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The study of once- and twice-daily biphasic insulin aspart 30 (BIAsp 30) with sitagliptin, and twice-daily BIAsp 30 without sitagliptin, in patients with type 2 diabetes uncontrolled on sitagliptin and metformin—The Sit2Mix trial

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ABSTRACT

Aims: Investigate efficacy and tolerability of intensifying diabetes treatment with once- or twice-daily biphasic insulin aspart 30 (BIAsp 30) added to sitagliptin, and twice-daily BIAsp 30 without sitagliptin in patients with type 2 diabetes (T2D) inadequately controlled on sitagliptin.

Methods: Open-label, three-arm, 24-week trial; 582 insulin-naïve patients were randomized to twice-daily BIAsp 30 + sitagliptin (BIAsp BID + Sit), once-daily BIAsp 30 + sitagliptin (BIAsp QD + Sit) or twice-daily BIAsp 30 without sitagliptin (BIAsp BID), all with metformin.

Results: After 24 weeks, HbA_{1c} reduction (%) was superior with BIAsp BID + Sit vs. BIAsp QD + Sit (BIAsp BID + Sit minus BIAsp QD + Sit difference: −0.36 [95% CI −0.54; −0.17], $P < 0.001$) and BIAsp BID (BIAsp BID minus BIAsp BID + Sit difference: 0.24 [0.06; 0.43], $P = 0.01$). Observed final HbA_{1c} values were 6.9%, 7.2% and 7.1% (baseline 8.4%), and 59.8%, 46.5% and 49.7% of patients achieved HbA_{1c} <7.0%, respectively. Confirmed hypoglycaemia was lower with BIAsp QD + Sit vs. BIAsp BID ($P = 0.015$); rate: 1.17 (BIAsp QD + Sit), 1.50 (BIAsp BID + Sit) and 2.24 (BIAsp BID) episodes/patient-year. Difference in bodyweight change favoured BIAsp QD + Sit vs. both BID groups ($P < 0.001$).

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Conclusions: Adding BIAsp 30 to patients with T2D poorly controlled with sitagliptin and metformin is efficacious and well tolerated; however, while BIAsp BID + Sit showed superior glycaemic control, BIAsp QD + Sit had a lower rate of hypoglycaemia and showed no weight gain.

1. Introduction

Treatment of patients with type 2 diabetes (T2D) aims to reduce insulin resistance and enhance beta-cell secretion through lifestyle modification and use of metformin, followed by the combination of other oral antidiabetic drugs (OADs). Nevertheless, due to the progressive deterioration in glycaemic control, insulin therapy is often required to achieve glycaemic goals [1]. Lowering glucose levels to the recommended HbA_{1c} level <7.0% is associated with reduction in microvascular complications and, if achieved in a timely manner after diagnosis, may also improve macrovascular outcomes [1].

Sitagliptin, a widely used, highly selective oral dipeptidyl peptidase-4 (DPP-4) inhibitor, can be used in dual or triple therapy when glycaemic control is not attained with metformin [1,2]. Although DPP-4 inhibitors are weight-neutral and have a low hypoglycaemia risk, they are associated with modest glucose-lowering activity (HbA_{1c} reduction 0.5–0.9%) [3,4]. In a head-to-head comparison, significantly better glycaemic control was achieved with insulin glargine versus sitagliptin, both with metformin, in insulin-naïve patients with T2D, although symptomatic hypoglycaemia was also significantly greater with this insulin-based regimen [5]. In insulin-naïve patients with T2D, improved glycaemic control has also been demonstrated when starting insulin detemir in combination with sitagliptin [6], and when adding insulin glargine to patients uncontrolled on metformin and DPP-4 inhibitors [7]. Despite these findings, there is no clear guidance on whether to withdraw DPP-4 inhibitors and add insulin therapy, or to combine these treatments when intensification is required in patients with poor glycaemic control on metformin.

Premixed insulin or basal insulin are often considered first-line therapy options for patients with T2D requiring insulin treatment [8]. Biphasic insulin aspart 30 (BIAsp 30) is a premixed insulin containing soluble insulin aspart and protamine-crystallized insulin aspart in a 30/70 ratio, thus providing prandial and basal glucose coverage, respectively, that can be administered once, twice or three-times daily. Adding BIAsp 30 has demonstrated significant improvements in glycaemic control versus OADs alone in poorly controlled insulin-naïve patients with T2D [9–11]; however, clinical data on the combination of premixed insulins and sitagliptin are limited. The Sit2Mix trial aimed to investigate efficacy and tolerability of intensifying diabetes treatment with once- or twice-daily BIAsp 30 by either adding BIAsp 30 to sitagliptin or substituting BIAsp 30 for sitagliptin in patients with T2D inadequately controlled on sitagliptin and metformin.

2. Materials and methods

2.1. Study protocol

Sit2Mix was a randomized, open-label, three-arm, parallel-group stratified, multicentre trial conducted in Argentina, Australia, Brazil, Greece, India, Korea, Malaysia, Portugal, Thailand and Turkey between 2012 and 2013. A 2-week screening period was followed by a 24-week treatment period during which patients were randomized (1:1:1) to BIAsp 30 (NovoMix 30, Novo Nordisk, Bagsværd, Denmark) administered twice daily + sitagliptin + metformin (BIAsp BID + Sit), BIAsp 30 administered once daily + sitagliptin + metformin (BIAsp QD + Sit), or BIAsp 30 administered twice daily + metformin but without sitagliptin (BIAsp BID). Participants were stratified according to prior OAD treatment besides sitagliptin and metformin. All other OADs were discontinued at randomization. The trial was conducted in compliance with Good Clinical Practice, local regulatory requirements and the Declaration of Helsinki.

2.2. Participants

Participants were eligible for inclusion if diagnosed with T2D for ≥6 months before the study, ≥18 years of age, HbA_{1c} 7.0–10.0% and BMI ≤40.0 kg/m^2. Patients were required to be insulin-naïve (short-term insulin use due to intermittent illness of ≤14 days allowed) and stable on treatment with a total daily dose of at least 1000 mg of metformin (± additional OADs) unchanged for ≥3 months prior to the study and treatment with ≥100 mg sitagliptin/day for ≥3 months before study; also to be able and willing to (1) administer subcutaneous injections daily, (2) eat at least two main meals daily and (3) perform self-measured blood glucose (SMPG) measurements. Exclusion criteria included: thiazolidinedione or glucagon-like-peptide-1 treatment within the 3 months before the study; cardiac disease within the last 6 months (defined as decompensated heart failure New York Heart Association class III or IV); unstable angina pectoris; myocardial infarction; severe hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg); change in dose of any systemic treatment with products which, in the investigator's opinion, could interfere with glucose metabolism; clinically significant diseases which, in the investigator's opinion, may confound the results of the trial or pose additional risk in administering trial product(s); impaired hepatic function (aspartate aminotransferase or alanine aminotransferase >2.5 times upper normal range); impaired renal function (serum creatinine levels ≥133 μmol/L [males], ≥124 μmol/L [females] or estimated creatinine clearance below 60 mL/min).

Withdrawal was at the discretion of the investigator or if non-compliance was reported.

2.3. Treatment regimen and dosing

All participants receiving BIAsp 30 had their insulin dose titrated by the investigator in accordance with titration guidelines [12]. Starting dose for BIAsp 30 was 6 U pre-breakfast and 6 U pre-dinner in the BID groups, and 12 U pre-dinner in the QD group. The BIAsp 30 dose was adjusted according to SMPG measurements taken on any 3 days in the week prior to a site visit/phone contact. This was conducted weekly for the first 6 weeks, and every second week thereafter. BIAsp 30 dose was adjusted by –2 U if pre-meal SMPG was <4.4 mmol/L, 0 U if 4.4–6.1 mmol/L, +2 U if 6.2–7.8 mmol/L, +4 U if 7.9–10 mmol/L and +6 U if >10 mmol/L. All participants received a stable dose of metformin 1000 mg/day. In the BIAsp 30 + sitagliptin arms, the dose of sitagliptin was 100 mg/day.

2.4. Endpoints

The primary endpoint was change from baseline in HbA_{1c} after 24 weeks of treatment. Secondary efficacy endpoints included the proportion of subjects achieving HbA_{1c} <7.0%, and the proportion achieving HbA_{1c} <7.0% without hypoglycaemia (any symptomatic hypoglycaemia with a plasma glucose value ≤3.9 mmol/L or any single plasma glucose value <3.1 mmol/L in the last 3 months of treatment), change from baseline in fasting plasma glucose (FPG), total daily insulin dose and 7-point self-measured capillary SMPG profiles. Safety endpoints included adverse events (AEs), changes from baseline in bodyweight, daytime and nocturnal treatment-emergent hypoglycaemic episodes, physical examination, vital signs, and changes in haematology and biochemistry measurements. Laboratory analyses were performed by a central laboratory. Confirmed hypoglycaemia was defined post hoc and comprised all episodes with a plasma glucose measurement <3.1 mmol/L (regardless of symptoms) and any episodes considered severe (requiring third-party assistance). Nocturnal hypoglycaemia was deemed to occur if the episode took place between 00:01 and 05:59 h (inclusive). Other endpoints included the change from baseline in treatment satisfaction using the self-reported Treatment Related Impact Measure – Diabetes (TRIM-D) [13] and a general health-economic analysis of the average cost related to each treatment regimen (costs based on drug prices from 13 September 2013 from MIMS database).

2.5. Statistical analysis

Efficacy and safety endpoints were analyzed using the full analysis dataset and safety analysis dataset, respectively. All analyses consisted of pair-wise two-sided tests with 5% significance level. Missing values were imputed using last observation carried forward. Sample size was based on change in primary endpoint and a clinically relevant treatment difference of 0.4%; a minimum sample size of 573 was required to meet the primary objective with 90% power. Normal linear regression models with treatment, strata and region as factors, and relevant baseline measurements as covariate were used for analyses of change in HbA_{1c}, FPG, bodyweight and TRIM-D scores. Analysis of 7-point SMPG profiles was conducted using a mixed-effects model with treatment, time, interaction between treatment and time, strata and region as fixed factors and subject as random. Responder analyses were analyzed based on a logistic regression model using treatment, strata and region as factors, and baseline HbA_{1c} as covariate. Hypoglycaemia was analyzed using a negative binomial regression model with treatment, strata and region as factors, and the logarithm of the time period for which a hypoglycaemic episode was considered treatment-emergent as offset. SAS version 9.3 was used to perform the analyses and all *P*-values <0.05 were considered statistically significant.

3. Results

3.1. Study population

804 participants were screened, of which 582 were randomized (BIAsp BID + Sit, $n = 195$; BIAsp QD + Sit, $n = 193$; BIAsp BID, $n = 194$) and 575 exposed to treatment. Overall, 46 participants withdrew from the trial: 13 in the BIAsp BID + Sit group, 12 in BIAsp QD + Sit and 21 in BIAsp BID (Fig. 1). Baseline characteristics were broadly comparable between groups, although gender distribution (male vs. female) varied slightly: 60% vs. 40% in the BIAsp BID group and 50% vs. 50% in the other two groups (Table 1). Baseline HbA_{1c} in all groups was 8.4 ± 0.8% and approximately 70% of participants in each group were receiving OADs before the study. At baseline, 2.6–6.2% of patients across the three groups experienced nephropathy, 10.8–13.5% neuropathy, 7.7–9.3% retinopathy and 1.5–6.2% macroangiopathy.

3.2. Glycaemic control

Observed final HbA_{1c} values after 24 weeks were 6.9%, 7.2% and 7.1% for BIAsp BID + Sit, BIAsp QD + Sit and BIAsp BID, respectively. Estimated HbA_{1c} change (%) was statistically superior with BIAsp BID + Sit versus BIAsp QD + Sit (−1.51 vs. −1.15, difference: −0.36 [95% CI −0.54; −0.17], $P < 0.001$) and versus BIAsp BID (−1.27 vs. −1.51, difference: 0.24, [95% CI 0.06; 0.43], $P = 0.01$) (Fig. 2). HbA_{1c} change was not significantly different between BIAsp QD + Sit and BIAsp BID (difference −0.11 [95% CI −0.30; 0.07], $P = 0.231$). There was a comparable FPG reduction across all treatment arms (final observed mean value: 7.0 mmol/L). After 24 weeks, 7-point SMPG (mmol/L) reported in the BIAsp BID + Sit arm was significantly lower versus the BIAsp QD + Sit arm 90 min after breakfast (difference: −1.07 [95% CI −1.65; −0.50]), before lunch (difference: −1.12 [95% CI −1.56; −0.67]), 90 min after lunch (difference: −1.29 [95% CI −1.81; −0.78]) and before dinner (difference: −1.25 [95% CI −1.74; −0.76]). A similar trend was observed for the comparison between BIAsp BID and BIAsp QD + Sit, but the BID groups were not significantly different to each other (Fig. 3).

The proportion of HbA_{1c} responders (<7.0%) was 59.8% with BIAsp BID + Sit, 46.5% with BIAsp QD + Sit and 49.7% with BIAsp BID. The odds of reaching HbA_{1c} <7.0% with BIAsp BID + Sit were significantly higher versus BIAsp BID (BIAsp

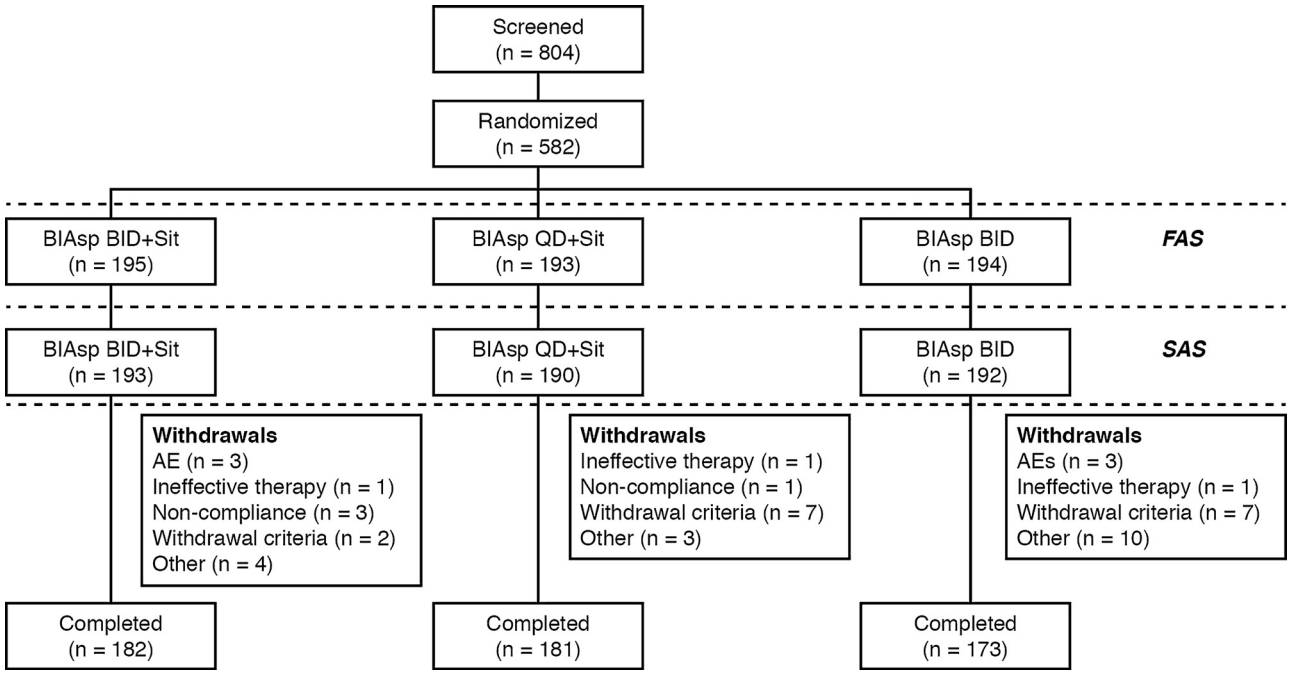

Fig. 1 – Participant flow from screening to study completion. AE, adverse event; BID, twice daily; BIAsp, biphasic insulin aspart; FAS, full analysis set; QD, once daily; SAS, safety analysis set; Sit, sitagliptin.

BID vs. BIASp BID + Sit odds ratio [OR] 0.60 [95% CI 0.39; 0.93], $P = 0.022$) and vs. BIAsp QD + Sit (OR 1.85 [95% CI 1.20; 2.85], $P = 0.005$); however, as observed with the primary endpoint, the BIAsp QD + Sit group was not significantly different versus the BIAsp BID group. The proportion of responders achieving HbA_{1c} <7.0% without hypoglycaemia was 41.5% with BIAsp BID + Sit, 39.2% with BIAsp QD + Sit and 27.9% with BIAsp BID. The odds for reaching target without hypoglycaemia were significantly higher with BIAsp BID + Sit versus BIAsp BID (BIASp BID vs. BIAsp BID + Sit OR 0.48 [95% CI 0.30; 0.76], $P = 0.002$), but were not significantly different versus BIAsp QD + Sit (OR 1.13 [95% CI 0.73; 1.75], $P = 0.595$). In contrast to the trend observed with the primary endpoint, the odds for reaching target without hypoglycaemia with BIAsp QD + Sit were significantly higher versus BIAsp BID (BIASp BID vs. BIASp QD + Sit OR 0.54 [95% CI 0.34; 0.86], $P = 0.009$) by the end of the study.

3.3. *Safety*

Overall confirmed hypoglycaemia rates were 1.17, 1.50 and 2.24 episodes/patient-year in the BIAsp QD + Sit, BIAsp BID + Sit and BIAsp BID groups, respectively (Table 2). The rate of confirmed hypoglycaemic episodes was significantly lower in the BIAsp QD + Sit group versus the BIAsp BID group (BIAsp BID vs. BIAsp QD + Sit rate ratio 1.84 [95% CI 1.12; 3.01], $P = 0.015$), but there was no significant difference versus the BIAsp BID + Sit group or between the two BID groups. Too few severe hypoglycaemia episodes were reported for statistical analysis. No significant differences in nocturnal hypoglycaemia were reported.

The proportion of patients who experienced treatment-emergent AEs was similar across groups: 44.6% with BIAsp BID + Sit, 47.4% with BIAsp QD + Sit and 50.0% with BIAsp BID, with corresponding event rates of 209.9, 281.2 and 262.2

Table 1 – Baseline characteristics of the Sit2Mix trial.

	BIAsp BID + Sit	BIAsp QD + Sit	BIAsp BID	Total
Number of subjects	195	193	194	582
Age, years	56.3 (10.2)	55.7 (10.4)	54.8 (9.5)	55.6 (10.0)
Sex, % (M/F)	48.2/51.8	49.7/50.3	57.2/42.8	51.7/48.3
Bodyweight, kg	78.3 (16.1)	77.5 (16.8)	79.4 (15.8)	78.4 (16.2)
BMI, kg/m^2	29.4 (4.5)	29.4 (5.0)	29.3 (4.3)	29.4 (4.6)
HbA_{1c}, %	8.4 (0.8)	8.4 (0.8)	8.4 (0.8)	8.4 (0.8)
FPG, mmol/L	9.3 (2.8)	8.7 (2.7)	8.9 (2.2)	9.0 (2.6)
Strata, %				
+OADs	69.7	69.9	67.5	69.1
−OADs	30.3	30.1	32.5	30.9

Data are mean (SD).
BID, twice daily; BIAsp, biphasic insulin aspart; FPG, fasting plasma glucose; OAD, oral antidiabetic drug; QD, once daily; Sit, sitagliptin.

Table 2 – Rates of confirmed hypoglycaemia after 24 weeks' treatment with BIAsp BID + Sit, BIAsp QD + Sit and BIAsp BID.

	BIAsp BID + Sit				BIAsp QD + Sit				BIAsp BID			
	N	%	*E*	*R*	*N*	%	*E*	*R*	*N*	%	*E*	*R*
Confirmed	50	25.9	129	1.50	37	19.5	100	1.17	70	36.5	186	2.24
Severe	1	0.5	1	0.01	2	1.1	6	0.07	1	0.5	1	0.01
Minor	50	25.9	128	1.49	36	18.9	94	1.10	70	36.5	185	2.23
Nocturnal severe	0	–	–	–	1	0.5	3	0.04	0	–	–	–
Nocturnal minor	8	4.1	14	0.16	9	4.7	23	0.27	11	5.7	21	0.25

Post hoc defined endpoint confirmed hypoglycaemia comprised episodes with a plasma glucose measurement <3.1 mmol/L (regardless of symptoms) and severe episodes (requiring assistance from another person). A nocturnal hypoglycaemic episode had a time of onset between 00:01 and 05:59 h (both included).
%, percentage of subjects; BID, twice daily; BIAsp, biphasic insulin aspart; *E*, number of episodes; FPG, fasting plasma glucose; *N*, number of subjects with at least one episode; QD, once daily; *R*, episodes per subject exposure-year; Sit, sitagliptin.

events/100 subject exposure-years, respectively. AEs reported in ≥5% of the study population included nasopharyngitis (4.2–5.7%), influenza (2.6–5.7%), headache (3.6–5.7%) and diarrhoea (0.5–5.3%). 21 serious adverse events were reported, of which six (all related to hypoglycaemia) were possibly/probably related to trial treatment.

3.4. *Change in bodyweight, insulin dose and treatment satisfaction*

After 24 weeks, mean change in bodyweight from baseline was +1.4 kg in the BIAsp BID + Sit group (difference vs. BIAsp QD + Sit: 1.51 [95% CI 0.82; 2.21], $P < 0.001$), +2.1 kg for BIAsp BID (difference vs. BIAsp QD + Sit: 2.19 [95% CI 1.49; 2.89], $P < 0.001$) and −0.1 kg for BIAsp QD + Sit. No significant difference was reported between the two BID groups. Final total daily dose was 0.66 U/kg, 0.72 U/kg and 0.39 U/kg, respectively, from a baseline of 0.16 U/kg. In the BID groups, the morning dose increased from 0.08 U/kg to 0.35 U/kg (BIAsp BID + Sit) and 0.39 U/kg (BIAsp BID), while the evening dose increased from 0.08 U/kg to 0.31 U/kg (BIAsp BID + Sit) and 0.34 U/kg (BIAsp BID).

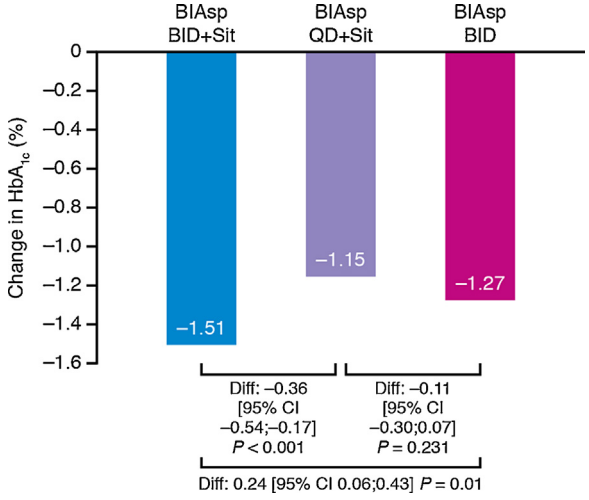

Fig. 2 – Change in HbA_{1c} after 24 weeks' treatment with BIAsp BID + Sit, BIAsp QD + Sit and BIAsp BID. BID, twice daily; BIAsp, biphasic insulin aspart; CI, confidence interval; QD, once daily; Sit, sitagliptin.

There were no significant differences in TRIM-D scores among the treatment groups. The overall TRIM-D score after 24 weeks was 76.64, 77.79 and 76.46 in the BIAsp BID + Sit, BIAsp QD + Sit and BIAsp BID groups, respectively, with baseline values of 70.28, 72.40 and 69.30.

3.5. *Costs*

Average total medicine costs in each arm (in subjects exposed ≥20 weeks) were GBP 345.7 for BIAsp BID + Sit, GBP 287.9 for BIAsp QD + Sit and GBP 160.0 for BIAsp BID. No further cost analyses were conducted.

4. Discussion

Clinicians need to balance risks, costs and benefits of different treatment approaches when choosing a suitable treatment plan for patients with diabetes. Moreover, individual circumstances should be considered, i.e. age, comorbidities, baseline HbA_{1c}, ability to adhere to complex regimens, to optimize outcomes when choosing an antihyperglycaemic strategy [2]. Sit2Mix included a relatively homogenous population at baseline and investigated three distinct intensification regimens

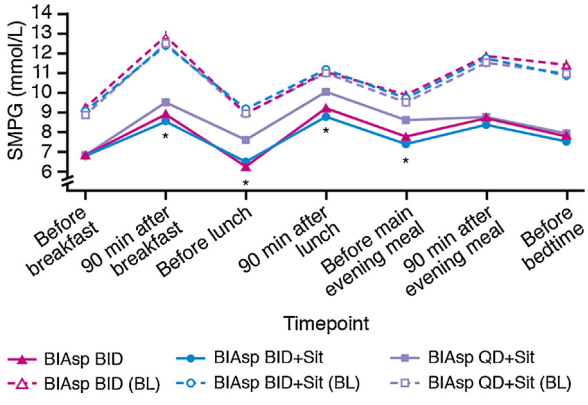

Fig. 3 – 7-point SMPG profiles at baseline and end of trial. *Significant treatment difference between BIAsp BID + Sit vs. BIAsp QD + Sit and BIAsp QD + Sit vs. BIAsp BID. BID, twice daily; BIAsp, biphasic insulin aspart; QD, once daily; Sit, sitagliptin; SMPG, self-measured blood glucose; BL, baseline.

in patients with T2D failing to be controlled on sitagliptin and metformin in combination with other OADs. All regimens were efficacious and well tolerated after 24 weeks of treatment, but each presented a different profile in terms of treatment benefits and risks. The BIAsp BID + Sit regimen showed greater improvement in glycaemic control versus BIAsp QD + Sit and BIAsp BID. Nevertheless, HbA_{1c} change in both the BIAsp QD + Sit and BIAsp BID groups was ≥1.0% and a change of this magnitude is associated with reduced risk for microvascular and macrovascular complications [14]. The improvement observed in mean SMPG after breakfast and lunch, and before lunch and dinner, in the BID groups is likely a reflection of the different dose-administration timings with BID and QD regimens (dosing before breakfast and dinner vs. dosing before dinner only, respectively). Although a greater proportion of patients achieved the recommended HbA_{1c} target <7.0% in the BIAsp BID + Sit group (approximately 60%) versus the other groups, this trend was not maintained upon examination of those patients who achieved target without hypoglycaemia. For this endpoint, the proportions of responders in the BIAsp BID + Sit and BIAsp QD + Sit groups were comparable (39–41.5%), yet the proportion in the QD group was greater than in the BIAsp BID group. The driving factor of this finding is likely the reported reduction in hypoglycaemia rate in the BIAsp QD + Sit group versus the BIAsp BID group. Also noteworthy, the change in bodyweight was significantly less in the BIAsp QD + Sit group versus the BID groups. Furthermore, according to TRIM-D questionnaire results, the impact on the patient is broadly similar regardless of treatment, suggesting that changing to a BIAsp 30-based regimen in these patients is not burdensome, and compliance and convenience are not compromised.

Our findings support different intensification regimens with BIAsp 30 that could be used in the treatment continuum of T2D. It should be noted, however, that although other regimens can be considered when starting insulin therapy e.g. basal insulin [1,2], our findings are relevant for those patients where premix insulin has been selected as the starting insulin of choice. Given the limited guidance from the ADA/EASD consensus algorithm regarding withdrawing DPP-4 inhibitors or adding on insulin therapy when intensification is required, we consider the presented data to be an important source of evidence to help guide clinicians and support individualized decisions based on endpoints that are pertinent to a patient's wellbeing and management of their diabetes. Adding BIAsp 30 BID to sitagliptin plus metformin would be the most effective choice (versus the other groups studied here) if targeting glycaemic control was the main concern; however, relative risk of hypoglycaemia and weight gain are also greater with this regimen and should be taken into consideration, along with patients' circumstances, when devising a treatment plan. Conversely, our data suggest that patients concerned about weight gain and/or those more prone to hypoglycaemia may benefit more from adding BIAsp QD to sitagliptin, although the extent of improvement in HbA_{1c} is not as considerable versus a BID BIAsp regimen with or without sitagliptin. Discontinuing sitagliptin followed by initiation of BIAsp BID (while continuing metformin) had similar efficacy, but a significantly greater change in bodyweight, versus adding BIAsp QD to sitagliptin and metformin. The treatment costs associated with discontinuing sitagliptin and starting BIAsp BD were 1.8- and 2.1-fold lower versus the BIAsp QD + Sit and BIAsp BID + Sit groups, respectively, thus the impact of costs also needs to be weighed against the clinical benefits and risks when comparing regimens.

To our knowledge, this is the first randomized, global study evaluating the combination of BIAsp 30 and sitagliptin, and the substitution of sitagliptin with BIAsp 30, thus providing valuable evidence for clinicians who would consider this approach for poorly controlled, insulin-naïve patients with T2D. However, the study does have limitations, including the absence of a sitagliptin-only control group and a restricted cost-analysis, which only considers the cost of the medicine itself and excludes costs associated with general diabetes management and complications. In addition, too few severe hypoglycaemic episodes were reported to allow for statistical analysis, which was also the case in the findings from Garber and colleagues who, in an observational study, reported few major hypoglycaemic episodes and no major nocturnal hypoglycaemic episodes during intensification of once-daily BIAsp 30 to twice- or three-times daily regimens [15]. Furthermore, our findings are specific to sitagliptin and BIAsp 30, so results cannot be extrapolated to other DPP-4 inhibitors or different ratio premix insulins.

In conclusion, intensification with BIAsp 30 in patients with T2D inadequately controlled with sitagliptin and metformin was shown to be efficacious and well tolerated using three distinct intensification regimens. The balance of benefits vs. risks was different for each of the studied regimens, providing evidence-supported therapy options for clinicians when tailoring a treatment plan for patients poorly controlled on sitagliptin and metformin.

Conflict of interest statement

S. Linjawi has received funding for advisory activities from Novo Nordisk A/S, and speaker activities from Novo Nordisk A/S, Novartis Pharma AG, Roche Pharmaceuticals, and AstraZeneca Pharmaceuticals LP. R. Sothiratnam has received funding for advisory activities from AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, and Merck Sharp and Dohme Limited; research activities from Merck Sharp and Dohme Limited and Novo Nordisk A/S; and speaker activities from AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly and Company, Merck Sharp and Dohme Limited, and Novo Nordisk A/S. R. Sari has no conflicts of interest to declare. H. Andersen and L. Hiort are employees and shareholders of Novo Nordisk A/S. P.V. Rao has received research support from Novo Nordisk A/S and the Indian Council of Medical Research, and is a Research Society for the Study of Diabetes in India board member.

Contributor statements

S. Linjwai, R. Sothiratnam, R. Sari and P.V. Rao were part of the team who conducted the trial, had full access to data and had final responsibility for manuscript content and submission. H. Andersen and L. Hiort are Novo Nordisk employees, and

as such were responsible for study design, data analysis, and manuscript review and submission.

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REFERENCES

[1] American Diabetes Association, Standards of Medical Care in, Diabetes – 2014, Diabetes Care 37 (2014) S14–S80.
[2] A.J. Garber, M.J. Abrahamson, J.I. Barzilay, et al., American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement, Endocr. Pract. 19 (2013) 1–48.
[3] B. Ahrén, Clinical results of treating type 2 diabetic patients with sitagliptin, vildagliptin or saxagliptin – diabetes control and potential adverse events, Best Pract. Res. Clin. Endocrinol. Metab. 23 (2009) 487–498.
[4] C.F. Deacon, Dipeptidyl peptidase-4 inhibitors in the treatment of type 2 diabetes: a comparative review, Diabetes Obes. Metab. 13 (2011) 7–18.
[5] P. Aschner, J. Chan, D.R. Owens, et al., Insulin glargine versus sitagliptin in insulin-naive patients with type 2 diabetes mellitus uncontrolled on metformin (EASIE): a multicentre randomised open-label trial, Lancet 379 (2012) 2262–2269.
[6] P. Hollander, K. Raslova, T.V. Skjøth, et al., Efficacy and safety of insulin detemir once daily in combination with sitagliptin and metformin: the TRANSITION randomized controlled trial, Diabetes Obes. Metab. 13 (2011) 268–275.
[7] J. Seufert, K. Pegelow, P. Bramlage, Efficacy and safety of insulin glargine added to a fixed-dose combination of metformin and a dipeptidyl peptidase-4 inhibitor: results of the GOLD observational study, Vasc. Health Risk Manag. 9 (2013) 711–717.
[8] P. Levy, Insulin analogs or premixed insulin analogs in combination with oral agents for treatment of type 2 diabetes, Med. Gen. Med. 9 (2007) 12.
[9] M. Kvapil, A. Swatko, C. Hilberg, M. Shestakova, Biphasic insulin aspart 30 plus metformin: an effective combination in type 2 diabetes, Diabetes Obes. Metab. 8 (2006) 39–48.
[10] I. Raz, U. Mouritzen, J. Vaz, et al., Addition of biphasic insulin aspart 30 to rosiglitazone in type 2 diabetes mellitus that are poorly controlled with glibenclamide monotherapy, Clin. Ther. 25 (2003) 3109–3123.
[11] I. Raz, S. Stranks, R. Filipczak, et al., Efficacy and safety of bisphasic insulin aspart 30 combined with pioglitazone in type 2 diabetes poorly controlled on glibenclamide (glyburide) monotherapy or combination therapy: an 18-week, randomised, open-label study, Clin. Ther. 27 (2005) 1432–1443.
[12] Novo Nordisk, Insulin NovoMix 30 SmPC, 2014, Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000308/WC500029441.pdf (accessed June 2014).
[13] M. Brod, T. Christensen, M. Hammer, et al., Examining the ability to detect change using the TRIM-Diabetes and TRIM-Diabetes Device measures, Qual. Life Res. 20 (2011) 1513–1518.
[14] I.M. Stratton, A.I. Adler, A.W. Neil, et al., Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study, BMJ 321 (2000) 405–412.
[15] A.J. Garber, J. Wahlen, T. Wahl, et al., Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily dosing with biphasic insulin aspart 70/30 (the 1-2-3 study), Diabetes Obes. Metab. 8 (2006) 58–66.