JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

# Safety and effectiveness of dulaglutide 0.75 mg in Japanese patients with type 2 diabetes in real-world clinical practice: 36 month post-marketing observational study

Rina Chin[1]*, Soshi Nagaoka[1], Haru Nakasawa[1], Yoko Tanaka[1], Nobuya Inagaki[2]

[1]Japan Drug Development and Medical Affairs, Eli Lilly Japan, Kobe, Japan, and [2]Division of Diabetes, Metabolism and Endocrinology, Kyoto University, Kyoto, Japan

**Keywords**
Diabetes type 2, Dulaglutide, Glucagon-like peptide-1 receptor

***Correspondence**
Rina Chin
Tel.: +81-(0)3-5574-9185
Fax: +81-(0)3-5574-9979
E-mail address:
chin_rina@lilly.com

*J Diabetes Investig* 2023; 14: 247–258

doi: 10.1111/jdi.13932

## ABSTRACT

**Aims/Introduction:** This study evaluated the safety and effectiveness of dulaglutide in patients with type 2 diabetes in the real-world setting in Japan.

**Materials and Methods:** This prospective, observational post-marketing surveillance study was conducted for 36 months (July 2016 to July 2021) in Japan. Investigators reported data *via* an electronic data capture system. Data were analyzed by overall population and age group (<65, ≥65 to <75, and ≥75 years).

**Results:** The analysis population ($N$ = 3,136) included 1,538 (49.04%), 869 (27.71%), and 729 (23.25%) patients aged <65 years, ≥65 to <75 years, and ≥75 years, respectively. Overall, 231 patients (7.37%) experienced ≥1 adverse drug reactions, with the highest frequency in the ≥75 years group. The most common adverse drug reactions were gastrointestinal disorders ($n$ = 106; 3.38%). Severe hypoglycemia ($n$ = 4; 0.13%), major adverse cardiovascular events ($n$ = 4; 0.13%), and acute pancreatitis ($n$ = 1; 0.03%) were uncommon. The mean glycated hemoglobin and bodyweight were reduced from baseline by −0.76% and −1.6 kg, respectively (last observation carried forward). The rate of dulaglutide continuation at 36 months was 58.03% overall and 59.43%, 63.13%, and 48.88% in the <65, ≥65 to <75, and ≥75 years groups, respectively. A factor analysis showed age ≥65 years was associated with a greater incidence of gastrointestinal adverse drug reactions as well as larger reductions in glycated hemoglobin and bodyweight.

**Conclusions:** The current real-world data are in accordance with clinical trial findings and further confirm the safety and effectiveness of dulaglutide for elderly patients, whose numbers were limited in the clinical trials.

## INTRODUCTION

The incidence of type 2 diabetes (T2D) is estimated at 14.6% in Japan[1], increasing over the past 50 years due to an aging population and lifestyle changes[2]. Patients with type 2 diabetes are at higher risk for severe comorbidities, including cardiovascular disease and chronic kidney disease (CKD). Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by the gastrointestinal tract in response to food ingestion. GLP-1 enhances glucose-dependent secretion of insulin, inhibits glucagon secretion, and suppresses gastric emptying[3]. GLP-1 receptor agonists (GLP-1 RAs) are used as antidiabetic therapeutics based on their ability to lower blood glucose levels and to facilitate weight loss[3]. Clinical studies indicate GLP-1 RAs are also associated with a reduced frequency of major adverse cardiovascular events (MACE) and a reduced progression of CKD in patients with type 2 diabetes[4–10].

Dulaglutide is a long-acting, once-weekly GLP-1 RA used to treat type 2 diabetes worldwide. Dulaglutide comprises a fusion protein of a GLP-1 (7–37) analogue covalently linked to the Fc region of human immunoglobulin G4, which protects the GLP-1 moiety from dipeptidyl peptidase-4 (DPP4)-mediated inactivation[11]. Phase 3 studies in Japanese patients with type 2

Received 3 July 2022; revised 26 September 2022; accepted 11 October 2022

diabetes demonstrated that once-weekly dulaglutide is safe and efficacious as monotherapy or in combination with other antidiabetic medications[12–15]. However, in these studies, elderly patients were under-represented, with only approximately 25% of patients aged ≥65 years and 3% aged ≥75 years[16]. The risk management plan in Japan for dulaglutide identified safety in elderly patients and patients with renal impairment as important missing information[17]. Limited data are also available on the long-term safety and effectiveness of dulaglutide when administered to Japanese patients in the real-world setting.

This post-marketing observational study of dulaglutide was conducted as an additional pharmacovigilance activity in the real-world setting. We reported previously on this study, specifically focusing on safety during the first 3 months of dulaglutide usage in patients aged ≥75 years[16] and on the therapeutic switch to dulaglutide from DPP4 inhibitors or other GLP-1 RAs at interim analysis[18]. The current manuscript reports the final analysis of the study, evaluating the safety of dulaglutide through 36 months of treatment, with a focus on age-related differences. This study also included patients with severe renal impairment, who are usually omitted from clinical trials.

## MATERIALS AND METHODS

### Study design and patients

This was a prospective, post-marketing observational study conducted in Japan from July 2016 to July 2021 at 468 clinics and hospital departments that treat type 2 diabetes. Enrollment continued through May 2018. Patients with type 2 diabetes were eligible if they were dulaglutide naïve and considered by investigators to be appropriate for dulaglutide treatment prior to enrollment. The observation period was 36 months after starting dulaglutide. Adult patients ordinarily received 0.75 mg dulaglutide once weekly by subcutaneous injection. If dulaglutide was discontinued, the observation period ended on the day of discontinuation.

This study was a drug-use survey, stipulated in the risk management plan[17] as a condition of dulaglutide approval in Japan, and was conducted in compliance with the Ministry of Health, Labour and Welfare ordinance on Good Post-marketing Study Practice[19]. Patients' written informed consent was not required for participation.

### Data collection

Investigators enrolled patients in a central registry. Registration was required ≤2 weeks after starting dulaglutide. Investigators entered the patients' data into an electronic case report form (eCRF) in an electronic data capture system. The study sponsor conducted the investigation with some activities (e.g., eCRF collection) outsourced to Sumitomo Pharma. Data were collected on patient demographics and baseline clinical characteristics, concomitant medications and therapies, dulaglutide usage, vital signs, clinical laboratory tests, electrocardiograms, and safety. Concomitant medications and therapies initiated after discontinuation of dulaglutide were excluded.

All adverse events (AEs), serious AEs, AE of special interests (AESIs), adverse drug reactions (ADRs), and serious ADRs (SADRs) were collected. AESIs for dulaglutide included severe hypoglycemia (assessed according to American Diabetes Association guidelines)[20], acute pancreatitis, MACE, gastrointestinal disorders, and injection site and hypersensitivity reactions. Of these, severe hypoglycemia, acute pancreatitis, and MACE were predefined as important events of interest. Hypoglycemia that met the serious criteria was considered severe hypoglycemia, with details recorded in the eCRF as an AE. Data on vital signs and clinical laboratory tests were collected at baseline and at every visit during the observation period. The criteria for the severity of renal impairment were based on estimated glomerular filtration rates (eGFRs), adapted from the Evidence-Based Clinical Practice Guideline for CKD 2013[21], with data summarized by eGFR categories (≥90, 60–89, 45–59, 30–44, 15–29, <15 mL/min/1.73m$^2$).

Effectiveness was assessed by glycated hemoglobin (HbA1c)-based glycemic control and changes in bodyweight.

### Statistical analyses

Continuous variables were summarized using mean (standard deviation [SD]) and median (range). Categorical variables were summarized using frequency and incidence. As there was no control group, statistical significance was determined for reference purposes only, and multiplicity adjustments were not made. The level of significance was set as $P < 0.05$. Missing data were imputed by the last observation carried forward (LOCF) analyses.

The AEs and ADRs were classified according to the Medical Dictionary for Regulatory Activities, Version 24.0. Data were analyzed by overall population and by '<65 years', '≥65 to <75 years', and '≥75 years' age-group categories. Data were additionally analyzed by prior treatment, which included three categories: patients switching from DPP4 inhibitors, patients switching from other GLP-1 RAs, and 'others' (i.e., patients not in the other two categories). Treatment persistence rates were estimated using the Kaplan–Meier method.

Factor analyses were conducted to examine how key demographic and baseline characteristics were related to the frequency of ADRs of gastrointestinal disorders and change from baseline in HbA1c and bodyweight, as described previously[22]. Incidence proportion plus 95% confidence intervals are presented for ADR frequency, with *P* values derived from Fisher's exact tests. The least squares mean plus 95% confidence intervals are shown for change from baseline HbA1c and bodyweight (LOCF), with *P* values derived from *t*-tests or analysis of variance. Statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, USA).

## RESULTS

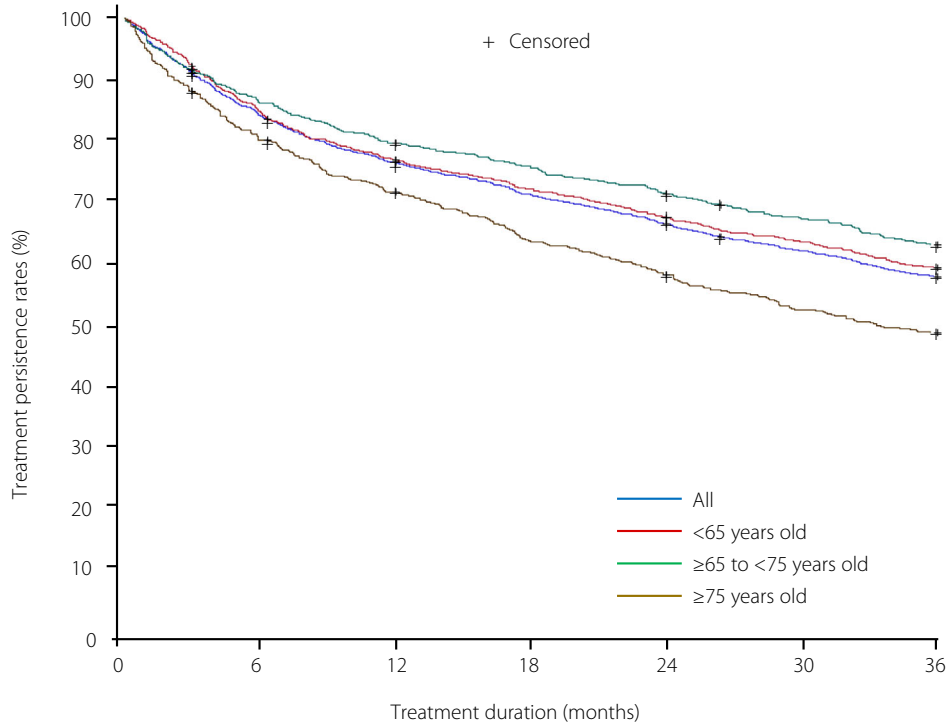
### Patient disposition and dulaglutide usage

Of 3,277 patients who were registered, eCRFs were collected from 3,247, 111 of whom were excluded from analysis,

including 28 for lack of treatment with dulaglutide (Figure S1), to give 3,136 in the safety and effectiveness analysis populations. Over the 36 month study period, 1,295 (41.29%) patients discontinued from the study, the reasons for which included AEs ($n$ = 140; 10.81%), lack of efficacy ($n$ = 189; 14.59%), lost to follow-up ($n$ = 514; 39.69%), symptoms improved ($n$ = 81; 6.25%), death ($n$ = 36; 2.78%), physician decision ($n$ = 151; 11.66%), patient decision ($n$ = 179; 13.82%), no visits after enrollment ($n$ = 4; 0.31%), and not determined ($n$ = 1; 0.08%). Dulaglutide continuation is shown in Figure 1. The rate of continuation at 36 months was 58.03% overall and 59.43%, 63.13%, and 48.88% in the <65, ≥65 to <75, and ≥75 years groups, respectively.

### Patient characteristics

In the subgroups, 1,538 (49.04%), 869 (27.71%), and 729 (23.25%) were aged <65, ≥65 to <75, and ≥75 years, respectively, with an overall median age of 65.0 years (range 16–108 years; Table 1). The ratio of males to females was slightly imbalanced (56.76% to 43.24%, respectively; Table 1). The




| | All | | <65 years | | ≥65 to <75 years | | ≥75 years | |
|---|---|---|---|---|---|---|---|---|
| Months | At risk (n) | Persistence rate (%) | At risk (n) | Persistence rate (%) | At risk (n) | Persistence rate (%) | At risk (n) | Persistence rate (%) |
| 0 | 3136 | | 1538 | | 869 | | 729 | |
| 6 | 2621 | 84.13 | 1302 | 84.76 | 742 | 86.25 | 577 | 80.27 |
| 12 | 2382 | 76.55 | 1181 | 77.01 | 686 | 79.74 | 515 | 71.77 |
| 18 | 2184 | 71.19 | 1090 | 72.23 | 648 | 75.64 | 446 | 63.64 |
| 24 | 2038 | 66.52 | 1020 | 67.59 | 609 | 71.42 | 406 | 58.36 |
| 30 | 1874 | 62.15 | 944 | 63.61 | 569 | 67.39 | 361 | 52.67 |
| 36 | 1750 | 58.03 | 882 | 59.43 | 533 | 63.13 | 335 | 48.88 |

**Figure 1** | Time-dependent changes in dulaglutide continuation rates by age group (safety population). Treatment persistence rates were estimated using the Kaplan–Meier method. For the patients who discontinued dulaglutide treatment, the date of discontinuation of treatment was defined as an event. For patients who completed the study or were lost to follow-up, patients were censored at the last visit date. *N*, number of patients in category.

mean HbA1c at baseline was similar across age groups (mean [SD]: overall, 8.5% [1.7]; <65 years, 8.5 [1.7]; ≥65 to <75 years, 8.3 [1.6]; ≥75 years, 8.6 [1.7]). The mean bodyweight decreased with age (mean [SD]: 79.8 [18.4], 66.2 [13.5], and 59.7 [12.0] kg in the <65, ≥65 to <75, and ≥75 years age groups, respectively) whereas the mean (SD) BMI was 29.2 (5.8), 26.2 (4.9), and 29.8 (4.3) kg/m$^2$, respectively.

The study included patients with lower eGFR (Table 1), including 53 (1.69%) who received concomitant dialysis during the study. At baseline, the proportion of patients in each eGFR category was similar across the age groups except a higher proportion of patients with eGFR ≥90 mL/min/1.73 m$^2$ were reported in the <65 years group (22.37%) compared with the ≥65 to <75 (9.44%) and ≥75 years (4.39%) groups. A lower proportion of patients aged <65 years had cardiovascular complications at baseline compared with the other age groups, but the proportions of diabetic complications were similar among age groups (Table 1).

Of the 3,136 patients enrolled, 1,296 (41.33%) switched from DPP4 inhibitors to dulaglutide, 627 (20.00%) switched from other GLP-1 RAs, and 1,216 (38.78%) were in the 'others' category (Table S1). Baseline clinical characteristics were relatively balanced across prior treatment categories except mean HbA1c was lower in patients switching from other GLP-1 RAs (mean [SD] 7.7% [1.4]) compared with those switching from DPP4 inhibitors or other drugs (8.6% [1.5] and 8.7% [1.9], respectively).

### Concomitant medications

Overall, 87.56% of patients received concomitant medications during the treatment period, with similar proportions in each age group (Table 2). Other antidiabetes medications were commonly used, with the highest proportions receiving biguanides (overall: 48.72%) or sodium glucose cotransporter-2 (SGLT2) inhibitors (overall: 37.76%). The percentage of patients receiving concomitant antidiabetic medications was generally similar among the age groups, but the concomitant use of biguanides or SGLT2 inhibitors decreased with increasing age. Concomitant antihypertensive use was also common (50.92%). The proportions of patients who received concomitant medications were generally similar across prior treatment categories, but a higher proportion of patients who switched from other GLP-1 RAs received concomitant biguanides or SGLT2 inhibitors compared with those who switched from DPP4 inhibitors or other regimens (Table S2).

### Safety

The reported ADRs and SADRs are summarized in Table S3. The incidence was 7.37% (231/3136) for ADRs and 1.12% (35/3136) for SADRs. The percentage of patients who experienced ADRs and SADRs increased with age (Table 3). In the overall population, 48 deaths (1.53%) were reported, including those as outcomes of AEs. Of these, seven deaths (0.22%) occurred for which the investigators could not rule out a causal relationship with dulaglutide: one death each (0.03%) were due to lung cancer and acute myocardial infarction and five (0.16%) were due to unknown causes. In total, 106 patients discontinued due to ADRs, most frequently gastrointestinal ADRs, including nausea ($n$ = 25; 23.58%), decreased appetite ($n$ = 12; 11.32%), and vomiting ($n$ = 11; 10.38%).

Severe hypoglycemia was reported in four patients (0.13%; Table 3). All ADRs of hypoglycemia were reported as resolved or resolving except for one patient (0.03%) whose condition was not resolved and worsened in association with underlying disease. One patient (0.14%) in the ≥75 years category experienced an ADR of acute pancreatitis, which was reported as resolved. Four patients (0.13%) experienced ADRs of MACE, including acute myocardial infarction ($n$ = 3) and brainstem hemorrhage ($n$ = 1). One ADR of acute myocardial infarction occurred in the ≥75 years category and was fatal, whereas the other three events were reported as resolving.

The most common ADRs of special interest were gastrointestinal disorders, which were reported in 106 patients (3.38%) in the overall population (58 [1.85%] resolved, 32 [1.02%] resolving; 13 [0.41%] not resolved; 3 [0.10%] unknown), most commonly nausea (1.66%; $n$ = 52), vomiting (0.54%; $n$ = 17), constipation (0.48%; $n$ = 15), or diarrhea (0.41%; $n$ = 13). Onset data were available for 74 patients experiencing gastrointestinal ADRs, which indicated most gastrointestinal ADRs (56/74; 75.68%) had an initial onset within 3 months of starting dulaglutide. ADRs of gastrointestinal disorders were reported in increasing frequency with age (Table 3). Five ADRs of gastrointestinal disorders were considered serious ($n$ = 1 each of gastric ulcer, mechanical ileus, impaired gastric emptying, colitis ischemic, and nausea).

More patients who switched from DPP4 inhibitors to dulaglutide reported ADRs and ADRs of special interest compared with patients who switched from other GLP-1 RAs or other regimens (Table S4).

### Effectiveness

At the LOCF endpoint, HbA1c had decreased from baseline in all age groups (mean decrease [SD]: overall, −0.76% [1.71]; $P$ < 0.001; Figure 2a). Statistically significant decreases in HbA1c occurred within 1 month of starting dulaglutide, with stable glycemic control from 3 months onwards (Table S5). The mean (SD) bodyweight also decreased over 36 months in each of the age categories (Figure 2b). Significant decreases were evident within 1 month of starting dulaglutide, with an overall mean (SD) change from baseline of −1.6 (4.9) kg ($P$ < 0.001) observed at the LOCF endpoint (Table S5). Analysis of bodyweight loss by baseline BMI showed a greater bodyweight loss in patients with a BMI ≥25 kg/m$^2$ (mean [SD] at LOCF: −2.1 [5.1]) compared with patients with a BMI <25 kg/m$^2$ (mean [SD] at LOCF: −0.8 [4.3]; $P$ < 0.001), with similar trends observed in each of the age groups (Table S6). Patient numbers within BMI categories at baseline and LOCF are shown by age in a cross-table in Table S7.

**Table 1** | Demographics and baseline characteristics by age group (safety population)

| Characteristic | Group | <65 years | ≥65 to <75 years | ≥75 years | Overall |
|---|---|---|---|---|---|
| *N* | Safety population | 1,538 | 869 | 729 | 3,136 |
| Sex, *n* (%) | Male | 957 (62.22) | 452 (52.01) | 371 (50.89) | 1780 (56.76) |
| | Female | 581 (37.78) | 417 (47.99) | 358 (49.11) | 1,356 (43.24) |
| Age (years) | <65 | 1,538 (100) | 0 | 0 | 1,538 (49.04) |
| | ≥65 | 0 | 869 (100) | 729 (100) | 1,598 (50.96) |
| Duration of type 2 diabetes (years) | *Nx* | 1,053 | 573 | 424 | 2050 |
| | <5 | 219 (14.24) | 52 (5.98) | 36 (4.94) | 307 (9.79) |
| | ≥5 to <10 | 303 (19.70) | 92 (10.59) | 53 (7.27) | 448 (14.29) |
| | ≥10 to <15 | 269 (17.49) | 111 (12.77) | 78 (10.70) | 458 (14.60) |
| | ≥15 to <20 | 143 (9.30) | 108 (12.43) | 74 (10.15) | 325 (10.36) |
| | ≥20 | 119 (7.74) | 210 (24.17) | 183 (25.10) | 512 (16.33) |
| Bodyweight (kg) | *Nx* | 1,362 | 750 | 602 | 2,714 |
| | Mean (SD) | 79.8 (18.4) | 66.2 (13.5) | 59.7 (12.0) | 71.6 (18.0) |
| BMI category (kg/m$^2$) | *Nx* | 1,295 | 709 | 563 | 2,567 |
| | <18.5 | 14 (0.91) | 27 (3.11) | 31 (4.25) | 72 (2.30) |
| | ≥18.5 to <22.0 | 67 (4.36) | 98 (11.28) | 127 (17.42) | 202 (9.31) |
| | ≥22.0 to <25.0 | 220 (14.30) | 197 (22.67) | 153 (20.99) | 570 (18.18) |
| | ≥25.0 to <30.0 | 508 (33.03) | 250 (28.77) | 182 (24.97) | 940 (29.97) |
| | ≥30.0 to <35.0 | 309 (20.09) | 94 (10.82) | 58 (7.96) | 461 (14.70) |
| | ≥35.0 to <40.0 | 114 (7.41) | 35 (4.03) | 12 (1.65) | 161 (5.13) |
| | ≥40 | 63 (4.10) | 8 (0.92) | 0 | 71 (2.26) |
| HbA1c (%) | *Nx* | 1,412 | 797 | 639 | 2,848 |
| | <7.0 | 217 (14.11) | 129 (14.84) | 84 (11.52) | 430 (13.71) |
| | ≥7.0 to <8.0 | 378 (24.58) | 234 (26.93) | 146 (20.03) | 758 (24.17) |
| | ≥8.0 to <9.0 | 361 (23.47) | 231 (26.58) | 195 (26.75) | 787 (25.10) |
| | ≥9.0 | 456 (29.65) | 203 (23.36) | 214 (29.36) | 873 (27.84) |
| eGFR (mL/min/1.73m$^2$) | *Nx* | 1,043 | 612 | 502 | 2,157 |
| *n* (%) | ≥90 | 344 (22.37) | 82 (9.44) | 32 (4.39) | 458 (14.60) |
| | 60–89 | 507 (32.96) | 275 (31.65) | 214 (29.36) | 996 (31.76) |
| | 45–59 | 79 (5.14) | 139 (16.00) | 127 (17.42) | 345 (11.00) |
| | 30–44 | 53 (3.45) | 74 (8.52) | 69 (9.47) | 196 (6.25) |
| | 15–29 | 26 (1.69) | 24 (2.76) | 39 (5.35) | 89 (2.84) |
| | <15 | 34 (2.21) | 18 (2.07) | 21 (2.88) | 73 (2.33) |
| Complications, *n* (%) | Total | 1,284 (83.49) | 768 (88.38) | 660 (90.53) | 2,712 (86.48) |
| | Hypertension | 826 (53.71) | 580 (66.74) | 478 (65.57) | 1884 (60.08) |
| | Dyslipidemia | 618 (40.18) | 334 (38.43) | 275 (37.72) | 1,227 (39.13) |
| | Cardiovascular (including vascular disease of the extremities) | 206 (13.39) | 240 (27.62) | 249 (34.16) | 695 (22.16) |
| | Diabetic neuropathy | 116 (7.54) | 79 (9.09) | 54 (7.41) | 249 (7.49) |
| | Diabetic retinopathy | 109 (7.09) | 69 (7.94) | 42 (5.76) | 220 (7.02) |
| | Diabetic nephropathy | 150 (9.75) | 83 (9.55) | 59 (8.09) | 292 (9.31) |

BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; *N*, number of patients in analysis population; *n*, number of patients in category; *Nx*, number of patients with data; SD, standard deviation.

**Table 2** | Concomitant medications by age group (safety population)

| | <65 years | ≥65 to <75 years | ≥75 years | Overall |
|---|---|---|---|---|
| Number of patients | 1,538 | 869 | 729 | 3,136 |
| Patients using concomitant medications, *n* (%) | 1,359 (88.36) | 764 (87.92) | 623 (85.46) | 2,746 (87.56) |
| Hypoglycemic agents, *n* (%) | | | | |
| Biguanides | 944 (61.38) | 404 (46.49) | 180 (24.69) | 1,528 (48.72) |
| Sulfonylureas | 368 (23.93) | 231 (26.58) | 194 (26.61) | 793 (25.29) |
| DPP4 inhibitors | 69 (4.49) | 41 (4.72) | 36 (4.94) | 146 (4.66) |
| Glinides | 163 (10.60) | 130 (14.96) | 123 (16.87) | 416 (13.27) |
| α-Glucosidase inhibitors | 224 (14.56) | 166 (19.10) | 147 (20.16) | 537 (17.12) |
| Thiazolidinediones | 174 (11.31) | 96 (11.05) | 64 (8.78) | 334 (10.65) |
| SGLT2 inhibitors | 762 (49.54) | 286 (32.91) | 136 (18.66) | 1,184 (37.76) |
| Rapid-acting insulin secretagogues | 160 (10.40) | 85 (9.78) | 54 (7.41) | 299 (9.53) |
| Insulin preparations | 509 (33.09) | 322 (37.05) | 225 (30.86) | 1,056 (33.67) |
| Antihypertensives *n* (%) | 703 (45.71) | 491 (56.50) | 403 (55.28) | 1,597 (50.92) |
| ACE inhibitors | 63 (4.10) | 47 (5.41) | 32 (4.39) | 142 (4.53) |
| ARBs | 547 (35.57) | 380 (43.73) | 276 (37.86) | 1,203 (38.36) |
| CCBs | 459 (29.84) | 337 (38.78) | 286 (39.23) | 1,082 (34.50) |
| Diuretics | 122 (7.93) | 120 (13.81) | 106 (14.54) | 348 (11.10) |
| Statins | 622 (40.44) | 402 (46.26) | 293 (40.19) | 1,317 (42.00) |

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; DPP4, dipeptidylpeptidase-4; *n*, number of patients in category; SGLT2, sodium-glucose cotransporter 2.

The HbA1c and bodyweight were also decreased significantly in all prior treatment categories over 36 months, but the magnitude of the changes from baseline was much lower for patients switching from other GLP-1 RAs compared with patients switching from DPP4 inhibitors or other medications (Figure S2).

### Other findings

Renal function decreased slightly over the 36 month treatment period (overall mean [SD] change in eGFR at LOCF: −2.7 [14.1] mL/min/1.73m$^2$; Table S5), with similar reductions observed in all baseline CKD categories except the ≥90 mL/min/1.73m$^2$ category, which showed a slight increase in the mean eGFR (Figure 3). The mean total cholesterol and other lipids also decreased significantly with dulaglutide, evident within 1 month of starting dulaglutide (Table S5; total cholesterol, mean [SD] change: −6.9 [36.4] mg/dL at LOCF, $P < 0.001$). Small, statistically significant decreases from baseline were observed in diastolic blood pressure throughout the 36 month study (mean [SD] change: −0.51 [11.8] mmHg at LOCF) and in systolic blood pressure through 18 months (mean [SD] change: −1.4 [17.3] mmHg; Table S5). Mean pulse rate was transiently increased at 1 and 3 months (mean [SD] change: 1.0 [9.8] and 0.7 [10.3], respectively) but was not significantly changed from baseline at later time points (Table S5).

### Factor analyses

For some baseline clinical data categories, data were not measured or reported for a proportion of patients, notably duration of type 2 diabetes data (36.63%; Table 1). In the factor analyses, females had significantly more gastrointestinal ADRs than males (Figure 4a; $P < 0.05$). Other factors associated with a greater incidence of gastrointestinal ADRs included age ≥65 years, bodyweight <70 kg, BMI <25 kg/m$^2$, and type 2 diabetes duration ≥10 years. Patients who switched from DPP4 inhibitors also had more gastrointestinal ADRs compared with those who switched from other medications ($P < 0.001$). Patients aged ≥65 years exhibited larger reductions in both HbA1c and bodyweight compared with those aged <65 years (Figure 4b,c; $P < 0.05$). Additionally, larger reductions in HbA1c were also associated with type 2 diabetes duration <10 years, baseline bodyweight <70 kg, baseline BMI <25 kg/m$^2$, and baseline HbA1c >8.5%. In contrast, larger reductions in bodyweight were associated with baseline bodyweight ≥70 kg and BMI ≥25 kg/m$^2$.

A COVID-19 pandemic impact statement is included in the Supplemental Materials.

## DISCUSSION

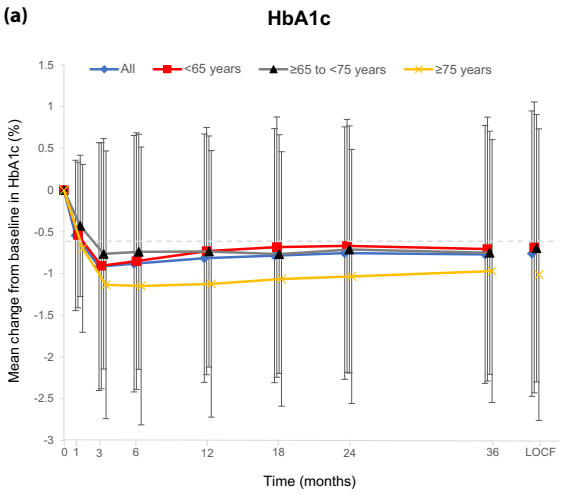
The current results indicate that the real-world safety and effectiveness of dulaglutide are in accordance with the findings of previous clinical trials in Japanese patients, which reported results up to 52 weeks[12–15]. This study additionally included a larger proportion of elderly patients (approximately 50% aged ≥65 years and 25% aged ≥75 years) than prior clinical studies and patients with different levels of kidney function, including those with CKD and on dialysis. As such, this study was able to confirm dulaglutide treatment up to 36 months was safe and effective in Japanese patients with type 2 diabetes, including in elderly patients and those with poorer renal function.

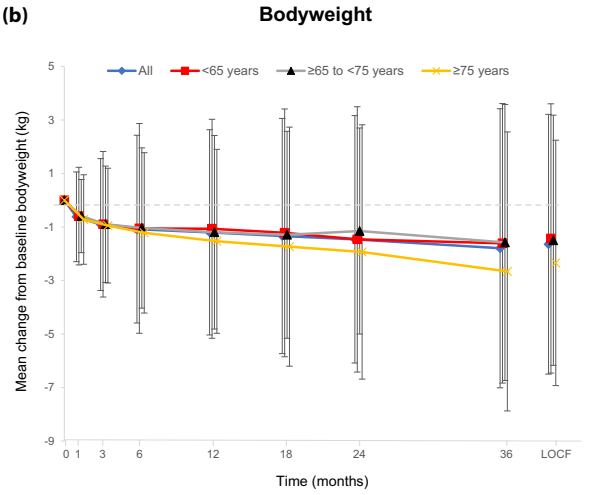
**Table 3** | Safety summary by age category (safety population)

| | | <65 years | ≥65 to <75 years | ≥75 years | Overall |
|---|---|---|---|---|---|
| Number of patients | | 1,538 | 869 | 729 | 3,136 |
| Patients with any ADR, *n* (%) | | 91 (5.92) | 68 (7.83) | 72 (9.88) | 231 (7.37) |
| Patients with any SADR, *n* (%) | | 11 (0.72) | 12 (1.38) | 12 (1.65) | 35 (1.12) |
| ADRs of special interest, *n* (%) | | | | | |
| Hypoglycemia | Hypoglycemia | 2 (0.13) | 1 (0.12) | 1 (0.14) | 4 (0.13) |
| Acute pancreatitis | Acute pancreatitis | 0 | 0 | 1 (0.14) | 1 (0.03) |
| MACE | Total | 2 (0.13) | 0 | 2 (0.27) | 4 (0.13) |
| | Acute myocardial infarction | 1 (0.07) | 0 | 2 (0.27) | 3 (0.10) |
| | Brainstem hemorrhage | 1 (0.07) | 0 | 0 | 1 (0.03) |
| Arrythmia and cardiac conduction disorders | Total | 1 (0.07) | 0 | 2 (0.27) | 3 (0.10) |
| | Atrial fibrillation | 1 (0.07) | 0 | 0 | 1 (0.03) |
| | Bundle branch block left | 0 | 0 | 1 (0.14) | 1 (0.03) |
| | Syncope | 0 | 0 | 1 (0.14) | 1 (0.03) |
| Gastrointestinal disorders | Total | 40 (2.60) | 34 (3.91) | 32 (4.39) | 106 (3.38) |
| | Nausea | 23 (1.50) | 15 (1.73) | 14 (1.92) | 52 (1.66) |
| | Vomiting | 8 (0.52) | 3 (0.35) | 6 (0.82) | 17 (0.54) |
| | Constipation | 6 (0.39) | 4 (0.46) | 5 (0.69) | 15 (0.48) |
| | Diarrhea | 4 (0.26) | 4 (0.46) | 5 (0.69) | 13 (0.41) |
| | Abdominal discomfort | 1 (0.07) | 6 (0.69) | 1 (0.14) | 8 (0.26) |
| | Feces soft | 2 (0.13) | 1 (0.12) | 0 | 3 (0.10) |
| | Abdominal pain | 1 (0.07) | 0 | 1 (0.14) | 2 (0.06) |
| | Abdominal distention | 0 | 2 (0.23) | 0 | 2 (0.06) |
| | Chronic gastritis | 0 | 1 (0.12) | 1 (0.14) | 2 (0.06) |
| | Gastrointestinal disorder | 1 (0.07) | 1 (0.12) | 0 | 2 (0.06) |
| | Abdominal pain upper | 0 | 1 (0.12) | 0 | 1 (0.03) |
| | Colitis ischemic | 0 | 1 (0.12) | 0 | 1 (0.03) |
| | Dyspepsia | 1 (0.07) | 0 | 0 | 1 (0.03) |
| | Gastric ulcer | 0 | 0 | 1 (0.14) | 1 (0.03) |
| | Gastroesophageal reflux disease | 0 | 1 (0.12) | 0 | 1 (0.03) |
| | Impaired gastric emptying | 0 | 1 (0.12) | 0 | 1 (0.03) |
| | Intestinal obstruction | 1 (0.07) | 0 | 0 | 1 (0.03) |
| | Mechanical ileus | 1 (0.07) | 0 | 0 | 1 (0.03) |
| Injection site reactions | Total | 8 (0.52) | 3 (0.35) | 1 (0.14) | 12 (0.38) |
| | Injection site pruritus | 3 (0.20) | 3 (0.35) | 1 (0.14) | 7 (0.22) |
| | Injection site induration | 2 (0.13) | 0 | 0 | 2 (0.06) |
| | Injection site pain | 2 (0.13) | 0 | 0 | 2 (0.06) |
| | Injection site erythema | 1 (0.07) | 0 | 0 | 1 (0.03) |
| Hypersensitivity reactions | Total | 4 (0.26) | 3 (0.35) | 3 (0.41) | 10 (0.32) |
| | Rash | 2 (0.13) | 3 (0.35) | 2 (0.27) | 7 (0.22) |
| | Blood pressure decreased | 1 (0.07) | 0 | 0 | 1 (0.03) |
| | Hypersensitivity | 0 | 0 | 1 (0.14) | 1 (0.03) |
| | Urticaria | 1 (0.07) | 0 | 0 | 1 (0.03) |

MedDRA 24.0. ADR, adverse drug reaction; MACE, major adverse cardiovascular events; *n*, number of patients in category; SADR, serious adverse drug reaction.

Some differences were observed across age groups both at baseline and with treatment. At baseline, clinical characteristics were relatively balanced across age groups, but the <65 years group had a higher bodyweight and lower rates of cardiovascular and renal complications compared with older patients. In addition, the proportion of patients who received concomitant medications with dulaglutide was high in all age groups (>87% overall). Many patients received concomitant antidiabetic drugs, most commonly biguanides (48.72%) or SGLT2 inhibitors (37.76%), and the proportion of patients using both classes of drugs was highest in the <65 years group. The multifaceted influence of patient characteristics and concomitant medication on the response and adherence to type 2 diabetes treatments is well recognized[23], and these baseline differences should be considered when interpreting the current results on dulaglutide.




| All | Baseline | 1 month | 3 months | 6 months | 12 months | 18 months | 24 months | 36 months | LOCF |
|---|---|---|---|---|---|---|---|---|---|
| N | 2848 | 2354 | 2523 | 2312 | 2172 | 1866 | 1871 | 1658 | 2774 |

| HbA1c, % | All | <65 years | ≥65 to <75 years | ≥75 years |
|---|---|---|---|---|
| N | 2774 | 1390 | 773 | 611 |
| Baseline mean | 8.5 | 8.5 | 8.3 | 8.6 |
| Mean ± SD change from baseline (LOCF) | -0.76 ± 1.71 *** | -0.69 ± 1.74 *** | -0.70 ± 1.60 *** | -1.01 ± 1.75 *** |

| All | Baseline | 1 month | 3 months | 6 months | 12 months | 18 months | 24 months | 36 months | LOCF |
|---|---|---|---|---|---|---|---|---|---|
| N | 2714 | 2310 | 2339 | 2133 | 2000 | 1753 | 1695 | 1508 | 2620 |

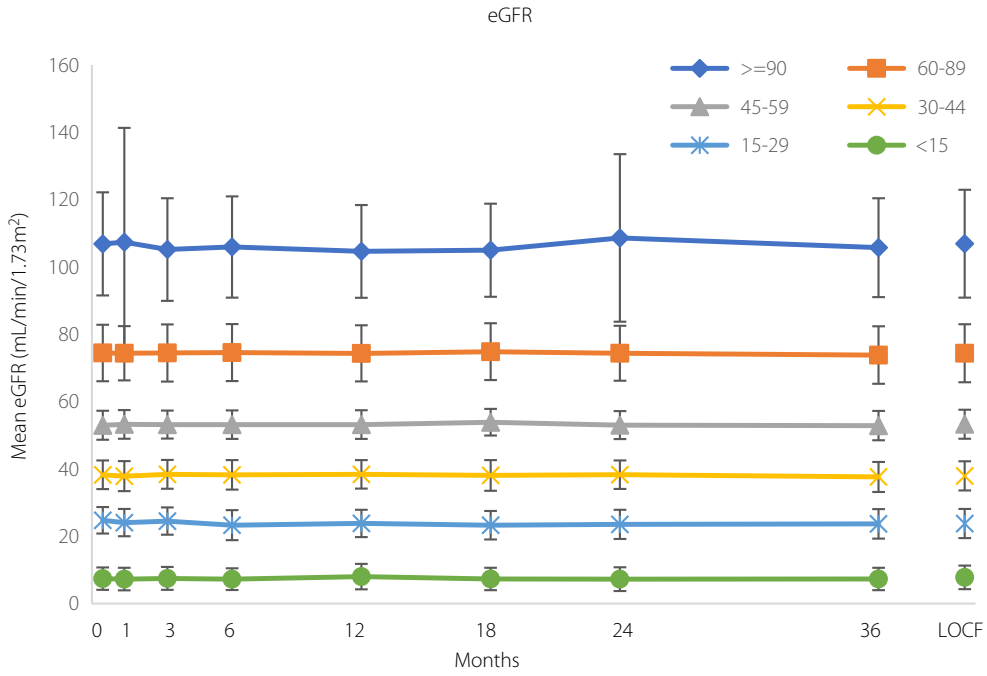
| Bodyweight, kg | All | <65 years | ≥65 to <75 years | ≥75 years |
|---|---|---|---|---|
| N | 2620 | 1328 | 727 | 565 |
| Baseline mean | 71.6 | 79.8 | 66.2 | 59.7 |
| Mean ± SD change from baseline (LOCF) | -1.6 ± 4.9 *** | -1.4 ± 5.0 *** | -1.5 ± 4.7 *** | -2.3 ± 4.6 *** |

**Figure 2** | HbA1c and bodyweight over time by age category (effectiveness population). (a) HbA1c, (b) bodyweight. Mean (SD) shown. HbA1c, glycated hemoglobin; LOCF, last observation carried forward; *N*, number in analysis population; SD, standard deviation. **P* < 0.05; ***P* < 0.01; ****P* < 0.001 by *t*-tests.

An important aspect of this study was the determination of real-world treatment persistence for dulaglutide up to 36 months, as treatment persistence beyond 12 months has not been well studied for GLP-1 RAs. In the overall population, the continuation rate for dulaglutide was 76.6% at 12 months and 58.0% at 36 months. These data are consistent with previous findings of high persistence rates with dulaglutide, which are significantly higher than those of other GLP-1 RAs[24]. Although methodology differences should be considered, treatment persistence for dulaglutide in the current study was also higher than all classes of oral antidiabetic medications at 12 (~ ≤ 60%) and 30 (~ ≤ 50%) months in a retrospective study of Japanese patients with type 2 diabetes using a real-world claims-based database[25]. In the current study, the total administration time for dulaglutide was slightly lower in the ≥75 years group compared with the other age groups, and the proportion of patients continuing treatment decreased more rapidly and to a greater degree in the ≥75 years group. Nevertheless, nearly 50% of patients aged ≥75 years continued treatment through 36 months, suggesting a significant proportion of Japanese patients, including elderly patients, could tolerate and continue to benefit from long-term dulaglutide use.

The safety profile of dulaglutide for Japanese patients in the real-world setting was generally manageable. The frequency of ADRs and SADRs increased with age. Gastrointestinal disorders were the most common ADRs reported in all age groups, and a higher incidence was associated with being female, age ≥65 years, bodyweight <70 kg, BMI <25 kg/m$^2$, and type 2 diabetes duration ≥10 years. These findings are in keeping with the literature on GLP-1 RAs, which indicates gastrointestinal events are common ADRs associated with this drug class[26]. Furthermore, a *post hoc* analysis of three Japanese phase 3 studies on dulaglutide 0.75 mg similarly found nausea to be significantly more common in patients who were female, of bodyweight <70 kg, and with type 2 diabetes duration ≥7 years and non-significantly more common for those ≥65 years old[22]. However, as there could be confounding occurring between these variables, it is difficult to specify which factors influenced the incidence of gastrointestinal ADRs. Current Japanese treatment guidelines for elderly patients with diabetes indicate GLP-1 RAs be used cautiously due to the potential for gastrointestinal ADRs and associated weight loss[27], and clinicians prescribing dulaglutide should carefully monitor elderly patients for these events.

The predefined important events of interest were rare. Of note, the four patients who experienced severe hypoglycemia also used concomitant insulin preparations and/or sulfonylureas, and prior clinical trials have indicated a low incidence of hypoglycemia with dulaglutide treatment, which is elevated by the concomitant use of insulin secretagogues or insulin




Patient numbers

| CKD category | Baseline | 1 month | 3 months | 6 months | 12 months | 18 months | 24 months | 36 months | LOCF |
|---|---|---|---|---|---|---|---|---|---|
| ≥90 | 458 | 379 | 378 | 360 | 336 | 271 | 262 | 227 | 479 |
| 60 -89 | 996 | 827 | 907 | 899 | 817 | 717 | 714 | 639 | 1220 |
| 45 -59 | 345 | 313 | 329 | 317 | 322 | 279 | 285 | 258 | 454 |
| 30 -44 | 196 | 185 | 195 | 195 | 165 | 165 | 149 | 129 | 243 |
| 15 -29 | 89 | 73 | 79 | 71 | 72 | 60 | 64 | 57 | 114 |
| <15 | 73 | 68 | 68 | 61 | 62 | 49 | 52 | 43 | 104 |

| eGFR mL/min/1.73m² | ≥90 | 60 -89 | 45 -59 | 30 -44 | 15 -29 | <15 |
|---|---|---|---|---|---|---|
| n | 359 | 952 | 349 | 193 | 100 | 88 |
| Mean ± SD change from baseline (LOCF) | 4.1 ± 19.7 *** | -3.0 ± 12.5 *** | -5.0 ± 11.5 *** | -5.7 ± 11.2 *** | -7.8 ± 10.6 *** | -4.7 ± 11.3 ** |

**Figure 3** | eGFR over time by CKD category (safety population). Mean (SD) shown. CKD categories correspond to the severity of renal impairment based on eGFR and were adapted from Japanese guidelines for management of CKD[21]. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LOCF, last observation carried forward; *n*, number of patients in category; SD, standard deviation. ** $P < 0.01$; *** $P < 0.001$ by *t*-tests.

preparations[13,28]. Of the patients experiencing MACE, three had relevant cardiovascular risk factors[18]. Of relevance, the REWIND trial reported a 12% relative risk reduction on 3-component MACE in patients with diabetes on dulaglutide 1.5 mg who had established cardiovascular disease or multiple cardiovascular risk factors[5]. Mean blood pressure was not clinically meaningfully changed in the current study, in accordance with the findings of prior dulaglutide 0.75 mg clinical trials in

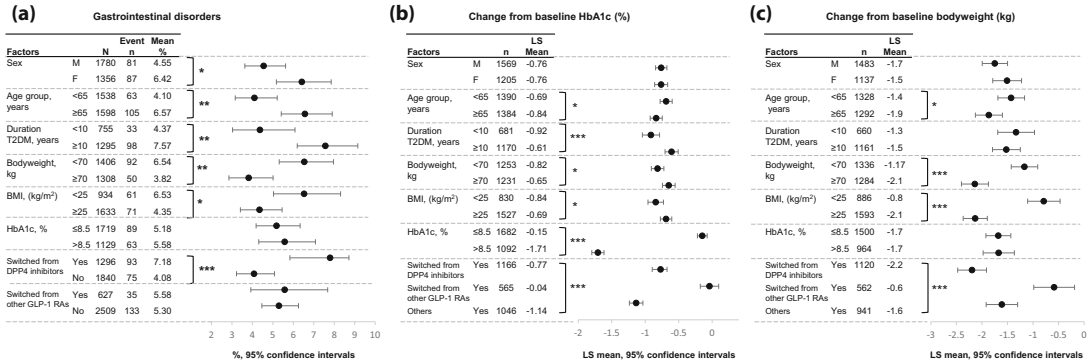



**Figure 4** | Analysis of results by baseline characteristics category. (a) Frequency of gastrointestinal disorders; (b) LS mean change from baseline (LOCF) in HbA1c; and (c) LS mean change from baseline (LOCF) in bodyweight. Means (95% confidence intervals) by baseline characteristic category are shown. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ by Fisher's exact test in (a) and by *t*-tests or ANOVA, as appropriate, in (b) and (c). ANOVA, analysis of variance; BMI, body mass index; DPP4, dipeptidylpeptidase-4, F, female; GLP-1 RA, glucagon like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; LOCF, last observation carried forward; LS, least squares; M, male; *N*, number in analysis population; *n*, number of events in (a) and number of patients with postbaseline data in (b) and (c); T2D, type 2 diabetes.

Japan[12–15]. Mean pulse rate was also not meaningfully changed in this study whereas pulse rate was elevated ~3 bpm in clinical studies[12–15].

The maximal mean reduction in eGFR was −3.4 at 36 months, with all eGFR categories showing little change in mean eGFR (i.e., ≤8 mL/min/1.73m$^2$), including patients in categories with the poorest renal function at baseline. These data are consistent with findings from the AWARD 7 trial, which showed higher eGFR following 52 weeks on dulaglutide 1.5 mg and 0.75 mg compared with insulin glargine in patients with diabetes and moderate-to-severe kidney disease[29]. Collectively, the data suggest dulaglutide is an appropriate therapeutic option for patients at risk for or with established CKD.

The current results indicate dulaglutide was effective in Japanese patients in the real-world setting. HbA1c and bodyweight were significantly decreased from baseline over 36 months, beginning at 1 month after starting dulaglutide, with similar trends observed across all age and prior treatment categories. An analysis of the baseline factors associated with dulaglutide effectiveness revealed patients aged ≥65 years generally showed larger reductions in both HbA1c and bodyweight compared with those aged <65 years. Additionally, larger reductions in HbA1c were associated with type 2 diabetes duration <10 years, baseline bodyweight <70 kg, baseline BMI <25 kg/m$^2$, and baseline HbA1c >8.5%. In contrast, larger reductions in bodyweight were associated with baseline bodyweight ≥70 kg and BMI ≥25 kg/m$^2$. Importantly, elderly patients with baseline BMI ≥25 kg/m$^2$ were confirmed to show substantially greater bodyweight loss than those with BMI <25 kg/m$^2$.

This study had several limitations. As a post-marketing surveillance study, the design was observational and lacked a control group. Furthermore, the differences noted in baseline characteristics and concomitant medication usage across age categories may have confounded interpretation of the outcomes. In addition, some baseline clinical data categories had missing data, which prevented multivariate analyses from being conducted and needs to be taken into consideration when interpreting the results of the factor analyses. Nevertheless, this study provides long-term safety data on dulaglutide in the real-world setting in Japan, including in elderly patients and those with poor renal function who were not well-represented in prior clinical studies.

## CONCLUSION

The safety and effectiveness profiles in this study in the real-world in Japan was in accordance with the results from clinical trials. The results of this study indicate elderly patients derive benefit from dulaglutide in terms of HbA1c reduction, and dulaglutide can safely be prescribed to this patient population, with consideration of potential gastrointestinal symptoms and reductions in bodyweight.

## DISCLOSURE

Nobuya Inagaki reports honoraria from Kyowa Kirin, MSD, Astellas Pharma, Novo Nordisk, Ono Pharmaceutical, Nippon Boehringer Ingelheim, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma, Sumitomo Pharma, Sanofi, and Eli Lilly Japan; research funding from Terumo, Drawbridge, and Asken; and subsidies/donations from Kissei Pharmaceutical, Sanofi, Daiichi-Sankyo, Mitsubishi Tanabe Pharma, Takeda Pharmaceutical, Japan Tobacco, Kyowa Kirin, Sumitomo Pharma, Astellas Pharma, MSD, Ono Pharmaceutical, Sanwa Kagaku

Kenkyusho, Nippon Boehringer Ingelheim, Novo Nordisk, Kowa, Novartis, and LifeScan Japan.
Rina Chin, Soshi Nagaoka, Haru Nakasawa, and Yoko Tanaka are employees of Eli Lilly Japan and minor shareholders of Eli Lilly and Company.

## ACKNOWLEDGMENTS

Medical writing (Kaye Stenvers) and editing (Dana Schamberger) were provided by Syneos Health and funded by Eli Lilly Japan.

## ETHICS STATEMENT

Research protocol approval: N/A.
Informed consent: Not required in accordance with the Ministry of Health, Labour and Welfare ordinance on Good Postmarketing Study Practice.
Registry approval date and number: N/A.
Animal studies: N/A.

## FUNDING INFORMATION

This study was funded by Eli Lilly Japan.

## REFERENCES

1. Ministry of Health Labour and Welfare. National nutrition survey: Ministry of Health, Labour and Welfare 2019 (Japanese).
2. Kohsaka S, Morita N, Okami S, *et al*. Current trends in diabetes mellitus database research in Japan. *Diabetes Obes Metab* 2021; 23(Suppl 2): 3–18.
3. Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: Physiology, pathophysiology, and response to therapeutic interventions. *Lancet Diabetes Endocrinol* 2016; 4: 525–536.
4. Gerstein HC, Colhoun HM, Dagenais GR, *et al*. Dulaglutide and renal outcomes in type 2 diabetes: An exploratory analysis of the REWIND randomised, placebocontrolled trial. *Lancet* 2019; 394: 131–138.
5. Gerstein HC, Colhoun HM, Dagenais GR, *et al*. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double-blind, randomised placebocontrolled trial. *Lancet* 2019; 394: 10193.
6. Gorriz JL, Romera I, Cobo A, *et al*. Glucagon-like peptide-1 receptor agonist use in people living with type 2 diabetes mellitus and chronic kidney disease: A narrative review of the key evidence with practical considerations. *Diabetes Ther* 2022; 13: 389–421.
7. Mann JFE, Fonseca V, Mosenzon O, *et al*. Effects of liraglutide versus placebo on cardiovascular events in patients with type 2 diabetes mellitus and chronic kidney disease. *Circulation* 2018; 138: 2908–2918.
8. Marso SP, Bain SC, Consoli A, *et al*. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; 375: 1834–1844.
9. Marso SP, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; 375: 311–322.
10. Shaman AM, Bain SC, Bakris GL, *et al*. Effect of the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide on kidney outcomes in patients with type 2 diabetes: Pooled analysis of SUSTAIN 6 and LEADER. *Circulation* 2022; 145: 575–585.
11. Glaesner W, Vick AM, Millican R, *et al*. Engineering and characterization of the long-acting glucagon-like peptide-1 analogue LY2189265, an fc fusion protein. *Diabetes Metab Res Rev* 2010; 26: 287–296.
12. Araki E, Inagaki N, Tanizawa Y, *et al*. Efficacy and safety of once-weekly dulaglutide in combination with sulphonylurea and/or biguanide compared with once-daily insulin glargine in Japanese patients with type 2 diabetes: A randomized, open-label, phase III, non-inferiority study. *Diabetes Obes Metab* 2015; 17: 994–1002.
13. Emoto M, Terauchi Y, Ozeki A, *et al*. A 1-year safety study of dulaglutide in Japanese patients with type 2 diabetes on a single oral hypoglycemic agent: An open-label, nonrandomized, phase 3 trial. *Endocr J* 2015; 62: 1101–1114.
14. Miyagawa J, Odawara M, Takamura T, *et al*. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide is non-inferior to once-daily liraglutide and superior to placebo in Japanese patients with type 2 diabetes: A 26-week randomized phase III study. *Diabetes Obes Metab* 2015; 17: 974–983.
15. Odawara M, Miyagawa J, Iwamoto N, *et al*. Once-weekly glucagon-like peptide-1 receptor agonist dulaglutide significantly decreases glycated haemoglobin compared with once-daily liraglutide in Japanese patients with type 2 diabetes: 52 weeks of treatment in a randomized phase III study. *Diabetes Obes Metab* 2016; 18: 249–257.
16. Taki K, Tsujimoto N, Kobayashi M, *et al*. The safety of dulaglutide 0.75 mg in patients with type 2 diabetes mellitus as assessed in initial analyses from a post marketing safety study in Japan. *Prog Med* 2018; 38: 629–641 (Japanese).
17. Eli Lilly Japan K.K.: Risk Management Plan (RMP) for Trulicity®, subcutaneous injection 0.75mg. ATEOS'.
18. Chin R, Nagaoka S, Kobayashi M, *et al*. Safety and effectiveness of dulaglutide 0.75 mg in Japanese patients with type 2 diabetes mellitus - an interim analysis from post-marketing surveillance. *Japanese Pharmacology and Treatment* 2021; 49: 875–888 (Japanese).
19. Good Post-marketing Study Practice (GPSP Ordinance) (Ministry of Health, Labour and Welfare Ordinance No. 171, dated December 20, 2004).
20. Seaquist ER, Anderson J, Childs B, *et al*. Hypoglycemia and diabetes: A report of a workgroup of the American Diabetes Association and the Endocrine Society. *Diabetes Care* 2013; 36: 1384–1395.

21. Japanese Society of Nephrology. Evidence-Based Clinical Practice Guideline for CKD 2013. Tokyo: Tokyo Igakusha. Ltd, 2013.
22. Onishi Y, Oura T, Nishiyama H, *et al*. Subgroup analysis of phase 3 studies of dulaglutide in Japanese patients with type 2 diabetes. *Endocr J* 2016; 63: 263–273.
23. Wibowo M, Yasin NM, Kristina SA, *et al*. Exploring of determinants factors of antidiabetic medication adherence in several regions of Asia - a systematic review. *Patient Prefer Adherence* 2022; 16: 197–215.
24. Lee DSU, Lee H. Adherence and persistence rates of major antidiabetic medications: A review. *Diabetol Metab Syndr* 2022; 14: 12.
25. Kadowaki T, Sarai N, Hirakawa T, *et al*. Persistence of oral antidiabetic treatment for type 2 diabetes characterized by drug class, patient characteristics and severity of renal impairment: A Japanese database analysis. *Diabetes Obes Metab* 2018; 20: 2830–2839.
26. Bettge K, Kahle M, Abd El Aziz MS, *et al*. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: A systematic analysis of published clinical trials. *Diabetes Obes Metab* 2017; 19: 336–347.
27. Japan Geriatrics Society/Japan Diabetes Society (Eds): Practice Guideline for the Treatment for Elderly Diabetes in Japan 2017. Tokyo: Nankodo Co., Ltd, (Japanese), 2017.
28. Ishii H, Onishi Y, Oura T, *et al*. Once-weekly dulaglutide with insulin therapy for type 2 diabetes: Efficacy and safety results from a phase 4, randomized, placebocontrolled study. *Diabetes Ther* 2020; 11: 133–145.
29. Tuttle KR, Lakshmanan MC, Rayner B, *et al*. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): A multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018; 6: 605–617.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** | Demographics and baseline characteristics by prior treatment category (safety population)

**Table S2** | Concomitant medication by prior treatment category (safety population)

**Table S3** | Adverse drug reactions and serious adverse drug reactions by system organ class (safety population)

**Table S4** | Safety summary by prior treatment category (safety population)

**Table S5** | Change from baseline in selected clinical and laboratory results

**Table S6** | Weight loss by baseline body mass index (effectiveness population)

**Table S7** | Cross table of patient numbers within body mass index categories at baseline and LOCF by age group (effectiveness population)

**Figure S1** | Patient disposition. AE, adverse event; eCRF, electronic case report form; *N*, number in analysis population; T2D, type 2 diabetes.

**Figure S2** | HbA1c and bodyweight over time by prior treatment category (effectiveness population). (a) HbA1c; (b) bodyweight. Mean (SD) shown. DPP4, dipeptidylpeptidase-4; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; LOCF, last observation carried forward; *N*, number in analysis population; SD, standard deviation. $^{**}P < 0.01$; $^{***}P < 0.001$ by *t*-test.

COVID-19 impact statement.