INCRETIN-BASED therapies (glucagon-like peptide-1 [GLP-1] receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) are used for the treatment of type 2 diabetes (T2D). The potential risk of pancreatitis with these therapies is currently being evaluated. Patients who met any of the predefined criteria (clinical signs/symptoms of acute pancreatitis, confirmed amylase or lipase level ≥3 times the upper limit of normal [ULN], abdominal imaging of the pancreas) were adjudicated for acute pancreatitis by a blinded external committee. A total of 43 events in 40 patients (dulaglutide, 35/917 patients; liraglutide, 2/137 patients; insulin glargine, 2/180 patients; and placebo, 2/70 patients) were adjudicated (1 patient had events adjudicated during both placebo and dulaglutide treatment); 2 patients treated with dulaglutide had acute pancreatitis confirmed (2/917 [0.2%]; 2.651 patients/1,000 patient-years). One of these patients was diagnosed by the investigator with acute pancreatitis related to dulaglutide, but there was no typical abdominal pain. The event in the other patient occurred following an endoscopic ultrasound-guided fine needle aspiration. Transient increases in lipase ≥3×ULN were observed in 2% of patients in both the dulaglutide and liraglutide groups; the incidence in dulaglutide-treated patients was not significantly different from the incidences in liraglutide, placebo-, or insulin glargine-treated patients. Results of systematic assessments of pancreatic safety in 3 phase 3 studies for up to 52 weeks do not suggest an increased risk of acute pancreatitis in Japanese patients treated with dulaglutide.
Design of studies
This analysis combines data from 3 phase 3 studies of once weekly dulaglutide 0.75 mg (dulaglutide) in Japanese patients with T2D: a 52-week study (primary endpoint at 26 weeks), referred to here as “the monotherapy study” [24, 25]; a 26-week study, referred to here as “the combination study” [26], and a 52-week study, referred to here as “the safety study” [27] (Table 1). All 3 studies were registered with ClinicalTrials.gov (NCT01558271, NCT01584232, NCT01468181).

For each of the studies a common protocol was approved at each site by an institutional review board, and the studies were performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice [24-27]. All patients provided written informed consent before participation.

Patient population
All 3 studies enrolled Japanese men and women with T2D, aged ≥20 years, with a body mass index (BMI) ≥18.5 and <35.0 kg/m². The monotherapy study and the combination study enrolled patients with glycated hemoglobin (HbA1c) ≥7.0 and ≤10.0% (confirmed at randomization in the monotherapy study and measured at screening in the combination study); the safety study enrolled patients with HbA1c at screening ≥7.0 and ≤11.0%. Patients with a medical history of acute or chronic pancreatitis, as assessed by the investigators, were excluded from all of the studies. Key inclusion and exclusion criteria for each of the studies are presented in the primary manuscripts [24, 26, 27].

Evaluation of pancreatic events of interest
In each of the 3 study protocols, blinded adjudication by a committee independent of the sponsor was specified for patients with any of the following pancreatic events of interest: a) severe or serious abdominal pain for which there was no associated diagnosis, or the occurrence of other clinical signs/symptoms suggestive of acute pancreatitis; b) confirmed elevation in amylase and/or lipase ≥3×upper limit of normal [ULN]; c) abdominal imaging (computerized tomography [CT] or magnetic resonance imaging [MRI]) performed.

Events of interest were submitted for adjudication to the Duke Clinical Research Institute Clinical Event Classification Group (CEC; Duke Clinical Research Institute, North Carolina, USA), which was comprised

Materials and Methods


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Events of interest were submitted for adjudication to the Duke Clinical Research Institute Clinical Event Classification Group (CEC; Duke Clinical Research Institute, North Carolina, USA), which was comprised
of board-certified physicians with expertise in the field of gastroenterology and prior CEC experience. In all 3 Japanese studies, as in the global dulaglutide clinical development program, 2 of the following 3 criteria were required for confirmation of acute pancreatitis upon adjudication: (a) abdominal pain, (b) serum amylase and/or lipase ≥3×ULN, and (c) characteristic findings of acute pancreatitis on CT scan or MRI.

**Evaluation of pancreatic enzymes**

In addition to detailed evaluation of pancreatic symptoms, serial pancreatic enzyme measurements were performed during the studies to detect cases of asymptomatic, clinically relevant increases from baseline. Lipase and total amylase were collected in all 3 studies; pancreatic amylase was collected only in the safety study. Measurements were performed at screening, baseline, during treatment (weeks 14, 26, 38, and 52 depending on study duration), and at the end-of-treatment and safety follow-up (approximately 4 weeks after cessation of treatment) visits. In the safety study, measurements were also performed at weeks 4, 8, and 20. Blood samples for all patients were analyzed at a central laboratory (Quintiles Laboratories Europe, West Lothian, United Kingdom); for expeditious evaluation of patients’ clinical conditions, confirmatory tests of elevated values may have been performed at a local laboratory. Normal laboratory ranges used as reference limits by the central laboratory were 0-60 U/L for lipase, 20-112 U/L for total amylase, and 13-53 U/L for pancreatic amylase.

**Statistical analysis**

All pancreatic events of interest occurring at any time during the studies, including events observed at the safety follow-up visit, are reported here; confirmed and non-confirmed (as determined by adjudication) events are presented separately. Exposure-adjusted rates (per 1,000 patient-years of study drug exposure) were computed.

Pancreatic enzyme measurements analyzed by a central laboratory were plotted over time for individual patients from all 3 studies. For the evaluations of changes from baseline and incidence of elevations in pancreatic enzymes, only data from the 2 randomized, controlled studies were included because of the differences in study designs between those studies and the safety study, which was nonrandomized and non-controlled and had more frequent pancreatic enzyme measurements. Proportions of patients with abnormal pancreatic enzymes (thresholds >1×ULN and/or ≥3×ULN) were summarized for each treatment group at baseline and during the treatment period; Fisher’s
exact test was used to conduct pairwise comparisons between the treatment groups. Analysis of variance using rank-transformed data was used to conduct pairwise comparisons between the treatments for changes from baseline in pancreatic enzymes.

Results

Patients

Overall, 917 patients received at least 1 dose of dulaglutide (754 total patient-years exposure): 855 patients received dulaglutide for up to 26 or 52 weeks from the beginning of the treatment period, and 62 patients in the monotherapy study received placebo for 26 weeks followed by dulaglutide for up to 26 weeks (Table 2). A total of 387 patients received active comparators or placebo (liraglutide [up to 52 weeks per patient], 137 [127 patient-years]; insulin glargine [up to 26 weeks per patient], 180 [89 patient-years]; placebo [up to 26 weeks per patient], 70 [32 patient-years]).

Patient baseline characteristics, including proportions of patients with risk factors for acute pancreatitis (alcohol use, dyslipidemia, cholelithiasis), were similar between the groups (Table 2).

Adjudicated events of pancreatitis

A total of 43 events in 40 patients (dulaglutide, 35/917 patients; liraglutide, 2/137 patients; insulin glargine, 2/180 patients; and placebo, 2/70 patients) were adjudicated by the CEC (Table 3). Three patients each had 2 events adjudicated: 2 patients receiving dulaglutide and 1 patient who was adjudicated while receiving placebo and again while receiving dulaglutide. The majority of events were sent for adjudication because the patients had pancreatic imaging performed (with or without symptoms) and/or confirmed asymptomatic pancreatic enzyme increases; one of the events (in the safety study) was reported by the investigator as a treatment-emergent adverse event of acute pancreatitis related to dulaglutide.

No cases were identified by the committee as having insufficient information for adjudication. Out of the 43 events adjudicated, 41 were determined not to be pancreatitis; 2 events, both in patients in the dulaglutide and sulfonylurea combination group in the safety study, were confirmed as acute pancreatitis after adjudication (2/917 [0.2%], 2.651 patients/1,000 patient-years). One of the events was in a 45-year-old male, reported by the investigator as drug-induced acute pancreatitis related to treatment with dulaglutide; the patient had no typical abdominal pain. The other was an event in a 73-year-old female, considered iatrogenic (due to the procedure of examination for pancreatic tumors, which resulted in pancreatic amylase and lipase levels of 1,035 IU/L and 3,157 U/L, respectively [measured at a local laboratory]). Both of these cases are presented in more detail in Table 4.

Table 2  Baseline characteristics by treatment in 3 studies

|               | Dulaglutide 0.75 mg N=855 a | Liraglutide 0.9 mg N=137 b | Insulin glargine N=180 c | Placebo N=70 b, d |
|---------------|-----------------------------|---------------------------|--------------------------|------------------|
| Sex           |                             |                           |                          |                  |
| Male, n (%)   | 649 (76)                    | 113 (83)                  | 133 (74)                 | 55 (79)          |
| Female, n (%) | 206 (24)                    | 24 (18)                   | 47 (26)                  | 15 (21)          |
| Age, years    | 57.3 (10.4)                 | 57.9 (10.4)               | 56.1 (11.3)              | 57.7 (8.3)       |
| Body weight, kg| 71.3 (13.1)                 | 70.2 (12.5)               | 71.1 (13.8)              | 69.3 (11.6)      |
| Body mass index, kg/m² | 25.9 (3.6)   | 25.5 (3.5)               | 25.9 (3.9)               | 25.2 (3.2)       |
| HbA1c, %      | 8.3 (1.0)                   | 8.1 (0.9)                 | 8.0 (0.9)                | 8.2 (0.8)        |
| Duration of diabetes, years | 7.6 (6.2) | 6.3 (6.0)               | 8.8 (6.1)                | 6.3 (5.1)        |
| Alcohol intake, n (%) | 223 (48.4) e | 67 (48.9)               | 95 (52.8)                | 36 (51.4)        |
| Dyslipidemia, n (%) f | 556 (65.0) | 89 (65.0)               | 108 (60.0)               | 43 (61.4)        |
| Cholelithiasis, n (%) | 15 (1.8)   | 7 (5.1)                 | 3 (1.7)                  | 2 (2.9)          |

HbA1c, glycated hemoglobin; MedDRA, Medical Dictionary for Regulatory Activities; SD, standard deviation. Data are mean (SD) unless otherwise stated. a Patients treated in any of the 3 studies (monotherapy study [only patients randomized to dulaglutide], combination study, safety study). b Patients treated in the monotherapy study. c Patients treated in the combination study. d After the 26-week placebo administration period, 62 of these patients received treatment with dulaglutide 0.75 mg for up to 26 weeks. e Data available from monotherapy study and combination study only (total n for dulaglutide=461). f Patients with pre-existing condition (MedDRA [v16.1] preferred term of dyslipidemia or hyperlipidemia).
Pancreatic enzyme profiles through 26 weeks of treatment in 2 randomized, controlled studies

After taking the different designs of the 3 Japanese phase 3 studies into consideration, pancreatic enzyme profiles through 26 weeks of treatment were evaluated across the 4 treatment groups using pooled data from the 2 randomized, controlled studies: the combination study and the first 26 weeks of the monotherapy study (Table 5 and Table 6). Median baseline values were similar across the 4 treatments for both enzymes across the 2 studies. Serum total amylase and lipase were significantly increased in the dulaglutide and liraglutide groups compared to the insulin glargine and placebo groups after 26 weeks ($p<0.002$) (Table 5). Further, lipase was significantly increased in the liraglutide group compared to the dulaglutide group ($p<0.001$).
### Table 5 Summary of pancreatic enzymes at baseline and week 26 (LOCF) in 2 randomized, controlled studies

| Treatment                  | Total amylase (U/L) | Lipase (U/L) |
|----------------------------|---------------------|--------------|
|                            | Median (IQR)        | Median (IQR) |
| **Baseline**               |                     |              |
| Dulaglutide 0.75 mg        | 58.0 (46.0, 71.0)   | 33.0 (26.0, 41.0) |
| Liraglutide 0.9 mg         | 62.0 (47.0, 77.0)   | 33.0 (27.0, 42.0) |
| Insulin glargine           | 60.0 (49.5, 78.0)   | 34.0 (27.0, 44.0) |
| Placebo                    | 55.0 (41.0, 69.0)   | 32.0 (26.0, 43.0) |
| **Change from baseline at 26 weeks (LOCF)** |                     |              |
| Dulaglutide 0.75 mg        | 7.0 (2.0, 15.0)     | 7.0 (1.0, 15.0) |
| Liraglutide 0.9 mg         | 7.0 (1.0, 15.0)     | 11.0 (5.0, 21.0) |
| Insulin glargine           | 3.0 (-2.0, 9.0)     | -1.0 (-6.0, 3.0) |
| Placebo                    | 0.0 (-6.0, 6.0)     | 1.0 (-6.0, 5.0) |

#### Pairwise p-value

- vs. dulaglutide 0.75 mg: N/A 0.353 <0.001 <0.001
- vs. liraglutide 0.9 mg: 0.353 N/A 0.002 <0.001

Includes data from the monotherapy study and the combination study. IQR, interquartile range; LOCF, last observation carried forward; N/A, not applicable. a Number of patients randomized and treated. b p-values are from analysis of variance on rank-transformed data, Model: Change = Treatment.

### Table 6 Summary of patients with abnormally elevated postbaseline pancreatic enzymes through 26 weeks in 2 randomized, controlled studies

| Treatment                  | Total amylase | Lipase |
|----------------------------|---------------|--------|
|                            | n/N (%)       | n/N (%)|
| **Total amylase**          |               |        |
| Patients with enzyme >1×ULN at baseline | 24/461 (5.2) | 66/461 (14.3) |
| Patients with enzyme >1×ULN postbaseline through 26 weeks on treatment b | 39/450 (8.7) | 122/450 (27.1) |
| Pairwise p-value vs. dulaglutide 0.75 mg c | N/A | N/A |
| Pairwise p-value vs. liraglutide 0.9 mg c | 0.861 | 0.124 |
| Patients with treatment-emergent enzyme >1×ULN postbaseline through 26 weeks on treatment d | 25/430 (5.8) | 88/410 (21.5) |
| Pairwise p-value vs. dulaglutide 0.75 mg c | N/A | N/A |
| Pairwise p-value vs. liraglutide 0.9 mg c | 0.830 | 0.067 |
| Patients with enzyme ≥3×ULN postbaseline through 26 weeks on treatment b | 0/450 (0.0) | 10/450 (2.2) |
| Pairwise p-value vs. dulaglutide 0.75 mg c | N/A | N/A |
| Pairwise p-value vs. liraglutide 0.9 mg c | N/A | 1.000 |
| **Patients with enzyme >1×ULN at baseline** | 66/461 (14.3) | 17/137 (12.4) |
| Patients with enzyme >1×ULN postbaseline through 26 weeks on treatment b | 122/450 (27.1) | 45/131 (34.4) |
| Pairwise p-value vs. dulaglutide 0.75 mg c | N/A | N/A |
| Pairwise p-value vs. liraglutide 0.9 mg c | 0.124 | 0.067 |
| Patients with treatment-emergent enzyme >1×ULN postbaseline through 26 weeks on treatment d | 88/410 (21.5) | 36/121 (29.8) |
| Pairwise p-value vs. dulaglutide 0.75 mg c | N/A | N/A |
| Pairwise p-value vs. liraglutide 0.9 mg c | 0.067 | 0.067 |
| Patients with enzyme ≥3×ULN postbaseline through 26 weeks on treatment b | 10/450 (2.2) | 2/131 (1.5) |
| Pairwise p-value vs. dulaglutide 0.75 mg c | N/A | N/A |
| Pairwise p-value vs. liraglutide 0.9 mg c | 1.000 | 1.000 |

Includes data from the monotherapy study and the combination study. n, number of patients in category; N/A, not applicable; ULN, upper limit of normal. a Number of patients randomized and treated. b Denominator is number of patients who had at least 1 postbaseline value. c p-values are from Fisher’s exact test. d Denominator is number of patients who had a normal value at baseline and at least 1 postbaseline value.
Fig. 1 and Fig. 2 plot total amylase and lipase values, respectively, over time for individual patients with a total amylase or lipase value, respectively, ≥3×ULN by treatment and study for all 3 studies (no patients who received liraglutide in the monotherapy study and no patients in the combination study had total amylase ≥3×ULN). Supplemental Fig. 1 and Supplemental Fig. 2 plot total amylase and lipase values, respectively, over time for individual patients by treatment and study for all 3 studies.

There were no significant differences between dulaglutide or liraglutide and insulin glargine or placebo in the proportions of patients (<10%) who had total amylase >1×ULN (overall or treatment-emergent) (Table 6). Significantly greater proportions of patients in the dulaglutide and liraglutide groups (21.5 to 34.4%) had lipase levels >1×ULN compared to the insulin glargine and placebo groups (3.6 to 9.5%; p<0.001). Across both studies, total amylase levels ≥3×ULN were observed in the placebo group only (1.5% of patients). There were no significant differences in the proportions of patients who had lipase levels ≥3×ULN between the dulaglutide (2.2%) or liraglutide (1.5%) and insulin glargine (0.6%) or placebo (0.0%) groups.

Total amylase and lipase values ≥3×ULN in patients treated with dulaglutide (across all 3 studies) or liraglutide (in the monotherapy study) were generally confirmed as resolved based on repeated collection of pancreatic enzymes during continued treatment (Fig. 1 and Fig. 2) and were thus considered transient overall. Similar transient increases in pancreatic amylase were observed through 52 weeks of treatment with dulaglutide in the safety study, as shown in Fig. 3 (all patients with any value ≥3×ULN) and Supplemental Fig. 3 (all patients). There were 3 exceptions to transient enzyme elevations ≥3×ULN among dulaglutide-treated patients. Two of the patients had no clinical observations related to pancreatitis during the study (Supplemental Table 1, Fig. 1 and Fig. 3) and the third had elevations related to pancreatic cancer (Table 7 and Fig. 2A).

Pancreatic enzyme profiles based on data from all 3 studies (data not shown) appeared consistent with the profiles presented in Table 5 and Table 6 based on data from the 2 randomized, controlled studies.
Fig. 2  Lipase values (U/L) from central laboratory over time in patients with lipase ≥3×ULN at any time (includes all values from screening through 4-week safety follow-up visit off study drug)

(A) Monotherapy study (B) Combination study (C) Safety study.

Lower dotted line, ULN, upper dotted line, 3×ULN. Dark bar on x-axis: treatment period (weeks 0-26)/(weeks 0-52). DU 0.75 mg, once weekly dulaglutide 0.75 mg. LIRA 0.9 mg, once daily liraglutide 0.9 mg. ULN, upper limit of normal. * Plac/DU 0.75 mg, placebo for 26 weeks followed by dulaglutide 0.75 mg for 26 weeks. ** All patients were also receiving 1 oral hypoglycemic agent.
**Cases of pancreatic carcinoma**

Two patients (one dulaglutide-treated patient and one liraglutide-treated patient, both in the monotherapy study) were diagnosed with pancreatic carcinoma; the case in the dulaglutide group was considered related to study drug by the investigator, while the case in the liraglutide group was considered not related to study drug (Table 7).

**Discussion**

Systematic assessments of pancreatic safety in 3 phase 3 studies up to 52 weeks in duration were conducted in Japanese patients treated with dulaglutide. The incidence of acute pancreatitis (confirmed by adjudication by an independent committee) in Japanese patients treated with dulaglutide was very low (2/917 patients). Increases from baseline in amylase and lipase were observed in patients treated with dulaglutide or liraglutide in the Japan studies, consistent with previous studies of dulaglutide and other GLP-1 receptor agonists [14-17]. One case of pancreatic carcinoma, considered treatment-related by the investigator, was observed in a dulaglutide-treated patient in the phase 3 studies in Japan (overall incidence 1/917 patients).

The comprehensive strategy used to assess pancreatic safety in these prospective studies of dulaglutide provides important data for the management of patients with T2D in Japan. This strategy included serial assessment of pancreatic enzymes through up to 52 weeks of treatment as well as assessments for up to 4 weeks after the end of study treatment. It also included the use of an independent, blinded committee to adjudicate cases of increased pancreatic enzymes or pancreatic-related symptoms.

Out of 43 pancreatic events in 40 patients adjudicated by the CEC, 2 were confirmed as acute pancreatitis (0.2%; 2.651 patients/1,000 patient-years); both patients had been treated with dulaglutide and sulfonylurea in the safety study. One of the cases was considered related to treatment with dulaglutide by the investigator; the other was considered to be iatrogenic, due to the procedure of examination for pancreatic tumors. The exposure-adjusted incidence rate of acute pancreatitis in dulaglutide-treated patients with T2D in the 3 Japanese phase 3 studies was
2.651 patients/1,000 patient-years; the reported incidence in an observational study in Japanese patients with T2D was 4.75 patients/1,000 patient-years [13]. Rates of acute pancreatitis reported in observational studies in patients with T2D in other countries include the following: Taiwan: 2.77 patients/1,000 patient-years [28]; Canada, United States, and the United Kingdom: 1.49 patients/1,000 patient-years [29]. The exposure-adjusted incidence rates of acute pancreatitis in patients treated with liraglutide or exenatide have been reported as 1.6 cases and 5.7 cases/1,000 patient-years, respectively [5, 7].

In global phase 3 studies of incretin-based therapies, including dulaglutide, amylase and lipase have been assessed together, and increases in both have been observed with GLP-1 receptor agonists (dulaglutide, liraglutide, and exenatide) and DPP-4 inhibitors (sitagliptin) [15, 17, 23]. Few clinical trials of GLP-1 receptor agonists in Asian patients with T2D have assessed both amylase and lipase; in a study of liraglutide in Japan, small median increases in amylase and lipase within normal limits were observed with liraglutide treatment [14]. In our analysis using pooled data from 26 weeks of treatment in 2 randomized, controlled phase 3 dulaglutide studies in Japan, in the dulaglutide and liraglutide groups, significantly greater increases from baseline in both serum total amylase and lipase were observed compared to the insulin glargine and placebo groups; further, lipase was significantly increased in the liraglutide group compared to the dulaglutide group (Table 5). Also, significantly greater proportions of patients in the dulaglutide and liraglutide groups had elevated serum lipase (>1×ULN) compared to the insulin glargine and placebo groups (Table 6). In both the dulaglutide and liraglutide groups, the proportions of patients with elevated lipase were greater than the proportions with elevated amylase; this may have been due to the fact that while lipase is secreted primarily by the pancreas, less than half of amylase is secreted by the pancreas.

Table 7 Listing of pancreatic carcinoma cases in 3 studies

| Pat | Study | Patient characteristics | Event start day * | Diagnostic criteria | Risk factors |
|-----|-------|-------------------------|-------------------|---------------------|-------------|
|     | Trt   | Sex Age BMI | Diab dur |             |             |
| 1   | Mono  | M 65 23.1 5.0 393 |         | At the follow-up visit on Day 393 (approximately 1 month after completion of 52 weeks of study treatment), blood test results indicated increased total amylase and lipase levels (232 U/L [>2×ULN] and 748 U/L [>12×ULN], respectively), and on Day 418 he was diagnosed with pancreatic cancer (a pancreas tumor). On Day 464, pancreaticoduodenectomy was performed, and he was diagnosed with cancer of the head of the pancreas. On Day 645, the investigator stated that the patient was not recovered. The investigator determined that the event was related to study drug. | Tobacco use, Alcohol use, Diabetes |
| 2   | Mono  | F 67 23.5 0.1 106 | The patient received treatment for approximately 15 weeks. At the 15-week visit, weight loss was noted despite no impaired appetite, so abdominal ultrasonography and tumour marker measurements were performed to exclude malignant disease. On Day 108, endoscopy was performed. A submucosal tumor of the duodenum was diagnosed, along with chronic and acute gastritis and polyp and adenoma of the descending colon. On Day 135, as a result of endoscopic retrograde cholangiopancreatography and pancreatic juice cytology, the patient was diagnosed with adenocarcinoma. As of Day 223, the investigator stated that the patient was not recovered. The investigator considered the event not related to study drug. | Diabetes |

BMI, body mass index; Diab dur, duration of diabetes; F, female; Lira, once daily liraglutide 0.9 mg; M, male; Mono, 52-week monotherapy study; Pat, patient; Plac/DU, placebo for 26 weeks followed by dulaglutide 0.75 mg for 26 weeks; Trt, treatment; ULN, upper limit of normal. * Relative to first day of treatment.
While this analysis presents results through 26 weeks of treatment with dulaglutide, median changes from baseline and proportions of patients with abnormal elevations in total amylase and lipase (≥1×ULN and ≥3×ULN) through 52 weeks of treatment were previously reported for patients randomized to dulaglutide or liraglutide in the monotherapy study [25] and for the 5 combination therapy groups in the safety study [27]. These results were similar to those reported here through 26 weeks. There were no clear trends in the timing of onset of increased pancreatic enzymes after initiation of dulaglutide treatment or in the duration of elevations during treatment. In the majority of cases, the increases in enzymes did not last long, and the values spontaneously decreased while dulaglutide treatment continued (Fig. 1 through Fig. 3, Supplemental Fig. 1 through Supplemental Fig. 3). In addition, no consistent clinical signs or symptoms related to these changes in enzymes were observed.

These studies were not designed to detect the mechanism behind the increased pancreatic enzymes observed with dulaglutide treatment. However, no immediate cause was apparent, and there seem to be several possible clinical explanations. For instance, the increases may have resulted directly, from the receptor-mediated effect of dulaglutide, or indirectly, due to alterations in food intake or to GLP-1-mediated stimulation of the vagal nerve [30] or components of the enteric endocrine system such as cholecystokinin [31], both of which may have increased secretion of pancreatic enzymes during treatment [32, 33].

Other limitations of this analysis included the sample size (approximately 900 patients) and length of the treatment periods (maximum 52 weeks), which were insufficient to accurately assess long-term effects of dulaglutide on the pancreas. Further, patients with a history of pancreatitis were excluded from the studies. As stated earlier, the incidence of acute pancreatitis is generally low, even in patients with T2D, so a large sample size and long exposure period in clinical and pharmaco-epidemiological studies will be required to appropriately estimate the risk of pancreatitis and monitor other effects of GLP-1 receptor agonist treatment on the pancreas in humans. A multinational cardiovascular outcomes study in which approximately 5,000 patients are expected to have approximately 6.5 years of exposure to dulaglutide each is currently ongoing and will provide substantial additional information [34].

In conclusion, in 3 studies of once weekly dulaglutide 0.75 mg in Japanese patients with T2D treated for up to 52 weeks, transient increases in pancreatic enzymes (≥3×ULN) were observed, and 2/917 (0.2%) dulaglutide-treated patients were confirmed with acute pancreatitis after adjudication; one of the cases was considered related to dulaglutide by the investigator. Results of systematic assessments of pancreatic safety in 3 phase 3 studies up to 52 weeks in duration do not suggest an increased risk of acute pancreatitis in Japanese patients treated with dulaglutide. It appears that routine repeated measurements of pancreatic enzymes in asymptomatic patients with T2D treated with GLP-1 receptor agonists such as dulaglutide have limited clinical value for predicting cases of acute pancreatitis.

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Declaration of Interest

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Author Contributions

M.E. was a trial investigator and participated in data collection. T.O., A.M., H.K., and N.I. prepared the first draft of the manuscript. T.O. was responsible for statistical considerations. All authors participated in reviewing and interpreting the data and providing comments and revisions to the manuscript. All authors approved the final version of the manuscript and take full responsibility for the content.
Supplemental Fig. 1  Total amylase values (U/L) from central laboratory over time (includes all values from screening through 4-week safety follow-up visit off study drug)

(A) Monotherapy study

(B) Combination study

(C) Safety study

Lower dotted line: ULN, upper dotted line: 3×ULN, solid dark line: median. Dark bar on x-axis: treatment period (weeks 0-26)/(weeks 0-52). α-GI, alpha glucosidase inhibitors; BG, biguanides; DU 0.75 mg, once weekly dulaglutide 0.75 mg; GLN, glinides; LIRA 0.9 mg, once daily liraglutide 0.9 mg; SU, sulfonylureas; TZD, thiazolidinediones; ULN, upper limit of normal. * Placebo/DU 0.75 mg, placebo for 26 weeks followed by dulaglutide 0.75 mg for 26 weeks.
Supplemental Fig. 2  Lipase values (U/L) from central laboratory over time (includes all values from screening through 4-week safety follow-up visit off study drug)

(A) Monotherapy study

(B) Combination study

(C) Safety study

Lower dotted line: ULN, upper dotted line: 3×ULN, solid dark line: median. Dark bar on x-axis: treatment period (weeks 0-26)/(weeks 0-52). α-GI, alpha glucosidase inhibitors; BG, biguanides; DU 0.75 mg, once weekly dulaglutide 0.75 mg; GLN, glinides; LIRA 0.9 mg, once daily liraglutide 0.9 mg; SU, sulfonylureas; TZD, thiazolidinediones; ULN, upper limit of normal. * Plac/DU 0.75 mg, placebo for 26 weeks followed by dulaglutide 0.75 mg for 26 weeks.
Supplemental Fig. 3  Pancreatic amylase values (U/L) from central laboratory over time in the safety study (includes all values from screening through 4-week safety follow-up visit off study drug).

Lower dotted line: ULN, upper dotted line: 3×ULN, solid dark line: median. Dark bar on x-axis: treatment period (weeks 0-52). α-GI, alpha glucosidase inhibitors; BG, biguanides; DU 0.75 mg, once weekly dulaglutide 0.75 mg; GLN, glinides; SU, sulfonylureas; TZD, thiazolidinediones; ULN, upper limit of normal.

Supplemental Table 1  Dulaglutide-treated patients with sustained or non-treatment-emergent elevations in pancreatic enzymes and no clinical observations related to pancreatitis in 3 studies

| Pat Study | Patient characteristics | Event start day* | Results of interest |
|-----------|-------------------------|------------------|--------------------|
|           | Trt | Sex | Age (yr) | BMI (kg/m²) | Diab dur (yr) |           |                    |
| 1 Safety DU+TZD | M 49 | 23.4 | 6.0 | 21 | The patient experienced sustained elevated total and pancreatic amylase levels from screening through the safety follow-up period (approximately 15 months). His lipase levels were normal at screening and baseline and <2×ULN for the majority of the treatment period. His baseline total amylase value was 277 U/L (>2×ULN). His total amylase values remained elevated throughout the study period, and treatment with dulaglutide did not result in remarkable changes from baseline (treatment period values: 270-468 U/L [range approximately 2-4×ULN], follow-up period values: 255 and 268 U/L [both <3×ULN]); his pancreatic amylase values were similar (including some >3×ULN). He had no clinical findings and completed the study. His case was adjudicated by the CEC but was not confirmed as pancreatitis. |
| 2 Safety DU+TZD | M 73 | 20.3 | 6.1 | 400 | The patient had a total amylase value of 864 U/L one month after completion of 52 weeks of study treatment. At that time, pancreatic amylase and lipase values were within normal limits (41 U/L and 22 U/L, respectively). One week later, the total amylase value was 232 U/L. Lipase and pancreatic amylase values remained within normal limits throughout the study. Upon CT there was no observation of pancreatitis. Since pancreatic amylase was not increased, the CEC denied the possibility of pancreatitis upon adjudication. |

BMI, body mass index; CEC, Clinical Event Committee; CT, computed tomography; Diab dur, duration of diabetes; DU+TZD, once weekly dulaglutide 0.75 mg + thiazolidinedione; M, male; Pat, patient; Safety, 52-week safety study; Trt, treatment; ULN, upper limit of normal. * Relative to first day of treatment.
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