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Exploring insulin analogue safety and effectiveness in a Maghrebian cohort with type 2 diabetes: results from the A_1chieve study

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ABSTRACT

Aim: To evaluate the safety and effectiveness of insulin analogues in patients with type 2 diabetes (T2D) from Morocco, Algeria and Tunisia that formed the Maghrebian cohort of the 24-week, non-interventional A_1chieve study.

Methods: Patients starting biphasic insulin aspart, insulin detemir and insulin aspart, alone or in combination, were included. The primary outcome was the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic events. Secondary outcomes included hypoglycaemia, glycated haemoglobin A_{1c} (HbA_{1c}), fasting plasma glucose (FPG), postprandial plasma glucose (PPPG), systolic blood pressure (SBP), body weight and lipids. Quality of life (QoL) was evaluated using the EQ-5D questionnaire.

Results: Overall, 3720 patients with a mean age of 58.6 years, body mass index of 27.7 kg/m^2 and diabetes duration of 11.5 years were enrolled. Pre-study, insulin-experienced patients had a mean±SD dose of 0.54±0.27 U/kg. In the entire cohort, the mean dose was 0.42±0.27 U/kg at baseline, titrated to 0.55±0.30 U/kg by Week 24. Twenty-six SADRs were reported during the study. There was a significant decrease in the proportion of patients reporting overall hypoglycaemia from baseline to Week 24 (18.3% to 13.8%, $p < 0.0001$). The mean HbA_{1c} improved significantly from 9.5±1.8% to 7.9±1.4% ($p < 0.001$). The mean FPG, PPPG, SBP, total cholesterol and QoL also improved significantly (all $p < 0.001$), while the mean body weight increased by 0.9±3.9 kg ($p < 0.001$).

Conclusion: Insulin analogue therapy was well-tolerated and was associated with improved glycaemic control.

1. Introduction

Glycaemic control worsens over time in type 2 diabetes (T2D) due to declining insulin sensitivity and waning beta-cell activity [1]. Uncontrolled T2D has grave implications for patient health with 4.8 million deaths worldwide attributed to diabetes in 2012 [2]. Early and aggressive treatment of T2D is known to be linked with better health outcomes in the long term [3]. However, although most patients ultimately require insulin therapy, clinical inertia on the part of physicians and erratic patient schedules, fear of hypoglycaemia and injection pain often comprise barriers to successful T2D management [4,5]. International treatment guidelines recommend targeting glycated haemoglobin A_{1c}

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(HbA_{1c}) levels of <7.0% (<53 mmol/mol) with corresponding fasting plasma glucose (FPG) levels of <130 mg/dL and postprandial plasma glucose (PPPG) of <180 mg/dL [6], but data from routine clinical practice show that patients seldom achieve these targets [7].

The Middle East and North Africa region has been profoundly affected by the global T2D epidemic. In 2011, this region was found to have the highest diabetes prevalence in the world, after age-standardization to the world population [8]. Morocco, Algeria and Tunisia have all reported high diabetes prevalences (6.8%, 6.9% and 9.5%, respectively) in 2011. It is further estimated that these figures will rise to 7.9%, 7.7% and 11.2%, respectively, over the next 20 years. Some prominent reasons for the rise in T2D prevalence include aging populations, increasing obesity and reduced physical activity. Dietary habits have also changed in developing countries, with more people consuming refined carbohydrates or foods high in saturated fat compared to traditional grain-based diets [9]. The 2008 DiabCare study in Algeria identified some key deficiencies in T2D care, including overly cautious approaches to treatment intensification and dosing on the part of physicians and low levels of understanding regarding the disease and its management among patients [10].

Recent research has emphasized the importance of modifying therapeutic regimens to suit the needs of individual patients with T2D [11]. The insulin analogues, premix biphasic insulin aspart 30 (BIAsp 30), basal insulin detemir (IDet) and bolus insulin aspart (IAsp), are linked to more predictable pharmacological action compared to human insulin [12]. Also, BIAsp 30 is known to provide better PPPG control with a lower risk of hypoglycaemia compared to biphasic human insulin (BHI) [13,14]. Transferring therapy to IDet from neutral protamine Hagedorn (NPH) insulin or the basal analogue, insulin glargine (IGlar), was associated with improved glycaemic control and reduced overall hypoglycaemia in a large observational study [15].

The global, non-interventional A_1chieve study evaluated the performance of a portfolio of insulin analogues (BIAsp 30, IDet and IAsp alone or combined with basal insulin) in routine treatment of T2D in different countries [16]. Complete study results are available online under www.A1chieve.com. In light of the high T2D prevalence in the Maghreb region, it is important to characterise the prevailing state of T2D management in order to identify possible areas of improvement. This sub-analysis in Moroccan, Algerian and Tunisian patients aimed to evaluate the safety and effectiveness of insulin analogue therapy over 24 weeks and to analyse the baseline T2D status of this cohort.

2. Methods

2.1. Study design

The prospective, open-label A_1chieve study evaluated the clinical safety and effectiveness of BIAsp 30 (NovoMix® 30, Novo Nordisk A/S, Denmark), IDet (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 T2D patients over 24 weeks [16]. This sub-analysis was conducted in Maghrebian patients recruited between 1 March 2009 and 7 January 2011 from 208 centres across Morocco, Algeria and Tunisia.

Patients initiated treatment with commercially available study insulins based upon the clinical judgment of the consulting physicians. The physicians selected the dose and administration frequency of the study insulins and all concomitant OGLDs, in accordance with the local regulatory guidelines.

As the study was non-interventional, no special investigations were planned. The physicians performed all safety and effectiveness assessments at routine visits and recorded the data from their clinical notes and patient examinations at baseline, Week 12 (interim visit) and Week 24 (final visit) in standard case report forms.

2.2. Patient eligibility

Patients who started treatment with any of the study insulins within 4 weeks prior to baseline were eligible for inclusion at the discretion of their physicians. Pregnant or lactating women and women who planned to become pregnant within the following 6 months were excluded from participation. Patients with hypersensitivity to any of the study insulins or excipients were also excluded.

All patients provided signed informed consent and the study was approved by the ethics committees of Morocco, Algeria and Tunisia.

2.3. Assessments and outcomes

The primary objective of the study was the evaluation of insulin analogue safety based upon the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemia. Secondary safety outcomes included changes in the number of overall hypoglycaemic events and nocturnal hypoglycaemic events during the last 4 weeks prior to baseline and Week 24, and the number of serious adverse events (SAEs) during the study.

Effectiveness of therapy was evaluated based upon the change from baseline to Week 24 in HbA_{1c}, FPG, post-breakfast PPPG, body weight, systolic blood pressure and lipids. Quality of life (QoL) was measured using the visual analogue scale (VAS) of the validated EQ-5D questionnaire. The VAS measures the current health state of individual patients on a scale of 0 to 100 where 0 represents the lowest score and 100 the highest.

2.4. Statistical analysis

Statistical analyses were performed for the entire cohort on study insulins and also for patients switching treatment from prior insulin treatment (with or without OGLDs) to the study insulins, wherever the number of patients was >100. Comparisons between groups are reported descriptively.

The number of insulin-naive patients on IAsp + basal insulin and insulin-naive and insulin-experienced patients

Table 1 – Baseline demographics and characteristics – entire cohort

Parameter	Entire cohort (n = 3720, 100%)	Insulin-naive (n = 1926, 51.8%)	Insulin-experienced (n = 1794, 48.2%)
Gender (male/female), %	42.1/57.9	44.6/55.4	39.4/60.6
Age, years	58.6 (11.7)	58.7 (11.1)	58.4 (12.3)
Body weight, kg	74.7 (13.0)	73.6 (13.0)	75.9 (12.9)
Body mass index, kg/m^2	27.7 (4.8)	27.2 (4.7)	28.3 (4.8)
Duration of diabetes, years	11.5 (7.3)	9.6 (6.4)	13.5 (7.6)
Time to insulin initiation, years	9.3 (6.5)	9.5 (6.5)	9.1 (6.5)
Duration on insulin, years	2.3 (4.2)	0.1 (0.5) [a]	4.5 (5.0)
HbA_{1c}, %	9.5 (1.8)	9.7 (1.8)	9.3 (1.7)
HbA_{1c}, mmol/mol	80 (20)	83 (20)	78 (19)
Duration on OGLDs, years	9.4 (6.6)	8.9 (6.3)	10.1 (6.9)
OGLDs, n (%)			
Metformin	1799 (80.4)	1080 (79.5)	719 (81.8)
Sulfonylurea	1126 (50.3)	859 (63.3)	267 (30.4)
Thiazolidinediones	26 (1.2)	18 (1.3)	8 (0.9)
1 OGLD	1158 (51.8)	535 (39.4)	623 (70.9)
2 OGLDs	1014 (45.3)	773 (56.9)	241 (27.4)
>2 OGLDs	65 (2.9)	50 (3.7)	15 (1.7)

HbA_{1c}, glycated haemoglobin A_{1c}; OGLDs, oral glucose-lowering drugs.
Data are presented as mean (SD) unless specified otherwise.
[a] Some patients were on insulin for a short period in the past, but were not on insulin when they were enrolled into the study.

on IAsp was very low; hence these data are not presented in this paper. P-values are not presented when the number of patients analysed was less than 100.

Descriptive statistics and frequency tables (n, %) were used to summarise continuous and discrete variables, respectively.

The change from baseline to Week 24 in effectiveness parameters and QoL was evaluated using a paired t-test. The change from baseline to Week 24 in the proportion of patients reporting at least one hypoglycaemic event was evaluated using McNemar's test for paired samples. Two-sided alternatives with a 5% significance level were used. All analyses were performed by Novo Nordisk A/S using SAS® Version 9.1.3.

3. Results

3.1. Patient characteristics

Overall, 3720 patients started insulin analogue therapy in the Maghrebian cohort. The cohort was composed of 1926 insulin-naive patients and 1794 insulin-experienced patients. Demographic and baseline characteristics are reported in Table 1 for the entire cohort, insulin-naive patients and insulin-experienced patients.

At baseline in the insulin-experienced subgroup, 152 patients switched therapy from NPH insulin to BIAsp 30, 358 patients switched from BHI to BIAsp 30, 129 patients switched from IGlar to BIAsp 30, 190 patients switched from NPH insulin to IDet and 159 patients switched from IGlar to IDet. The remaining patients were on other combinations of insulin prior to and during the study, and are not discussed in this paper as the number in each insulin switch group was below 100.

The average duration of diabetes was 11.5 years and baseline HbA_{1c} level was 9.5% (80 mmol/mol) in the entire cohort (Table 1). The average baseline HbA_{1c} was >8.0% (>64 mmol/mol) for patients in the switch groups (Table 4, below).

Physicians reported that 92.3% of patients in the entire cohort started study insulin therapy to improve glycaemic control.

3.2. OGLDs

The OGLDs taken at baseline are presented in Table 1 for the entire cohort and by pre-study therapy type. At baseline, 79.5% and 63.3% of insulin-naive patients were on metformin and sulphonylurea, respectively, while 81.8% and 30.4% of insulin-experienced patients were on metformin and sulphonylurea, respectively.

3.3. Insulin dose and dosing frequency

The mean total daily insulin doses by weight are presented in Table 2 for pre-study, baseline and Week 24. Pre-study, insulin-experienced patients had a mean±SD dose of 0.54±0.27 U/kg, while at baseline the mean dose was 0.55±0.27 U/kg, titrated up to 0.67±0.31 U/kg at Week 24.

Insulin-naive patients had a starting dose of 0.31±0.22 U/kg, titrated up to 0.43±0.24 U/kg at Week 24.

The mean insulin dose for each study insulin regimen is presented in Table 3 and that for the switch groups in Table 4. Of patients switched to BIAsp 30 from pre-study NPH insulin, BHI and IGlar, 85.2%, 87.4% and 77.6%, respectively, dosed

Table 2 – Baseline and 24-week data for effectiveness and safety outcomes – entire cohort

		Entire cohort	Insulin-naive	Insulin-experienced
Insulin dose by weight, U/kg	n	3631	1873	1759
	Pre-study	0.54 (0.27)	–	0.54 (0.27)
	Baseline	0.42 (0.27)	0.31 (0.22)	0.55 (0.27)
	Week 24	0.55 (0.30)	0.43 (0.24)	0.67 (0.31)
HbA_{1c}, %/mmol/mol	n	2421	1278	1143
	Baseline	9.5 (1.8)/80 (20)	9.7 (1.8)/83 (20)	9.3 (1.7)/78 (19)
	Week 24	7.9 (1.4)/63 (15)	7.7 (1.2)/61 (13)	8.0 (1.5)/64 (16)
	Change	–1.7 (1.9)/–19 (21)	–2.0 (1.9)/–22 (21)	–1.3 (1.8)/–14 (20)
	p	<0.001	<0.001	<0.001
FPG, mg/dL	n	2724	1445	1279
	Baseline	205.6 (75.9)	220.0 (74.7)	189.3 (73.9)
	Week 24	141.7 (49.6)	138.3 (45.5)	145.5 (53.6)
	Change	–63.9 (86.2)	–81.6 (81.4)	–43.9 (87.1)
	p	<0.001	<0.001	<0.001
PPPG, mg/dL	n	1624	855	769
	Baseline	267.1 (84.8)	277.2 (84.6)	255.9 (83.7)
	Week 24	187.5 (63.3)	185.6 (60.8)	189.6 (66.1)
	Change	–79.6 (100.4)	–91.6 (99.6)	–66.3 (99.7)
	p	<0.001	<0.001	<0.001
Weight, kg	n	2999	1559	1440
	Baseline	74.7 (13.0)	73.6 (13.0)	75.9 (12.9)
	Week 24	75.6 (12.5)	75.0 (12.3)	76.2 (12.6)
	Change	0.9 (3.9)	1.3 (4.0)	0.4 (3.8)
	p	<0.001	<0.001	<0.001
SBP, mmHg	n	2863	1473	1390
	Baseline	133.2 (18.0)	133.3 (17.4)	133.2 (18.6)
	Week 24	131.1 (19.4)	131.5 (22.4)	130.7 (15.7)
	Change	–2.1 (20.9)	–1.8 (23.8)	–2.5 (17.3)
	p	<0.001	0.004	<0.001
Total cholesterol, mmol/L	n	1401	752	649
	Baseline	4.7 (1.2)	4.7 (1.2)	4.7 (1.2)
	Week 24	4.5 (1.0)	4.5 (1.0)	4.5 (1.0)
	Change	–0.2 (1.2)	–0.2 (1.2)	–0.2 (1.2)
	p	<0.001	<0.001	<0.001
Triglycerides, mmol/L	n	1455	782	673
	Baseline	1.6 (0.9)	1.7 (0.9)	1.6 (0.9)
	Week 24	1.5 (0.6)	1.5 (0.7)	1.5 (0.6)
	Change	–0.1 (0.9)	–0.2 (0.8)	–0.1 (0.9)
	p	<0.001	<0.001	0.04
HDL cholesterol, mmol/L	n	928	478	450
	Baseline	1.1 (0.4)	1.1 (0.4)	1.1 (0.5)
	Week 24	1.1 (0.4)	1.1 (0.3)	1.1 (0.4)
	Change	0.0 (0.5)	0.0 (0.5)	0.0 (0.6)
	p	0.114	0.568	0.112
LDL cholesterol, mmol/L	n	884	467	417
	Baseline	2.9 (1.3)	2.9 (1.2)	2.8 (1.4)
	Week 24	2.7 (1.1)	2.8 (1.1)	2.7 (1.2)
	Change	–0.1 (1.5)	–0.1 (1.4)	–0.1 (1.6)
	p	0.014	0.034	0.167

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Table 2 – (*continued*)

		Entire cohort	Insulin-naive	Insulin-experienced
Hypoglycaemia (events per patient-year/percent with at least one event)				
Overall	Baseline	8.23/18.3	3.01/7.5	13.83/29.8
	Week 24	4.10/13.8	2.99/11.1	5.31/16.9
	p[a]	<0.0001	<0.0001	<0.0001
Major	Baseline	1.22/5.5	0.58/3.0	1.91/8.1
	Week 24	0.05/0.2	0.02/0.1	0.09/0.2
	p[a]	<0.0001	<0.0001	<0.0001
Minor	Baseline	7.00/17.7	2.43/7.4	11.91/28.8
	Week 24	4.05/13.7	2.97/11.0	5.23/16.7
	p[a]	<0.0001	<0.0001	<0.0001
Nocturnal	Baseline	3.30/11.6	1.11/5.2	5.66/18.5
	Week 24	1.28/5.4	0.99/4.3	1.59/6.7
	p[a]	<0.0001	0.0624	<0.0001

FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPPG, postprandial plasma glucose; SBP, systolic blood pressure.
Baseline, Week 24 and change data are mean (SD).
[a] p-value is from McNemar's test on paired proportions of patients experiencing hypoglycaemia.

BIAsp 30 twice daily at Week 24. Of patients switched from pre-study NPH insulin and IGlar to IDet, 78.0% and 77.8%, respectively, dosed IDet once daily at Week 24.

3.4. SAEs and SADRs

Of the 98 SAEs reported in 43 patients during the study, 26 events in 12 patients were SADRs. Twenty-four SADRs were considered probably related to the study insulins and 2 events were considered possibly related. The remaining 72 SAEs were considered unlikely to be related to the study insulins. Fatal outcomes were reported in 12 patients due to 32 events. The most commonly reported event types were metabolism and nutrition disorders (16 events), cardiac disorders (9 events) and neoplasms (5 events).

3.5. Hypoglycaemia

The proportion of patients with at least one event of overall hypoglycaemia decreased significantly from 18.3% at baseline to 13.8% at Week 24 in the entire cohort ($p < 0.0001$, Table 2). From baseline to Week 24, there was an increase in the proportion of insulin-naive patients (7.5% vs. 11.1%) and a reduction in the proportion of insulin-experienced patients (29.8% vs. 16.9%) with at least one event of overall hypoglycaemia (both $p < 0.0001$).

There was a significant decrease in the proportion of patients reporting major hypoglycaemia from baseline to Week 24 in the entire cohort, insulin-naive patients and insulin-experienced patients ($p < 0.0001$, Table 2).

Across study insulin regimens, there was an increase in the proportions of insulin-naive patients reporting overall hypoglycaemia from baseline to Week 24, and a decrease in the proportions of insulin-experienced patients reporting overall hypoglycaemia (Table 3).

From baseline to Week 24, the proportion of patients reporting overall hypoglycaemia decreased significantly for all switch groups (Table 4), except for an increase in patients switching from pre-study IGlar to BIAsp 30 therapy (10.9% at baseline vs. 24.1% at Week 24, $p = 0.0053$).

3.6. HbA_{1c}, FPG and PPPG

Significant improvements in HbA_{1c} (–1.7±1.9%/–19±21 mmol/mol, $p < 0.001$), FPG (–63.9±86.2 mg/dL, $p < 0.001$) and post-breakfast PPPG (–79.6±100.4 mg/dL, $p < 0.001$) were reported after 24 weeks of study insulin therapy in the entire cohort (Table 2).

Also, 635 patients (22.9%) achieved the HbA_{1c} target of <7.0% (<53 mmol/mol) at Week 24 compared to 134 patients (4.4%) at baseline.

Clear improvements in glycaemic parameters were also noted among insulin-naive and -experienced patients across regimens ($p < 0.001$, Table 3).

Improvements in HbA_{1c}, FPG and post-breakfast PPPG also occurred for patients in the switch groups (Table 4). The greatest improvements were noted in patients switched from NPH insulin to BIAsp 30 (HbA_{1c}: –1.8±1.9%/–20±21 mmol/mol, FPG: –62.3±90.9 mg/dL, PPPG: –82.4±108.2 mg/dL).

3.7. Body weight, SBP and lipids

Results for body weight, SBP and lipids are presented in Table 2 for the entire cohort, Table 3 by study insulin regimen and Table 4 for the switch groups.

In the entire cohort, mean body weight increased over 24 weeks (0.9±3.9 kg, $p < 0.001$, Table 2).

The mean body weight increased significantly for insulin-naive patients across regimens and for insulin-experienced patients on BIAsp 30 (all $p < 0.001$, Table 3). However, there was a decrease in weight for insulin-experienced patients on IDet (–0.6±3.3 kg, $p < 0.001$), while there was no significant change for insulin-experienced patients on IAsp + basal insulin.

Table 3 – Baseline and 24-week data for effectiveness and safety outcomes by study insulin regimen

		Insulin-naive		Insulin-experienced		
		Biphasic insulin aspart 30	Insulin detemir	Biphasic insulin aspart 30	Insulin detemir	Insulin aspart + basal insulin
Insulin dose by weight, U/kg	n	572	1194	755	458	326
	Pre-study	–	–	0.56 (0.25)	0.38 (0.21)	0.67 (0.30)
	Baseline	0.50 (0.18)	0.19 (0.11)	0.58 (0.20)	0.32 (0.15)	0.73 (0.26)
	Week 24	0.61 (0.22)	0.33 (0.16)	0.67 (0.22)	0.43 (0.21)	0.91 (0.36)
HbA_{1c}, %/mmol/mol	n	326	892	477	298	227
	Baseline	10.2 (2.0)/88 (22)	9.5 (1.7)/80 (19)	9.4 (1.8)/79 (20)	8.8 (1.6)/73 (17)	9.6 (1.7)/81 (19)
	Week 24	7.7 (1.1)/61 (12)	7.8 (1.3)/62 (14)	7.9 (1.4)/63 (15)	8.2 (1.7)/66 (19)	7.9 (1.5)/63 (16)
	Change	−2.5 (2.0)/−27 (22)	−1.7 (1.7)/−19 (19)	−1.4 (1.8)/−15 (20)	−0.6 (1.7)/−7 (19)	−1.7 (2.0)/−19 (22)
	p	<0.001	<0.001	<0.001	<0.001	<0.001
FPG, mg/dL	n	419	951	554	340	250
	Baseline	241.7 (80.6)	207.4 (64.4)	195.0 (74.7)	170.6 (65.5)	191.1 (74.7)
	Week 24	142.1 (48.3)	136.6 (44.4)	147.3 (50.9)	147.3 (62.3)	137.0 (45.9)
	Change	−99.5 (91.0)	−70.8 (70.9)	−47.8 (87.3)	−23.3 (84.2)	−54.1 (83.3)
	p	<0.001	<0.001	<0.001	<0.001	<0.001
PPPG, mg/dL	n	260	553	362	181	141
	Baseline	302.8 (85.2)	263.8 (80.2)	262.8 (85.4)	228.6 (65.9)	259.1 (85.9)
	Week 24	183.7 (57.8)	188.7 (62.7)	189.7 (64.8)	200.5 (70.3)	175.5 (60.7)
	Change	−119.1 (102.1)	−75.1 (94.5)	−73.1 (100.2)	−28.0 (88.7)	−83.6 (98.9)
	p	<0.001	<0.001	<0.001	<0.001	<0.001
Weight, kg	n	453	1021	622	374	278
	Baseline	72.0 (12.9)	74.5 (13.0)	76.1 (12.4)	76.2 (13.0)	75.5 (13.4)
	Week 24	74.2 (11.8)	75.3 (12.6)	76.8 (12.3)	75.6 (12.8)	75.8 (12.9)
	Change	2.2 (4.6)	0.8 (3.5)	0.8 (3.9)	−0.6 (3.3)	0.3 (3.7)
	p	<0.001	<0.001	<0.001	<0.001	0.135
SBP, mmHg	n	381	1010	580	382	272
	Baseline	133.9 (17.9)	132.7 (16.9)	132.2 (16.8)	134.0 (19.5)	133.5 (21.0)
	Week 24	130.7 (14.1)	131.7 (25.3)	130.3 (15.5)	131.2 (16.2)	131.0 (15.5)
	Change	−3.2 (16.9)	−0.9 (26.2)	−1.9 (16.8)	−2.7 (17.5)	−2.5 (18.5)
	p	<0.001	0.252	0.005	0.002	0.029
Total cholesterol, mmol/L	n	159	551	281	164	143
	Baseline	5.0 (1.2)	4.6 (1.1)	4.7 (1.2)	4.6 (1.1)	4.7 (1.4)
	Week 24	4.7 (0.9)	4.4 (1.1)	4.5 (1.0)	4.4 (1.0)	4.4 (1.1)
	Change	−0.3 (1.2)	−0.2 (1.2)	−0.1 (1.2)	−0.1 (1.2)	−0.2 (1.3)
	p	0.005	0.001	0.057	0.233	0.04
Triglycerides, mmol/L	n	157	581	290	170	152
	Baseline	1.7 (1.0)	1.7 (0.9)	1.5 (0.9)	1.7 (1.1)	1.5 (0.9)
	Week 24	1.5 (0.5)	1.5 (0.7)	1.5 (0.6)	1.5 (0.6)	1.5 (0.6)
	Change	−0.2 (0.9)	−0.1 (0.8)	−0.0 (0.8)	−0.2 (1.1)	−0.1 (0.9)
	p	0.001	<0.001	0.459	0.052	0.447
HDL cholesterol, mmol/L	n	114	336	202	109	97
	Baseline	1.1 (0.3)	1.1 (0.4)	1.2 (0.5)	1.0 (0.4)	1.1 (0.5)
	Week 24	1.2 (0.4)	1.1 (0.3)	1.1 (0.4)	1.1 (0.5)	1.2 (0.5)
	Change	0.0 (0.5)	0.0 (0.4)	−0.0 (0.5)	0.1 (0.6)	0.1 (0.6)
	p	0.278	0.768	0.541	0.122	–[a]

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Table 3 – *(continued)*

		Insulin-naive		Insulin-experienced		
		Biphasic insulin aspart 30	Insulin detemir	Biphasic insulin aspart 30	Insulin detemir	Insulin aspart + basal insulin
LDL cholesterol, mmol/L	n	110	328	179	103	89
	Baseline	3.1 (1.2)	2.8 (1.2)	2.9 (1.6)	2.8 (1.0)	2.8 (1.5)
	Week 24	2.9 (0.8)	2.7 (1.2)	2.8 (1.3)	2.6 (0.8)	2.7 (1.3)
	Change	–0.3 (1.1)	–0.1 (1.6)	–0.1 (2.0)	–0.2 (1.0)	–0.1 (1.6)
	p	0.006	0.358	0.473	0.072	–[a]
Hypoglycaemia (events per patient-year/percent with event)						
Overall	Baseline	5.39/14.9	1.76/4.2	12.20/29.4	11.73/30.6	21.54/32.2
	Week 24	4.89/21.9	1.97/6.1	6.00/19.5	2.93/9.8	6.64/19.4
	p[b]	0.0002	0.0348	<0.0001	<0.0001	<0.0001
Major	Baseline	1.39/7.4	0.16/0.7	1.87/8.2	1.66/7.9	2.19/7.8
	Week 24	0.05/0.4	0.00/0.0	0.18/0.3	0.00/0.0	0.05/0.3
	p[b]	<0.0001	0.0047	<0.0001	<0.0001	<0.0001
Minor	Baseline	4.00/14.7	1.60/4.1	10.33/28.5	10.07/29.8	19.34/31.0
	Week 24	4.84/21.7	1.97/6.1	5.82/19.3	2.93/9.8	6.59/19.1
	p[b]	0.0001	0.0263	<0.0001	<0.0001	0.0002
Nocturnal	Baseline	2.35/11.0	0.49/2.5	5.47/19.1	4.31/16.6	8.85/21.1
	Week 24	1.37/8.1	0.81/2.6	1.84/8.5	1.24/3.5	1.58/7.3
	p[b]	0.006	0.7855	<0.0001	<0.0001	<0.0001

FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PPPG, postprandial plasma glucose; SBP, systolic blood pressure.
Baseline, Week 24 and change values are mean (SD).
[a] p-values are not presented when the number of patients analysed was less than 100.
[b] p-value is from McNemar's test on paired proportions of patients experiencing hypoglycaemia.

In the switch groups, mean body weight changed significantly only for patients switching from IGlar to BIAsp 30 (+2.3±4.0 kg, $p < 0.001$) and from IGlar to IDet (–0.8±3.8 kg, $p = 0.017$, Table 4).

The mean SBP improved significantly in the entire cohort (–2.1±20.9 mmHg, $p < 0.001$, Table 2) and also across study insulin regimens ($p < 0.05$, Table 3), with the exception of insulin-naive patients on IDet where no significant change was seen. In the switch groups, SBP improved significantly only for patients switching from BHI to BIAsp 30 (–2.6±16.8 mmHg, $p = 0.014$, Table 4) and from NPH insulin to IDet (–3.0±15.5 mmHg, $p = 0.018$).

The mean total cholesterol levels decreased significantly (–0.2±1.2 mmol/L, $p < 0.001$, Table 2) in the entire cohort. By study insulin regimen, total cholesterol decreased significantly among insulin-naive patients ($p < 0.01$, Table 3), but not among insulin-experienced patients. There was no statistically significant change in total cholesterol in any of the switch groups (Table 4).

3.8. Quality of life

From baseline to Week 24, improvements were noted in the mean QoL in the entire cohort (from 62.1±17.7 points to 74.3±14.5 points), insulin-naive patients (from 62.0±17.7 points to 75.6±14.0 points) and insulin-experienced patients (from 62.2±17.8 points to 72.8±14.9 points, all $p < 0.001$). QoL also improved significantly from baseline across the study insulin regimens and switch groups (all $p < 0.001$).

4. Discussion

This sub-analysis demonstrated the safety and effectiveness of insulin analogue therapy in the Maghrebian cohort of the A_1chieve study. Patients treated with the study insulins showed significant improvements in glycaemic parameters and a reduced risk of overall and major hypoglycaemia as also observed in the entire A_1chieve cohort [16]. Study insulin therapy was associated with a low incidence of SADRs and SAEs in this cohort.

Glycaemic control was poor at baseline, echoing the results reported from other global observational studies [7,16]. Although the average diabetes duration was 11.5 years, 51.8% of patients were insulin-naive with a mean HbA_{1c} level of 9.7% (83 mmol/mol) at baseline. These data depict the sub-optimal state of T2D management in the Maghrebian region.

Treatment with study insulins was associated with significant improvements in HbA_{1c}, FPG and PPPG, in the entire cohort, irrespective of prior insulin use, as well as in groups switching from other insulins. This improved glycaemic control was accompanied by a reduced risk of overall hypoglycaemia after 24 weeks in the entire cohort. As anticipated, among insulin-naive patients the proportion experiencing overall hypoglycaemia increased from 7.5% at baseline to 11.1% at Week 24; however, the absolute incidence of events remained low (3.01 vs. 2.99 events per patient-year). Decreases in the event rates of

Table 4 – Baseline and 24-week data for effectiveness and safety outcomes for patients switching insulins

Parameter		NPH to BIAsp 30	BHI to BIAsp 30	IGlar to BIAsp 30	NPH to IDet	IGlar to IDet
Insulin dose by weight, U/kg	n	151	351	129	186	158
	Pre-study	0.50 (0.24)	0.60 (0.20)	0.39 (0.24)	0.37 (0.19)	0.32 (0.14)
	Baseline	0.55 (0.20)	0.60 (0.19)	0.50 (0.23)	0.33 (0.15)	0.32 (0.15)
	Week 24	0.62 (0.22)	0.69 (0.21)	0.66 (0.24)	0.44 (0.21)	0.44 (0.20)
HbA_{1c}, %/mmol/mol	n	94	211	93	117	111
	Baseline	10.0 (1.8)/86 (20)	8.9 (1.6)/74 (17)	9.6 (1.7)/81 (19)	8.8 (1.7)/73 (19)	8.5 (1.5)/69 (16)
	Week 24	8.2 (1.4)/66 (15)	7.6 (1.1)/60 (12)	8.1 (1.4)/65 (15)	8.3 (1.9)/67 (21)	8.0 (1.4)/64 (15)
	Change	−1.8 (1.9)/−20 (21)	−1.3 (1.8)/−14 (20)	−1.4 (1.7)/−15 (19)	−0.6 (1.8)/−7 (20)	−0.5 (1.7)/−5 (19)
	p	– [a]	<0.001	– [a]	<0.001	0.002
FPG, mg/dL	n	109	257	97	138	127
	Baseline	209.5 (83.3)	187.7 (70.1)	195.1 (71.0)	176.1 (74.7)	163.6 (57.9)
	Week 24	147.2 (48.1)	144.9 (49.2)	147.6 (50.0)	150.0 (66.3)	140.3 (48.9)
	Change	−62.3 (90.9)	−42.9 (81.2)	−47.5 (87.5)	−26.1 (90.3)	−23.3 (73.6)
	p	<0.001	<0.001	– [a]	<0.001	<0.001
PPPG, mg/dL	n	64	176	74	64	83
	Baseline	262.2 (96.6)	258.7 (78.5)	264.3 (87.3)	234.2 (67.8)	226.7 (61.8)
	Week 24	179.8 (51.5)	183.1 (49.3)	207.6 (82.1)	198.1 (74.9)	203.9 (70.8)
	Change	−82.4 (108.2)	−75.5 (88.7)	−56.7 (115.1)	−36.1 (83.6)	−22.9 (92.8)
	p	– [a]	<0.001	– [a]	– [a]	– [a]
Weight, kg	n	115	287	115	152	142
	Baseline	75.9 (12.2)	75.3 (12.3)	76.7 (13.0)	75.2 (13.8)	76.9 (11.8)
	Week 24	76.2 (12.0)	75.8 (11.6)	79.0 (13.8)	74.9 (13.3)	76.1 (11.6)
	Change	0.3 (3.4)	0.4 (3.8)	2.3 (4.0)	−0.3 (2.9)	−0.8 (3.8)
	p	0.279	0.057	<0.001	0.24	0.017
SBP, mmHg	n	118	248	112	153	140
	Baseline	134.8 (17.3)	131.6 (16.5)	130.4 (16.6)	135.7 (18.6)	131.3 (20.8)
	Week 24	132.6 (17.0)	129.0 (15.2)	128.3 (15.0)	132.7 (16.1)	128.3 (17.4)
	Change	−2.2 (17.2)	−2.6 (16.8)	−2.1 (15.2)	−3.0 (15.5)	−2.9 (18.9)
	p	0.178	0.014	0.143	0.018	0.067
Total cholesterol, mmol/L	n	59	116	61	52	83
	Baseline	4.9 (1.4)	4.7 (1.1)	4.5 (1.0)	4.5 (1.2)	4.5 (1.0)
	Week 24	4.6 (1.0)	4.6 (0.8)	4.4 (0.9)	4.6 (1.1)	4.4 (0.9)
	Change	−0.3 (1.4)	−0.1 (1.2)	−0.1 (0.9)	0.1 (1.5)	−0.2 (1.0)
	p	– [a]	0.254	– [a]	– [a]	– [a]
Triglycerides, mmol/L	n	57	121	67	54	87
	Baseline	1.4 (0.7)	1.5 (0.8)	1.6 (1.3)	1.6 (0.8)	1.7 (1.3)
	Week 24	1.4 (0.6)	1.5 (0.6)	1.4 (0.6)	1.6 (0.7)	1.4 (0.6)
	Change	−0.1 (0.7)	−0.0 (0.7)	−0.2 (1.2)	0.0 (0.9)	−0.3 (1.2)
	p	– [a]	0.904	– [a]	– [a]	– [a]
HDL cholesterol, mmol/L	n	43	75	47	43	49
	Baseline	1.1 (0.4)	1.3 (0.6)	1.0 (0.4)	1.0 (0.4)	1.1 (0.4)
	Week 24	1.1 (0.3)	1.2 (0.3)	1.1 (0.4)	1.1 (0.4)	1.1 (0.3)
	Change	−0.1 (0.5)	−0.1 (0.6)	0.1 (0.4)	0.1 (0.5)	0.0 (0.5)
	p	– [a]	– [a]	– [a]	– [a]	– [a]

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Table 4 – *(continued)*

Parameter		NPH to BIAsp 30	BHI to BIAsp 30	IGlar to BIAsp 30	NPH to IDet	IGlar to IDet
LDL cholesterol, mmol/L	n	32	79	48	35	49
	Baseline	2.8 (1.4)	2.7 (1.0)	2.9 (1.8)	2.7 (1.1)	2.8 (0.9)
	Week 24	2.6 (1.0)	2.7 (0.7)	3.0 (2.3)	2.5 (0.8)	2.7 (0.8)
	Change	−0.2 (1.4)	−0.0 (1.1)	0.1 (3.0)	−0.3 (1.1)	−0.1 (0.9)
	p	–[a]	–[a]	–[a]	–[a]	–[a]
Hypoglycaemia (events per patient-year/percent with event)						
Overall	Baseline	13.86/30.3	13.87/35.2	3.02/10.9	14.23/33.7	6.95/22.0
	Week 24	3.73/13.9	5.97/22.7	10.53/24.1	1.95/7.5	4.69/13.2
	p[b]	0.0002	<0.0001	0.0053	<0.0001	0.009
Major	Baseline	1.28/5.9	2.76/12.0	0.00/0.0	2.53/10.5	0.41/2.5
	Week 24	0.00/0.0	0.34/0.3	0.11/0.9	0.00/0.0	0.00/0.0
	p[b]	0.0027	<0.0001	0.3173	0.0003	0.0455
Minor	Baseline	12.57/30.3	11.11/33.5	3.02/10.9	11.70/32.6	6.54/20.8
	Week 24	3.73/13.9	5.64/22.3	10.42/24.1	1.95/7.5	4.69/13.2
	p[b]	0.0002	<0.0001	0.0053	<0.0001	0.0236
Nocturnal	Baseline	5.90/19.7	6.06/22.9	1.91/7.0	6.16/21.6	2.29/6.9
	Week 24	0.85/4.9	1.89/10.0	4.03/13.8	0.73/1.9	2.35/6.3
	p[b]	0.0002	<0.0001	0.0896	<0.0001	0.6171

BHI, biphasic human insulin; BIAsp 30, biphasic insulin aspart 30; FPG, fasting plasma glucose; HbA_{1c}, glycated haemoglobin A_{1c}; HDL, high-density lipoprotein; IDet, insulin detemir; IGlar, insulin glargine; LDL, low-density lipoprotein; NPH, neutral protamine Hagedorn insulin; PPPG, postprandial plasma glucose; SBP, systolic blood pressure.
Baseline, Week 24 and change values are mean (SD).
[a] p-values are not presented when the number of patients analysed was less than 100.
[b] p-value is from McNemar's test on paired proportions of patients experiencing hypoglycaemia.

overall hypoglycaemia were also noted in patients switching from pre-study BHI and NPH insulin to BIAsp 30 and IDet therapy, respectively, concordant with the results from other studies [17,18]. The proportion of patients reporting major hypoglycaemic events decreased at Week 24 in the entire cohort and among insulin-naive and -experienced patients.

A modest increase in mean body weight was observed following 24 weeks of study insulin therapy in the entire cohort along with significant improvements in the mean SBP and the total cholesterol levels. Switching from IGlar to IDet was also associated with a small but significant reduction in mean body weight, in line with the known effects of IDet therapy [19].

The starting dose of the study insulins was 0.42±0.27 U/kg, titrated up to 0.55±0.30 U/kg by Week 24. Although glycaemic parameters improved compared to baseline in this Maghrebian cohort, patients still failed to achieve the internationally recommended levels for optimal glycaemic control, possibly reflecting the trend of inadequate dose optimisation noted in the 2008 DiabCare Algeria study [10]. A more active approach to dose intensification may well benefit these patients and enable them to reach the glycaemic targets.

Health-related QoL is an important aspect of diabetes care. It is recognised that QoL is linked to improved health and to patients' perceptions of their ability to control their disease [20]. In this sub-analysis, significant improvements in QoL were noted in the entire cohort, irrespective of pre-study therapy type.

Some limitations of this observational study design include the absence of control groups and non-standardized data collection methods. Also, data for endpoints such as hypoglycaemia were collected retrospectively, which may have led to the introduction of a recall bias in the reported incidence of hypoglycaemic events. However, the study offered an opportunity to explore the safety and effectiveness of the insulin analogues in a heterogeneous population and to examine the level of local clinical care in the Maghrebian region. In conclusion, therapy with the study insulins was well-tolerated and improved glycaemic control over 24 weeks in this Maghrebian cohort.

Conflict of interest statement

Mohamed Belhadj is a board member and speaker for Novo Nordisk and has received funding from Novo Nordisk for advisory and educational activities. Henda Jamoussi had no conflicts of interest to disclose. Amine Dahaoui is employed by Novo Nordisk. This study was sponsored by Novo Nordisk A/S, Denmark. The sponsor took part in the development of the protocol, the process of data collection and analysis, funding of medical writing services, and in reviewing the manuscript, but not in participant selection, choice of therapies (study or otherwise), provision of therapies, including insulin, or continuing clinical management of the participants. Ahmed Farouqi received funding from Novo Nordisk and other insulin manufacturers for his research, advisory and educational activities.

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