SUPPLEMENTARY DATA

Supplementary Table 1. Baseline clinical characteristics by development of pancreatic events

Characteristic	No pancreatic event (*N*=14613)	Pancreatitis adjudicated yes (*N*=35)	Pancreatic cancer adjudicated yes (*N*=23)	*P**
Age, years	65 (60, 71)	66 (60, 73)	66 (63, 74)	0.61
Female sex	4282/14613 (29.3)	10/35 (28.6)	5/23 (21.7)	0.73
Race				0.016
White	9910/14613 (67.8)	25/35 (71.4)	22/23 (95.7)	
Black	443/14613 (3.0)	4/35 (11.4)	0/23 (0)	
Asian	3259/14613 (22.3)	5/35 (14.3)	1/23 (4.3)	
Other	1001/14613 (6.9)	1/35 (2.9)	0/23 (0)	
Hispanic or Latino	1794/14613 (12.3)	3/35 (8.6)	1/23 (4.3)	0.54
Duration of diabetes, years	10 (5, 16)	9 (5, 16)	11 (5, 20)	0.59
Qualifying HbA1c, %	7.2 (6.8, 7.7)	7.3 (6.7, 8.0)	7.5 (6.9, 7.9)	0.18
Qualifying HbA1c, mmol/mol	55.2 (50.8, 59.6)	57.4 (51.5, 60.7)	56.3 (51.9, 59.6)	0.59
Body mass index, kg/m^2	29.5 (26.3, 33.3)	30.7 (26.7, 35.8)	29.4 (26.2, 35.9)	0.33
eGFR, mL/min/1.73 m^2	73 (60, 88)	72.5 (69.0, 91.0)	75 (60, 94)	0.36
Triglycerides, mg/dL	142 (103, 199)	124 (101, 189)	161 (100, 212)	0.70
Previous cardiovascular disease	10810/14576 (74.2)	32/35 (91.4)	21/23 (91.3)	0.011
Previous cerebrovascular disease	3575/14613 (24.5)	8/35 (22.9)	5/23 (21.7)	0.93
Previous peripheral arterial disease	2428/14613 (16.6)	5/35 (14.3)	0/23 (0)	0.095
Cigarette smoking				0.015
Never smoked	7128/14613 (48.8)	16/35 (45.7)	5/23 (21.7)	
Previous smoker	5818/14613 (39.8)	11/35 (31.4)	15/23 (65.2)	
Current smoker	1667/14613 (11.4)	8/35 (22.9)	3/23 (13.0)	
Medications				
Metformin	11924/14613 (81.6)	25/35 (71.4)	17/23 (73.9)	0.19
Sulfonylurea	6621/14613 (45.3)	15/35 (42.9)	9/23 (39.1)	0.80
Thiazolidinedione	394/14613 (2.7)	2/35 (5.7)	0/23 (0)	0.34
Insulin	3388/14613 (23.2)	11/35 (31.4)	9/23 (39.1)	0.10
Diuretic	5997/14613 (41.0)	13/35 (37.1)	10/23 (43.5)	0.87
Statin	11666/14613 (79.8)	31/35 (88.6)	22/23 (95.7)	0.073

Data are median (IQR) or *n/N* (%). *Kruskal-Wallis *P*-value for continuous variables and chi-square or Fisher's exact test for categorical variables.

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Supplementary Table 2. Characteristics of events submitted for adjudication for possible pancreatitis that were NOT confirmed

Sex	Age (years)	BMI (kg/m^2)	Treatment group	Investigator-reported etiology	Investigator-reported symptoms	Investigator-reported imaging findings	Amylase (% of ULN)	Lipase (% of ULN)	Investigator reported medications at time of event	TECOS completion status
M	73	33.5	Placebo	Unknown	Dizziness and unsteadiness	No visible findings	117%	715%	ARB, statin	Withdrew for AE with no positively adjudicated pancreatic event
M	65	31.3	Placebo	Unknown	Mass	Pancreatic abscess			ARB, statin, thiazide	Completed study with no positively adjudicated pancreatic event
M	73	31	Placebo	Unknown	Serum creatinine increased after rehydration	Acute development of pancreatic pseudocyst		1538%	ARB, statin	Withdrew for AE with no positively adjudicated pancreatic event
M	77	36.2	Placebo	Gallstones or biliary tract disease	Diarrhea and serum creatinine increased after rehydration	Focal, diffuse or inhomogenous gland enlargement	244%	200%	None	Completed study with no positively adjudicated pancreatic event
F	70	42.5	Placebo	Gallstones or biliary tract disease	Pain	Focal, diffuse or inhomogenous gland enlargement	32%		ACE inhibitor, antimicrobial agent, thiazide, metformin, verapamil, omeprazole	Completed study with no positively adjudicated pancreatic event
M	66	32.8	Placebo	Viral gastroenteritis	Pain, vomiting, weight loss, headache, myalgias, low grade fever, nausea, slight loose stools, and decreased appetite	Not done	149%	200%	ARB, statin	Withdrew by physician decision with no positively adjudicated pancreatic event
F	71	47	Placebo	Unknown	Vomiting	Not done			Unknown	GI death with no positively adjudicated pancreatic event
F	51	36.8	Placebo	Unknown	Pain and vomiting	Not done		153%	Statin, aspart insulin, NPH insulin, lisinopril, aspirin,	Completed study with no positively adjudicated pancreatic event

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									paracetamol, codeine, vitamin D	
F	57	45.5	Placebo	Prior pancreatitis	Pain	Not done		182%	Loop diuretic, NSAID, statin, aripiprazole, esomeprazole, fluoxetine, vitamin D, ondansetron, clonidine, metformin, metoprolol, potassium	Confirmed pancreatitis event before this one
F	76	29.5	Placebo	Gallstones or biliary tract disease	Pain	No visible findings	258%	172%	ARB, statin	Completed study with no positively adjudicated pancreatic event
M	56	27	Placebo	Unknown	Pain and vomiting	No visible findings	114%	148%	ACE inhibitor, statin, thiazide	Withdrew for other reason with no positively adjudicated pancreatic event
F	66	34.8	Placebo	Gallstones or biliary tract disease	Pain and vomiting	No visible findings	42%	99%	None	Completed study with no positively adjudicated pancreatic event
F	67	40.4	Placebo	Unknown	Pain and vomiting	Focal, diffuse or inhomogenous gland enlargement	16%		ACE inhibitor, loop diuretic, NSAID, opioid, statin, glargine, lispro, metoclopramide	Confirmed pancreatic cancer event later in the study
F	74	30.8	Placebo	Unknown	Pain, bloating, mass and icterus or tea-colored urine	Focal, diffuse or inhomogenous gland enlargement and pancreatic necrosis or hemorrhagic pancreatitis	66%	51%	ACE inhibitor, opioid, statin, thiazide, gabapentin, glargine	Pancreatic cancer death
M	64	27.5	Placebo	Prior pancreatitis	Pain	Acute development of pancreatic pseudocyst	103%	110%	Statin, glargine, gabapentin, pancrease, aspirin, dipyridamole, citalopram	Withdrew by physician decision with no positively adjudicated pancreatic event
M	.	37.1	Placebo	Unknown	Pain, diarrhea, and weight loss	Focal, diffuse or inhomogenous gland enlargement	26%		ACE inhibitor, dutasteride	Sudden cardiac death with no positively adjudicated pancreatic event

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M	67	32.7	Placebo	Gallstones or biliary tract disease	Pain	Focal, diffuse or inhomogenous gland enlargement			None	Completed study with no positively adjudicated pancreatic event
M	69	41.7	Sitagliptin	Unknown	Diarrhea	No visible findings		498%	ARB, loop diuretic, statin, thiazide, vitamin K antagonist	Withdrew by physician decision with no positively adjudicated pancreatic event
M	70	31.2	Sitagliptin	Unknown	Icterus or tea-colored urine	No visible findings	150%	298%	Statin, fibrate, thiazide, clopidrogrel, acetylsalicylic acid, lansoprazole	Completed study with no positively adjudicated pancreatic event
M	61	26.5	Sitagliptin	Prior pancreatitis	Pain and vomiting	Not done			ACE inhibitor, statin, fibrate, aspirin. bisoprolol, amlodipine, glibenclamide, metformin	Completed study with no positively adjudicated pancreatic event
M	50	23.6	Sitagliptin	Alcohol	Vomiting	Not done			Loop diuretic, statin, thiazide	Completed study with no positively adjudicated pancreatic event
M	50	30.1	Sitagliptin	Unknown	Pain	Not done	189%		ACE inhibitor, statin	Completed study with no positively adjudicated pancreatic event
M	52	26.7	Sitagliptin	Prior pancreatitis	Pain	Not done		211%	ACE inhibitor, statin	Confirmed pancreatitis event before this one
M	52	26.7	Sitagliptin	Prior pancreatitis	Pain	Not done		138%	ACE inhibitor, statin, opioid	Confirmed pancreatitis event before this one
M	52	26.7	Sitagliptin	Prior pancreatitis	Pain	Not done		199%	ACE inhibitor, aspirin, glipizide, quetiapine, citalopram, gabapentin, alprazolam, pioglitazone, metformin	Confirmed pancreatitis event before this one
F	80	28.1	Sitagliptin	Gallstones or biliary tract disease	Pain and vomiting	Not done			ACE inhibitor	Confirmed pancreatitis event before this one
M	65	30.9	Sitagliptin	Alcohol	Pain	No visible findings	227%	917%	Statin, thiazide, metformin, aspirin, metoprolol,	Completed study with no positively adjudicated pancreatic event

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									clopidogrel, albuterol inhaler	
F	64	34	Sitagliptin	Prior pancreatitis	Pain	No visible findings	50%		ACE inhibitor, statin	Completed study with no positively adjudicated pancreatic event
M	54	33.2	Sitagliptin	Prior pancreatitis	Pain, diarrhea, and vomiting	No visible findings	38%	116%	Hydromorphone	Withdrew by physician decision with no positively adjudicated pancreatic event
M	70	29.8	Sitagliptin	Gallstones or biliary tract disease	Pain and dark stool	Focal, diffuse or inhomogenous gland enlargement and pancreatic abscess	48%	64%	ACE inhibitor, statin	Pancreatic cancer death
M	73	30.8	Sitagliptin	Unknown	Pain, diarrhea, and vomiting	Acute development of pancreatic pseudocyst	48%	137%	ACE inhibitor, statin, thiazide	Completed study with no positively adjudicated pancreatic event
M	67	30.4	Sitagliptin	Gallstones or biliary tract disease	Pain and vomiting	Focal, diffuse or inhomogenous gland enlargement	234%		ACE inhibitor, fibrate, loop diuretic, NSAID, statin, thiazide, aspirin, dipyridamole, carvedilol, digoxin, isosorbide mononitrate	Sudden cardiac death with no positively adjudicated pancreatic event
M	57	29.6	Sitagliptin	Prior pancreatitis	Pain and vomiting	Focal, diffuse or inhomogenous gland enlargement	81%	127%	Statin, atenonol, ezetimibe, aspirin	Confirmed pancreatitis event later in the study

BMI=body mass index, ULN=upper limits of normal, ARB=angiotensin receptor blocker, ACE=angiotensin converting enzyme, NPH=neutral protamine Hagedorn insulin, NSAID=non-steroidal anti-inflammatory drug, AE=adverse event, GI=gastrointestinal.

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Definitions From TECOS Charter

Acute Pancreatitis

Reported events of acute pancreatitis will be adjudicated based on clinical symptoms, serologic markers and radiographic findings. Confirmed cases of acute pancreatitis will be further categorized as mild or severe based on evidence of organ failure or radiographic criteria.

To confirm a diagnosis of acute pancreatitis, the following criteria must be present:

i. Symptoms of abdominal pain **OR** vomiting

AND

i. Objective evidence of pancreatic inflammation

1. Elevated pancreatic enzymes, defined by
   a. Amylase OR Lipase > 3× the upper limit normal.
   b. In patients with chronic pancreatitis, enzyme elevations >2× the upper limit normal

OR

2. Evidence of pancreatitis documented by imaging
   a. Abdominal CT, MRI or ultrasound showing focal, diffuse and inhomogeneous gland enlargement

Confirmed acute pancreatitis will be graded as mild, severe or unknown. To confirm severe pancreatitis, the following criteria must be present:

1. Evidence of organ failure (at least one of the following)
   a. Shock: systolic BP < 90 mm Hg
   b. Pulmonary insufficiency: Pa02 < 60 mm Hg
   c. Renal failure: serum creatinine > 2 mg/dl after rehydration
   d. Gastrointestinal bleeding: > 500 ml/24 hours

OR

2. Local complications demonstrated on abdominal CT, MRI, or ultrasound (at least one of the following)
   a. Pancreatic necrosis (note: hemorrhagic pancreatitis is a pathologic term often used synonymously with pancreatic necrosis)
   b. Pancreatic abscess
   c. (Acute) Pancreatic pseudocyst

Confirmed cases of acute pancreatitis not meeting criteria for severe pancreatitis will be classified as mild pancreatitis.

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Malignancy

The following definitions will be utilized by the CEC for purposes of adjudication of malignancies:

I. Charter-Defined Malignancy

The CEC will classify the event as a **charter-defined malignancy** if the subject has either evidence of a new malignancy or the first recurrence (during the study period) of a previous cancer.

A. New malignancies:

1. New primary cancer in patients with or without pre-existing cancer, or
2. New metastatic cancer in patients without previous diagnosis of cancer, or
3. New metastatic cancer of a clearly distinct histology from any pre-existing cancer

B. First recurrence of previous cancer:

1. Evidence of first recurrence of a pre-existing cancer during the study period (histological, imaging, or clinical), AND
2. History of this pre-existing cancer at the time of randomization (i.e. diagnosis of original cancer predates randomization), AND
3. No evidence to indicate based on histological type or clinical picture that this is a different cancer.

II. Benign Neoplasm

Non-malignant neoplasms which are reported should be classified as benign neoplasms.

III. Progression of Existing Disease

Progression of a prior malignancy does not meet the TECOS charter definition of malignancy. Such occurrences will be classified as progression of existing disease.

IV. Neoplasm Details

A. Date of Initial Detection: This will be the date of initial detection by a treating physician, when the patient demonstrated either clinical symptoms or diagnostic testing results (for example, imaging, laboratory) with evidence of neoplasm that allows for a probable clinical diagnosis. Whichever date can be confirmed to occur first will be used.

B. Date of histological diagnosis: This will be the date that the diagnosis of Neoplasm was documented by histological and/or cytological evidence.

C. Status of Disease:

1. No evidence of disease: A patient who after treatment has normal tumor markers and no evidence of disease on physical exam or imaging studies.
2. Active disease: A patient who has evidence of disease and has either had a new and/or change in treatment since their previous evaluation or could be eligible for a new and/or change in treatment but either refused or did not receive the therapy for another clinical reason (e.g. terminal disease for which alteration in treatment would not be expected to meaningfully prolong life expectancy).
3. Stable/Inactive disease: A patient that has evidence of disease, but is not progressing, and has had no new and/or change in treatment since their previous evaluation.
4. Cannot be determined: Is used to describe cases for which there is not enough information to indicate a classification.