypoglycaemia also increased significantly from baseline to Week 24 in the overall A_1chieve cohort on BIAsp 30 therapy [11].

Fasting and postprandial glucose levels reduced markedly in the Jordanian subgroup following 24 weeks' treatment with BIAsp 30. The reductions in FPG and PPPG were accompanied by reductions in the HbA_{1c} levels in these Jordanian patients as well, triggering improvements in mean HbA_{1c} by −2.5% ± 1.3% in insulin-naïve patients and –1.9% ± 1.4% in insulin-experienced patients. Furthermore, 112 patients in the entire subgroup achieved the HbA_{1c} target level of <7.0% by Week 24 compared to only 6 patients at baseline. These results are particularly noteworthy in the light of findings from the United Kingdom Prospective Diabetes Study that linked a 1% reduction in mean HbA_{1c} to a 37% risk reduction for microvascular complications and a 14% risk reduction for myocardial infarction [12].

Hypercholesterolaemia and hypertriglyceridaemia are common co-morbidities for T2D patients. A 2006 study revealed that dyslipidaemia was highly prevalent among Jordanian T2D patients (reported in over 90% of patients) and high LDL cholesterol levels were the most common form (reported in 91.5% of patients) [13]. In this sub-analysis, Jordanian patients presented with high lipid levels at baseline, while at Week 24, significantly lower levels of total cholesterol, LDL cholesterol and triglycerides were observed. The mean SBP also improved by an average of −6.1 ± 16.1 mmHg, suggesting that patients may have initiated lifestyle changes during the study. As expected, mean body weight increased in the entire subgroup, primarily due to an increase (~2.0 kg) in insulin-naïve patients following the start of insulin therapy.

Fluctuating blood glucose levels and the complications associated with T2D can significantly affect patients' well-being [14]. However, following 24 weeks of BIAsp 30 therapy, patient QoL, assessed using the validated EQ-5D questionnaire, improved noticeably from baseline levels. It is possible that the demonstrated improvements in blood glucose and lipid levels and the low incidence of hypoglycaemia may have contributed to the greater positive patient responses at Week 24.

This sub-analysis is subject to certain limitations of the non-interventional design of the A_1chieve study. The study lacked a control arm. Concomitant medication and dietary intake were not controlled and data collection was largely based on patient recall, diaries or self-reported information. The incidence of hypoglycaemia was collected based on the patients' recall of the past 4 weeks prior to the study visit, which may have led to an underestimation of the actual occurrence rate of hypoglycaemic events. Nevertheless, this study provided an opportunity to evaluate treatment strategies for T2D in routine clinical care in Jordan. The results of this sub-analysis demonstrate the safety and effectiveness of BIAsp 30 in a setting that is close to real life and in a patient group not restricted by strict selection criteria. These results can also provide evidence for framing clinical poli-

cies in Jordan. In summation, starting BIAsp 30 therapy improved glycaemic control and was not associated with any issues of tolerability or safety in this Jordanian subgroup.

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Conflict of Interest

Jihad Haddad is an advisory board member for Novo Nordisk and Merck, and is on the speaker's bureau for Novo Nordisk, Merck, Novartis, Astra Zeneca, Merck Sharp & Dohme, and Menarini. Levent Sandalci is employed by Novo Nordisk. Fares H. Haddad, Rashad Nasser, Abdel-Ellah Al-Shudifat, Firas Abbas Annavi and Moawia Al-Kilani have no conflicts of interest to declare.

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