SUPPLEMENTARY DATA

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

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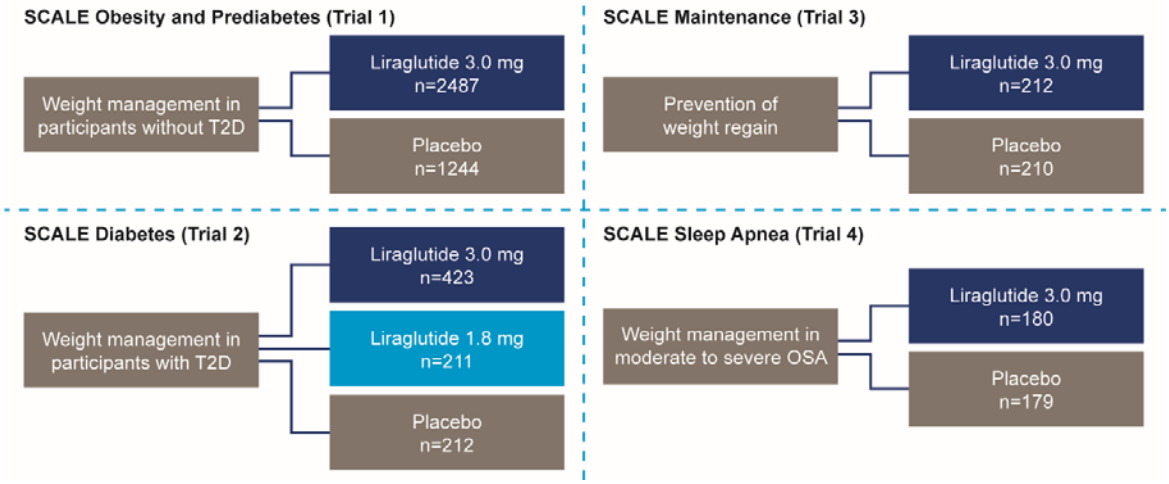
Supplementary Figure 1. Overview of the SCALE phase 3a clinical trial program.



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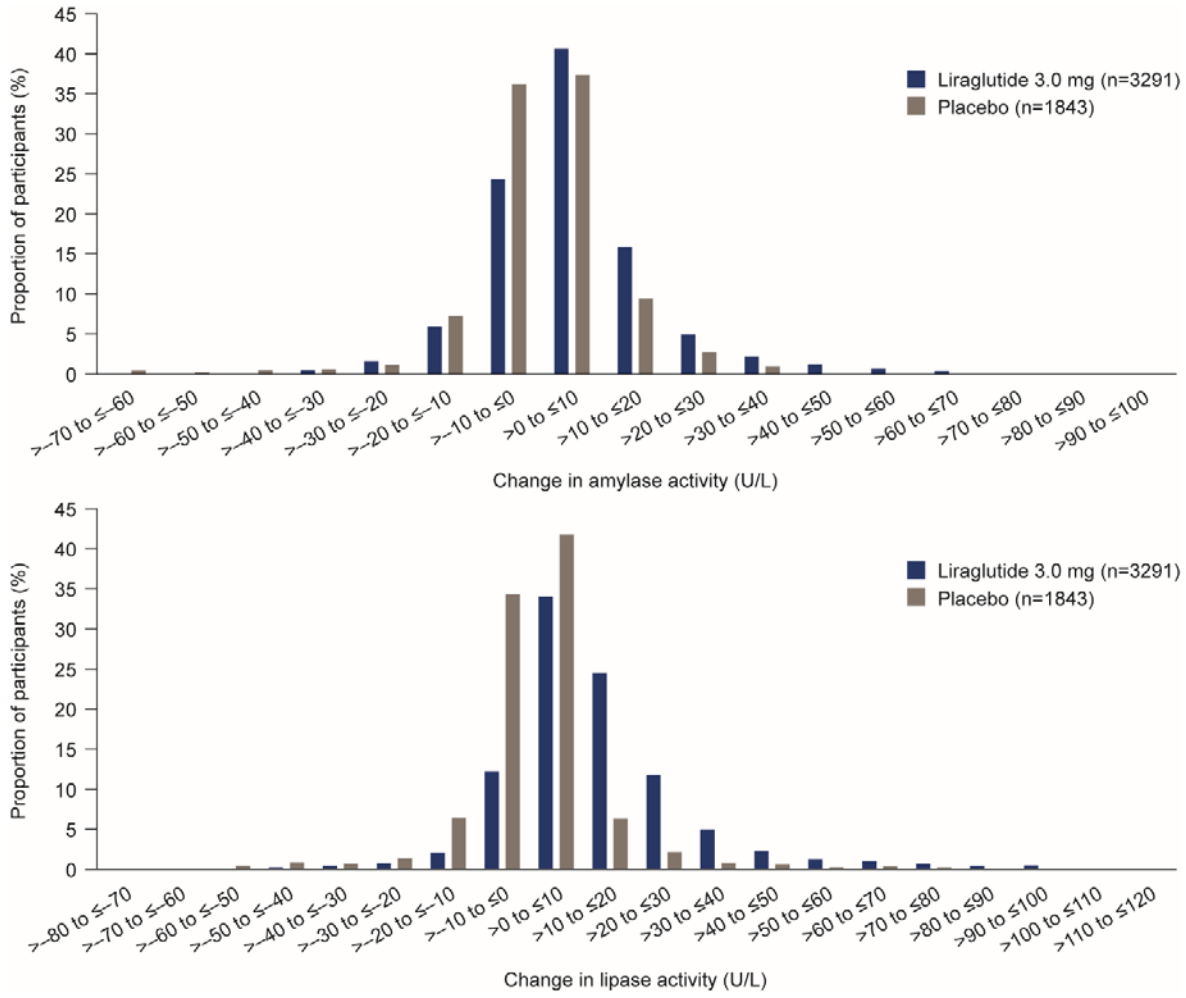
Supplementary Figure 2. Incremental changes in amylase and lipase activity from baseline to end of treatment (pooled data from Trials 1-4).



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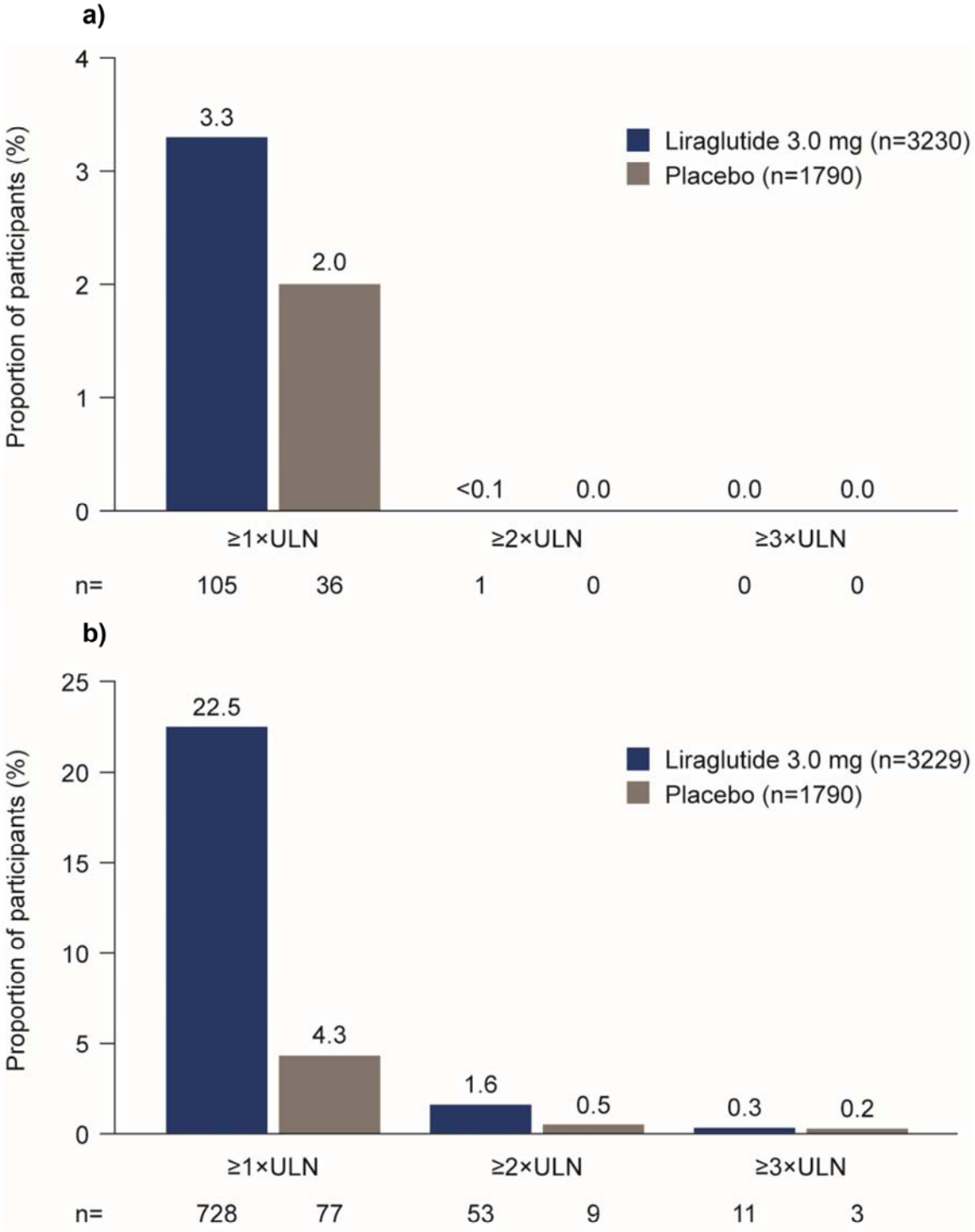
Supplementary Figure 3. Recurrent elevations of (a) amylase and (b) lipase (at two or more consecutive visits).



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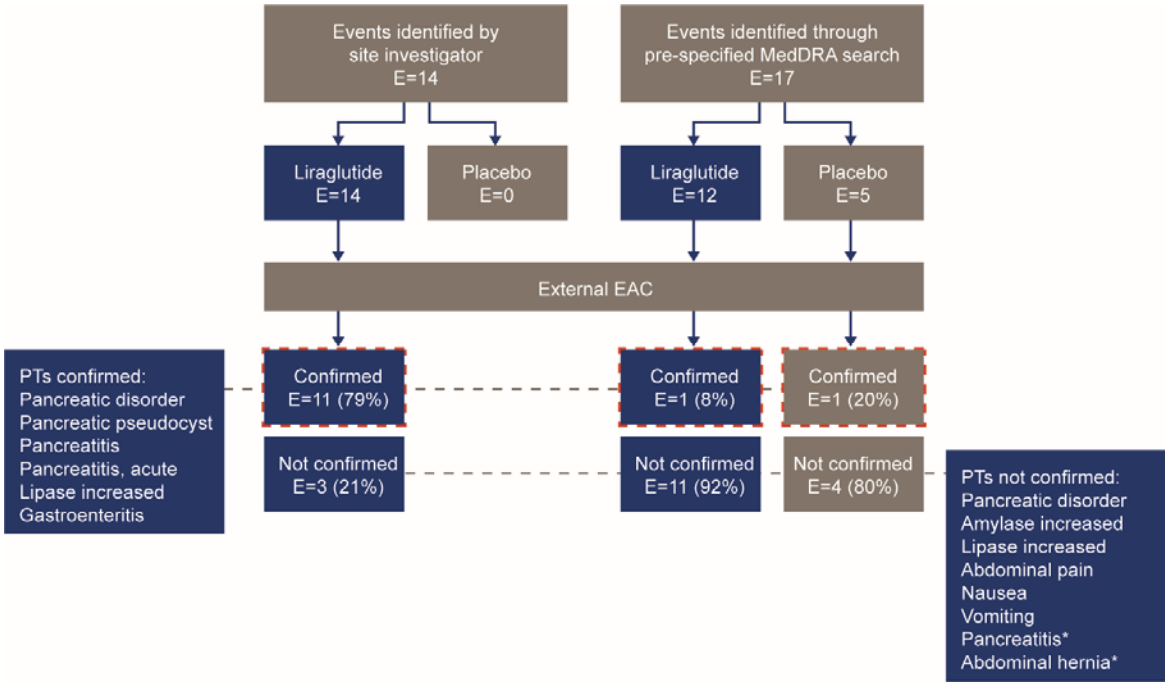
Supplementary Figure 4. Overview of the pancreatitis events sent for adjudication.



*Could not be adjudicated due to incomplete source documentation. E, number of pancreatitis events; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term (from MedDRA).

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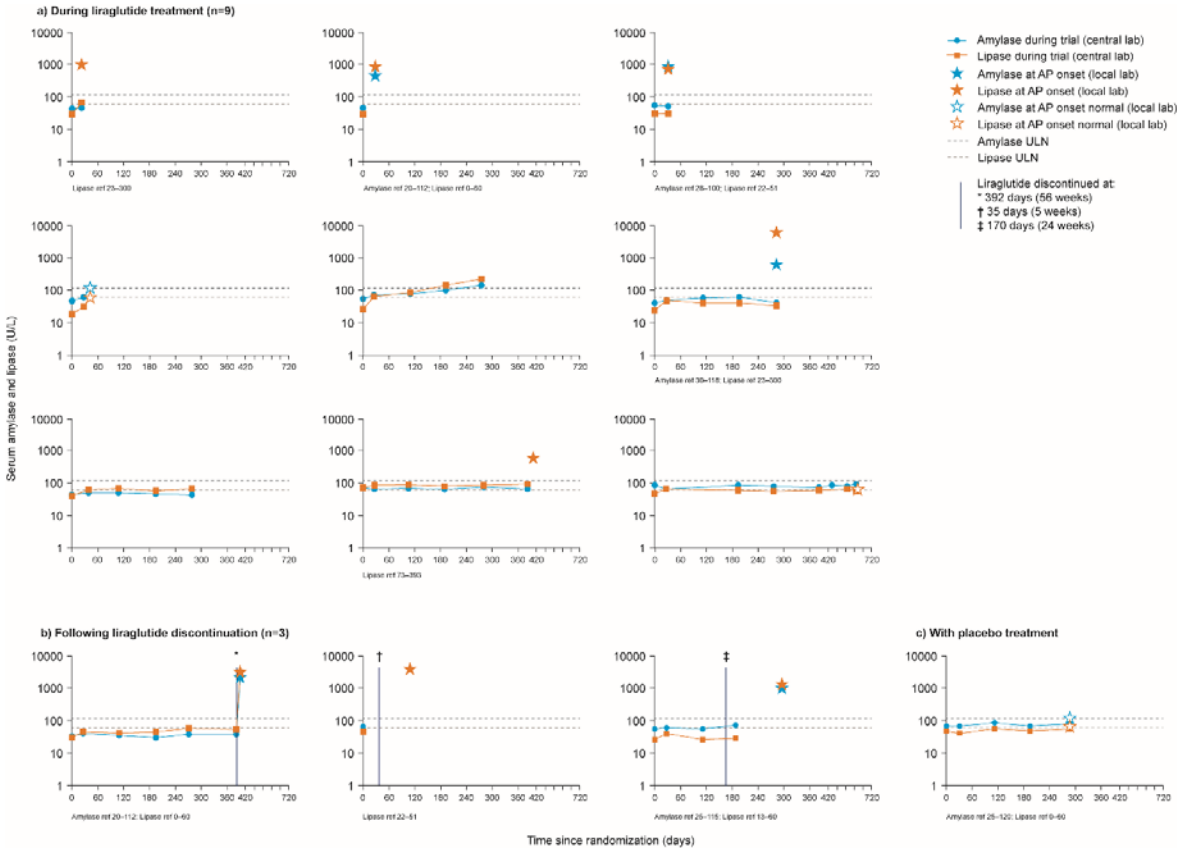
Supplementary Figure 5. Semi-logarithmic plot of amylase and lipase serum levels for the 13 participants who experienced AP: (a) during liraglutide treatment (n=9); (b) following liraglutide discontinuation (n=3); and (c) with placebo treatment (n=1).



ULN for amylase and lipase: 112U/L and 60U/L (all AP events occurred in Trial 1). Amylase and lipase values plotted on a logarithmic scale. Timescale after 420 days has been compressed. Individual panel footnotes refer to the reference interval for local lab measurements. Amylase level at AP event not reported for patient data in panels 1, 5, 7-9, and 11. Lipase level at AP event not reported for patient data in panels 5 and 7

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Supplementary Table 1. Relationship between patient characteristics at baseline and baseline amylase/lipase activity

	Amylase			Lipase		
	Ratio (relative to reference group)	95% CI	Two-sided test for no effect (*p* value)	Ratio (relative to reference group)	95% CI	Two-sided test for no effect (*p* value)
Age group (years)						
<45 / ≥65	0.89	0.85; 0.93		0.87	0.83; 0.91	
45-54 / ≥65	0.92	0.88; 0.97	<0.0001	0.94	0.89; 0.98	<0.0001
55-64 / ≥65	0.95	0.91; 1.00		0.99	0.94; 1.03	
Sex						
Female/Male	0.97	0.95; 0.99	0.0137	0.95	0.93; 0.98	0.0003
Race						
Asian/White	1.14	1.08; 1.21		0.90	0.85; 0.95	
Black or African American/White	1.37	1.33; 1.42	<0.0001	0.86	0.83; 0.89	<0.0001
Other/White	1.13	1.05; 1.21		0.90	0.84; 0.97	
BMI (kg/m^2)						
<30 / ≥40	1.27	1.20; 1.33		1.20	1.14; 1.26	
30-34 / ≥40	1.17	1.15; 1.20	<0.0001	1.13	1.10; 1.16	<0.0001
35-39 / ≥40	1.10	1.08; 1.13		1.05	1.03; 1.08	
Dyslipidemia						
Yes/no	1.03	1.01; 1.06	0.0039	1.09	1.06; 1.11	<0.0001
Hypertension						
Yes/no	1.03	1.01; 1.05	0.0063	1.05	1.03; 1.07	<0.0001
Renal impairment						
Mild/normal	1.07	1.05; 1.09		1.10	1.07; 1.12	
Moderate/normal	1.20	1.14; 1.26	<0.0001	1.29	1.23; 1.36	<0.0001
Severe/normal	1.55	1.12; 2.15		1.24	0.89; 1.74	
Glycemic status						
Prediabetes/ normoglycemia	0.98	0.96; 1.01	0.0721	1.02	1.00; 1.05	<0.0001
Diabetes/ normoglycemia	0.96	0.93; 1.00		1.20	1.15; 1.24	

Safety analysis set

SUPPLEMENTARY DATA

Supplementary Table 2. Relationship between patient characteristics and change in amylase/lipase activity from baseline associated with liraglutide

		Amylase			Lipase		
		Treatment ratio (liraglutide 3.0mg/placebo)	95% CI	Two-sided test for no characteristic and treatment interaction (*p* value)	Treatment ratio (liraglutide 3.0mg/placebo)	95% CI	Two-sided test for no characteristic and treatment interaction (*p* value)
Age group (years)	<45	1.05	1.03; 1.07	0.0027	1.26	1.22; 1.29	0.0002
	45-54	1.08	1.06; 1.10		1.35	1.31; 1.40	
	55-64	1.08	1.06; 1.11		1.31	1.26; 1.37	
	≥65	1.15	1.09; 1.20		1.47	1.36; 1.58	
Sex	Female	1.06	1.05; 1.08	0.0363	1.30	1.27; 1.33	0.2226
	Male	1.09	1.07; 1.12		1.34	1.29; 1.39	
Race	White	1.07	1.06; 1.08	0.6514	1.30	1.27; 1.33	0.2515
	Asian	1.08	1.01; 1.16		1.37	1.22; 1.53	
	Black or African-American	1.09	1.06; 1.13		1.36	1.28; 1.45	
	Other	1.05	0.97; 1.14		1.42	1.24; 1.63	
BMI (kg/m^2)	<30	1.10	1.05; 1.16	0.6712	1.35	1.24; 1.47	0.7196
	30-34	1.08	1.05; 1.10		1.32	1.28; 1.37	
	35-39	1.07	1.04; 1.09		1.31	1.26; 1.35	
	≥40	1.07	1.05; 1.09		1.29	1.25; 1.34	
Dyslipidemia	No	1.07	1.05; 1.08	0.1846	1.31	1.28; 1.34	0.8393
	Yes	1.08	1.06; 1.11		1.31	1.27; 1.36	
Hypertension	No	1.07	1.06; 1.09	0.7800	1.31	1.28; 1.35	0.8189
	Yes	1.08	1.06; 1.10		1.31	1.27; 1.35	
Renal impairment	Normal	1.07	1.05; 1.09	0.8771	1.29	1.25; 1.32	0.1287
	Mild	1.08	1.06; 1.10		1.34	1.30; 1.38	
	Moderate	1.06	1.00; 1.13		1.35	1.22; 1.49	
	Severe	0.98	0.68; 1.42		0.91	0.50; 1.67	
Glycemic status	Normoglycemia	1.04	1.02; 1.06	0.0045	1.28	1.24; 1.32	0.2248
	Prediabetes	1.08	1.06; 1.10		1.33	1.29; 1.36	
	Diabetes	1.10	1.06; 1.14		1.29	1.22; 1.37	

Safety analysis set

SUPPLEMENTARY DATA

Supplementary Table 3. Positive predictive value of increased amylase levels for EAC confirmed pancreatitis

	Liraglutide 3.0 mg (N=3291)	
	N	(%)
Amylase ≥1 ULN during trial	373	
Subsequent pancreatitis	1	(0.3)
Amylase ≥2 ULN during trial	27	
Subsequent pancreatitis	0	(0.0)
Amylase ≥3 ULN during trial	4	
Subsequent pancreatitis	0	(0.0)

Safety analysis set; All phase 3 trials; All events of pancreatitis (including treatment-emergent and non-treatment-emergent events); Amylase measurements include unscheduled visits; observed data including the 120-day regulatory safety update period. Upper limit of normal (ULN) for amylase: 100 U/L (Trials 3 and 4) and 112U/L (Trials 1 and 2).

SUPPLEMENTARY DATA

Supplementary Table 4. Positive predictive value of increased lipase levels for EAC confirmed pancreatitis

	Liraglutide 3.0 mg (N=3291)	
	N	(%)
Lipase ≥ 1ULN during trial	1536	
Subsequent pancreatitis	4	(0.3)
Lipase ≥ 2ULN during trial	317	
Subsequent pancreatitis	1	(0.3)
Lipase ≥ 3ULN during trial	137	
Subsequent pancreatitis	1	(0.7)

Safety analysis set; All phase 3 trials; All events of pancreatitis (including treatment-emergent and non-treatment-emergent events); Lipase measurements include unscheduled visits; observed data including the 120-day regulatory safety update period. Upper limit of normal (ULN) for lipase: 60U/L.