Impact of Liraglutide on Amylase, Lipase, and Acute Pancreatitis in Participants With Overweight/Obesity and Normoglycemia, Prediabetes, or Type 2 Diabetes: Secondary Analyses of Pooled Data From the SCALE Clinical Development Program

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OBJECTIVE

To describe amylase/lipase activity levels and events of acute pancreatitis (AP) in the SCALE (Satiety and Clinical Adiposity—Liraglutide Evidence in individuals with and without diabetes) weight-management trials.

RESEARCH DESIGN AND METHODS

Secondary analyses were performed on pooled data from four trials (*N* = 5,358 with BMI ≥30, or 27 to <30 kg/m^2 with ≥1 comorbidity). Of these, 1,723 had normoglycemia, 2,789 had prediabetes, and 846 had type 2 diabetes. Participants were randomized to liraglutide 3.0 mg (*n* = 3,302), liraglutide 1.8 mg (*n* = 211, only type 2 diabetes), or placebo (*n* = 1,845). Relationships between baseline characteristics and amylase/lipase activity at baseline and during treatment were investigated.

RESULTS

Over 56 weeks, liraglutide 3.0 mg versus placebo was associated with increases in mean levels of 7% (amylase) and 31% (lipase), respectively. Similar changes in amylase/lipase levels were observed with liraglutide 1.8 mg. More participants receiving liraglutide 3.0 mg versus placebo experienced amylase (9.4% vs. 5.9%) and lipase (43.5% vs. 15.1%) elevations greater than or equal to the upper limit of normal (ULN); few had elevations ≥3 × ULN for amylase (<0.1% with liraglutide 3.0 mg or placebo) or lipase (2.9% vs. 1.5%, respectively). After liraglutide discontinuation, enzymes returned to baseline levels. Thirteen participants developed AP: 12 on (*n* = 9, 0.3%) or after (*n* = 3, 0.1%) liraglutide 3.0 mg treatment and one (0.1%) with placebo. A total of 6/13 participants with AP (5/12 liraglutide; 1 placebo) had gallstone disease evident at AP onset. Amylase/lipase elevations either 1 × ULN or ≥3 × ULN before AP onset had very low positive predictive value for AP (<1%).

CONCLUSIONS

Liraglutide resulted in dose-independent, reversible increases in amylase/lipase activity, unrelated to baseline characteristics, not predicting AP onset. Gallstones possibly contributed to 50% of AP cases. Data provide no basis for amylase/lipase level monitoring in liraglutide treatment except in suspected AP.

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The relationship between incretin-based therapies and the risk of acute pancreatitis (AP) has been the topic of research, debate, and regulatory review (1–6). All currently marketed glucagon-like peptide 1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase 4 inhibitors carry label warnings concerning AP (5). Based on review of all available evidence and types of data (including nonclinical toxicology studies, clinical trial data, and epidemiologic data), the U.S. Food and Drug Administration (FDA) and the European Medicines Agency concluded that the data at the time did not support a causal relationship between incretin-based drugs and AP (4). However, although the totality of reviewed data provides reassurance, pancreatitis continues to be considered a risk until more data become available (4,5).

Amylase and lipase, as biomarkers of pancreatic inflammation, are routinely measured in clinical trials of incretin-based therapies as a regulatory requirement (7). Elevations, mostly within the range of greater than or equal to the upper limit of normal (ULN) to 2 × ULN, predominantly with lipase, have been described following treatment with GLP-1RAs and dipeptidyl peptidase 4 inhibitors (8–10). Little is known, however, about amylase or lipase activity in individuals with overweight/obesity without type 2 diabetes or whether routinely monitoring these enzymes can predict subsequent AP onset.

Liraglutide is an acylated human GLP-1 analog that binds to and activates the GLP-1 receptor (11,12). It lowers body weight through decreased caloric intake while stimulating insulin secretion and reducing glucagon via a glucose-dependent mechanism (13,14). Liraglutide at doses up to 1.8 mg has been licensed for treatment of type 2 diabetes since 2009 (15,16). Liraglutide 3.0 mg was recently approved for chronic weight management in adults with overweight (BMI ≥27 kg/m^2) and ≥1 weight-related comorbidity, or with obesity (BMI ≥30 kg/m^2), as an adjunct to a reduced-calorie diet and increased physical activity (11,12). As with other GLP-1RAs, AP has been reported in clinical trials and postmarketing use of liraglutide (11,12).

The aims of this exploratory analysis of pooled data from the SCALE (Satiety and Clinical Adiposity—Liraglutide Evidence in individuals with and without diabetes) program were to *1*) describe baseline and longitudinal on-treatment amylase and lipase data from phase 3a clinical trials of liraglutide in weight management, including dose-response and potential relationships with baseline characteristics, and *2*) investigate any association between treatment-related increases in amylase and lipase activity and subsequent AP occurrence.

RESEARCH DESIGN AND METHODS

Participants

This analysis includes four randomized, placebo-controlled trials comprising the SCALE phase 3a clinical trial program of liraglutide 3.0 mg for weight management (Supplementary Fig. 1). The design and primary results from the trials have been published previously (17–20):

- SCALE Obesity and Prediabetes (Trial 1). This 56-week, randomized, parallel-group trial (*n* = 3,731, ClinicalTrials.gov identifier NCT00422058) investigated the efficacy and safety of liraglutide 3.0 mg versus placebo (each as an adjunct to diet and exercise) in people with BMI ≥30 kg/m^2, or ≥27 kg/m^2 and ≥1 weight-related comorbidity. Participants with type 2 diabetes were excluded. After 56 weeks, participants on liraglutide without prediabetes at randomization were rerandomized to either continue liraglutide 3.0 mg or switch to placebo for an additional 12 weeks; placebo participants continued on placebo (17). Participants with prediabetes at randomization were studied for up to 3 years for new onset of diabetes.
- SCALE Diabetes (Trial 2). This 56-week, randomized, parallel-group trial (*n* = 846, ClinicalTrials.gov identifier NCT01272232) investigated the efficacy and safety of liraglutide 3.0 mg versus liraglutide 1.8 mg or placebo (each as an adjunct to diet and exercise) in people with type 2 diabetes and BMI ≥27 kg/m^2 (19). After 56 weeks, participants were studied for an additional 12 weeks off treatment.
- SCALE Maintenance (Trial 3). This 56-week randomized, parallel-group trial (*n* = 422, ClinicalTrials.gov identifier NCT00781937) examined prevention of weight regain following a low-calorie diet run in with liraglutide 3.0 mg versus placebo (each as an adjunct to diet and exercise) in people with BMI ≥30 kg/m^2, or ≥27 kg/m^2 and ≥1 weight-related comorbidity (18). Participants with type 2 diabetes were excluded. After 56 weeks, participants were studied for an additional 12 weeks off treatment.
- SCALE Sleep Apnea (Trial 4). This 32-week, randomized, parallel-group trial (*n* = 359, ClinicalTrials.gov identifier NCT01557166) investigated the efficacy and safety of liraglutide 3.0 mg versus placebo (each as an adjunct to diet and exercise) in people with BMI ≥30 kg/m^2 and moderate to severe obstructive sleep apnea (20). Participants with type 2 diabetes were excluded.

Participants in all trials were prescribed a 500 kcal/day deficit diet (maximum ~30% energy from fat, 20% energy from protein, 50% energy from carbohydrates) and increased physical activity (≥150 min/week brisk walking). People with a history of idiopathic AP or chronic pancreatitis were excluded from the SCALE program. There were no exclusion criteria based on elevated amylase/lipase levels (17–20).

Assessments

Serum amylase and lipase were measured at screening and randomization and monitored approximately once every 3 months during treatment, at end of treatment, and at follow-up (2 weeks and 3 months after last dose [Trials 1–3]) (7). Amylase and lipase activity were measured using enzymatic colorimetric assay (Roche Diagnostics, Mannheim, Germany) performed by a central laboratory. ULN for amylase were 100 units/L (Trial 3) and 112 units/L (Trials 1, 2, 4) and for lipase 60 units/L (Trials 1–4). Elevated amylase/lipase levels ≥3 × ULN were to be reported as "medical events of special interest," irrespective of gastrointestinal tract symptoms, but would lead to treatment discontinuation only if AP was suspected. For other trial assessments, see respective publications (17–20).

Evaluation of Pancreatitis

Across the SCALE trials, suspicion of pancreatitis was predefined as a "medical event of special interest" to ensure timely and systematic collection of relevant information for in-depth evaluation (7). The diagnosis of AP was based on meeting two or more of the following three

criteria: *1*) characteristic abdominal pain, *2*) amylase and/or lipase >3 × ULN, and/or *3*) characteristic findings on pancreas imaging (ultrasound, computed tomography, MRI). All potential cases of pancreatitis were adjudicated by an independent, blinded adjudication committee (7). Severity was classified by an expert pancreatologist according to revised Atlanta criteria, using available information in source documents (7,17,21). Trial 3 (the first initiated of the four trials) was ongoing at adjudication implementation, and therefore events were adjudicated post hoc in this trial, following the same blinded process and charter as the other three prospectively adjudicated trials as far as possible (7). All suspected drugs (including protocol-permitted drugs) were to be discontinued if pancreatitis was suspected. Participants were withdrawn if a pancreatitis diagnosis was confirmed.

The sponsor took measures to identify potential events of pancreatitis not already identified by study investigators (7). During conduct of Trials 1, 2, and 4, the sponsor performed ongoing blinded searches, using a predefined Medical Dictionary for Regulatory Activities (MedDRA) search, in the clinical database for potential events of pancreatitis not already identified by investigators. This search included AEs of increased amylase/lipase with concomitant reporting of AEs of abdominal pain or vomiting (occurring within a time window of ±30 days of elevated amylase/lipase). A similar retrospective search was carried out for Trial 3.

For completeness, all events with onset through the data cutoff for the regulatory 120-day safety update report to the FDA (corresponding to 1,621 additional person-years-of-observation [PYO] in Trial 1) were included in this analysis.

Statistical Analyses

All analyses are based on pooled liraglutide 3.0 mg and pooled placebo data from all four trials, adjusting for trial. Data from the liraglutide 1.8 mg group (Trial 2) are also reported. Geometric mean amylase/lipase activity levels were calculated based on scheduled visits; outlier (categorical) analyses also included data from unscheduled visits. The following definitions were used in the categorical analyses of amylase or lipase: ≥1 × ULN, ≥2 × ULN, and ≥3 × ULN. Exploratory subgroup analyses were used to investigate the relationship between baseline characteristics and amylase/lipase activity at baseline and during treatment. These analyses used an ANCOVA model of log-transformed baseline amylase/lipase, or amylase/lipase relative change from baseline, with trial and baseline characteristics as factors, or trial, treatment, baseline characteristics, and treatment × baseline characteristics interaction as factors and baseline amylase/lipase as covariates, respectively. Incidence was calculated in terms of PYO, covering the period from the start of treatment until the final contact with the patient (including off-drug follow-up). The positive predictive value (PPV) for AP was defined as the number of participants with at least one amylase/lipase value ≥1 × ULN, or ≥3 × ULN, at scheduled visits who subsequently developed AP (numerator) divided by the total number of participants (participants with and without subsequent AP) who had an amylase/lipase value ≥1 × ULN or ≥3 × ULN at any time during the study (denominator). Finally, a simple estimate of the number needed to harm (NNH) for AP was derived with the function $1/(P_{lira} - P_{placebo})$, where P_{lira} and $P_{placebo}$ are the yearly AP incidence rates based on observation time from treatment start until last participant contact. Amylase/lipase measurements from Trial 1 through the regulatory 120-day safety update were included when calculating the PPV for AP; all other changes from baseline data are based on randomization to end of treatment (Trials 1–3: 0–56 weeks; Trial 4: 0–32 weeks).

The following definitions were used for subgroup analyses: age-group, years (<45, 45–54, 55–64); sex (male, female); race (Asian, black/African American, other, white); BMI, kg/m^2 (<30, ≥30 to <35, ≥35 to <40, ≥40); dyslipidemia, LDL ≥160 mg/dL and/or triglycerides ≥150 mg/dL and/or HDL <40 mg/dL for males, <50 mg/dL for females (yes/no); hypertension, systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg (yes/no); renal impairment, mild (estimated glomerular filtration rate [eGFR] 60–89 mL/min/1.73 m^2), moderate (30–59 mL/min/1.73 m^2), or severe (15–29 mL/min/1.73 m^2); and glycemic status (normoglycemia, prediabetes, diabetes) (eGFR calculated via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Eq. [22]). Normoglycemia (relevant for Trials 1, 3, 4) was defined as not having prediabetes or diabetes; in Trial 1 this equated to meeting all three of the following criteria: HbA_{1c} <5.7%; fasting glucose <100 mg/dL; 2-h plasma glucose measurement <140 mg/dL during a 75-g oral glucose tolerance test (OGTT). Prediabetes (relevant for Trials 1, 3, 4) was defined as having impaired fasting plasma glucose (FPG) (100–125 mg/dL) and/or impaired glucose tolerance (2-h plasma glucose 140–199 mg/dL [OGTT], Trial 1 only) and/or HbA_{1c} 5.7–6.4% (39–46 mmol/mol) (17,23). Diabetes was defined as having a diagnosis at least 3 months prior to screening (Trial 2); diabetes was an exclusion criterion in Trial 1 (based on meeting ≥1 of the following: FPG ≥126 mg/dL; 2-h plasma glucose ≥200 mg/dL [OGTT]; HbA_{1c} ≥6.5%) and in Trials 3 and 4 (diagnosis of type 1 diabetes or type 2 diabetes by the investigator; FPG ≥126 mg/dL).

RESULTS

Baseline Characteristics

In total, 5,358 participants were randomized to liraglutide 3.0 mg (*n* = 3,302), liraglutide 1.8 mg (*n* = 211), or placebo (*n* = 1,845) in the SCALE trials (Supplementary Fig. 1). In total, 1,723 participants had normoglycemia, 2,789 had prediabetes, and 846 had type 2 diabetes (Table 1). Mean age was 47 years; 70.8% were female; 83.9% were white; mean body weight was 106.5 kg; and mean BMI was 38.0 kg/m^2. It should be noted that the participants in the diabetes trial (Trial 2) were older (mean age 54.9 years) and that Trial 2, together with Trial 4, had more males compared with the other trials (Table 1). Overall, 52.4% of participants had normal renal function, while 43.0, 4.5, and 0.1% had mild, moderate, and severe renal impairment, respectively. Trials 1, 2, and 4 showed similar proportions of participants across renal function status, but in Trial 3, the majority of participants (86.2%) had normal renal function (Table 1). Baseline characteristics are summarized in further detail in Table 1.

Amylase/Lipase Activity at Baseline

Table 1 shows the mean values and categorical distributions of amylase/lipase in Trials 1, 2, 3, and 4. At baseline, the mean

Table 1—Baseline characteristics and categorical distribution of amylase and lipase activity for randomized participants of the phase 3 clinical trials

	Trial 1		Trial 2	Trial 3	Trial 4	
	Weight loss in participants without type 2 diabetes		Weight loss in participants with type 2 diabetes	Prevention of weight regain	Weight loss in participants with OSA	All trials combined
	(*N* = 3,731)		(*N* = 846)	(*N* = 422)	(*N* = 359)	(*N* = 5,358)
Glycemic status	Participants with normoglycemia (*N* = 1,446)	Participants with prediabetes (*N* = 2,285)	Participants with type 2 diabetes (*N* = 846)	Participants with normoglycemia (*N* = 150) or prediabetes (*N* = 272)	Participants with normoglycemia (*N* = 127) or prediabetes (*N* = 232)	
Mean age at screening, years (SD)	41.5 (11.6)	47.4 (11.8)	54.9 (10.5)	46.2 (11.5)	48.5 (9.7)	47.0 (12.2)
Age-group, *n* (%)						
18 to <65	1,402 (97.0)	2,124 (93.0)	689 (81.4)	401 (95.0)	359 (100.0)	4,975 (92.9)
≥65 to <75	44 (3.0)	154 (6.7)	142 (16.8)	21 (5.0)	0 (0.0)	361 (6.7)
≥75	0 (0.0)	7 (0.3)	15 (1.8)	0 (0.0)	0 (0.0)	22 (0.4)
Sex, female	1,191 (82.4)	1,737 (76.0)	421 (49.8)	343 (81.3)	101 (28.1)	3,793 (70.8)
Race, *n* (%)						
White	1,257 (86.9)	1,911 (83.6)	705 (83.3)	355 (84.1)	265 (73.8)	4,493 (83.9)
Black/African American	136 (9.4)	220 (9.6)	98 (11.6)	56 (13.3)	69 (19.2)	579 (10.8)
Asian	21 (1.5)	115 (5.0)	19 (2.2)	1 (0.2)	16 (4.5)	172 (3.2)
American Indian/ Alaska Native	2 (0.1)	7 (0.3)	4 (0.5)	0 (0.0)	0 (0.0)	13 (0.2)
Native Hawaiian/ Pacific Islander	2 (0.1)	2 (0.1)	0 (0.0)	2 (0.5)	3 (0.8)	9 (0.2)
Other	28 (1.9)	30 (1.3)	20 (2.4)	8 (1.9)	6 (1.7)	92 (1.7)
Ethnicity						
Hispanic or Latino	177 (12.2)	216 (9.5)	87 (10.3)	28 (6.6)	43 (12.0)	551 (10.3)
Not Hispanic or Latino	1,269 (87.8)	2,069 (90.5)	756 (89.4)	394 (93.4)	316 (88.0)	4,804 (89.7)
Not applicable*	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)	3 (<0.1)
Mean body weight, kg (SD)	103.9 (20.5)	107.7 (21.8)	105.9 (21.5)	99.6 (21.0)	117.6 (24.2)	106.4 (21.8)
Mean BMI, kg/m^2 (SD)	37.5 (6.2)	38.8 (6.4)	37.1 (6.8)	35.6 (5.9)	39.1 (6.9)	38.0 (6.5)
Renal function (based on eGFR), *n* (%)						
Normal	799 (55.3)	1,095 (47.9)	410 (48.5)	363 (86.2)	141 (39.3)	2,808 (52.4)
Mild	605 (41.8)	1,076 (47.1)	368 (43.5)	55 (13.1)	197 (54.9)	2,301 (43.0)
Moderate	41 (2.8)	111 (4.9)	66 (7.8)	3 (0.7)	21 (5.8)	242 (4.5)
Severe	1 (0.1)	3 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	6 (0.1)
Amylase						
Mean, units/L	57.2	56.2	56.4	54.6	59.4	56.6
≥1 × ULN, *n* (%)	35 (2.4)	52 (2.3)	26 (3.1)	17 (4.0)	19 (5.3)	149 (2.8)
≥2 × ULN, *n* (%)	0 (0.0)	1 (<0.1)	1 (0.1)	1 (0.2)	1 (0.3)	4 (0.1)
≥3 × ULN, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lipase						
Mean, units/L	34.4	35.3	43.1	33.9	35.5	36.2
≥1 × ULN, *n* (%)	64 (4.4)	117 (5.1)	101 (11.9)	21 (5.0)	20 (5.6)	323 (6.0)
≥2 × ULN, *n* (%)	7 (0.5)	11 (0.5)	20 (2.4)	2 (0.5)	2 (0.6)	42 (0.8)
≥3 × ULN, *n* (%)	2 (0.1)	5 (0.2)	11 (1.3)	0 (0.0)	1 (0.3)	19 (0.4)

OSA, obstructive sleep apnea. *Ethnicity data were not collected at French sites in Trial 2. ULN for amylase were 100 units/L (Trial 3) and 112 units/L (Trials 1, 2, and 4) and for lipase 60 units/L (Trials 1–4).

amylase value across the four trials was 56.6 units/L, and 149 participants (2.8%) had amylase ≥1 × ULN, 4 participants (0.1%) had ≥2 × ULN, and no participants had values ≥3 × ULN (Table 1). For lipase, the mean value at baseline across the four trials was 36.2 units/L, and 323 (6%) had lipase ≥1 × ULN, 42 (0.8%) had ≥2 × ULN, and 19 (0.4%) had values ≥3 × ULN (Table 1).

Relationship Between Baseline Characteristics and Baseline Amylase/Lipase Activity

The following variables were associated with statistically higher amylase/lipase

levels at baseline: increasing age ($P < 0.0001$); being male ($P < 0.05$); being Asian, black, African American, or other race versus being white ($P < 0.0001$); decreasing BMI category ($P < 0.0001$); having dyslipidemia ($P < 0.05$); having hypertension ($P < 0.05$); and increasing degree of renal impairment ($P < 0.0001$) (Supplementary Table 1).

In addition, there was a significant effect of worsening glycemic status (having prediabetes or diabetes vs. normoglycemia, defined according to the American Diabetes Association 2010 criteria [23]) on baseline lipase (20% higher lipase levels in individuals with type 2 diabetes vs. those with normoglycemia; $P < 0.0001$); no glycemic status effect was observed with amylase (Supplementary Table 1).

Changes in Amylase/Lipase Activity Over Time

The time course and magnitude of mean change from baseline in amylase/lipase activity were similar across trials (P value for trial by treatment interaction > 0.05): as an illustration, data are shown for Trials 1 (without type 2 diabetes, Fig. 1*A* and *B*) and 2 (with type 2 diabetes, Fig. 1*C* and *D*). Based on pooled data from the SCALE phase 3 program, liraglutide 3.0 mg was associated with an amylase increase of 7% and a lipase increase of 31%, relative to placebo ($P < 0.001$). These mean changes in amylase/lipase activity were not driven by a few outlying data points but rather a general right-shifted distribution, as shown in Supplementary Fig. 2.

For both enzymes, the mean increase in activity with liraglutide was evident at the first scheduled measurement (4 weeks), and activity was consistently above baseline and placebo for as long as participants remained on treatment (Fig. 1*B*–*D*). Mean amylase/lipase activity returned toward baseline values once liraglutide treatment was discontinued (i.e., during 12-week off-treatment follow-up periods) (Fig. 1*A*–*D*). Treatment effects appeared similar in participants with normoglycemia, prediabetes, and diabetes (Trials 1 and 2) (Fig. 1*A*–*D*), and there was no evidence of a dose-response between liraglutide 1.8 mg and 3.0 mg (Trial 2) (Fig. 1*C* and *D*).

Figure 2 shows that while on treatment, 9.4% of participants on liraglutide 3.0 mg had amylase $\geq 1 \times$ ULN vs. 5.9% for placebo; 0.5% vs. 0.2% had amylase $\geq 2 \times$ ULN; and $<0.1\%$ had amylase $\geq 3 \times$ ULN. For lipase, 43.5% of participants on liraglutide 3.0 mg vs. 15.1% on placebo had an elevation of lipase $\geq 1 \times$ ULN at any time during treatment, while 7.7% vs. 3.5% and 2.9% vs. 1.5% had a $\geq 2 \times$ ULN and $\geq 3 \times$ ULN lipase elevation, respectively. It should be noted that, irrespective of treatment and possibly due to their higher baseline values, a relatively higher proportion of participants in Trial 2 (participants with type 2 diabetes) versus those in the pooled data set had elevations of lipase ($\geq 1 \times$ ULN, $\geq 2 \times$ ULN, $\geq 3 \times$ ULN) (Trial 2: 56.4%, 15.6%, 7.6% on liraglutide 3.0 mg; 56.2%, 16.2%, 9.5% on liraglutide 1.8 mg; and 29.7%, 10.8%, and 6.1% on placebo, respectively).

The majority of elevations were not sustained. No participants treated with liraglutide 3.0 mg experienced recurrent elevated amylase $\geq 3 \times$ ULN over ≥ 2 visits (Supplementary Fig. 3). Eleven (0.3%) and 3 (0.2%) of the participants in the liraglutide 3.0 mg and placebo groups, respectively, experienced lipase $\geq 3 \times$ ULN over ≥ 2 visits (Supplementary Fig. 3).

Relationship Between Baseline Characteristics and Changes in Amylase/Lipase Activity Changes Over Time

The following characteristics were associated with greater increases in amylase following treatment with liraglutide: increasing age, male sex, and worsening glycemic status (Supplementary Table 2). Only increasing age was associated with greater increases in lipase with liraglutide (Supplementary Table 2).

Relationship Between Low-Calorie Diet–Induced Weight Loss and Change in Amylase/Lipase Activity

We also speculated whether the treatment-related increases in pancreatic enzyme levels could be related to treatment-related improvement in glycemia and/or body weight. While the first hypothesis could not be tested with the current trials, based on results from Trial 3, a diet-induced weight loss of $\geq 5\%$ was not associated with changes in amylase or lipase activity (data not shown).

Confirmed Pancreatitis Events

An overview of all AEs sent for adjudication on suspicion of pancreatitis and their outcome is in Supplementary Fig. 4. In total, 31 cases were reviewed by the external event adjudication committee, 14 of which were initially identified by the investigator and 17 by standardized MedDRA search in the AE database; 13 cases were confirmed as AP, 12 in participants who were either on treatment with liraglutide 3.0 mg at onset of the event ($n = 9$, 0.3%) or had previously been treated with liraglutide 3.0 mg ($n = 3$, 0.1%), and 1 treated with placebo (0.1%) (Table 2). All confirmed cases were from Trial 1. If all 12 cases associated with liraglutide are included, the event rates for liraglutide 3.0 mg, 1.8 mg, and placebo are 2.65, 0, and 0.44/1,000 PYO, respectively. Based on AP events with onset in the main-treatment and follow-up periods, the NNH for AP with liraglutide 3.0 mg is 322. There were no confirmed cases of chronic pancreatitis (not unexpected given the short exposure time).

In the 12 liraglutide-treated participants who developed AP, two latency periods (interval between drug initiation and developing pancreatitis) were observed. In 4/12 participants, pancreatitis developed <60 days after starting liraglutide, while 7/12 had a latency period of at least 5–6 months (Table 2). Six participants (five liraglutide-treated) had gallstone-associated pancreatitis, as indicated by presence of gallstones on imaging, alanine aminotransferase levels that were $\geq 3 \times$ ULN, or both (24). All but one case were mild in severity according to Atlanta classification; the remaining case was classified as moderately severe (21). All events occurred in people without type 2 diabetes; 10/12 had prediabetes, and two had normoglycemia.

Supplementary Fig. 5 shows amylase and lipase levels measured during the regular protocol–scheduled visits as well as local measurements at admission (if available) for participants who experienced AP.

PPV of Amylase or Lipase Elevations for AP

Most amylase or lipase elevations $\geq 3 \times$ ULN occurred once or twice during treatment and were unaccompanied by signs and symptoms of pancreatitis. The PPV for amylase $\geq 3 \times$ ULN and subsequent AP was 0%. For lipase $\geq 3 \times$ ULN, the PPV was 0.7%. The PPVs for amylase and lipase values $\geq 1 \times$ ULN were 0.3% and 0.3%, respectively (Supplementary Tables 3 and 4).

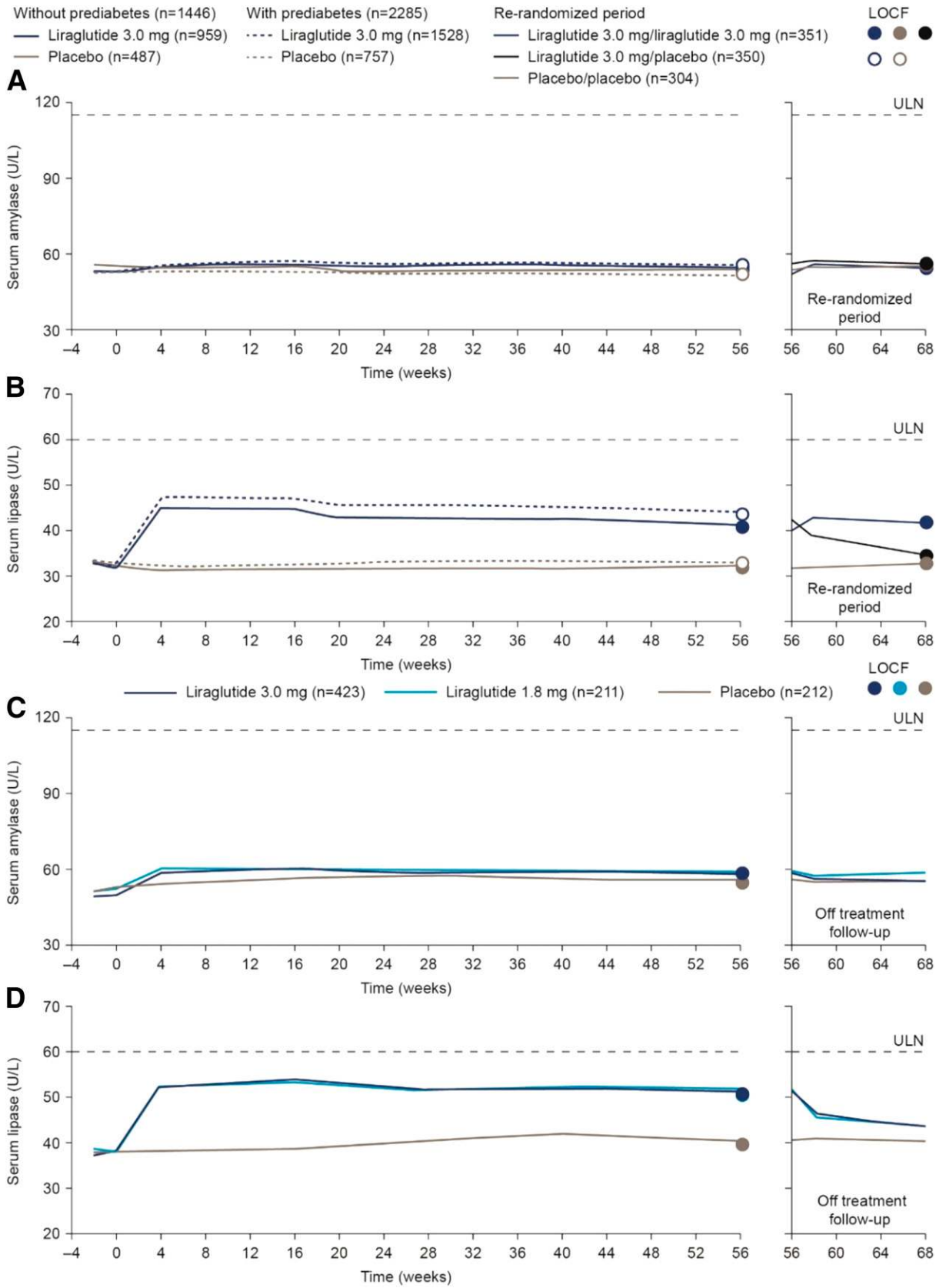

Figure 1—Mean change from baseline in amylase and lipase activity over time in Trial 1 (*A* and *B*) and Trial 2 (*C* and *D*). *A* and *B*: Safety analysis set. Graphs are geometric means. Circles are geometric means with last observation carried forward (LOCF). Amylase ULN defined as 112 units/L. Lipase ULN defined as 60 units/L. At week 56, participants without prediabetes on liraglutide were rerandomized 1:1 to liraglutide or placebo. *C* and *D*: Safety analysis set. Graphs are geometric means. Circles are geometric means with LOCF. Amylase ULN defined as 112 units/L. Lipase ULN defined as 60 units/L. The liraglutide 1.8-mg and 3.0-mg graphs are virtually superimposed.

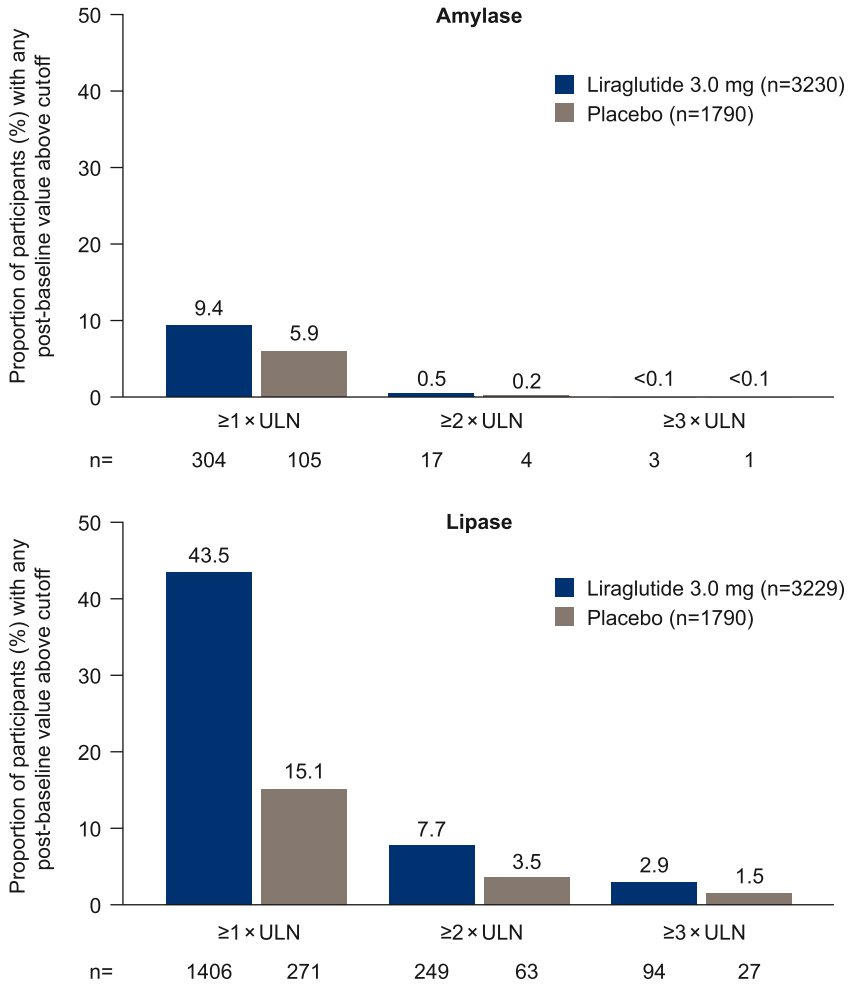

Figure 2—Amylase and lipase elevations at any time during treatment (pooled data from Trials 1–4).

CONCLUSIONS

This analysis was undertaken to better understand the nature of treatment-related increases in amylase/lipase activity with liraglutide 3.0 mg in people with overweight or obesity conditions, as well as any potential relationships between elevated amylase/lipase levels and subsequent occurrence of AP. To the best of our knowledge, this is the first time such data have been reported in people without diabetes (but with and without prediabetes).

On average, amylase/lipase activity increased by 7% and 31%, respectively, with liraglutide 3.0 mg relative to placebo, corresponding to treatment-related increases in the range of 0–10 units/L for both amylase and lipase. Similar increases were observed with liraglutide 1.8 mg, indicating no dose-response of the effect. While incidental increases in amylase/lipase ≥1 × ULN were quite common (~9% and ~44% of participants treated with liraglutide, respectively), sustained elevations were uncommon, as were elevations ≥3 × ULN (<0.1% and 2.9%, respectively). Elevations were reversible upon treatment discontinuation; most values had returned to normal within 12 weeks.

Increasing age, male sex, non-white origin, lower BMI, having dyslipidemia and/or hypertension, and renal impairment were associated with modestly higher amylase/lipase levels at baseline. In addition, data from the present analysis suggest that worsening glycemia was associated with modestly higher baseline lipase levels. These findings are consistent with findings from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, which also demonstrated that asymptomatic enzyme elevations, including ≥3 × ULN, are not uncommon in people with type 2 diabetes and significant cardiovascular risk (25). Baseline characteristics had no material influence on amylase or lipase excursions on treatment.

Importantly, the current analysis provided no indication that routinely measured amylase or lipase values 3 × ULN predict occurrence of AP in people treated with liraglutide 3.0 mg (PPV 0.7% for lipase).

The mechanism by which liraglutide causes increased amylase/lipase in the blood is unknown. One possibility is that this GLP-1RA causes subclinical pancreatic inflammation leading to enzyme elevation. We consider this unlikely as the enzymes rise almost immediately after administration, stay elevated for as long as the agent is given, and return to normal levels as soon as the agent is stopped. These elevations were unaccompanied by the development of AP in the vast majority of cases. This is further corroborated by the recently published long-term LEADER trial that showed that despite liraglutide-induced elevations of amylase/lipase for a mean of 3.5 years (the length of the study), there was no increased rate of AP compared with placebo (25). Nevertheless, at this point in time, we cannot rule out persistent low grade inflammation.

GLP-1 receptors are weakly expressed on the acinar cells in the human pancreas (26), and in mice, short-term GLP-1 receptor activation leads to increased acinar cell amylase secretion (27). Also in mice, short-term administration of GLP-1RAs increases pancreas protein synthesis with no signs of an inflammatory state (28). Similarly, in nonhuman primates, chronic administration of liraglutide or semaglutide showed no histopathological changes in the pancreas (29). However, even if enzyme production in the acinar tissue is increased with continued GLP-1 receptor stimulation, it does not explain an increase in enzymes in the blood. Acini discharge their contents into the pancreatic ductules, and from there to the small bowel where the enzymes are not absorbed into the blood. It is possible that liraglutide (and other incretin-based therapies) might facilitate the transfer of acinar enzymes across the basolateral membrane of the pancreas and into the blood. This is a theory that has not yet been explored. Other explanations include the possibility that these drugs may affect the metabolism and excretion of lipase and or amylase from the kidney or peripheral tissues.

The absolute risk of AP in the SCALE program was low, but numerically higher

Table 2—Case details for confirmed AP events

Treatment	Exposure to liraglutide (days)	Age/sex/ BMI	Glycemic status	Peak amylase/ lipase*	Diagnostic criteria fulfilled			Severity (Atlanta criteria†)	Gallstones	
					Abdominal pain	Enzymes	Imaging		By imaging	Elevated LFTs
During liraglutide 3.0 mg treatment (n = 9)	24	32/F/38.9	Normal	43/64	✓	✓	NA	Mild	NA	NA
	29	51/M/32.7	Prediabetes	43/28	✓	✓	NA	Mild	NA	NA
	31	52/M/62.9	Prediabetes	51/28	✓	✓	NA	Mild	NA	✓ALT 4 × ULN
	43	58/M/34.7	Prediabetes	56/30	✓	NA	✓	Mild	NA	NA
	277	51/F/48.6	Prediabetes	130/213	✓	✓	NA	Mild	NA	NA
	283	40/F/41.7	Prediabetes	56/43	✓	✓	✓	Moderately severe	✓	✓ALT 8 × ULN
	330	40/M/54.0	Prediabetes	45/63	✓	NA	✓	Moderately severe	NA	✓ALT <1.5 × ULN
	410	62/F/38.7	Prediabetes	7/88	✓	✓	NA	Mild	NA	NA
	626	48/F/45.1	Prediabetes	82/61	✓	NA	✓	Mild	NA	NA
After liraglutide discontinuation (n = 3)										
Liraglutide/ placebo	392 [12]‡	42/F/36.2	Normal	2,074/ 3,007	✓	✓	NA	Mild	NA	✓ALT 5 × ULN
Liraglutide 3.0 mg	35 [74]‡	64/M/38.1	Prediabetes	65/43	✓	✓	✓	Mild	NA	✓ALT 3 × ULN
	170 [124]‡	41/F/42.9	Prediabetes	65/36	✓	✓	✓	Moderately severe	✓	ALT unavailable, AST 24 × ULN
During placebo treatment (n = 1)	287	55/F/35.5	Prediabetes	76/52	✓	NA	✓	Mild	✓	✓ALT 2.5 × ULN

All patients recovered. ULN for amylase were 100 units/L (Trial 3) and 112 units/L (Trials 1, 2, and 4) and for lipase 60 units/L (Trials 1–4). ✓, yes; ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; LFT, liver function test; M, male; NA, information not available. *As measured during trial (central laboratory) prior to AP event. †Post hoc assessment by an expert pancreatologist according to the revised Atlanta criteria. ‡Exposure to liraglutide 3.0 mg after treatment discontinuation.

in liraglutide versus placebo (0.4% for liraglutide 3.0 mg, <0.1% for placebo; 2.65 cases/1,000 PYO for liraglutide 3.0 mg vs. 0.44 cases/1,000 PYO for placebo). The estimated incidence rate includes the three participants in the liraglutide group who were off the medication for 35–392 days before the event of AP. In comparison, the estimated frequency of AP in the Liraglutide Effect and Action in Diabetes (LEAD) program was 1.6 cases/1,000 patient-years exposure for liraglutide 1.8 mg versus 0.7 cases/1,000 patient-years exposure for total active comparators (5). However, in the LEAD trial program, AP cases were not adjudicated. Using similar methodology for ascertainment and adjudication as in the SCALE program, the LEADER trial, by far the largest and longest GLP-1RA trial to date (~9,300 people with type 2 diabetes, 1:1 randomized, median follow-up 3.5 years) showed no imbalance in AP for liraglutide 1.8 mg versus placebo (0.4% for liraglutide 1.8 mg, 0.5% for placebo) (17,30). Likewise, in the SUSTAIN-6 trial in which 3,297 participants with type 2 diabetes and high cardiovascular risk were randomly assigned to semaglutide, a once-weekly GLP-1RA, or placebo for 104 weeks, adjudicated AP rates were also similar between groups (0.5% for semaglutide, 0.7% for placebo) (31). Generally, it may be difficult to extrapolate incidence rates from a clinical trial setting to clinical practice in the real world, and the low number of cases in the SCALE program precludes any firm conclusions as to the risk of AP with liraglutide 3.0 mg.

It has recently been suggested that use of GLP-1 analogs is associated with an increased risk of biliary tract disease (32). Liraglutide has been associated with a doubling of gallstone-related AE frequency in recent clinical trials (17,30). This has been attributed to the greater magnitude of weight loss seen with liraglutide, as well as potentially weight-loss–independent mechanisms (17). Five of the 12 participants in the liraglutide-treated group (and the one on placebo) who developed AP in this study (total of 6/13) had gallstones at the time of presentation either by imaging or based on typical liver-enzyme findings, suggesting an important contribution of gallstones to the pancreatitis episode. Moreover, the great majority of patients developing AP while on liraglutide do so after being on drug more than 6 months. It is conceivable that in a small number of patients, GLP-1RAs may predispose to gallstone formation or may worsen existing gallstone disease, induced or worsened either by weight loss or alterations in biliary motility or by an unknown mechanism that may increase slightly the risk of AP (33). Analysis of large-scale studies may help to elucidate these questions.

In conclusion, asymptomatic elevations of amylase/lipase did not predict subsequent AP in participants with overweight/obesity in the SCALE phase 3a clinical trial program. The PPV of an elevated amylase or lipase in predicting AP is negligible, and therefore there is little rationale in monitoring these enzymes while on treatment. Amylase and especially lipase increases are common with liraglutide treatment, are not dose-dependent, and return to baseline levels upon treatment discontinuation. The mechanism and clinical relevance of these observations remain unclear. The absolute risk of AP with liraglutide

3.0 mg is low but higher than placebo, and gallstones appear the most commonly identifiable etiological factor potentially contributing to nearly half the identified cases. Mechanistic data are required to further advance our understanding of these findings.

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