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ORIGINAL RESEARCH

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Effectiveness and safety of insulin glargine 300 unit/mL in Japanese type 2 diabetes mellitus patients: a 12-month post-marketing surveillance study (X-STAR study)

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ABSTRACT

Background: With limited real-world insulin glargine 300 unit/mL (Gla-300) data available, we assessed the effectiveness and safety of Gla-300 in the Japanese type 2 diabetes mellitus (T2DM) population.

Research design and methods: X-STAR was a prospective, observational, 12-month post-marketing study of Gla-300 from 2015 to 2018. T2DM patients received Gla-300 as the first insulin (insulin-naïve) or after treatment with another type of insulin (insulin-experienced).

Results: We identified 1,227 insulin-naïve and 3,394 insulin-experienced patients. Insulin-naïve group increased the Gla-300 starting dose by 2.80 U/day during 12 months (7.49 to 10.29 U/day). Mean HbA1c reduced by 1.99% (9.82 to 7.83%), and 28.4% showed HbA1c < 7.0%. Insulin-experienced group had a baseline insulin dose of 14.86 U/day, which increased by 0.73 U/day. Mean HbA1c reduced by 0.18% (7.99 to 7.81%), and 24.6% showed HbA1c < 7.0%. Adverse drug reactions occurred in 3.42% (insulin-naïve) and 4.45% (insulin-experienced); symptomatic hypoglycemia (2.93% and 3.86%, respectively) was the most common in both groups.

Conclusions: Gla-300, in clinical practice, provides an effective and safe therapy as HbA1c was reduced/maintained in insulin-naïve/experienced Japanese T2DM patients without new safety signal. This study provides insights into the current Japanese clinical practices where insulin use is delayed and conservative despite relatively low HbA1c achievement.

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Diabetes mellitus; Type 2; insulin glargine; product surveillance; postmarketing

1. Introduction

The management of type 2 diabetes mellitus (T2DM) patients focuses on achieving and maintaining good glycemic control in order to reduce the risk of developing microvascular and macrovascular complications [1,2]. T2DM, as a consequence of continued β-cell loss, is a progressive disease; therefore, escalation of therapy is required to maintain good glycemic control in a majority of patients. In fact, the algorithm for therapy escalation has been well described in the ADA/EASD guidelines, which have been broadly adopted worldwide [3].

Although insulin therapy is a logical and physiologically appropriate intervention for T2DM patients with low β-cell function, its initiation is often delayed for several years. Patients at the time of insulin initiation often have very poorly controlled diabetes with HbA1c levels >9% [4–7]. Even following the initiation of basal insulin, titration according to fasting plasma glucose (FPG) is insufficient, resulting in poor achievement of glycemic targets (HbA1c). Such a situation is referred to as 'clinical inertia' [8,9] and is seen in most countries worldwide, including Japan. It is well recognized that multiple factors, including fear of hypoglycemia, weight gain, treatment complexity, a lack of confidence/education, patient empowerment, and healthcare resources, contribute to clinical inertia. Due to these factors, patients cannot receive the full therapeutic benefits of insulin therapy. It is clear that all these factors need to be addressed to facilitate appropriate initiation and titration of insulin, thereby improving the management of T2DM.

Insulin glargine 300 U/mL (Gla-300, Toujeo® in the United States and Europe [Sanofi, Paris, France]; Lantus® XR in Japan [Sanofi K.K., Tokyo, Japan]), a second-generation basal insulin analog, has been available in Japan since 2015 and is licensed for the treatment of both type 1 diabetes mellitus (T1DM) and T2DM. Gla-300 has more constant and prolonged pharmacokinetic/pharmacodynamic profiles than insulin glargine 100 U/mL (Gla-100), the first-generation insulin analog, and provides a full 24-hour cover with a more stable glycemic profile, allowing the achievement of glycemic targets with a lower hypoglycemia risk [10]. The EDITION program and randomized controlled trials designed to compare Gla-300 with Gla-100 in T1DM and T2DM patients showed that Gla-300 is equally effective in lowering HbA1c and is associated with a lower risk of hypoglycemia, especially nocturnal hypoglycemia [11–

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Supplemental data for this article can be accessed here.

13]. Retrospective studies using real-world data from healthcare databases in the USA suggest that Gla-300 administration to T2DM patients was more beneficial than first-generation basal insulin, resulting in comparable glycemic control with fewer incidences of hypoglycemia [14,15]. However, similar studies to assess the effectiveness and safety of Gla-300 in a real-world clinical setting in Japan have not been reported.

The X-STAR study (Lantus® XR Post-Marketing Surveillance) was a 12-month, prospective, observational study of Gla-300 that assessed the effectiveness and safety of the drug in diabetes mellitus (DM) patients who had been newly prescribed Gla-300 in a Japanese clinical practice. This analysis focused on T2DM patients.

2. Patients and methods

2.1. Study design

The X-STAR study was a prospective, observational, 12-month study conducted from December 2015 to August 2018 in accordance with the pharmaceutical affairs law and the ministerial ordinance of Good Post-Marketing Study Practice in Japan. Ethical committee approval and written informed consent were waived for this study. DM patients to whom Gla-300 was newly prescribed were enrolled at the participating medical institutions under a contract with Sanofi K.K. (Tokyo, Japan) and were followed up for 12 months. The patients were centrally enrolled within 14 days from the day that Gla-300 was first administered, and their anonymized data were entered into an electronic data capturing system. The treating physicians managed the doses as they would in their routine practice in accordance with the Japanese package insert of Gla-300 [16].

2.2. Study population

Among the enrolled T2DM patients, those who had never received insulin prior to Gla-300 were categorized as 'insulin-naïve' and those who had been treated with other insulin products prior to Gla-300 were categorized as 'insulin-experienced.' In the insulin-experienced group, Gla-300 either replaced the other insulin product or was administered in combination with it.

To explore the association of antidiabetic medication prior to insulin initiation with the effectiveness of Gla-300, the insulin-naïve people were stratified according to their medication prior to Gla-300 prescription. First, patients who were treated with glucagon-like peptide-1 receptor agonist (GLP-1RA) were categorized as 'GLP-1RA/naïve.' Then, the remaining patients were further stratified by the number of oral antidiabetic drugs (OADs) prescribed: none (0-OAD/naïve), 1 (1-OAD/naïve), 2 (2-OADs/naïve), and ≥3 (≥3-OADs/naïve).

2.3. Data collection and assessments

Baseline demographics and clinical characteristics in this analysis included age, sex, duration of diabetes, body weight, height, complications, and details of prior medication. Data on Gla-300 treatment, such as the timing of injection and concomitant use of other antidiabetic medications (type, dose), were also collected. Doses of Gla-300 were monitored at months 1 (days 22–28), 3 (days 78–84), 6 (days 169–196), 9 (days 253–280), and 12 (days 337–364). HbA1c levels (National Glycohemoglobin Standardization Program) and FPG, including laboratory measurement or self-monitored plasma glucose (SMPG), and body weight were measured for the assessment of Gla-300 effectiveness. For the baseline, the latest data within 8 weeks prior to Gla-300 initiation were used. After Gla-300 initiation, data were collected at months 1 (± 4 weeks), 3 (−4 to +6 weeks), 6 (± 6 weeks), 9 (± 6 weeks), and 12 (± 6 weeks).

Adverse drug reactions (ADRs), including abnormal variations in laboratory test parameters, were recorded during the observation period. Treating physicians reported ADRs when these events were observed. Hypoglycemia was reported according to the manual issued by the Ministry of Health, Labour and Welfare of Japan [17]. Severe hypoglycemia was defined as an event that required assistance of another person. ADRs were classified based on the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J Ver.22.0).

Adherence of the enrolled patients to Gla-300 injection (adherent: ≥75%; sometimes non-adherent: 50% to <75%; non-adherent: <50%; and unknown) and exercise and diet modifications (not instructed; adherent: ≥75%; sometimes non-adherent: 50% to <75%; non-adherent: <50%; and unknown) were estimated by the treating physicians.

2.4. Statistical analysis

The sample size was set at 5,000 to have 95% power to detect ADRs with low incidence (0.1% or more). All data were expressed as mean ± standard deviation (SD) for continuous variables, or as number and proportion of patients in each category for categorical data. Proportions of insulin-naïve and insulin-experienced people who achieved HbA1c level <7.0% were calculated and further summarized with and without FPG measurement. To calculate Gla-300 dose as U/kg/day, body weight at baseline was used for the dose prior to baseline and the latest body weight measurement was used for the dose after baseline. The last observation carried forward (LOCF) approach was used for imputing the missing value and described as month 12 (LOCF). For comparison of data at month 12 (LOCF) with those at baseline, the paired t-test was used. All analyses were performed using the SAS software release 9.4 (SAS Institute, Inc., Cary, NC, USA). The significance level was defined as a two-sided p-value <0.05.

3. Results

3.1. Participant sample size

A total of 5,826 people with DM from 449 institutions were enrolled in the X-STAR study. From these, 4,621 T2DM (1,227 insulin-naïve and 3,394 insulin-experienced) patients were

analyzed to assess drug safety (Figure 1). After excluding those with incomplete medication records, 4,491 people (1,194 insulin-naïve and 3,297 insulin-experienced) were analyzed to assess effectiveness.

3.2. Demographics and clinical characteristics at baseline

Demographic and clinical characteristics at baseline of the insulin-naïve and insulin-experienced T2DM patients are shown in Table 1. Among participants, 65.6% of insulin-naïve and 59.4% of insulin-experienced patients were men. The insulin-naïve population tended to be younger (62.1 ± 14.1 years vs 64.9 ± 12.5 years) and have a shorter duration of diabetes (11.3 ± 8.8 years vs 16.3 ± 9.4 years) than the insulin-experienced population. The mean (± SD) body mass index (BMI) was 24.8 ± 4.7 kg/m^2 in the insulin-naïve group and 25.5 ± 4.7 kg/m^2 in the insulin-experienced group. At least one diabetic complication was seen in 47.8% of insulin-naïve patients and in 61.9% of insulin-experienced people. In the insulin-naïve and insulin-experienced patients, 1.1% and 10.1% had complained of hypoglycemia during the 3 months prior to Gla-300 initiation, respectively.

Stratification of insulin-naïve patients by the previous therapeutic regimen revealed that the duration of diabetes was longer and the proportion of any diabetic complications was higher in patients with more OADs.

3.3. Antidiabetic and concomitant medications

The antidiabetic medications of both groups are listed in Table 2. Prior to Gla-300 initiation, 67.7% of insulin-naïve patients and 100.0% of insulin-experienced patients were treated with antidiabetic medication. The dipeptidyl peptidase-4 inhibitor (DPP-4i) was most commonly used (60.2% in insulin-naïve and 44.6% in insulin-experienced), followed by sulfonylurea (SU) in the insulin-naïve (42.5%) and biguanide in the insulin-experienced (31.3%) patients. The use of OADs remained stable during the observation period, except for reduction in SU use to 28.6% in insulin-naïve people during 12 months.

Among the insulin-experienced people, 91.6% and 41.9% were receiving long-acting and rapid-acting insulin,

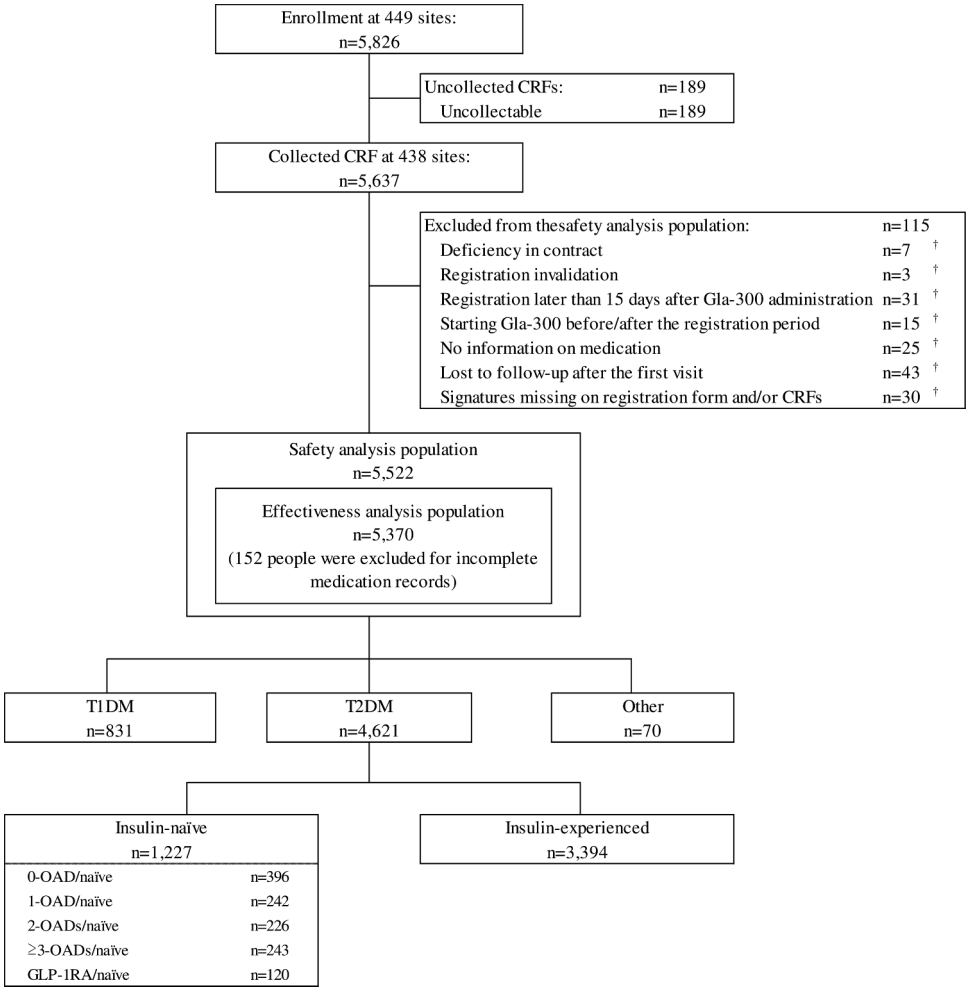


Figure 1. Participant disposition.

CRF: case report form; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; OAD: oral antidiabetic drug; GLP-1RA: glucagon-like peptide-1 receptor agonist

†Reasons for exclusion may be multiple.

Table 1. Baseline characteristics.

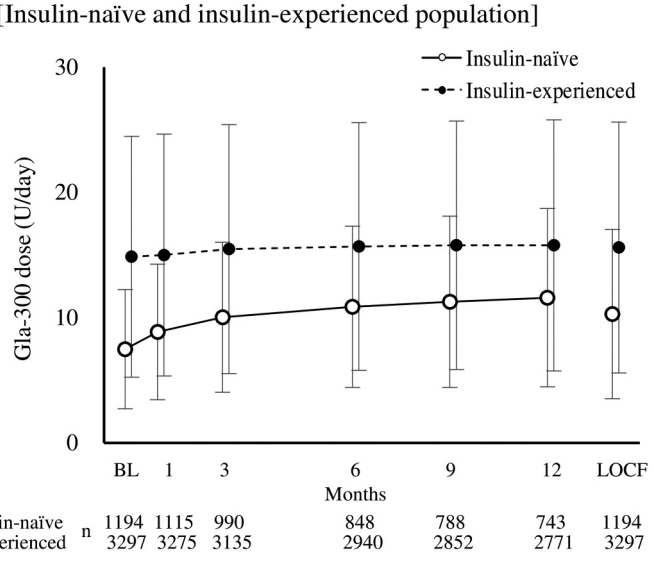
Characteristics	Insulin-naïve													
	Total (n = 1,227)		0-OAD/naïve (n = 396)		1- OAD/naïve (n = 242)		2-OADs/naive (n = 226)		≥3-OADs/naïve (n = 243)		GLP-1RA/naïve (n = 120)		Insulin-experienced (n = 3,394)	
Male, n (%)	805	(65.6)	281	(71.0)	145	(59.9)	140	(61.9)	163	(67.1)	76	(63.3)	2,015	(59.4)
Age														
mean ± SD, years	62.1	± 14.1	58.4	± 14.0	64.0	± 14.6	64.3	± 14.3	64.9	± 12.6	61.1	± 13.3	64.9	± 12.5
<65 years, n (%)	620	(50.5)	257	(64.9)	114	(47.1)	96	(42.5)	93	(38.3)	60	(50.0)	1,450	(42.7)
≥65 years, n (%)	607	(49.5)	139	(35.1)	128	(52.9)	130	(57.5)	150	(61.7)	60	(50.0)	1,944	(57.3)
Duration of diabetes, n	827	-	220	-	172	-	169	-	183	-	83	-	2,550	-
mean ± SD, years	11.3	± 8.8	7.0	± 7.9	10.1	± 8.6	12.7	± 8.8	14.5	± 8.0	14.6	± 8.8	16.3	± 9.4
Hospitalization, n (%)	174	(14.2)	67	(16.9)	36	(14.9)	30	(13.3)	30	(12.3)	11	(9.2)	121	(3.6)
Body weight, n	1022	-	298	-	198	-	206	-	217	-	103	-	2, 914	-
mean ± SD, kg	66.0	± 15.6	66.5	± 15.4	63.0	± 15.1	64.3	± 13.7	65.8	± 14.9	74.8	± 18.8	66.9	± 15.2
BMI[†], n	1022	-	298	-	198	-	206	-	217	-	103	-	2, 910	-
mean ± SD, kg/m^2	24.8	± 4.7	24.4	± 4.5	24.0	± 4.5	24.4	± 4.1	25.0	± 4.5	27.7	± 5.6	25.5	± 4.7
<22.0 kg/m^2, n (%)	286	(23.3)	96	(24.2)	68	(28.1)	57	(25.2)	53	(21.8)	12	(10.0)	620	(18.3)
22.0–< 25.0 kg/m^2, n (%)	303	(24.7)	81	(20.5)	58	(24.0)	66	(29.2)	71	(29.2)	27	(22.5)	882	(26.0)
25.0–<30.0 kg/m^2, n (%)	309	(25.2)	95	(24.0)	53	(21.9)	64	(28.3)	64	(26.3)	33	(27.5)	978	(28.8)
≥30.0 kg/m^2, n (%)	124	(10.1)	26	(6.6)	19	(7.9)	19	(8.4)	29	(11.9)	31	(25.8)	430	(12.7)
Diabetic complications, n (%)	587	(47.8)	136	(34.3)	99	(40.9)	126	(55.8)	153	(63.0)	73	(60.8)	2, 100	(61.9)
Retinopathy	274	(22.3)	67	(16.9)	46	(19.0)	51	(22.6)	75	(30.9)	35	(29.2)	1,242	(36.6)
Nephropathy	387	(31.5)	91	(23.0)	60	(24.8)	80	(35.4)	100	(41.2)	56	(46.7)	1, 445	(42.6)
Neuropathy	342	(27.9)	78	(19.7)	59	(24.4)	71	(31.4)	91	(37.4)	43	(35.8)	1, 208	(35.6)
Timing of the first Gla-300 injection, n (%)														
Morning	683	(55.7)	196	(49.5)	130	(53.7)	129	(57.1)	138	(56.8)	90	(75.0)	1,643	(48.4)
Lunch	40	(3.3)	16	(4.0)	8	(3.3)	5	(2.2)	9	(3.7)	2	(1.7)	47	(1.4)
Dinner	170	(13.9)	54	(13.6)	39	(16.1)	28	(12.4)	31	(12.8)	18	(15.0)	603	(17.8)
Bedtime	330	(26.9)	129	(32.6)	63	(26.0)	64	(28.3)	64	(26.3)	10	(8.3)	1,075	(31.7)
Morning and dinner	3	(0.2)	0	-	2	(0.8)	0	-	1	(0.4)	0	-	21	(0.6)
Morning and bedtime	1	(0.1)	1	(0.3)	0	-	0	-	0	-	0	-	4	(0.1)
Hypoglycemia during 3 months prior to Gla-300 administration, n (%)														
Yes	13	(1.1)	4	(1.0)	2	(0.8)	1	(0.4)	3	(1.2)	3	(2.5)	343	(10.1)
Unknown	79	(6.4)	27	(6.8)	22	(9.1)	14	(6.2)	7	(2.9)	9	(7.5)	113	(3.3)

OAD: oral antidiabetic drug; GLP-1RA: glucagon-like peptide-1 receptor agonist; SD: standard deviation; BMI: body mass index
Insulin-naïve people are stratified according to treatment prior to Gla-300 administration (0, 1, 2, and ≥3 OADs; and GLP-1RA irrespective of OAD administration)
[†]Body mass index is calculated as weight in kilograms divided by the square of the height in meters

Table 2. Antidiabetic medications used prior to the X-STAR study (pre-baseline) and those concomitantly used with Gla-300 at baseline and during 12 months of Gla-300 administration.

	Insulin-naïve (n = 1,227)						Insulin-experienced (n = 3,394)					
	Pre-baseline†		Baseline		During 12-month observation period		Pre-baseline†		Baseline		During 12-month observation period	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Use of other antidiabetic medications												
Yes	831	(67.7)	899	(73.3)	1,025	(83.5)	3, 394	(100.0)	3,162	(93.2)	3,205	(94.4)
GLP-1 receptor agonist	120	(14.4)	106	(11.8)	142	(13.9)	341	(10.0)	347	(11.0)	438	(13.7)
Insulin												
Long-acting	0		0		0		3,110	(91.6)	19	(0.6)	23	(0.7)
Intermediate	0		0		0		20	(0.6)	1	(0.0)	1	(0.0)
Premix	0		1	(0.1)	5	(0.5)	150	(4.4)	21	(0.7)	23	(0.7)
Regular	0		1	(0.1)	3	(0.3)	24	(0.7)	21	(0.7)	25	(0.8)
Rapid	0		103	(11.5)	159	(15.5)	1, 422	(41.9)	1,385	(43.8)	1,429	(44.6)
Other	0		0		0		2	(0.1)	0		0	
Oral antidiabetic drugs												
Sulfonylurea	353	(42.5)	271	(30.1)	293	(28.6)	470	(13.8)	456	(14.4)	467	(14.6)
Biguanide	339	(40.8)	310	(34.5)	402	(39.2)	1,061	(31.3)	1,055	(33.4)	1,107	(34.5)
DPP-4 inhibitor	500	(60.2)	484	(53.8)	607	(59.2)	1,514	(44.6)	1,489	(47.1)	1,573	(49.1)
SGLT2 inhibitor	136	(16.4)	125	(13.9)	189	(18.4)	530	(15.6)	533	(16.9)	654	(20.4)
Glinide	67	(8.1)	66	(7.3)	92	(9.0)	230	(6.8)	221	(7.0)	255	(8.0)
α-glucosidase inhibitor	122	(14.7)	112	(12.5)	152	(14.8)	485	(14.3)	467	(14.8)	494	(15.4)
Thiazolidinedione	73	(8.8)	60	(6.7)	71	(6.9)	190	(5.6)	179	(5.7)	190	(5.9)
FDC	88	(10.6)	81	(9.0)	115	(11.2)	252	(7.4)	253	(8.0)	286	(8.9)

GLP-1: glucagon-like peptide-1; DPP-4: dipeptidyl peptidase-4; SGLT2: sodium-glucose cotransporter-2; FDC: fixed-dose combination
†Pre-baseline refers to within 3 months prior to baseline

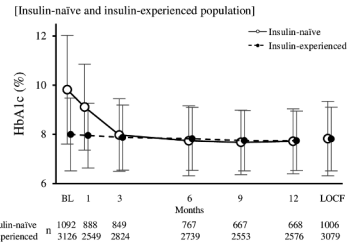


T2DM population	n	Baseline (U)		12 month (LOCF) (U)		Change (U)		Paired t-test, p-value
		mean	SD	mean	SD	mean	SD	
Insulin-naïve	1,194	7.49	4.76	10.29	6.76	2.80	5.82	p<0.001
0-OAD/naïve	386	7.73	4.51	9.61	5.99	1.89	5.11	p<0.001
1-OAD/naïve	235	7.99	5.43	9.88	7.01	1.89	5.33	p<0.001
2-OADs/naïve	220	7.57	4.59	10.67	6.44	3.10	5.69	p<0.001
≥3-OADs/naïve	237	6.11	3.66	10.84	7.41	4.73	6.97	p<0.001
GLP-1RA/naïve	116	8.34	5.82	11.53	7.64	3.19	5.69	p<0.001
Insulin-experienced	3,297	14.86	9.61	15.60	10.01	0.73	3.79	p<0.001

Figure 2. Dose change of Gla-300 over 12 months.

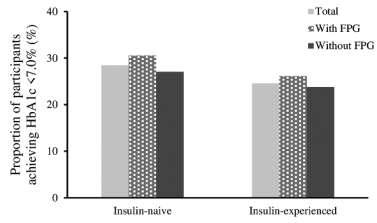
BL: baseline; T2DM: type 2 diabetes mellitus; SD: standard deviation; LOCF: last observation carried forward; OAD: oral antidiabetic drug; GLP-1RA: glucagon-like peptide-1 receptor agonist.
Participants included in the table are limited to those with data at the LOCF endpoint.
Insulin-naïve people are stratified according to treatment prior to Gla-300 administration (0, 1, 2, and ≥3 OADs; and GLP-1RA irrespective of OAD administration).

(a) HbA1c levels (%)



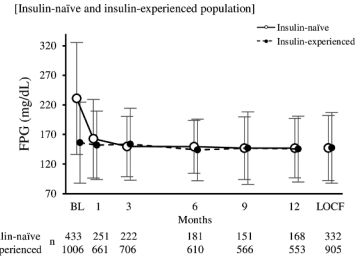
T2DM population	n	Baseline (%) mean	SD	Baseline (mmol/mol) mean	SD	Month 12 (LOCF) (%) mean	SD	Month 12 (LOCF) (mmol/mol) mean	SD	Change† (%) mean	SD	Change† (mmol/mol) mean	SD	Paired t-test, p-value
Insulin-naïve	1,006	9.82	2.19	83.84	23.96	7.83	1.52	62.07	16.58	-1.99	2.30	-21.77	25.17	p<0.001
0-OAD/naïve	290	10.86	2.43	95.24	26.53	7.62	1.68	59.76	18.32	-3.25	2.71	-35.48	29.61	p<0.001
1-OAD/naïve	199	9.73	2.23	82.89	24.42	7.86	1.56	62.44	17.08	-1.87	2.08	-20.45	22.76	p<0.001
2-OADs/naïve	197	9.51	2.01	80.43	21.97	7.93	1.36	63.15	14.83	-1.58	2.06	-17.28	22.51	p<0.001
≥3-OADs/naïve	215	9.20	1.57	77.03	17.18	7.87	1.33	62.48	14.52	-1.33	1.57	-14.55	17.21	p<0.001
GLP-1RA/naïve	105	8.97	1.76	74.50	19.20	8.09	1.57	64.87	17.16	-0.88	1.62	-9.62	17.76	p<0.001
Insulin-experienced	3,079	7.99	1.48	63.88	16.13	7.81	1.30	61.90	14.18	-0.18	1.21	-1.98	13.22	p<0.001

(b) <7.0% HbA1c achievement



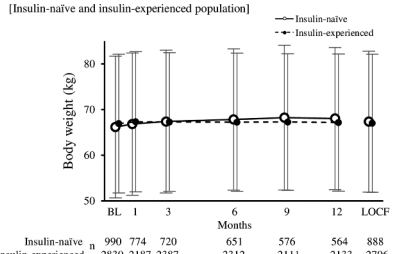
T2DM population	Insulin-naïve Total n (%)	Insulin-naïve With FPG‡ n (%)	Insulin-naïve Without FPG‡ n (%)	Insulin-experienced Total n (%)	Insulin-experienced With FPG‡ n (%)	Insulin-experienced Without FPG‡ n (%)
Achievement	286 (28.4)	119 (30.6)	167 (27.1)	756 (24.6)	254 (26.2)	502 (23.8)
Non-achievement	720 (71.6)	270 (69.4)	450 (72.9)	2,323 (75.4)	716 (73.8)	1,607 (76.2)

(c) FPG‡ levels (mg/dL)



T2DM population	n	Baseline (mg/dL) mean	SD	Baseline (mmol/L) mean	SD	Month 12 (LOCF) (mg/dL) mean	SD	Month 12 (LOCF) (mmol/L) mean	SD	Change† (mg/dL) mean	SD	Change† (mmol/L) mean	SD	Paired t-test, p-value
Insulin-naïve	332	229.2	91.6	12.7	5.1	147.2	55.0	8.2	3.1	-82.0	97.0	-4.5	5.4	p<0.001
0-OAD/naïve	101	251.3	89.5	13.9	5.0	141.7	56.1	7.9	3.1	-109.6	92.4	-6.1	5.1	p<0.001
1-OAD/naïve	71	241.8	104.2	13.4	5.8	149.6	48.7	8.3	2.7	-92.2	106.5	-5.1	5.9	p<0.001
2-OADs/naïve	66	216.9	79.4	12.0	4.4	149.0	54.2	8.3	3.0	-67.9	90.9	-3.8	5.1	p<0.001
≥3-OADs/naïve	60	209.8	83.7	11.6	4.6	151.6	65.0	8.4	3.6	-58.2	95.2	-3.2	5.3	p<0.001
GLP-1RA/naïve	34	195.2	88.9	10.8	4.9	147.7	47.4	8.2	2.6	-47.6	82.6	-2.6	4.6	p=0.002
Insulin-experienced	905	156.8	69.4	8.7	3.8	147.5	59.7	8.2	3.3	-9.3	69.5	-0.5	3.9	p<0.001

(d) Body weight (kg)



T2DM population	n	Baseline (kg) mean	SD	Month 12 (LOCF) (kg) mean	SD	Change† (kg) mean	SD	Paired t-test, p-value
Insulin-naïve	888	66.7	15.6	67.4	15.4	0.7	4.1	p<0.001
0-OAD/naïve	245	67.2	15.2	68.5	15.3	1.3	5.4	p<0.001
1-OAD/naïve	164	64.0	15.1	64.3	15.1	0.3	2.9	p=0.145
2-OADs/naïve	183	65.1	13.8	65.7	13.8	0.5	4.2	p=0.083
≥3-OADs/naïve	198	65.6	15.2	66.2	15.0	0.5	3.4	p=0.035
GLP-1RA/naïve	98	75.2	18.6	75.4	17.4	0.2	3.5	p=0.597
Insulin-experienced	2,706	67.2	15.2	67.0	15.1	-0.2	3.1	p=0.003

Figure 3. Change of HbA1c levels (a), <7.0% HbA1c achievement (b), FPG levels (c), and body weight (d) over 12 months after Gla-300 initiation.

HbA1c: hemoglobin A1c; BL: baseline; T2DM: type 2 diabetes mellitus; SD: standard deviation; LOCF: last observation carried forward; OAD: oral antidiabetic drug; GLP-1RA: glucagon-like peptide-1 receptor agonist; FPG: fasting plasma glucose

Participants included in the table are limited to those who had data at the LOCF endpoint.Insulin-naïve people are stratified according to treatment prior to Gla-300 administration (0, 1, 2, and ≥3 OADs; and GLP-1RA irrespective of OAD administration).

†Mean change was calculated for participants whose baseline and endpoint data were both collected.

‡FPG data are either laboratory- or self-measured values. 'With FPG' refers to people who have FPG data, and 'without FPG' refers to people who do not have FPG data.

respectively. In the insulin-experienced group, 95.2% replaced their insulin with Gla-300 and 4.8% added Gla-300 to their ongoing insulin regimen. In 94.2% of these patients 'insufficient glycemic control' accounted for the switch from other insulin products to Gla-300.

3.4. Change in Gla-300 dose

As shown in Figure 2, in insulin-naïve patients, the mean (± SD) starting dose was 7.49 ± 4.76 U/day (0.11 ± 0.08 U/kg/day), which increased to 10.29 ± 6.76 U/day (0.16 ± 0.10 U/kg/day) at month 12 (LOCF), with a mean change of 2.80 ± 5.82 U/day (0.04 ± 0.09 U/kg/day) ($p < 0.001$). Among the subgroups, ≥3-OADs/naïve patients started with the lowest initial dose (6.11 ± 3.66 U/day, 0.10 ± 0.06 U/kg/day), which increased the most (4.73 ± 6.97 U/day, 0.07 ± 0.10 U/kg/day, $p < 0.001$).

In the insulin-experienced patients, the mean basal insulin dose was 15.00 ± 9.67 U/day (0.22 ± 0.13 U/kg/day) prior to Gla-300 initiation. The starting dose at baseline was 14.86 ± 9.61 U/day (0.22 ± 0.13 U/kg/day), which increased to 15.60 ± 10.01 U/day (0.24 ± 0.14 U/kg/day), with a mean change of 0.73 ± 3.79 U/day (0.01 ± 0.06 U/kg/day) ($p < 0.001$). The distribution of Gla-300 dose at month 12 (LOCF) is shown in Supplementary figure 1.

3.5. Effectiveness assessment

As shown in Figure 3(a), in insulin-naïve patients, mean (± SD) HbA1c levels reduced from 9.82 ± 2.19% (83.84 ± 23.96 mmol/mol) at baseline to 7.83 ± 1.52% (62.07 ± 16.58 mmol/mol) at month 12 (LOCF), with a mean change of −1.99 ± 2.30% (−21.77 ± 25.17 mmol/mol) ($p < 0.001$). Insulin-experienced patients showed markedly smaller reduction (7.99 ± 1.48% [63.88 ± 16.13 mmol/mol] to 7.81 ± 1.30% [61.90 ± 14.18 mmol/mol]) in HbA1c levels, with a mean change of −0.18 ± 1.21% (−1.98 ± 13.22 mmol/mol) ($p < 0.001$). HbA1c levels <7.0% were achieved in 28.4% of insulin-naïve and 24.6% of insulin-experienced patients (Figure 3(b)). This HbA1c target was achieved in a greater proportion of patients with FPG data

in both the insulin-naïve (30.6% with FPG vs 27.1% without FPG) and insulin-experienced (26.2% with FPG vs 23.8% without FPG) groups than in those without FPG data.

Figure 3(c) shows that the mean (± SD) FPG levels reduced from 229.2 ± 91.6 mg/dL (12.7 ± 5.1 mmol/L) at baseline to 147.2 ± 55.0 mg/dL (8.2 ± 3.1 mmol/L) at month 12 (LOCF) in insulin-naïve patients. In insulin-experienced patients, it changed from 156.8 ± 69.4 mg/dL (8.7 ± 3.8 mmol/L) to 147.5 ± 59.7 mg/dL (8.2 ± 3.3 mmol/L). The mean (± SD) change in body weight was +0.7 ± 4.1 kg ($p < 0.001$) in insulin-naïve and −0.2 ± 3.1 kg ($p = 0.003$) in insulin-experienced patients (Figure 3(d)).

The 0-OAD/naïve patients showed the largest changes in mean HbA1c (−3.25 ± 2.71% [−35.48 ± 29.61 mmol/mol], $p < 0.001$), mean FPG (−109.6 ± 92.4 mg/dL [−6.1 ± 5.1 mmol/L], $p < 0.001$), and mean body weight (+1.3 ± 5.4 kg, $p < 0.001$) among all subgroups.

3.6. Safety assessment

Overall, 42 ADRs from 42 insulin-naïve patients (3.42%) and 155 from 151 insulin-experienced patients (4.45%) were reported (Table 3). In both groups, hypoglycemia was the most common (36, 2.93% in insulin-naïve patients and 131, 3.86% in insulin-experienced patients). Incidences of serious hypoglycemia were 2 (0.16%) in insulin-naïve patients and 8 (0.24%) in insulin-experienced patients, and those of severe hypoglycemia were 1 (0.08%) in insulin-naïve patients and 7 (0.21%) in insulin-experienced patients.

3.7. Adherence

Among the participants, 84.1% of insulin-naïve and 86.7% of insulin-experienced patients remained adherent to Gla-300 (Table 4). Regarding life style modification, 33.2% of insulin-naïve and 31.3% of insulin-experienced patients were adherent to instruction on exercise, and 24.8% of insulin-naïve and 23.9% of insulin-experienced patients did not receive instructions. Moreover, 39.0% of insulin-naïve and 37.6% of insulin-experienced patients were adherent to dietary instruction and 14.4% of insulin-naïve and 13.2% insulin-experienced patients did not receive instructions. There was no numerical difference between the groups.

4. Discussion

The X-STAR study investigated the effectiveness and safety of Gla-300 in Japanese DM patients in a real-world clinical setting. This analysis of insulin-naïve and insulin-experienced T2DM patients provides insights into the current diabetes management strategies used prior to and after commencing second-generation basal insulin in Japanese clinical practice.

In insulin-naïve T2DM patients, treatment with Gla-300 was associated with significant reduction in HbA1C from baseline to month 12 (−1.99% [−21.77 mmol/mol], 9.82% [83.84 mmol/mol] to 7.83% [62.07 mmol/mol]). These results are comparable with those from previous randomized controlled trials of Gla-300 [18–22]. The insulin-experienced group showed a statistically significant, but clinically diminutive, reduction in HbA1c levels (−0.18% [−1.98 mmol/mol], 7.99–-7.81% [63.88–61.90 mmol/mol]). Additionally, changes in body weight were clinically insignificant, and overall, no unprecedented safety concerns were reported.

Overall achievement of HbA1c level <7.0% was relatively low at month 12 (28.4% of insulin-naïve and 24.6% of insulin-experienced patients). In insulin-naïve patients, the final dose of Gla-300 was 10.29 U at month 12 (+2.80 U from 7.49 U at initiation). In insulin-experienced patients, the mean change in dose was small (+0.73 U, from 14.86 U to 15.60 U) although 'insufficient glycemic control' was the most common reason for the switch (94.2%). In the Japan Diabetes Clinical Data Management (JDDM) study [4], only 21% of patients with HbA1c at ≥7.0% 180 days after the initiation of basal insulin had their treatment intensified during the 1.5-year follow-up.

Table 3. ADR reported during 12 months from baseline.

	Insulin-naïve (n = 1,227)		Insulin-experienced (n = 3,394)	
ADRs	n	(%)	n	(%)
Number of patients with ADRs	42	(3.42)	151	(4.45)
Number of ADR events	42	-	155	-
Cardiac disorders	0		1	(0.03)
Acute myocardial infarction	0		1	(0.03)
Gastrointestinal disorders	1	(0.08)	3	(0.09)
Abdominal discomfort	1	(0.08)	0	
Abdominal distension	0		1	(0.03)
Nausea	0		2	(0.06)
General disorders and injection site conditions	1	(0.08)	3	(0.09)
Injection site erythema	1	(0.08)	1	(0.03)
Injection site pruritus	0		2	(0.06)
Injection site mass	0		1	(0.03)
Investigations	0		5	(0.15)
Blood glucose abnormality	0		1	(0.03)
Blood glucose increased	0		2	(0.06)
Glycosylated hemoglobin increased	0		1	(0.03)
Liver function tests increased	0		1	(0.03)
Infectious and infestations	2	(0.16)	1	(0.03)
Pneumonia	0		1	(0.03)
Pharyngitis	1	(0.08)	0	
Infectious pleural effusion	1	(0.08)	0	
Metabolism and nutrition disorders	36	(2.93)	133	(3.92)
Diabetes mellitus[†]	0		1	(0.03)
Hyperglycemia	0		1	(0.03)
Hypoglycemia	36	(2.93)	131	(3.86)
Hepatobiliary disorders	0		1	(0.03)
Liver disorder	0		1	(0.03)
Nervous system disorders	0		2	(0.06)
Dizziness	0		1	(0.03)
Headache	0		1	(0.03)
Skin and subcutaneous tissue disorders	2	(0.16)	5	(0.15)
Eczema	1	(0.08)	0	
Pruritus	0		2	(0.06)
Rash	0		2	(0.06)
Urticaria	1	(0.08)	1	(0.03)
Total hypoglycemia	36	(2.93)	131	(3.86)
Serious hypoglycemia	2	(0.16)	8	(0.24)
Severe hypoglycemia[‡]	1	(0.08)	7	(0.21)

ADR: adverse drug reaction
Individual ADRs were coded according to the MedDRA/J Ver.22.0 classified according to Preferred Term
[†]The primary disease, i.e. diabetes mellitus was exacerbated
[‡]Severe hypoglycemia was defined as an event that required assistance of another person

Table 4. Adherence status with treatment instructions during the 12 months after Gla-300 initiation.

	Insulin-naïve (n = 1,227)		Insulin-experienced (n = 3,394)	
Adherence status	n	(%)	n	(%)
Gla-300 administration				
Adherent (≥75%)	782	(84.1)	2,664	(86.7)
Sometimes non-adherent (50% to <75%)	101	(10.9)	302	(9.8)
Non-adherent (<50%)	22	(2.4)	56	(1.8)
Unknown	25	(2.7)	50	(1.6)
Exercise				
Not instructed	231	(24.8)	735	(23.9)
Adherent (≥75%)	309	(33.2)	960	(31.3)
Sometimes non-adherent (50% to <75%)	191	(20.5)	652	(21.2)
Non-adherent (<50%)	102	(11.0)	435	(14.2)
Unknown	97	(10.4)	290	(9.4)
Dietary				
Not instructed	134	(14.4)	404	(13.2)
Adherent (≥75%)	363	(39.0)	1,156	(37.6)
Sometimes non-adherent (50% to <75%)	244	(26.2)	854	(27.8)
Non-adherent (<50%)	97	(10.4)	408	(13.3)
Unknown	92	(9.9)	250	(8.1)

The discrepancy between the reason for the switch to Gla-300 and suboptimal up-titration of Gla-300 in real clinical practice suggests that there are barriers to effective diabetes management. In general, fear of hypoglycemia in both patients and clinicians is the most important factor that leads to insufficient up-titration of insulin dose even when suboptimal control is apparent [23]. It can be assumed that a substantial number of insulin-experienced patients have had hypoglycemia and have developed fear from the current data; >40% of them on rapid-acting insulin or complex regimen with multiple OADs including SU (Table 2). In insulin-naïve patients, there is a highly frequent use of SU (42.5%) before initiation of Gla-300, and then only approximately 12% of the patients discontinued SU after the initiation, which may lead to difficulty in achieving glycemic control in patients with delayed initiation of insulin. In addition, there was a high proportion of elderly people with T2DM (49.5% in insulin-naïve and 57.3% in insulin-experienced patients were ≥65-year old; Table 1), indicative of the aging Japanese society. The Japanese Diabetes Society guideline recommends that HbA1c targets should be set according to age, medication (in particular, SU and insulin), and cognitive function and activities of daily living [24]. The older age profile of the population could have contributed to the low rate of insulin intensification seen in the present study and further sub-analysis in elderly should be considered.

Given that dose of basal insulin is adjusted according to FPG in the titration algorithms [25], the achievement of optimal glycemic control may be related to the frequency of FPG measurement. Our findings in patients with or without FPG show the same trend (Figure 3(b)). However, any firm conclusions cannot be made due to the small size of FPG samples in this study (332/1,194, 27.8% in insulin-naïve and 905/3,297, 27.4% in insulin-experienced patients).

Previous reports have suggested that the initiation of insulin therapy in the early stage of the disease can help to achieve and maintain optimal glycemic control [26,27], possibly due to the preservation of β-cell function [28]. Despite these reports, the present study suggests that early intervention with insulin in T2DM is not a common practice in Japan. Baseline HbA1c levels of insulin-naïve patients started on Gla-300 were high (9.82%). This figure is comparable with results of previous studies published from 2004 to 2013 in Japan, including ALOHA (9.05%) [5], ALOHA-2 (9.58%) [6], JDDM (9.4%) [4], and the Diabetes Attitudes Wishes and Needs (DAWN) Japan study (9.69%) [7]. This delay in the escalation of therapy, combined with barriers to appropriate titration, may limit the impact of insulin treatment on the overall glycemic control and preservation of β-cell function. There are, of course, various other reasons for this 'clinical inertia.' In general, healthcare professionals and patients hesitate to use injectable therapies. Treatment complexity, inconvenience, weight gain, and hypoglycemia are all well-recognized barriers to insulin therapy [8]. Furthermore, hospitals and clinics in Japan are overcrowded and understaffed, and the initiation of insulin requires time for patient education on self-injection and the use of SMPG, which may be a logistical barrier to treatment intensification. Safe and effective drugs such as Gla-300 can be a viable therapeutic option to achieve glycemic control.

The present study has certain limitations. First, the incidences of ADRs, including hypoglycemia, may be underestimated. In post-marketing surveillance, data are collected at routine visits and the definition of hypoglycemia is not strictly specified, leading to underreporting in comparison with clinical trials. Second, this is an observational study and the lack of a control group prevents any comparative analysis. Last, because this is a post marketing surveillance conducted in Japan, our study results may not be generalizable.

5. Conclusions

In conclusion, the X-STAR study of T2DM patients showed that treatment with Gla-300 reduced or maintained HbA1c levels in insulin naïve or experienced patients, and no unprecedented safety concerns were reported during the study period of 12 months. This suggests that Gla-300 is a safe and effective basal insulin for the management of T2DM.

The study also indicates that in Japanese clinical practice, there is delayed initiation of insulin with high mean HbA1c (>9%) at initiation and very small up-titration of basal insulin despite low (<30%) achievement of glycemic targets (HbA1c < 7.0%). Although the age profile of the Japanese population affects individual glycemic targets, improved comprehensive strategies for glycemic control in Japanese T2DM patients are required, and Gla-300 is a viable therapeutic option.

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Author contributions

M Matsuhisa and Y Terauchi conceived and designed the study, interpreted the data, and critically revised the manuscript. M Odawara, T Hirose, and Y Tanaka interpreted the data and critically revised the manuscript. R Koshida interpreted the data, and drafted and critically revised the manuscript. M Senda conceived and designed the study, participated in data acquisition, analysis, and interpretation, and critically revised the manuscript. All authors approved the final version of the manuscript for publication and agreed to be accountable for the data presented herein.

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