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ORIGINAL RESEARCH

Improved Treatment Satisfaction and Self-reported Health Status after Introduction of Basal-Supported Oral Therapy Using Insulin Glargine in Patients with Type 2 Diabetes: Sub-Analysis of ALOHA2 Study

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ABSTRACT

Introduction: This study aimed to assess treatment satisfaction and self-reported health status in insulin-naïve patients with type 2 diabetes mellitus (T2DM) who started insulin glargine basal-supported oral therapy (BOT) with glycated hemoglobin (HbA1c) value of ≥6.5%, using data from Add-on Lantus® to Oral Hypoglycemic Agents 2 (ALOHA2) study, a 24-week single-arm, observational study of Japanese patients with T2DM, conducted as drug use surveillance in Japan.

Methods: Treatment satisfaction was measured using the Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) and change version (DTSQc) and self-reported health status using EuroQol 5 Dimension (EQ-5D). The results were compared between the groups stratified by HbA1c level at the final evaluation point: target-achieved (<7.0%) and target-not-achieved groups (≥7.0%).

Results: In 1251 patients (336 in the target-achieved group), scores of DTSQs, DTSQc, and EQ-5D indicated significant improvement from baseline to the final evaluation point (both $P < 0.01$). The mean change in DTSQs scale score, DTSQs item score, and EQ-5D index score, and mean DTSQc scale score were significantly improved in the target-achieved group compared with the target-not-achieved group ($P < 0.05$ for all). DTSQs scale score and HbA1c level showed the same pattern of chronological change. Data analysis in patients stratified by DTSQs score showed better glycemic control in the high satisfaction group.

Conclusion: Following insulin glargine BOT introduction, treatment satisfaction and health

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status were improved from patients' perspectives despite the need for daily injections. Based on the possible association between HbA1c 7.0% level achievement, treatment satisfaction, and health status, better glycemic control may be a key to successful treatment.

Keywords: Basal-supported oral therapy; Health status; Insulin glargine; Insulin naïve; Patient-reported outcome; Treatment satisfaction; Type 2 diabetes

INTRODUCTION

A goal of diabetes treatment is to prevent diabetes complications and maintain as good quality of life (QOL) as those without diabetes, beginning from the fundamental step to achieve and maintain good glycemic control [1]. Although diligent life-long self-management is required due to the progressive nature of diabetes [2, 3], better glycemic control is associated with treatment satisfaction [4] and with better physical and psychological health [5]. Therefore, assessing treatment satisfaction and one's perception, i.e., health status and QOL, using patient-reported outcome (PRO) measures as important outcomes and also as factors influencing disease and treatment outcomes is an important part of diabetes management [6].

Basal-supported oral therapy (BOT) in which long-acting insulin injection is added to ongoing treatment with oral antidiabetic drugs (OADs) has been widely adopted for patients with type 2 diabetes mellitus (T2DM) whose blood glucose control using OADs is insufficient [7]. The simple and less frequent administration is expected to lower a barrier to initiation derived from anticipated or actual physical and psychological burden of insulin treatment, and make the management easier, which can consequently encourage healthcare providers to initiate insulin treatment at early treatment stage. Insulin glargine, one of the long-acting insulin analogs most commonly used in BOT, can supplement endogenous basal insulin effectively to reduce glycemic levels for approximately 24 h by once-daily injection with smaller risk of hypoglycemia [8–11].

In Japan, Add-on Lantus® to Oral Hypoglycemic Agents 2 (ALOHA2) study, a 24-week, prospective, open-label multicenter, single-arm, observational study showed that insulin glargine BOT significantly improved blood glucose level in patients with T2DM, suggesting physiological efficacy and safety [12]. Although explored in other countries [13, 14], glargine BOT's influence on treatment satisfaction and health status lacks data in Japanese patients, warranting the investigation specifically in a Japanese population. Anxiety and fear of insulin are known to hinder the introduction of insulin therapy [15]. Investigating the influence of glargine BOT on treatment satisfaction and health status may give patients and their medical practitioners an incentive to introduce insulin without undue delay. In the present analysis, using a subset of data from the ALOHA2, we explored treatment satisfaction and self-reported health status in patients starting insulin glargine BOT.

METHODS

Study Design and Patients

The ALOHA2 study, a sequel of the ALOHA study [16–19], was conducted between 2012 and 2013 in 619 hospitals and clinics across Japan [12]. Participating patients were observed

in a clinical setting. Patients with T2DM were included if they: were aged 20 or older, were being treated with OAD therapy, had glycated hemoglobin (HbA1c) ≥6.5% during 4 weeks prior to the study, and were to start BOT with insulin glargine. For data analysis, in the case of HbA1c levels in Japan Diabetes Society and the International Federation of Clinical Chemistry values, they were converted into the National Glycohemoglobin Standardization Program values [20].

Summary Results of the ALOHA2 Study

Of the 2630 patients enrolled, 2602 and 1629 patients comprised the safety and efficacy analysis set, respectively (Fig. 1). Of patients included in the safety analysis set, 140 patients (5.38%) reported hypoglycemic events, including 11 patients (0.42%) with severe hypoglycemic events (0.019 event/patient-year). As to efficacy, HbA1c, FPG, and 2 h PPG levels significantly improved from baseline to the final evaluation point (9.6% to 7.9%; 203.0 to 148.6 mg/dL; and 267.0 to 192.5 mg/dL, respectively).

PRO Instruments

Patients' satisfaction and self-reported health status were measured using validated Japanese versions of three questionnaires: Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) and change version (DTSQc) [21] and EuroQol 5 Dimension (EQ-5D) in the original 3-level format [22]. DTSQs and EQ-5D were administered at baseline, week 10 and week 24 or the last visit (final evaluation point) and DTSQc at the final evaluation point.

DTSQ simply and comprehensively assesses satisfaction specifically with diabetes treatment [23]. DTSQs captures the current status and DTSQc the change in treatment satisfaction [23, 24]. The instruments contain 8 questions: (1) satisfaction with current treatment, (2) perceived frequency of hyperglycemia, (3) perceived frequency of hypoglycemia, (4) convenience of the treatment, (5) flexibility of the treatment, (6) understanding of diabetes mellitus, (7) willingness to recommend the treatment to others, and (8) satisfaction to continue the treatment. Each item scores from 0 to 6 and −3 to 3 in the DTSQs and DTSQc, respectively. Treatment satisfaction was evaluated based on the combined score of 6 treatment satisfaction items: item 1, and 4–8. Scale scores range from 0 to 36 and −18 to 18 in DTSQs and DTSQc, respectively. A higher score indicates greater satisfaction or greater improvement in satisfaction. Perceived frequency of hyperglycemia and hypoglycemia (item 2 and 3, respectively) were assessed independently; a lower score indicates fewer perceived episodes of hyperglycemia, hypoglycemia, or a reduction in the number of such episodes.

EQ-5D is a universally used tool to describe respondent's perceived health status [25]. The instrument includes the descriptive system and the visual analogue scale (EQ-VAS). The descriptive system consists of 5 dimensions: mobility, self-care, pain/discomfort, usual activities, and anxiety/depression, with three response levels: no problem, some problems, and extreme problems. The index score derived from the conversion of the total responses ranges from −0.11 to 1.00 in the Japanese population with the score of 1 denoting "full health" and 0 "death" [22]. EQ-VAS records respondent's general health ranging from 0 (worst imaginable health state) to 100 (best possible health state).

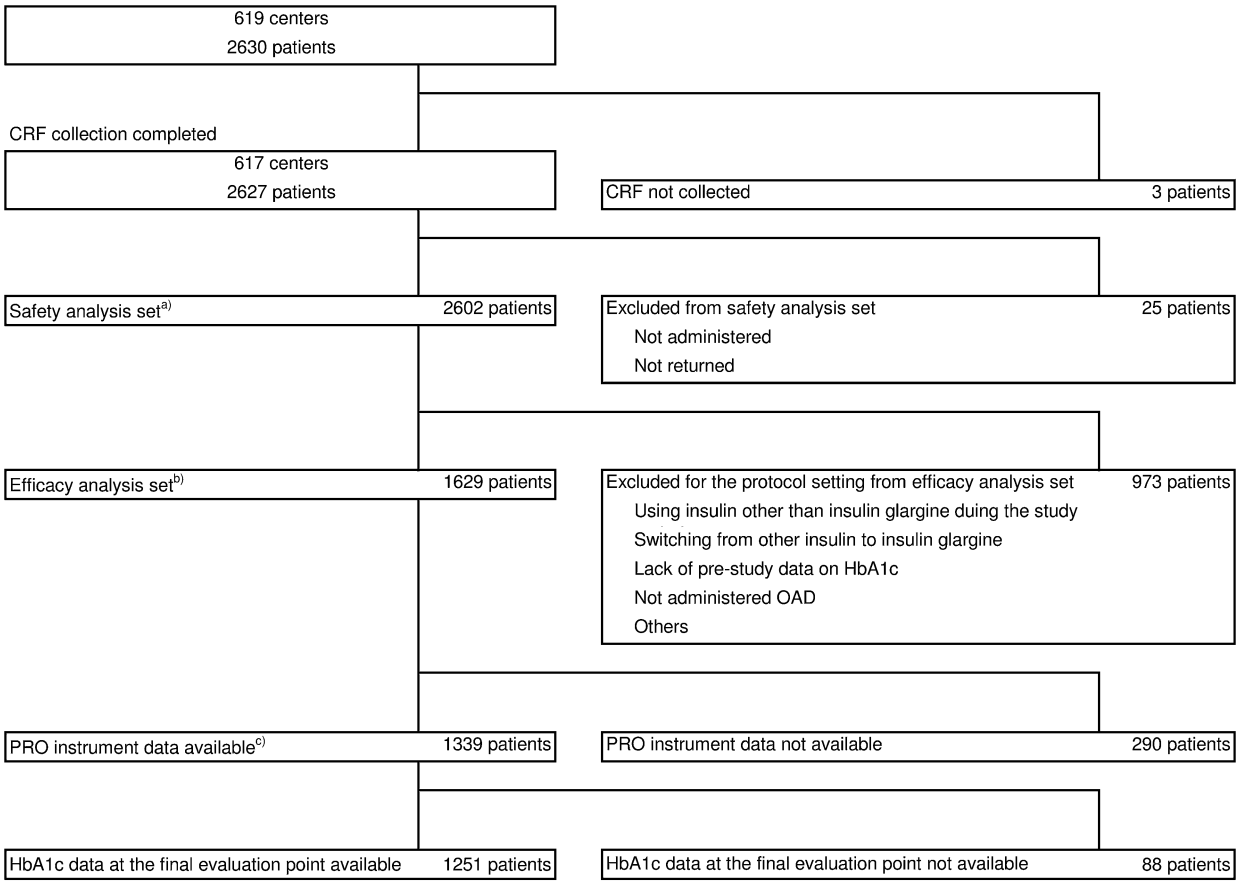


Fig. 1 Patient flow. *CRF* case report form, *HbA1c* glycated hemoglobin, *OAD* orally administered antidiabetic agent, *PRO* patient-reported outcome. *a* patients who had ever been administered insulin glargine. *b* patients who had not been treated with insulin previously and started insulin glargine basal-supported oral therapy during the observational period. *c* patients whose PRO instrument data were evaluable

Statistical Analysis

Of the efficacy analysis set insulin-naïve patients ($n = 1629$), patients with data on PRO instruments and HbA1c level at the final evaluation point available were analyzed. The patients were stratified according to the HbA1c level at the final evaluation point: <7.0% as target-achieved group, recommended level of glycemic control [1, 2, 26]; ≥7.0% as target-not-achieved group. Missing data were substituted by the data of the final evaluation point, using the last observation carried forward method. Data were compared between groups. Demographic and clinical characteristics were summarized descriptively and compared using Wilcoxon's rank-sum test for continuous variables and Fisher's exact test for nominal variables. The PRO score at baseline and the final evaluation point was compared using Wilcoxon signed-rank test (change in the DTSQc score was calculated based on the assumed baseline score of zero, indicating no change). The scores and their changes from baseline of each PRO instrument at the final evaluation point were compared using the Wilcoxon rank-sum test.

To explore possible factors that may influence treatment satisfaction, patients were stratified by tertiles of DTSQs satisfaction score

change from baseline to the final evaluation point: high, middle, and low satisfaction groups. Factors were compared between the three groups using the Fisher's exact test for nominal and Kruskal–Wallis test for continuous variables.

All statistical tests were conducted at a two-tailed significance level of 0.05 using SAS System software (version 9.2 or higher, SAS Institute, Cary, NC, 2006).

Compliance with Ethics Guidelines

This study was conducted as a special drug use surveillance in compliance with the pharmaceutical affairs law and the ministerial ordinance of "Good Post-Marketing Study Practice" in Japan, and conducted after a contract with each medical institution participating in the survey. Informed consent was obtained from all patients included in the study. All treatment decisions were made by each attending physician. Physicians and healthcare medical staff were blinded to the patients' response to questionnaires.

RESULTS

Patient Characteristics

Of the 1251 patients included in this analysis (Fig. 1), 336 patients (26.9%) achieved the target HbA1c level of <7.0%. Their baseline characteristics are summarized by target-achieved and target-not-achieved groups in Table 1. The disease seemed to have progressed less in the target-achieved than in the target-not-achieved group prior to baseline (i.e., a shorter duration of diabetes, fewer concomitant OAD, and lower percentage of patients with diabetic nephropathy ($P < 0.05$ for all).

Mean HbA1c level significantly decreased in both groups at the final evaluation point from baseline (paired t test, $P < 0.0001$) with significantly greater reduction in the target-achieved group ($P < 0.0001$) (Fig. 2). From baseline, both groups illustrated a similar trend of reduction (more than 1%) to week 12 and slight reduction (about 0.5%) in the target-achieved group and sideway shift with slight increase (less than 0.1%) in the target-not-achieved group onwards to the final evaluation point.

Although data from patients who answered the questionnaire were analyzed, data from those who did not answer did not show significantly poorer glycemic control or higher incidence of treatment-related adverse events in this particular group of patients ($P > 0.05$) (data not shown).

DTSQ

The mean DTSQs treatment satisfaction scale score significantly improved from baseline to the final evaluation point in overall patients (baseline vs final evaluation point: 21.8 vs 25.6, $P < 0.0001$) and also in the target-achieved and target-not-achieved group ($P < 0.0001$ for both) (Fig. 3a). The mean change from baseline to the final evaluation point was significantly greater in the target-achieved group (mean ± standard deviation: 5.3 ± 8.0 and 3.2 ± 7.6, $P = 0.001$). Over the study period, the treatment satisfaction scale score increased in both groups from baseline to week 10, and continued to increase slightly thereafter in the target-achieved group and almost leveled off in the target-not-achieved group, similar to the change in HbA1c level (Fig. 3a). Mean score of each item significantly improved from baseline to the final evaluation point ($P < 0.0001$ for all)

with significantly greater improvement in the target-achieved group ($P < 0.05$ for all) (Fig. 3b).

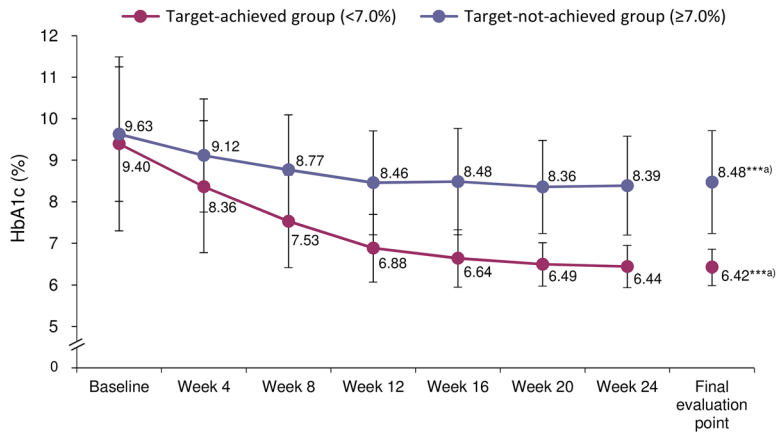
The mean DTSQs score of perceived frequency of hyperglycemia significantly improved from baseline to the final evaluation point in both groups ($P < 0.0001$ for both) (Fig. 3c) with significantly greater improvement in the target-achieved group ($P = 0.0014$). Mean score shift over time followed the same pattern as the treatment satisfaction scale score and the HbA1c level. Mean hypoglycemia scores increased in both groups from baseline to the final evaluation point with small changes in actual values (1.2 to 1.4 and 1.0 to 1.4) without significant inter-group difference in the change ($P = 0.6706$) (Fig. 3c).

The mean DTSQc treatment satisfaction scale score at the final evaluation point was 9.4 in overall patients. The score in the target-

Table 1 Baseline characteristics by the target-achieved and target-not-achieved group

	Overall (n = 1251)		**Target-achieved group (n = 336)**		**Target-not-achieved group (n = 915)**		***P* value**[a]
Sex							
Men	776	62.0%	228	67.9%	548	59.9%	*
Age (year)	1221	61.7 ± 12.4	325	62.8 ± 12.8	896	61.3 ± 12.2	ns
Duration of diabetes (year)	1011	11.5 ± 8.2	264	10.3 ± 8.2	747	11.9 ± 8.1	**
Number of concomitant OADs							
1	358	28.6%	117	34.8%	241	26.3%	*
2	451	36.1%	117	34.8%	334	36.5%	
3	334	26.7%	77	22.9%	257	28.1%	
≥4	108	8.6%	25	7.4%	83	9.1%	
BMI (kg/m^2)	1067	25.0 ± 4.7	286	24.3 ± 4.4	781	25.3 ± 4.8	**
HbA1c (%)	1251	9.6 ± 1.8	336	9.4 ± 2.1	915	9.6 ± 1.6	***
FPG (mg/dL)	457	202.3 ± 74.1	135	204.5 ± 82.5	322	201.5 ± 70.4	ns
2 h PPG (mg/dL)	315	274.6 ± 93.0	78	276.3 ± 101.5	237	274.0 ± 90.3	ns
Complications							
Diabetic retinopathy	190	15.2%	50	14.9%	140	15.3%	ns
Diabetic neuropathy	198	15.8%	48	14.3%	150	16.4%	ns
Diabetic nephropathy	298	23.8%	61	18.2%	237	25.9%	**
Renal dysfunction	307	24.5%	64	19.0%	243	26.6%	**
Ischemic heart disease	74	5.9%	16	4.8%	58	6.3%	ns
Ischemic cerebrovascular disorder	56	4.5%	23	6.8%	33	3.6%	*

Data are frequency and mean ± standard deviation or percentages. Totals may not sum to 100% due to rounding
OAD orally administered antidiabetic agent, *BMI* body mass index, *HbA1c* glycated hemoglobin, *FPG* fasting plasma glucose, *2 h PPG* 2 h postprandial plasma glucose, *ns* not significant
* <0.05, ** <0.01, *** <0.001
[a] The Fisher's exact test for nominal variables and Wilcoxon's rank-sum test for continuous variables were used



		Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Final evaluation point [b]
Target-achieved group (<7.0%)	n	336	256	252	230	231	216	281	336
Target-not-achieved group (≥7.0%)		915	716	703	632	601	605	752	915

Fig. 2 HbA1c level from baseline to the final evaluation point by the target-achieved and target-not-achieved group. ***$P < 0.0001$ (mean change target-achieved group vs target-not-achieved), Wilcoxon rank-sum test. *HbA1c* glycated hemoglobin. *a* Patients whose data both at baseline and the final evaluation point available were included in the inter-group comparison. Change from baseline to the final evaluation point (target-achieved vs target-not-achieved group, mean ± standard deviation): -2.98 ± 2.21 vs -1.15 ± 1.60%. *b* Final evaluation point: week 24 or the final visit in case of discontinuation

achieved and target-not-achieved group was 10.9 and 8.8, respectively, indicating significant improvement from baseline ($P < 0.0001$). The scale and each of the item scores were significantly greater in the target-achieved group indicating a greater improvement in satisfaction with the change in treatment (scale: $P < 0.0001$; item scores: $P < 0.001$ for all) (Fig. 3d, e). Mean hyperglycemia and hypoglycemia scores at the final evaluation point were significantly lower in the target-achieved than target-not-achieved group indicating a greater reduction in the perceived frequency of hyperglycemia and hypoglycemia in the target-achieved group (hyperglycemia: −0.9 and 0.0, respectively, $P < 0.0001$; hypoglycemia: −0.7 and −0.4, respectively, $P = 0.0041$) (Fig. 3f).

Of the data at baseline and final evaluation point analyzed to explore possible factors associated with treatment satisfaction by high, middle, and low satisfaction groups, the proportion of the patients with diabetic nephropathy and those with renal dysfunction were significantly smaller in the high satisfaction and larger in low satisfaction group ($P < 0.05$ for all) (Table 2). HbA1c and FPG levels were not significantly different at baseline between groups, although they were at the final evaluation point (highest in the low and lowest in the high satisfaction group, $P < 0.05$ for all). More patients in the low satisfaction group (8.6%) than the others (middle and high satisfaction groups: 5.3 and 4.7%, respectively) reported hypoglycemic events as treatment-related adverse events, but without significant inter-group difference ($P = 0.1613$).

EQ-5D

Overall patients reported relatively good health status (i.e., 75.9–94.8% of patients responded "No problem" in each item). The mean index

score significantly increased from 0.893 at baseline to 0.911 at the final evaluation point ($P = 0.0011$) in the whole sample and also increased in both target-achieved and target-not-achieved groups (from 0.872 to 0.917 and 0.891 to 0.908, $P = 0.0012$ and 0.0185, respectively). Mean change of EQ-5D index score from baseline to the final evaluation point was significantly greater in the target-achieved than in the target-not-achieved group (0.037 and 0.011, respectively, $P = 0.0185$) (Fig. 4a). In all dimensions in both groups, except self-care in the target archived group, the proportion of patients who answered that they had no problem increased from baseline to the final evaluation point (Table 3). Greatest mean change, about 10%, was observed in the anxiety/depression dimension in the target-achieved group among all the dimensions in the groups. At the final evaluation point, no patient in either the target-achieved or the target-not-achieved group answered that they had "extreme problems" in the anxiety/depression dimension.

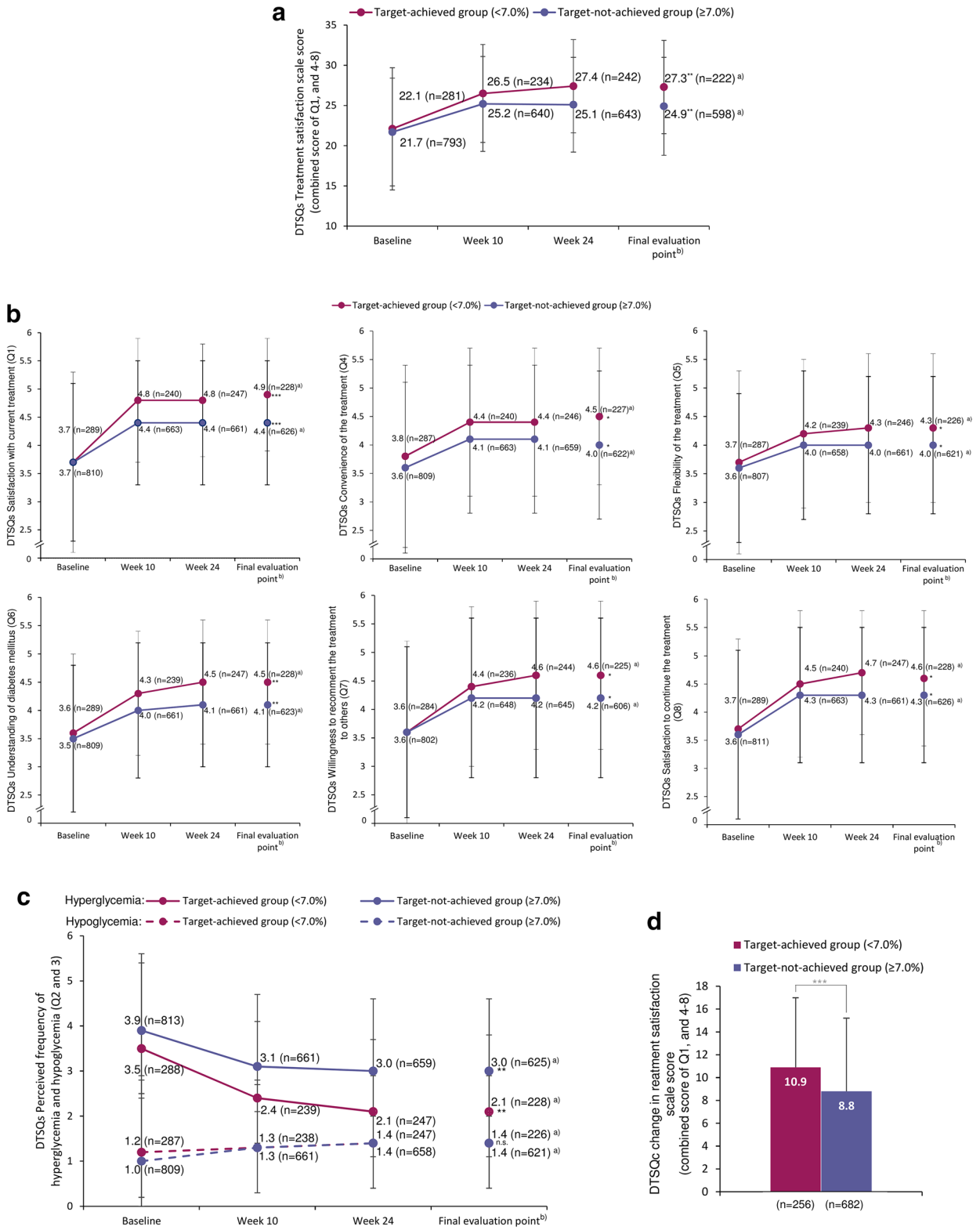
The mean EQ-VAS score significantly increased from baseline to the final evaluation point (61.19–69.46, $P < 0.0001$) across all samples and also increased in both groups (from 58.65 to 73.51 and from 62.10 to 68.01 in the target-achieved and target-not-achieved group, respectively, $P < 0.0001$ for both). Mean change in score was significantly greater in the target-achieved group ($P < 0.0001$), starting from the lower score at baseline (Fig. 4b).

DISCUSSION

In this sub-analysis using data from the ALOHA2 study, we explored treatment satisfaction and self-reported health status in patients with T2DM in whom the oral treatment failed and glargine BOT started. Improvement in treatment satisfaction was reflected in both DTSQs and DTSQc. Further significant improvement in EQ-5D index score (range −0.11 to 1.0) from a mean baseline score of more than 0.8, representing good health status, in both groups suggests that health further improved after starting glargine BOT even in the patients originally regarding themselves in a good health state. The results showed that treatment satisfaction and self-reported health status were not compromised but rather all improved following introduction of glargine BOT, representing the effectiveness of the treatment from patients' perspectives.

A possible reason for the improvement in treatment satisfaction and self-reported health status despite insulin introduction may be attributed to perceived low frequency of hypoglycemia in contrast to the often held negative impression of insulin [27, 28]. DTSQs hypoglycemia item score slightly deteriorated or did not change, although DTSQc equivalent did improve. This contradiction may be due in

Fig. 3 DTSQ treatment satisfaction score by the target-achieved and target-not-achieved groups. **a–c** DTSQs treatment satisfaction score by the target-achieved and target-not-achieved groups. **d–f** DTSQc treatment satisfaction score at the final evaluation point by the target-achieved and target-not-achieved groups. *DTSQ* Diabetes Treatment Satisfaction Questionnaire, *DTSQs* Diabetes Treatment Satisfaction Questionnaire status version, *DTSQc* Diabetes Treatment Satisfaction Questionnaire change version. *<0.05, **<0.01, ***<0.001, *ns* not significant, (mean change target-achieved vs target-not-achieved group), Wilcoxon rank-sum test. *a* Patients whose data both at baseline and the final evaluation point available were included in the inter-group comparison. Change from baseline to the final evaluation point [target-achieved vs target-not-achieved group, mean ± standard deviation (SD)]: 5.3 ± 8.0 vs 3.2 ± 7.6 (total satisfaction scale score), mean ± SD vs mean ± SD (item score). *b* Final evaluation point: week 24 or the final visit in case of discontinuation


a
Target-achieved group (<7.0%)
Target-not-achieved group (≥7.0%)
DTSQs Treatment satisfaction scale score (combined score of Q1, and 4-8)
22.1 (n=281)
26.5 (n=234)
27.4 (n=242)
27.3** (n=222) a)
21.7 (n=793)
25.2 (n=640)
25.1 (n=643)
24.9** (n=598) a)
Baseline
Week 10
Week 24
Final evaluation point b)
b
DTSQs Satisfaction with current treatment (Q1)
3.7 (n=289)
4.8 (n=240)
4.8 (n=247)
4.9 (n=228) a)
3.7 (n=810)
4.4 (n=663)
4.4 (n=661)
4.4 (n=626) a)
DTSQs Convenience of the treatment (Q4)
3.8 (n=287)
4.4 (n=240)
4.4 (n=246)
4.5 (n=227) a)
3.6 (n=809)
4.1 (n=663)
4.1 (n=659)
4.0 (n=622) a)
DTSQs Flexibility of the treatment (Q5)
3.7 (n=287)
4.2 (n=239)
4.3 (n=246)
4.3 (n=226) a)
3.6 (n=807)
4.0 (n=658)
4.0 (n=661)
4.0 (n=621) a)
DTSQs Understanding of diabetes mellitus (Q6)
3.6 (n=289)
4.3 (n=239)
4.5 (n=247)
4.5 (n=228) a)
3.5 (n=809)
4.0 (n=661)
4.1 (n=661)
4.1 (n=623) a)
DTSQs Willingness to recommend the treatment to others (Q7)
3.6 (n=284)
4.4 (n=236)
4.6 (n=244)
4.6 (n=225) a)
3.6 (n=802)
4.2 (n=648)
4.2 (n=645)
4.2 (n=606) a)
DTSQs Satisfaction to continue the treatment (Q8)
3.7 (n=289)
4.5 (n=240)
4.7 (n=247)
4.6 (n=228) a)
3.6 (n=811)
4.3 (n=663)
4.3 (n=661)
4.3 (n=626) a)
c
Hyperglycemia: Target-achieved group (<7.0%)
Target-not-achieved group (≥7.0%)
Hypoglycemia: Target-achieved group (<7.0%)
Target-not-achieved group (≥7.0%)
DTSQs Perceived frequency of hyperglycemia and hypoglycemia (Q2 and 3)
3.9 (n=813)
3.1 (n=661)
3.0 (n=659)
3.0 (n=625) a)
3.5 (n=288)
2.4 (n=239)
2.1 (n=247)
2.1 (n=228) a)
1.2 (n=287)
1.3 (n=238)
1.4 (n=247)
1.4 (n=226) a)
1.0 (n=809)
1.3 (n=661)
1.4 (n=658)
1.4 (n=621) a)
n.s.
Baseline
Week 10
Week 24
Final evaluation point b)
d
Target-achieved group (<7.0%)
Target-not-achieved group (≥7.0%)
***
DTSQc change in reatment satisfaction scale score (combined score of Q1, and 4-8)
10.9
8.8
(n=256) (n=682)

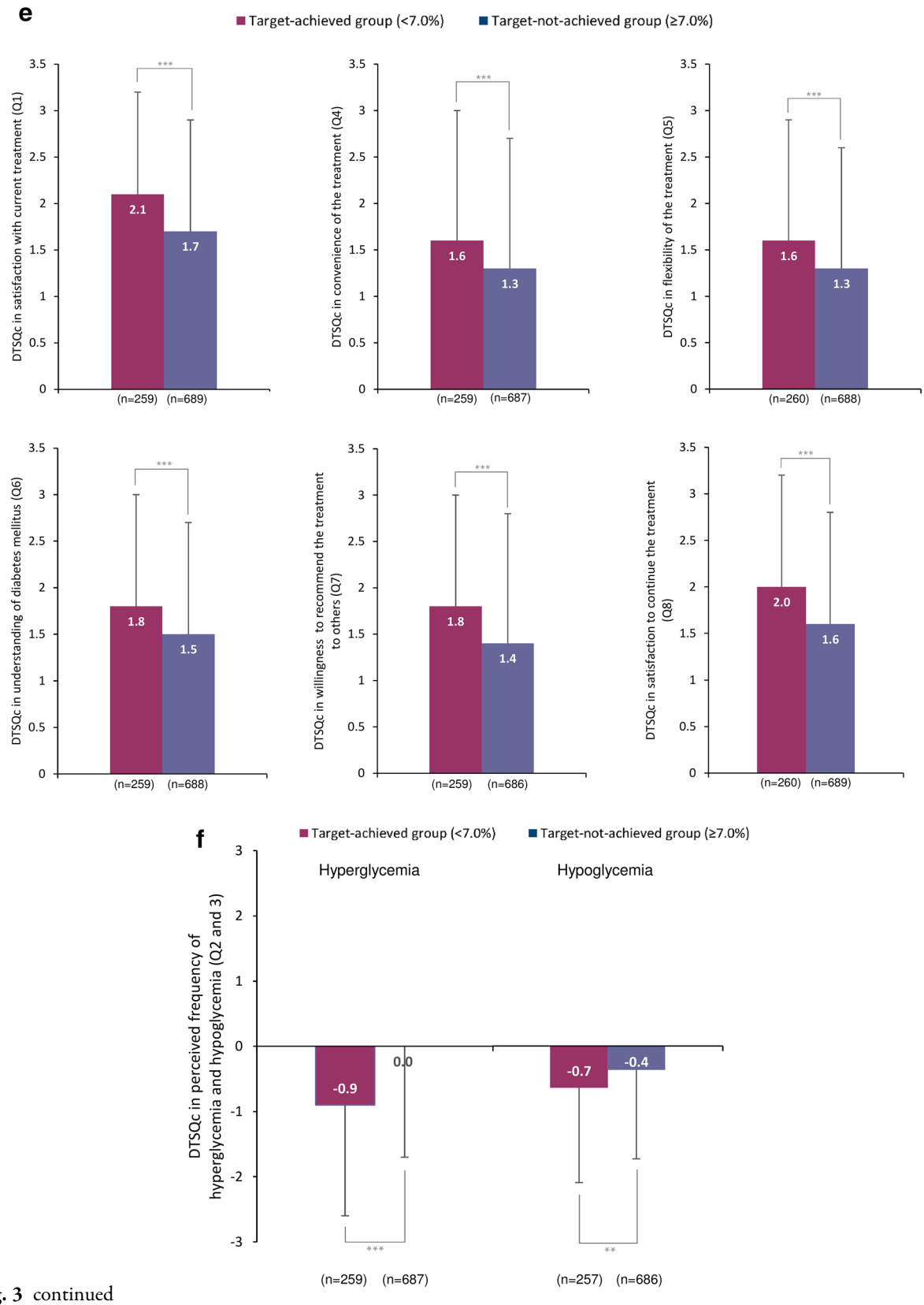


Fig. 3 continued

Table 2 Demographic and clinical characteristics of the groups by tertile of DTSQs satisfaction score change from baseline to the final evaluation point (high, middle, and low satisfaction groups)

	Overall ($n = 856$)	Low satisfaction group ($n = 234$)	Middle satisfaction group ($n = 321$)	High satisfaction group ($n = 301$)	*P* value[a]
Baseline					
Sex					
Men	63.6%	61.1%	65.7%	63.1%	ns
Age (year)	61.7 ± 12.0	61.1 ± 12.1	61.6 ± 11.9	62.1 ± 12.1	ns
Duration of diabetes (year)	11.5 ± 8.0	10.8 ± 8.0	11.9 ± 7.7	11.4 ± 8.5	ns
Insulin glargine dose per 1 kg body weight (U/kg)	0.10 ± 0.05	0.10 ± 0.05	0.10 ± 0.05	0.10 ± 0.06	ns
Timing of insulin glargine administration per day					
Morning	46.1%	42.7%	46.4%	48.5%	ns
Afternoon	2.7%	5.1%	0.9%	2.7%	
Night	14.4%	15.0%	14.0%	14.3%	
Before bedtime	36.6%	37.2%	38.3%	34.2%	
Morning + night	0.1%	0.0%	0.3%	0.0%	
Morning + before bedtime	0.0%	0.0%	0.0%	0.0%	
Unknown	0.1%	0.0%	0.0%	0.3%	
Number of concomitant OADs					
1	27.3%	28.6%	25.2%	28.6%	ns
2	37.6%	35.0%	38.0%	39.2%	
3	26.9%	26.5%	26.8%	27.2%	
≥4	8.2%	9.8%	10.0%	5.0%	
BMI (kg/m^2)	25.2 ± 4.6	25.4 ± 5.0	25.0 ± 4.3	25.2 ± 4.7	ns
HbA1c (%)	9.6 ± 1.8	9.6 ± 1.7	9.6 ± 1.9	9.6 ± 1.8	ns
FPG (mg/dL)	209.0 ± 75.8	208.1 ± 76.4	205.1 ± 73.8	213.8 ± 77.8	ns
Diabetic Retinopathy	15.1%	14.1%	16.8%	14.0%	ns
Diabetic Neuropathy	15.0%	16.2%	15.9%	13.0%	ns
Diabetic Nephropathy	22.4%	28.2%	22.1%	18.3%	*
Renal dysfunction	22.9%	28.2%	22.7%	18.9%	*
Ischemic heart disease	6.2%	7.7%	5.9%	5.3%	ns
Ischemic cerebrovascular disorder	4.3%	4.7%	4.4%	4.0%	ns

Table 2 continued

	Overall ($n = 856$)	Low satisfaction group ($n = 234$)	Middle satisfaction group ($n = 321$)	High satisfaction group ($n = 301$)	*P* value[a]
Final evaluation point[b]					
Insulin glargine dose per 1 kg body weight (U/kg)	0.15 ± 0.08	0.16 ± 0.08	0.15 ± 0.09	0.15 ± 0.07	ns
Timing of insulin glargine administration per day					
Morning	46.1%	41.5%	46.7%	49.2%	ns
Afternoon	2.1%	3.4%	0.6%	2.7%	
Night	14.6%	17.1%	14.0%	13.3%	
Before bedtime	35.9%	35.9%	37.4%	34.2%	
Morning + night	0.7%	1.3%	0.6%	0.3%	
Morning + before bedtime	0.5%	0.9%	0.6%	0.0%	
Unknown	0.1%	0.0%	0.0%	0.3%	–
Number of concomitant OADs					
1	23.8%	23.5%	22.4%	25.6%	ns
2	41.8%	41.9%	40.8%	42.9%	
3	26.1%	28.2%	26.2%	24.3%	
≥4	6.9%	5.6%	8.7%	6.0%	
HbA1c (%)	7.9 ± 1.3	8.2 ± 1.5	7.9 ± 1.4	7.6 ± 1.1	***
FPG (mg/dL)	143.8 ± 51.5	155.2 ± 60.2	147.9 ± 54.8	133.3 ± 40.0	*
Hypoglycemia (treatment-related adverse event)	6.0%	8.6%	5.3%	4.7%	ns

Final evaluation point: week 24 or the last visit in case of discontinuation

Data are frequency and mean ± standard deviation or percentages. Totals may not sum to 100% due to rounding

DTSQs Diabetes Treatment Satisfaction Questionnaire status version, *OAD* orally administered antidiabetic agent, *BMI* body mass index, *HbA1c* glycated hemoglobin, *FPG* fasting plasma glucose, *ns* not significant

* <0.05, ** <0.01, *** <0.001

[a] The Fisher's exact test for nominal variables and Kruskal–Wallis test for continuous variables for continuous variables were used

part to the floor effect with the DTSQs whereby many patients scored zero at baseline for perceived frequency of hypoglycemia and could not show an improvement, only a worsening. The DTSQc overcame this floor effect. A greater decrease in hypoglycemia frequency shown in DTSQc item 3 scores in the target-achieved group despite a similar proportion of patients who actually experienced one or more hypoglycemic events in the target-achieved and target-not-achieved groups (7.1% and 5.6%, respectively, $P = 0.3465$) (data not shown) may imply that better glycemic control achieved may have

given the retrospective impression that the hypoglycemia frequency had decreased and so imply importance of achieving glycemic control. DTSQc's higher responsiveness to change [24, 29] may support this inference. In addition to the improvement in HbA1c level, patients' perceived low frequency of hypoglycemia may have defied the anxiety toward insulin therapy, perhaps leading to improved treatment satisfaction and perceived health status. Our current findings along with previous consistent study results [13, 14, 30] may underscore the effectiveness and safety of insulin glargine added to OADs from both clinical and patient perspectives.

The current analysis suggests associations of HbA1c with treatment satisfaction and health status as reported in previous studies [31–34]. Treatment satisfaction and health status were more likely to improve in the target-achieved than in the target-not-achieved group based on the greater improvement in PRO scores in the target-achieved group; the similar improving trend over time traced by changes in HbA1c level and DTSQs except hypoglycemia frequency; and significant difference in the HbA1c and FPG level at the final evaluation point despite the non-significant difference at baseline in the DTSQs tertile group analysis. Improvement in the DTSQ treatment satisfaction scale and item scores encompassing various impressions, e.g., convenience of the treatment, in the target-achieved group may allow an interpretation that better glycemic control may have further lightened various burdens as well as hypoglycemia. The findings suggest better glycemic state may enhance treatment

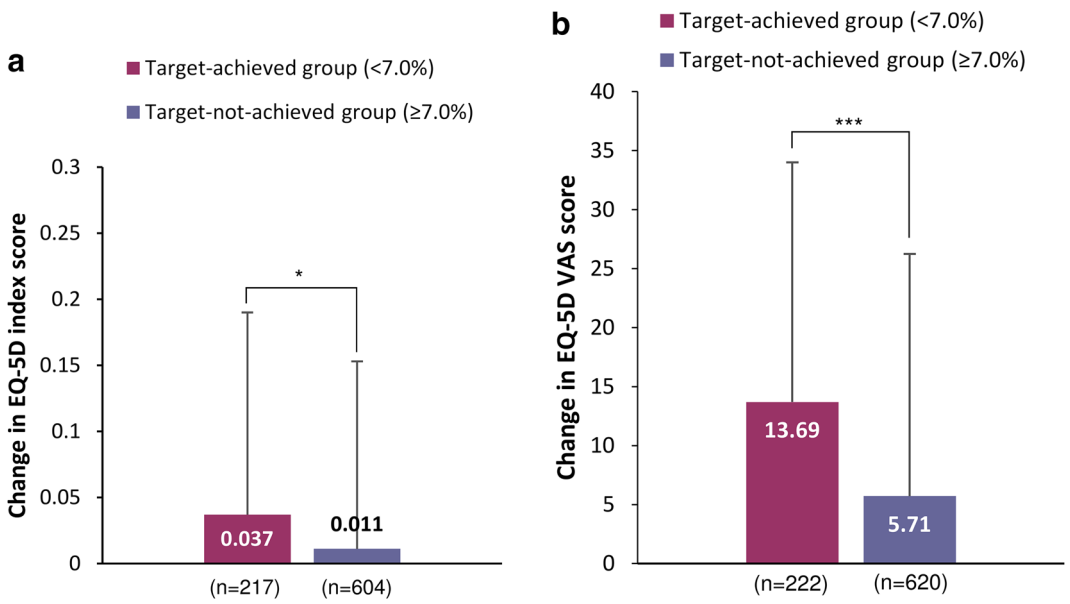


Fig. 4 EQ-5D score from baseline to the final evaluation point by the target-achieved and target-not-achieved group. *EQ-5D* EuroQol 5 dimension, *VAS* visual analogue scale *<0.05, **<0.01, ***<0.001, *ns* not significant, (mean change target-achieved vs target-not-achieved group), Wilcoxon rank-sum test. **a** Final evaluation point: week 24 or the final visit in case of discontinuation. **b** Patients whose data both at baseline and the final evaluation point available were included in the inter-group comparison. Change from baseline to the final evaluation point (target-achieved vs target-not-achieved group, mean ± standard deviation): 0.037 ± 0.153 vs 0.011 ± 0.142 (index score), 13.69 ± 20.31 vs 5.71 ± 20.53 (VAS score)

Table 3 Responses to each EQ-5D dimension by the target-achieved and target-not-achieved group

	Number of patients (%)			
	Target-achieved group		Target-not-achieved group	
	Baseline ($n = 286$)	Final evaluation point ($n = 269$)[a]	Baseline ($n = 806$)	Final evaluation point ($n = 711$)[a]
Mobility				
No problem	238 (83.2)	232 (86.2)	680 (84.4)	618 (86.9)
Some problem	44 (15.4)	34 (12.6)	119 (14.8)	90 (12.7)
Extreme problem	4 (1.4)	2 (0.7)	3 (0.4)	0 (0.0)
Self-care				
No problem	271 (94.8)	248 (92.2)	764 (94.8)	679 (95.5)
Some problem	11 (3.8)	18 (6.7)	35 (4.3)	28 (3.9)
Extreme problem	2 (0.7)	2 (0.7)	3 (0.4)	1 (0.1)
Usual activities				
No problem	236 (82.5)	231 (85.9)	684 (84.9)	618 (86.9)
Some problem	44 (15.4)	33 (12.3)	117 (14.5)	89 (12.5)
Extreme problem	5 (1.7)	3 (1.1)	3 (0.4)	3 (0.4)
Pain/discomfort				
No problem	215 (75.2)	214 (79.6)	614 (76.2)	544 (76.5)
Some problem	67 (23.4)	47 (17.5)	175 (21.7)	149 (21.0)
Extreme problem	4 (1.4)	5 (1.9)	12 (1.5)	12 (1.7)
Anxiety/depression				
No problem	221 (77.3)	236 (87.7)	666 (82.6)	615 (86.5)
Some problem	62 (21.7)	30 (11.2)	131 (16.3)	89 (12.5)
Extreme problem	3 (1.0)	0 (0.0)	6 (0.7)	0 (0.0)

EQ-5D EuroQol 5 dimension

[a] Final evaluation point: week 24 or the last visit in case of discontinuation

satisfaction and health status, or vice versa. Moreover, considering these links suggested in combination with better glycemic control achieved by earlier introduction of additional insulin on OAD treatment reported in several studies [35, 36] including ALOHA sub-analysis [19] may provide another perspective. Earlier insulin initiation may help achieve better glycemic status further leading to better treatment satisfaction and health status. The present findings may add to the collective evidence for recommending early insulin initiation. In addition, the associations between complications and reduced treatment satisfaction and impaired glycemic control are indicated by the higher proportion of patients with diabetic nephropathy and renal dysfunction at baseline in the lower satisfaction groups, and also a significantly higher proportion of patients with

complications at baseline in the target-not-achieved group. Having existing complications which are difficult to relieve may have prevented patients from feeling more satisfied with treatment.

The EQ-5D result suggests that anxiety and depression coexist in a certain proportion of patients with T2DM. Depression in patients with diabetes is twice as prevalent as in the counterparts without [37], although the association does not link to diabetes itself, but to complications [38–40]. Comorbidity of diabetes and depression may be associated with poor self-caring attitudes, treatment adherence, glycemic control, and eventually to onset or progression of vascular complications [41–45]. Greater improvement in the anxiety/depression dimension in those with better glycemic control may reinforce the relationships. Given a path to the goal of diabetes treatment intersected with various factors, e.g., glycemic control, complications, treatment satisfaction, and health status, comprehensive assessment encompassing subjective and objective parameters is important for successful diabetes management.

Some aspects may limit the interpretation of this sub-analysis. First, the design is single-arm observational and the aim itself does not lay in confirmation of superiority of insulin glargine BOT. Since the ALOHA2 study was conducted as post-marketing surveillance in a routine clinical setting after the drug was marketed, hypoglycemia was not strictly defined and counted unlike clinical trials. Therefore, hypoglycemia frequencies can be underestimated. Secondly, our analysis cannot fully explain associations found, since our results cannot suggest causality in the associations and our study may not have encompassed all the factors that may influence the relationships. Increased treatment satisfaction may also result in improved HbA1c leading to reduced anxiety. Consequently, treatment satisfaction or perceived health status could improve. Thirdly, findings associated with glargine BOT may not be generalizable to different insulin treatment modalities or analogs. Fourthly, although statistically significant, the change in the EQ-5D could not reach the minimal important difference in diabetes patients in the United Kingdom [46]. However, the originally perceived good health status may not have left sufficient room for further improvement. Finally, patients who participated in this study may be more proactive and the results may not generalize well.

CONCLUSION

In the patients with T2DM whose OAD treatment failed to achieve adequate glycemic control, introduction of insulin glargine BOT does not detract from treatment satisfaction or health status but rather benefits patients from their own perspectives with a minimal risk for hypoglycemia despite the negative impressions often associated with insulin treatment. Improvement in both treatment satisfaction and health status and glycemic control were associated. HbA1c achievement may relieve various burdens. Based on the possible association, a key to successful treatment may be found in achievement of target glycemic level and early initiation of insulin glargine BOT.

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Access to Questionnaires: DTSQs and DTSQc visit http://www.healthpsychologyresearch.com. EQ-5D visit http://www.euroqol.org/.

Conflict of interest. Shoko Tsukube is an employee of Sanofi K.K., Tokyo, Japan. Yukio Ikeda is also an employee of Sanofi K.K., Tokyo, Japan. Takashi Kadowaki has served on advisory panels for Boehringer Ingelheim, Daiichi-Sankyo, Novo Nordisk, Taisho, Takeda and Tanabe-Mitsubishi; has served as a consultant for Boehringer Ingelheim and MSD; has received research support from Astra Zeneca, Chugai, Daiichi-Sankyo, MSD, Ono, Sanofi, Takeda and Tanabe-Mitsubishi; and has served on speakers' bureaus for Astellas, Astra Zeneca, Boehringer Ingelheim, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Kowa, Kyowahakko Kirin, MSD, Novartis, Ono, Sanofi, Sanwa, Taisho, Takeda and Tanabe-Mitsubishi. Masato Odawara has served advisory panels for Astra Zeneca, Boehringer Ingelheim, Novo Nordisk, Sanofi, and Taisho; has received research support from Astellas, Astra Zeneca, Boehringer Ingelheim, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Kowa, Kyowahakko Kirin, MSD, Novartis, Ono, Sanofi, Taisho, Takeda and Tanabe-Mitsubishi; and has served on speakers' bureaus for Astellas, Astra Zeneca, Boehringer Ingelheim, Daiichi-Sankyo, Dainippon-Sumitomo, Eli Lilly, Kowa, Kyowahakko Kirin, MSD, Novartis, Ono, Sanofi, Taisho, Takeda and Tanabe-Mitsubishi.

Compliance with ethics guidelines. This study was conducted as a special drug use surveillance complied with the pharmaceutical affairs law and the ministerial ordinance of "Good Post-Marketing Study Practice" in Japan, and conducted after a contract was signed with each medical institution participating in the survey. Informed consent was obtained from all patients for being included in the study. Ethical consideration including confidentiality had been given in a course of the study implementation.

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