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A Randomized Controlled Phase 2 Dose-Finding Trial to Evaluate the Efficacy and Safety of Camostat in the Treatment of Painful Chronic Pancreatitis: The TACTIC Study

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BACKGROUND & AIMS: Chronic pancreatitis (CP) causes an abdominal pain syndrome associated with poor quality of life. We conducted a clinical trial to further investigate the efficacy and safety of camostat, an oral serine protease inhibitor that has been used to alleviate pain in CP. **METHODS:** This was a double-blind randomized controlled trial that enrolled adults with CP with a baseline average daily worst pain score ≥4 on a numeric rating system. Participants were randomized (1:1:1:1) to receive camostat at 100, 200, or 300 mg 3 times daily or placebo. The primary end point was a 4-week change from baseline in the mean daily worst pain intensity score (0–10 on a numeric rating system) using a mixed model repeated measure analysis. Secondary end points included changes in alternate pain end points, quality of life, and safety. **RESULTS:** A total of 264 participants with CP were randomized. Changes in pain from baseline were similar between the camostat groups and placebo, with differences of least squares means of −0.11 (95% CI, −0.90 to 0.68), −0.04 (95% CI, −0.85 to 0.78), and −0.11 (95% CI, −0.94 to 0.73) for the 100 mg, 200 mg, and 300 mg groups, respectively. Multiple subgroup analyses were similar for the primary end point, and no differences were observed in any of the secondary end points. Treatment-emergent adverse events attributed to the study drug were identified in 42 participants (16.0%). **CONCLUSION:** We were not able to reject the null hypothesis of no difference in improvements in pain or quality of life outcomes in participants with painful CP who received camostat compared with placebo. Studies are needed to further define mechanisms of pain in CP to guide future clinical trials, including minimizing placebo responses and selecting targeted therapies. ClinicalTrials.gov, Number: NCT02693093.

Keywords: Serine Protease Inhibitor; Analgesia; Morbidity; Quality of Life.

Chronic pancreatitis (CP) is a fibroinflammatory disease of the exocrine pancreas that is often accompanied by progressive, irreversible pancreatic insufficiencies. The cardinal symptom of CP is abdominal pain, which can develop early in the disease course and is a primary source of morbidity associated with decreased quality of life, higher likelihood of significant mental health disorders, and hospitalizations.[1–3] Proposed mechanisms for pain origination include inflammatory and neuropathic pathways.[4] In addition, there is a complex combination of factors in patients, including pancreatic duct obstruction; abnormalities in pain processing; and psychological distress, which are associated with cumulative detrimental effects on pain intensity and quality of life.[5] A pragmatic approach to improving pain in patients with CP involves trying to reduce the contribution of 1 or more initiating or propagating factors in the pain experience. In a recent Patient Focus Drug Development

Abbreviations used in this paper: **CP, chronic pancreatitis; FDA, US Food and Drug Administration; ITT, intention-to-treat; MMRM, mixed model repeated measure; RCT, randomized controlled trial; TEAE, treatment emergent adverse event.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Chronic pancreatitis is a condition commonly associated with a debilitating chronic abdominal pain syndrome for which there is no approved medical therapy.

NEW FINDINGS

This trial found that camostat (an oral medication used in some countries for this indication) did not improve pain or other patient-reported outcomes compared with placebo after 1 month of therapy.

LIMITATIONS

The analyses did not assess changes in potential inflammatory mediators of disease.

CLINICAL RESEARCH RELEVANCE

Although camostat was safe, there were no observed benefits with regard to symptom management for chronic pancreatitis. The high response rate in all groups, including placebo, warrants additional investigation to guide future trial design and execution in this study population.

BASIC RESEARCH RELEVANCE

Targeting the reduction of trypsin-mediated injury alone with an oral protease inhibitor does not clearly improve disease-related symptoms.

program, respondents with pancreatitis identified pain as the most desired area for further investigation.[6]

In the absence of consistently effective medical therapies for pain management in CP, it is common for patients to receive escalating doses of opioids and/or embark on endoscopic or surgical intervention. An oral, nonopioid medication that is safe and effective for managing pain in CP is highly desirable. In Japan, a medication named "camostat" (ie, camostat mesylate) has been approved since 1985 and is dosed at 200 mg 3 times daily for the treatment of acute pain associated with CP. Camostat is an oral serine protease inhibitor that has a number of potentially beneficial effects for pancreatitis, including inhibition of intra- and extracellular activation of trypsin and reduced activation of macrophages, monocytes, and neutrophils in pancreatic tissue.[7–10] It has a favorable safety profile and has been used for other indications, including recent studies in COVID-19.[11]

Because use of camostat is not approved, and it is not widely used, in countries outside of Japan, we conducted a double-blind, parallel-group, randomized controlled trial (RCT) to examine the efficacy and safety of camostat to relieve or reduce abdominal pain in participants with CP. The current phase 2 trial studied multiple dosages to guide planning for a potential phase 3 trial. In addition to studying various measures of the pain experience, we aimed to evaluate the effect of camostat vs placebo on quality of life.

Methods

Ethical Conduct

The study protocol was approved by a central Institutional Review Board (ie, Copernicus Group) with agreement from each participating center's Institutional Review Board or Ethics Committee. Written informed consent was obtained from participants before conducting any study procedures. The trial was prospectively registered at Clinicaltrials.gov (NCT02693093). All authors had access to the study data and reviewed and approved the final manuscript.

Study Design

The scientific rationale and study design for the phase 1/2 TACTIC (A Dose Ranging Study Evaluating Efficacy and Safety of Camostat) clinical trial have been described previously.[12] Study planning involved iterative discussions with multiple stakeholders, including the study sponsor, investigators, key opinion leaders in the field of pancreatitis-related pain, and patient stakeholders. Based on guidance from the US Food and Drug Administration (FDA), a phase 1 study was performed to assess the pharmacokinetic and safety profiles after administration of a single dose of camostat (100 mg, 200 mg, and 300 mg). Doses were administered to 6 participants with CP in each dosing treatment group.

After an interim analysis confirming safety and approval from FDA to proceed, a phase 2, double-blind, parallel-group RCT was performed from April 2017 to September 2021 in the United States, Ukraine, and Russia. All participants in phase 2 completed a 1-week, single-blind, placebo run-in period before randomization (Supplementary Figure 1). Group assignment was stratified on the basis of mean daily opioid dose (morphine-equivalent dose of 0–50 mg/d vs >50 to ≤100 mg/d) and randomized by block at each site. There were a total of 4 arms consisting of 3 times daily dosing of placebo or camostat (at doses of 100 mg, 200 mg, or 300 mg) for 28 days. Placebo tablets were made to be identical in appearance to the investigational drug and the total number of tablets per day was the same for participants in all arms.

Eligibility Criteria

Eligibility criteria for the phase 2 trial have been detailed previously (Supplementary Table 1).[12] In brief, adults (aged 18–85 years) with CP and a baseline pain score of ≥4 (on a numeric rating scale from 0 to 10) were eligible for participation. The study's definition of CP was adapted from the American Pancreatic Association's diagnostic guidelines, and included the presence of pancreatic parenchymal or intraductal calcifications, advanced ductal changes, or suggestive diagnostic features on endoscopic ultrasound with supportive evidence of exocrine pancreatic dysfunction or insufficiency.[13] For participants enrolled into phase 2, the baseline mean daily worst pain score had to be a minimum of 4 out of 10 during 4 or more days in the 7-day, single-blind run-in period, or they did not proceed with randomization. The use of opioid analgesics (up to a dose of 100 mg oral morphine-equivalent) was permitted during the study, and dose titrations (increase or decrease) during the intervention period were at the discretion of each participant's clinical provider.

Outcome Assessments

There are no standardized core outcome assessments for trials in recurrent acute or chronic pancreatitis.[14] Therefore, the primary outcome regarding efficacy was selected after consultations with the FDA, key opinion leaders, and study

investigators, and was defined as the change in mean daily worst pain intensity score (averaged over 7 days of the week) from the placebo run-in period (day −7 to day −1) to week 4 (day 22 to day 28).

Secondary efficacy variables included change from baseline in least pain score, mean pain score, and current pain score; responder rate; time to first rescue medication use (defined as time to first intravenous or intramuscular analgesic); change in quality of life from baseline (assessed using Pancreatitis Quality of Life Instrument) and the pain interference aspect of the Brief Pain Inventory); and change in mean morphine-equivalent daily opioid dose and gabapentin or pregabalin daily dose.[15] For the purposes of this study, a responder was defined as a participant who achieved ≥30% reduction in primary outcome from baseline for ≥2 of the 4 weeks of double-blind treatment.

Safety evaluations included physical examinations, vital sign measurements, adverse events, and concomitant medication evaluations, 12-lead electrocardiograms, and clinical laboratory tests. The safety population for the phase 2 study included all participants receiving at least 1 dose of camostat or placebo. Assessors were blinded to group assignments.

Sample Size Determination

There were limited data available on the SD of the primary efficacy end point before the study, so we planned a blinded, interim sample size re-estimation. The initial sample size estimation assumed a 1-unit difference between each camostat dose (100, 200, and 300 mg) and placebo and an SD of 1.16, which resulted in an initial sample size of 120 participants for the 4 arms combined. In the absence of a defined standard, the effect size was determined on the basis of iterative discussions, as discussed previously. We set a target sample size of 128 to accommodate a 5% dropout rate. A blinded power analysis completed in 2019 found a larger than assumed SD, so the sample size was increased to a total of 260 participants to yield approximately 80% power at an overall 2-sided type I error rate of 5% using Dunnett's procedure.

Statistical Analysis

Efficacy analyses were based on the intent-to-treat (ITT) analysis set and included all randomized participants. Analysis of the primary efficacy variable was repeated using a per-protocol set to test the robustness of results. The per-protocol set consisted of ITT participants who had no major protocol deviations that impacted the primary efficacy analysis, received the treatment to which they were randomly assigned, and had a baseline pain score and at least 1 post-baseline pain score.

The primary efficacy variable (change in mean daily worst pain intensity score from baseline to week 4) was analyzed using a restricted maximum likelihood–based repeated measures approach (ie, a mixed model repeated measure [MMRM] analysis). Missing data were imputed using the baseline observation carried forward. The MMRM analysis included treatment arm, stratification factor (ie, opioid dose category), baseline mean daily pain intensity score, visit, and treatment by visit interaction as fixed-effect explanatory variables and center as a random effect. The visit variable in the model contained a link between participants to facilitate the repeated measures analysis with an unstructured covariance matrix. Significance tests were based on least squares mean. The treatment comparisons were the contrast between treatment groups at week 4. Model-based point estimates and 95% CIs were calculated. Dunnett's procedure was used to control the overall familywise error rate at the 2-sided 5% level for the comparisons of the 3 camostat dose groups with placebo.

For change from baseline in continuous secondary end points, MMRM analyses similar to that used for the primary analysis were performed using the ITT analysis set. Binary end points were analyzed using a logistic regression model. Lastly, the Kaplan-Meier method was used to assess time to first rescue medication.

Results

Baseline Characteristics

A total of 264 participants were enrolled and randomized in this double-blind, placebo controlled trial (Figure 1). Mean age at enrollment was 51.8 years (Table 1). The study population was predominantly White (94.3%) with a slight male predominance (51.1%). With regard to the disease characteristics, the diagnosis of CP was confirmed by the presence of calcifications in 70% of participants. The median duration of CP was 4.2 years, with almost 30% reporting diabetes and almost three-quarters (72.0%) using pancreatic enzyme replacement therapy. More than one-half of participants (51.1%) had undergone prior invasive interventions for pain relief related to CP, including celiac plexus block (17.8%), other endoscopy therapy (27.3%), or pancreatic surgery (22.7%). The treatment arms were balanced with respect to demographic and baseline disease characteristics (Table 1).

Primary Efficacy Assessment

In the ITT analysis set, the mean daily worst pain intensity scores (assessed by MMRM analysis) at baseline were 5.56, 5.89, 5.82, and 5.83 for the groups receiving the placebo, camostat 100 mg, 200 mg, and 300 mg 3 times daily, respectively. Based on observed case data, mean changes from baseline were −2.03, −2.10, −1.97, and −2.21 at week 4 for the respective groups (Figure 2). These changes from baseline to week 4 were similar in all groups. Using an MMRM model analysis, there were no significant differences compared with placebo for any treatment group receiving camostat (Table 2). Similar analyses using the per-protocol study population for the primary end point also failed to show a statistically significant difference between camostat groups and placebo (data not shown).

Subgroup analyses based on sex, the morphine-equivalent dose at enrollment (0 mg/d, <0 to ≤50 mg/d, or >50 to ≤100 mg/d), pain duration (more than 4.2 years [observed median pain duration] vs less than 4.2 years), presence of calcifications (yes vs no), and geographic region (United States vs rest of the world) were also conducted on the ITT analysis set using observed case data and an MMRM model. No significant difference in changes from baseline were observed for participants treated with camostat compared with placebo for any subgroup analyzed (data not shown).

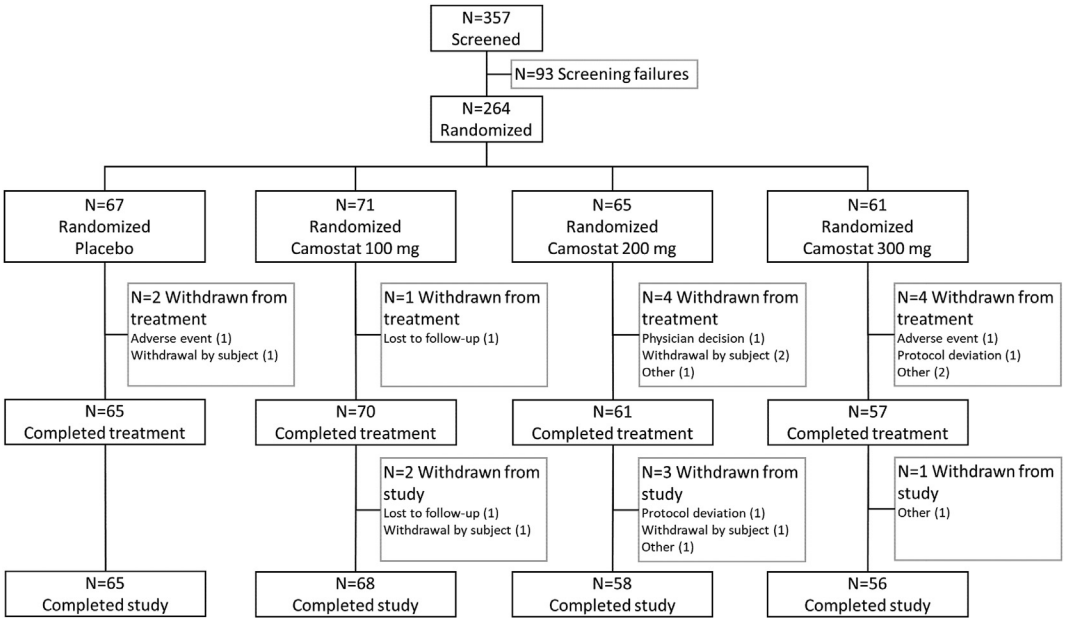

Figure 1. Final disposition of 264 randomized participants in ITT population of the TACTIC study.

Secondary Efficacy Assessments

There were no significant between-group differences in the secondary end points using alternate methods of assessing pain scores, including change from baseline in least pain score, mean pain score, and current pain score (Supplementary Figure 2). The responder rates ranged from 48% to 59% across the treatment arms. Odds ratios of being a responder were analyzed for each treatment group compared with placebo for the ITT analysis, and did not show a significant increase associated with any camostat arm (Table 3). There were only 5 events of first rescue for all groups (data not shown), so we did not have statistical power to assess whether there was a statistical difference in the time to first rescue with an intravenous or intramuscular analgesic. There were no changes in the mean daily doses of oral morphine-equivalent or gabapentin/pregabalin doses (data not shown). Lastly, the change in quality of life scores were similar between groups for both the total and subdomain scores (Supplementary Figure 3, Supplementary Table 2).

Safety

One randomized participant did not take any dose of study drug, so the safety population consisted of 263 participants. A total of 271 treatment-emergent adverse events (TEAEs) occurred in 109 participants (41.4%). The most commonly reported TEAEs were headache (7.2%), nausea (6.1%), and abdominal pain (5.7%) (Supplementary Table 3). More participants experienced TEAEs in groups receiving placebo or 100 mg camostat 3 times daily (43.3% and 46.5%, respectively) than 200 mg or 300 mg camostat 3 times daily (37.9% and 37.3%, respectively). The proportion of participants with TEAEs that were related to the study intervention were inversely proportional to the camostat dose received (10 [14.9%], 14 [19.7%], 10 [15.2%], and 8 [13.6%] for the groups receiving placebo, camostat 100 mg, 200 mg, and 300 mg 3 times daily, respectively).

Serious TEAEs showed a dose-dependent increase with 1.5%, 2.8%, 4.5%, and 6.8% of affected participants with placebo, camostat 100 mg, 200 mg, and 300 mg 3 times daily, respectively; none were adjudicated as related to the intervention by site investigators (Supplementary Table 4). Two participants discontinued the study because of a TEAE, 1 in the placebo group (due to nausea) and 1 in the 300 mg 3 times daily camostat group (due to finding of a pancreatic cyst). There were no safety events observed related to changes in laboratory values, vital signs, electrocardiogram readings, or deaths.

Discussion

In this double-blind, placebo controlled, randomized trial in painful CP, there was no significant improvement in the primary end point of mean daily worst pain score after 28 days at any of the studied dosages of camostat compared with placebo. Similarly, there were no improvements in subgroups or secondary efficacy end points, including alternate methods of assessing pain response, quality of life, and dosages of concomitant analgesic medications. The safety data confirmed it is generally safe to administer camostat at doses up to and including 300 mg 3 times daily. The observed responder rate was high in all groups, including the placebo arm, despite extensive efforts to minimize a placebo response. These results demonstrate the need to better understand the placebo response in this patient population, as well as highlight the critical need for placebo controls in all studies in CP.

Prior work supporting the use of camostat to relieve symptoms in CP has been conducted largely in preclinical models or outside the context of a controlled trial. Thus,

Table 1. Baseline Characteristics of the Intention-to-Treat Study Population (n = 264) for the Double-Blind Phase

Characteristic	Placebo TID (n = 67)	Camostat 100 mg TID (n = 71)	Camostat 200 mg TID (n = 65)	Camostat 300 mg TID (n = 61)
Age at enrollment, *y*, mean ± SD	51.0 ± 11.7	52.7 ± 11.9	53.1 ± 10.3	50.1 ± 12.3
Race, n (%)				
White	66 (98.5)	62 (87.3)	62 (95.4)	59 (96.7)
Black or African American	1 (1.5)	7 (9.9)	2 (3.1)	2 (3.3)
American Indian or Alaska Native	0	1 (1.4)	0	0
Native Hawaiian or other Pacific Islander	0	0	1 (1.5)	0
Multiple	0	1 (1.4)	0	0
Ethnicity, n (%)				
Hispanic or Latino	4 (6.0)	5 (7.0)	3 (4.6)	4 (6.6)
Not Hispanic or Latino	63 (94.0)	66 (93.0)	62 (95.4)	57 (93.4)
Male sex, n (%)	38 (56.7)	33 (46.5)	32 (49.2)	32 (52.5)
Body mass index at enrollment, mean ± SD	27.05 ± 5.65[a]	26.34 ± 6.60	26.50 ± 5.84	25.53 ± 4.21
Duration of pancreatitis, *y*, median	3.56	4.28[a]	4.15	4.85
Presence of calcifications on imaging, n (%)	47 (70.1)	48 (67.6)[a]	42 (64.6)	48 (78.7)
Etiology of chronic pancreatitis attributed to alcohol, n (%)	13 (19.4)	14 (19.7)[a]	13 (20.0)	12 (19.7)
Previous pancreatic surgery, n (%)	11 (16.4)	17 (24.6)[b]	16 (24.6)	16 (26.7)[a]
Current smoker, n (%)	15 (22.4)	19 (26.8)	16 (24.6)	24 (39.3)
Presence of diabetes, n (%)	16 (23.9)	21 (29.6)	24 (36.9)	16 (26.2)
Use of pancreatic enzyme replacement therapy, n (%)	46 (68.7)	54 (76.1)	47 (72.3)	43 (70.5)
Morphine-equivalent dose strata at enrollment, n (%)				
0 to <50 mg/d	59 (88.1)	65 (91.5)	62 (95.4)	60 (98.4)
50 to ≤100 mg/d	8 (11.9)	6 (8.5)	3 (4.6)	1 (1.6)
Baseline morphine-equivalent dose, *mg*, mean ± SD	8.18 ± 21.01	7.99 ± 17.55	7.95 ± 25.70	5.51 ± 12.82

TID, 3 times daily.
[a]Participants with missing data: n = 1.
[b]Participants with missing data: n = 2.

although the primary results are different than expected, there are potential biological and methodological explanations. First, prior preclinical studies primarily sought to understand the mechanistic pathways whereby camostat may disrupt the pathogenesis of pancreatitis. In our study, the primary goal was to demonstrate clinical efficacy. Therefore, we were unable to exclude the possibility that participants may have experienced biological benefits, which we were unable to observe clinically. For example, prior mechanistic studies examined changes in duodenal trypsin output with direct pancreas function testing and pancreas size with serial abdominal ultrasonography.[16,17] Although objective biological end points are desirable, efficient methods to assess such biological responses in larger clinical trials of CP without introducing excessive participant burden are needed. Next, most developmental studies in humans have used an open-label design, which is susceptible to, and we are unable to account for, the placebo response. For example, a recent trial that did not appear to be blinded showed pain improvement in participants with CP receiving a combination of camostat with pancreatic enzymes and a proton pump inhibitor.[18] Lastly, it is important to acknowledge most of the prior work has been conducted in Asia. Therefore, there is a possibility of potential differences in drug metabolism of camostat (and therefore different therapeutic responses) due to differences in pharmacogenetics, although this is speculative. Although we did not find benefit in a group using a camostat dose higher than that used in routine clinical practice (ie, 200 mg 3 times daily), our data cannot conclude this lack of response occurred despite achieving therapeutic levels of the active metabolite in circulation. Future investigations of camostat should consider the addition of pharmacodynamic studies for correlative work in this regard.

In the absence of a widely accepted core outcome for assessing pain in CP, we selected a series of primary and secondary assessments for pain based on consultation with the FDA, key opinion leaders, and study investigators. We conducted a series of subgroup analyses and sensitivity analyses for these various assessments, yet were unable to

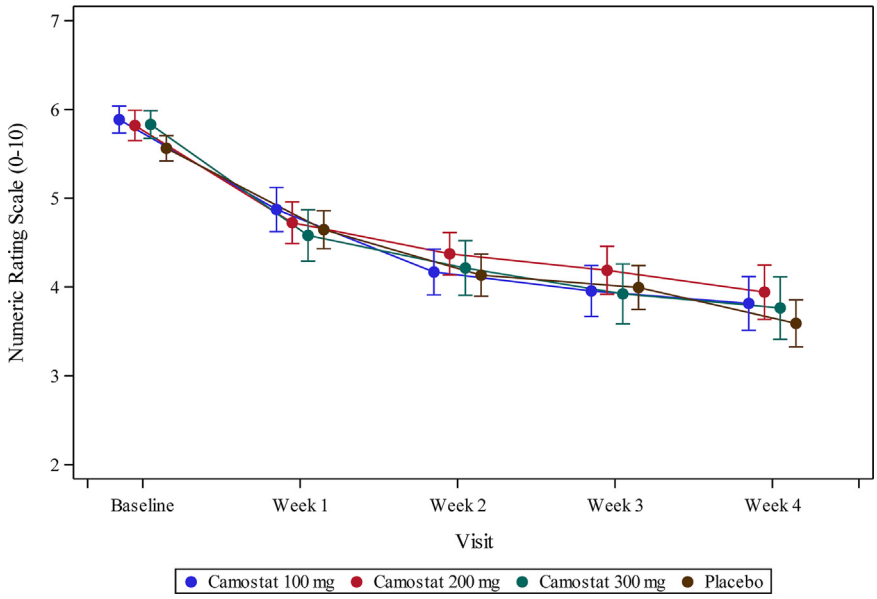

Figure 2. Plots of daily worst pain intensity score in the intention to treat analysis set. Data represent mean ± SE.

demonstrate increased efficacy of camostat compared with placebo. Notably, there were improvements in essentially all outcomes across all treatment arms. For example, the responder rate was 51%–59% in the 3 camostat arms and 48% in the placebo arm. This placebo response was present despite careful planning and execution of the RCT, which included double blinding, a 1-week run-in period for eligibility, and use of placebo-response reduction training of all

Table 2. A Mixed Model Repeated Measures Analysis of the Change From Baseline in Mean Daily Worst Pain Intensity Score in the Intention-to-Treat Population for the Double-Blind Phase

		Camostat		
Variable	Placebo TID (n = 67)	100 mg TID (n = 71)	200 mg TID (n = 65)	300 mg TID (n = 61)
Baseline				
Mean	5.56	5.89	5.82	5.83
SD	1.169	1.287	1.380	1.221
Wk 4				
Mean	3.51[a]	3.77[b]	3.77[c]	3.54[d]
SD	2.127	2.546	2.380	2.686
Change from baseline to wk 4				
Mean	–2.03[a]	–2.10[b]	–1.97[c]	–2.21[d]
SD	1.706	2.012	1.873	2.104
LS mean ± SE[e]	–1.53 ± 0.266	–1.64 ± 0.263	–1.57 ± 0.277	–1.64 ± 0.287
Difference of LS means (95% CI)[e]	—	–0.11 (–0.90 to 0.68)	–0.04 (–0.85 to 0.78)	–0.11 (–0.94 to 0.73)
Unadjusted P value vs placebo	—	.706	.899	.721
Adjusted P value vs placebo[f]	—	1.000	1.000	1.000

LS, least square.
[a]No. of participants with missing data: n = 2.
[b]No. of participants with missing data: n = 1.
[c]No. of participants with missing data: n = 3.
[d]No. of participants with missing data: n = 4.
[e]LS means, 95% CI, and *P* values were obtained from a restricted maximum likelihood-based repeated measures approach (ie, an MMRM analysis) on baseline observation carried forward data.
[f]The adjusted *P* value obtained from the Dunnett's procedure protects the overall familywise error rate by taking into account the multiple comparisons among the 3 camostat treatment groups with placebo.

Table 3. Proportion and Odds of Participants Achieving Study Definition for Response Based on Treatment Arm

Variable	Placebo TID (n = 67)	Camostat 100 mg TID (n = 71)	Camostat 200 mg TID (n = 65)	Camostat 300 mg TID (n = 61)
Achieved treatment response, n (%)	32 (47.8)	37 (52.1)	33 (50.8)	36 (59.0)
95% CI[a]	35.8–59.7	40.5–63.7	38.6–62.9	46.7–71.4
Adjusted odds ratio (camostat vs placebo)	—	1.56	1.37	2.11
95% CI[a]	—	0.75–3.24	0.65–2.90	0.98–4.57
P value	—	0.238	0.414	0.058
Adjusted *P* value[b]	—	0.476	0.476	0.174

TID, 3 times daily.
[a]The 95% CI for the proportions was based on the normal approximation to the binomial. The 95% CI for the adjusted odds ratio and the *P* value were obtained from a logistic regression model on baseline observation carried forward data with treatment, baseline mean pain intensity score, and center as factors.
[b]The adjusted *P* value, obtained with the Holm's step-down procedure, protects the overall familywise error rate by taking into account the multiple comparisons among the 3 camostat treatment groups with placebo.

research staff. Although the placebo response is higher than reported in a prior meta-analysis of placebo response (20%) in CP, this is likely due to a more stringent definition for pain remission used in the meta-analysis.[19] For comparison, the placebo response rate in the current trial was similar to what has been observed for analgesic trials in other diseases.

These findings have potentially broader implications for future trials and clinical practice. First, the high placebo response reveals a potential challenge of using patient-reported outcomes in clinical trials of pain in CP. This response should be taken into consideration for future trial design and may guide sample size calculations and other aspects of study design (eg, selection of alternative end points). Further research will be beneficial to help understand participant characteristics that are associated with a placebo response. Importantly, there is a need for additional deliberations among key stakeholders, including patient representatives, investigators, and regulatory agencies to collaboratively identify core outcome measures. The high placebo response highlights the need to reconsider approaches for treating pain in CP that are based on noncontrolled, observational studies (including total pancreatectomy and endoscopic therapies). Lastly, we did observe several cases of treatment-emergent abdominal pain and acute pancreatitis in the camostat arms. Without uniform cross-sectional imaging for all participants, it was not possible to definitively determine whether these events reflected the underlying natural history of their pancreatitis or were potentially caused by protease inhibition leading to onset of pancreatitis. Biological plausibility for a connection relates to prior studies finding that the pancreas can adapt to intraluminal protease inhibition, leading to increased duodenal lipase activity.[16,17] This potential signal requires further scrutiny in future trials.

There are additional limitations with our study. First, a consequence of the stringent eligibility criteria is that the results may not be generalizable to a broader patient population. As mentioned previously, we do not have correlative pharmacodynamic or translational studies to understand whether the doses studied were adequate to maintain sufficient levels of the active metabolite in circulation and/or produce the anticipated intracellular changes. Of note, camostat is rapidly metabolized to its active metabolite, 4-(4-guanidinobenzoyloxy) phenylacetate (referred to as FOY 251), which has inhibitory effects similar to those of trypsin.[20–23] Therefore, insufficient metabolite levels may explain the lack of demonstrated efficacy. A final challenge with all studies of pain in CP relates to the nonspecificity of the symptom and lack of understanding regarding mechanistic contributors in individual patients. Pancreatic quantitative sensory testing is a potentially meaningful tool under development to objectively characterize phenotypic patterns of pain, this was not accessible at that start of the current RCT and the feasibility of using this tool for stratification in an RCT has not been examined.[24,25]

There are several strengths to our study. First, it is a double-blind RCT in more than 250 participants with CP, which represents a large clinical trial for this patient population. Combining the low disease prevalence, stringent eligibility criteria, and COVID-19 pandemic, the study took 5 years to complete, which reflects the large collaborative effort of the study investigators and sponsor. Our null findings were consistent across numerable comparisons to investigate different aspects of pain and quality of life in the ITT group, as well as multiple subgroups of interest confirming results.

In summary, in this double-blind, randomized controlled phase 2 trial, we were not able to reject the null hypothesis of no difference in improvements in pain or quality of life

outcomes in participants with painful CP who received camostat compared with placebo. Treatment with camostat at doses up to 300 mg 3 times daily for 1 month was safe with a tolerable adverse effect profile. There is a need to further understand whether the absence of improvement was related to suboptimal drug dosing or other factors that prevented achieving therapeutic improvements. A high placebo response was observed in this study despite extensive efforts to minimize this effect, illustrating a key challenge with conducting clinical trials in pancreatitis, and further emphasizes that uncontrolled studies should not be relied on to guide clinical decision making as it relates to therapy.[14] Considering the high morbidity of pain in patients with CP, there remains an unmet need to better understand contributors to the experience of pain in CP and pain phenotypes to guide future clinical trials.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2023.12.008.

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Conflicts of interest
These authors disclose the following: Phil A. Hart received honoraria paid to his institution for consulting from KC Specialty Therapeutics, LLC and Kangen Pharmaceuticals America, LLC. Janet Nuttall received consulting fees from KC Specialty Therapeutics, LLC and Kangen Pharmaceticals America, LLC. The remaining authors disclose no conflicts.

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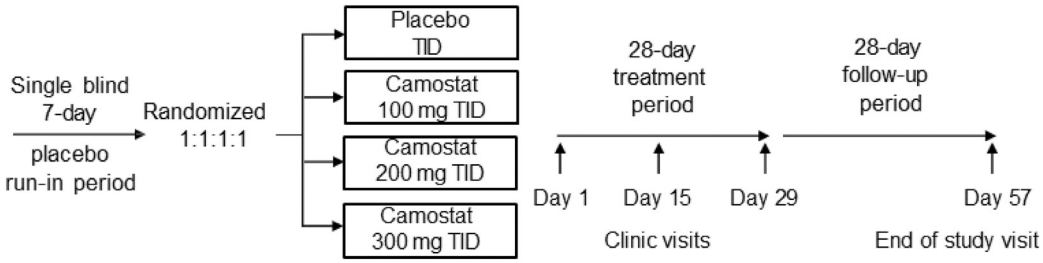
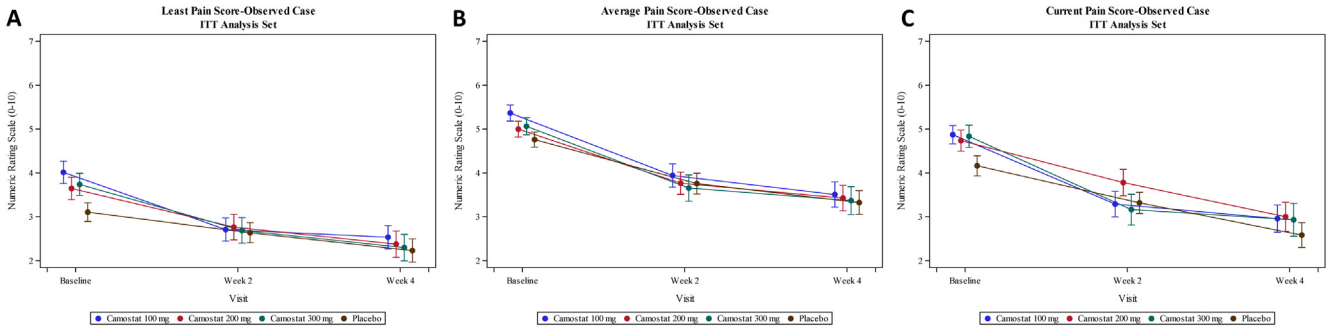
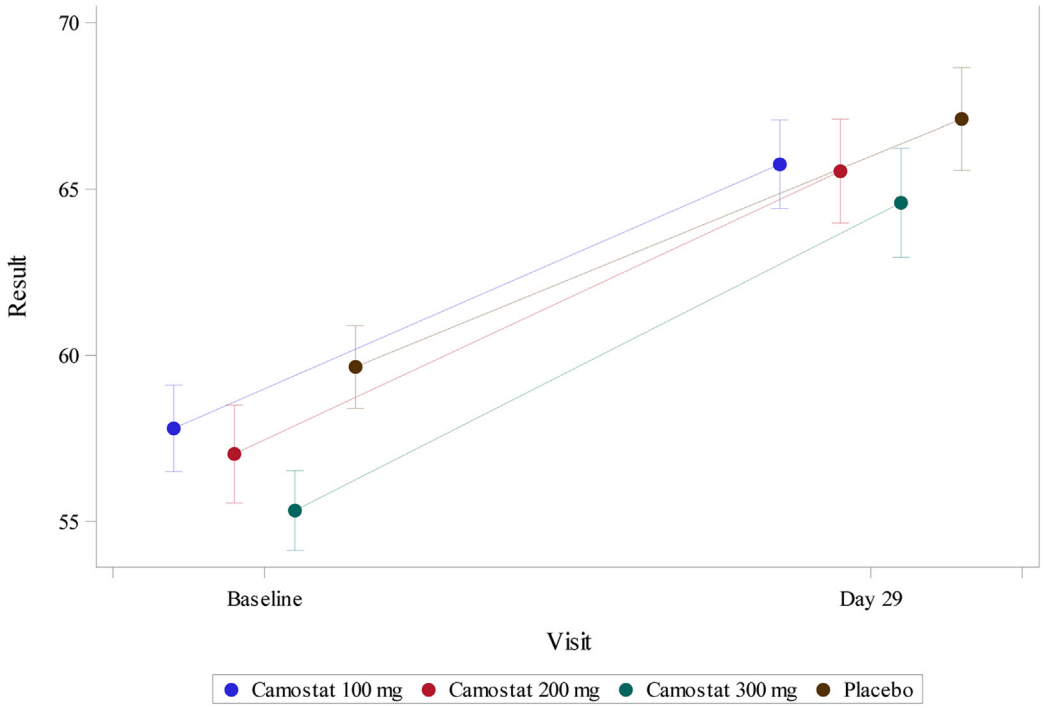
Data Availability
Individual participant data will not be shared.



Supplementary Figure 1. Study design for the phase 2 randomized controlled trial (TACTIC). TID, 3 times daily.



Supplementary Figure 2. Plots demonstrating the mean ± SE scores for least pain score (*A*), mean pain score (*B*), and current pain score (*C*) in the ITT analysis across the 4 treatment arms.



Supplementary Figure 3. Plots of mean ± SE total scores in the Pancreatitis Quality of Life Instrument from the ITT analysis population. Higher scores indicate a better quality of life.

Supplementary Table 1. Eligibility Criteria for the Phase 2 TACTIC Study

Inclusion criteria	Exclusion Criteria
Adults aged 18–85 years	Comorbid medical conditions, including clinically significant cardiovascular disease, active infection within 30 days of day 1, seizure within the past 12 months, pregnancy or planned pregnancy or active breastfeeding, history of malignancy within 5 years of study enrollment, or HIV infection.
Diagnosis of CP supported by a combination of cross-sectional imaging, endoscopic ultrasound, endoscopic retrograde pancreatography, and/or assessment of pancreatic function[12]	Renal or hepatic dysfunction: including stage IV chronic kidney disease (estimated using Cockcroft-Gault formula). Patients with active, chronic hepatitis B infection (surface antigen positivity) and chronic hepatitis C infection (including those with a detectable polymerase chain reaction level or undetectable levels in patients with advanced fibrosis (histologic grade 3–4/4) were excluded, as were those with cirrhosis based on previous evaluation, including biopsy, a noninvasive estimate of fibrosis, or radiographic features.
Mean baseline pain score $\geq$4 using a numeric rating scale (0–10) during the 7-day run in period	Diagnosis of autoimmune pancreatitis based on the International Consensus Diagnostic Criteria for Autoimmune Pancreatitis.
Stable analgesic regimen If oral narcotic analgesics are used, the daily oral morphine equivalent dose should not exceed 100 mg	Use of potentially confounding medications, including other experimental medications, recent change in selective serotonin reuptake inhibitor/serotonin and norepinephrine reuptake inhibitors dosage, systemic steroids, anti-epileptics, or antipsychotics.
Ability to use contraception method from screening until 28 day after completion of the study medication	Potential confounding of pain assessment, including the presence of generalized pain syndrome prohibiting the differentiation of abdominal pain, major abdominal surgery or endoscopic intervention (including celiac plexus block, sphincterotomy, and/or pancreatic duct stenting) within 90 days of enrollment.
Ability to understand and provide written informed consent	Substance abuse, including use of illegal substances, use of cannabinoids must have 28-day wash-out period and negative drug test at screening and at day 29, or alcohol use exceeding 2 drinks/d (or 14 drinks/wk). Miscellaneous: inadequate venous access, known hypersensitivity to camostat or one of its excipients, inability/unwillingness to comply with study restrictions, blood donation or transfusion within 7 days of enrollment.

Adapted from Ramsey et al.[12]

Supplementary Table 2. Changes in the Pancreatitis Quality of Life Instrument Total Scores and Domain Subscores During the TACTIC Study

Total score[a]	Placebo (n = 67)	Camostat 100 mg (n = 71)	Camostat 200 mg (n = 65)	Camostat 300 mg (n = 61)
Baseline				
Mean	59.7[b]	57.8[b]	57.0[b]	55.3
SD	10.10	10.90	11.78	9.38
Day 29 (week 4)				
Mean	67.1	65.7	65.5	64.6
SD	12.64	11.18	12.55	12.82
Change from baseline to day 29 (week 4)				
Mean	7.1[b]	8.2[b]	8.6[b]	9.3
SD	12.55	12.14	12.15	12.13
LS mean ± SE	7.6 ± 1.866	7.8 ± 1.883	7.9 ± 1.974	7.7 ± 2.054
LS MD (95% CI)	—	0.2 (–4.0 to 4.4)	0.3 (–4.1 to 4.6)	0.1 (–4.4 to 4.6)
Unadjusted *P* value	—	.906	.882	.957
Adjusted *P* value (compared with placebo)[c]	—	.999	.998	1.000
Physical function domain				
Baseline				
Mean	18.6	17.5	17.5[b]	16.9
SD	4.29	4.44	4.36	4.77
Day 29 (week 4)				
Mean	21.1	21.2	21.1	19.8
SD	4.72	4.59	4.52	5.33
Change from baseline to day 29 (week 4)				
Mean	2.5	3.7	3.7[b]	2.8
SD	4.91	4.94	4.52	5.10
LS mean ± SE	2.1 ± 0.699	2.8 ± 0.700	2.7 ± 0.745	1.5 ± 0.774
LS MD (95% CI)	—	0.7 (–0.9 to 2.3)	0.6 (–1.1 to 2.3)	–0.6 (–2.3 to 1.1)
Unadjusted *P* value	—	.313	.419	.420
Adjusted *P* value (compared with placebo)[c]	—	.617	.756	.757
Role function domain				
Baseline				
Mean	14.5	14.1	13.9[b]	14.3
SD	3.13	2.44	3.38	2.89
Day 29 (week 4)				
Mean	16.5	16.0	15.8	16.3
SD	3.19	2.97	3.84	3.59
Change from baseline to day 29 (week 4)				
Mean	2.0	1.9	1.9[b]	2.1
SD	4.29	3.72	4.47	4.51
LS mean ± SE	2.4 ± 0.560	1.9 ± 0.560	1.7 ± 0.595	2.3 ± 0.618
LS MD (95% CI)	—	–0.5 (–1.8 to 0.8)	–0.6 (–2.0 to 0.7)	–0.1 (–1.5 to 1.3)
Unadjusted *P* value	—	.379	.291	.876
Adjusted *P* value (compared with placebo)[c]	—	.709	.585	.997
Emotional function domain				
Baseline				
Mean	12.9[b]	12.8	12.9[b]	12.0
SD	4.68	4.66	4.74	3.94
Day 29 (week 4)				
Mean	15.0	14.5	14.7	14.5
SD	4.74	4.48	4.79	4.53
Change from baseline to day 29 (week 4)				
Mean	2.0[b]	1.7	1.8[b]	2.5
SD	4.32	4.60	4.03	4.46
LS mean ± SE	1.8 ± 0.653	1.6 ± 0.650	1.7 ± 0.689	1.9 ± 0.717
LS MD (95% CI)	—	–0.2 (–1.7 to 1.3)	–0.1 (–1.6 to 1.5)	0.1 (–1.5 to 1.7)
Unadjusted *P* value	—	.746	.910	.881
Adjusted *P* value (compared with placebo)[c]	—	.977	.999	.998

Supplementary Table 2. Continued

Total score[a]	Placebo (n = 67)	Camostat 100 mg (n = 71)	Camostat 200 mg (n = 65)	Camostat 300 mg (n = 61)
Self-worth domain				
Baseline				
Mean	13.8[b]	13.4[b]	12.7[b]	12.1
SD	3.05	2.76	3.36	2.90
Day 29 (week 4)				
Mean	14.5	14.1	14.0	14.0
SD	3.67	3.33	3.50	3.47
Change from baseline to day 29 (week 4)				
Mean	0.6[b]	0.8[b]	1.2[b]	1.9
SD	3.43	3.93	3.71	3.45
LS mean ± SE	1.2 ± 0.528	1.2 ± 0.536	1.3 ± 0.563	1.7 ± 0.590
LS MD (95% CI)	—	0.0 (–1.3 to 1.2)	0.1 (–1.2 to 1.4)	0.5 (–0.9–1.8)
Unadjusted *P* value	—	.932	.912	.426
Adjusted *P* value (compared with placebo)[c]	—	1.000	.999	.763

NOTE. LS means, SEs, and 95% CIs come from a baseline observation carried forward analysis using an analysis of covariance model with baseline score as covariate, both treatment and stratification factor (morphine equivalent dose 0–50 mg/d vs >50 mg/d to ≤100 mg/d) as a fixed effect, and center as a random effect.
LS, least square; MD, mean difference.
[a]Higher numbers indicate a better quality of life for the specified domain.
[b]Missing data: n = 1.
[c]Significance tests are based on LS MDs. The adjusted *P* value, obtained using the Dunnett's procedure, protects the overall familywise error rate by taking into account the multiple comparisons among the 3 camostat treatment groups with placebo.

Supplementary Table 3. Treatment Emergent Adverse Events During the Double-Blind Phase of the TACTIC Study

Variable	Placebo TID (n = 67)	Camostat 100 mg TID (n = 71)	Camostat 200 mg TID (n = 66)	Camostat 300 mg TID (n = 59)	Total
Patients with any TEAEs	29 (43.3)	33 (46.5)	25 (37.9)	22 (37.3)	109 (41.4)
Gastrointestinal disorders	17 (25.4)	20 (28.2)	12 (18.2)	12 (20.3)	61 (23.2)
Nausea	4 (6.0)	3 (4.2)	5 (7.6)	4 (6.8)	16 (6.1)
Abdominal pain	6 (9.0)	5 (7.0)	2 (3.0)	2 (3.4)	15 (5.7)
Vomiting	3 (4.5)	2 (2.8)	1 (1.5)	2 (3.4)	8 (3.0)
Diarrhea	0	2 (2.8)	2 (3.0)	3 (5.1)	7 (2.7)
Constipation	1 (1.5)	2 (2.8)	0	2 (3.4)	5 (1.9)
Pancreatitis acute	1 (1.5)	2 (2.8)	1 (1.5)	1 (1.7)	5 (1.9)
Abdominal pain upper	1 (1.5)	1 (1.4)	1 (1.5)	1 (1.7)	4 (1.5)
Pancreatitis, not otherwise specified	0	0	3 (4.5)	1 (1.7)	4 (1.5)
Infections and infestations	7 (10.4)	5 (7.0)	5 (7.6)	7 (11.9)	24 (9.1)
Nasopharyngitis	1 (1.5)	1 (1.4)	1 (1.5)	1 (1.7)	4 (1.5)
Upper respiratory tract infection	2 (3.0)	1 (1.4)	0	1 (1.7)	4 (1.5)
Bronchitis	0	2 (2.8)	1 (1.5)	0	3 (1.1)
Nervous system disorders	5 (7.5)	10 (14.1)	5 (7.6)	4 (6.8)	24 (9.1)
Headache	4 (6.0)	8 (11.3)	3 (4.5)	4 (6.8)	19 (7.2)
Dizziness	1 (1.5)	2 (2.8)	1 (1.5)	0	4 (1.5)
General disorders and administration site conditions	3 (4.5)	2 (2.8)	5 (7.6)	4 (6.8)	14 (5.3)
Fatigue	3 (4.5)	0	3 (4.5)	0	6 (2.3)
Pyrexia	0	0	2 (3.0)	1 (1.7)	3 (1.1)
Skin and subcutaneous tissue disorders	2 (3.0)	4 (5.6)	4 (6.1)	1 (1.7)	11 (4.2)
Rash	0	2 (2.8)	1 (1.5)	0	3 (1.1)
Respiratory, thoracic and mediastinal disorders	4 (6.0)	0	3 (4.5)	2 (3.4)	9 (3.4)
Cough	1 (1.5)	0	2 (3.0)	1 (1.7)	4 (1.5)
Metabolism and nutrition disorders	2 (3.0)	1 (1.4)	1 (1.5)	3 (5.1)	7 (2.7)
Decreased appetite	1 (1.5)	0	1 (1.5)	1 (1.7)	3 (1.1)
Injury, poisoning, and procedural complications	2 (3.0)	1 (1.4)	1 (1.5)	1 (1.7)	5 (1.9)
Ligament sprain	0	1 (1.4)	1 (1.5)	1 (1.7)	3 (1.1)

NOTE. Only TEAEs reported for >1% of the safety population (n = 263) are shown. Values are presented as n (%).
TID, 3 times daily.

Supplementary Table 4. Distribution of Serious Treatment Emergent Adverse Events in the Safety Population (n = 263)

Variable	Placebo TID (n = 67)	Camostat 100 mg TID (n = 71)	Camostat 200 mg TID (n = 66)	Camostat 300 mg TID (n = 59)	Total
Patients with any serious TEAEs	1 (1.5)	2 (2.8)	3 (4.5)	4[a] (6.8)	10 (3.8)
Abdominal pain	—	1 (1.4)	1 (1.5)	2 (3.4)	4 (1.5)
Diabetic ketoacidosis	—	—	—	1 (1.7)	1 (0.4)
Head injury	1 (1.5)	—	—	—	1 (0.4)
Nephrolithiasis	—	—	—	1 (1.7)	1 (0.4)
Pancreatic cyst	—	—	—	1 (1.7)	1 (0.4)
Pancreatitis	—	1 (1.4)	2 (3.0)	1 (1.7)	4 (1.5)

NOTE. Values are presented as n (%).
TID, 3 times daily.
[a]Abdominal pain, diabeteic ketoacidosis, and nephrolithiasis occurred in the same patient.

Update

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DOI: https://doi.org/10.1053/j.gastro.2024.06.002

Corrigendum

Morton JP, Jamieson NB, Karim SA, et al. LKB1 Haploinsufficiency Cooperates With *Kras* to Promote Pancreatic Cancer Through Suppression of p21-Dependent Growth Arrest. Gastroenterology 2010;139:586–597.e6.

During the preparation of the above article, the wrong image was included for IgfBP7 staining of KLC mice in Figure 5B. The authors have amended the figure to include the correct image. The updated Figure 5 is shown below.

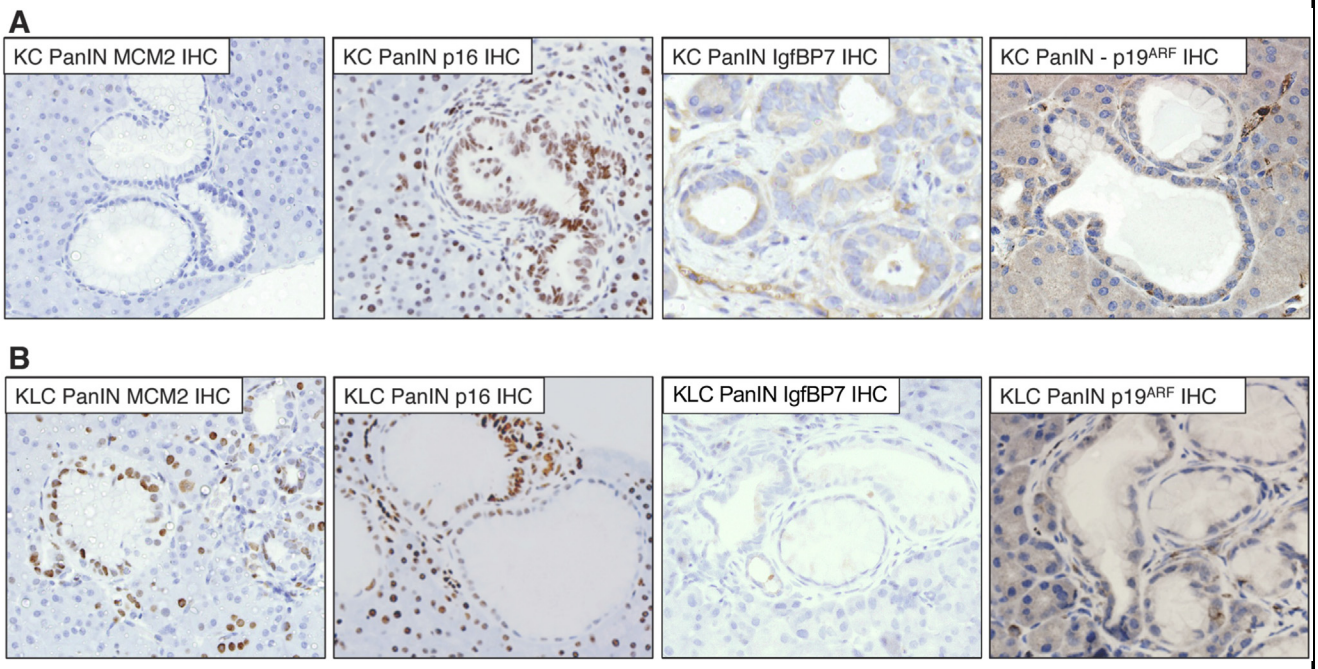

Figure 5.

The authors also have provided additional information in the legend for Figure 6E to highlight that a higher magnification image of KC PanIN is shown in Figure 4A.

The correct legend for Figure 6E is: "Senescence-associated β-gal staining in PanIN lesions from KC and KCp21 mice (higher magnification image of KC PanIN is shown in Figure 4A)."

The authors apologize for these errors and state that they do not affect the results described in the figures or the conclusions of the article.

Corrigendum

Hart PA, Osypchuk Y, Hovbakh I, et al. A Randomized Controlled Phase 2 Dose-Finding Trial to Evaluate the Efficacy and Safety of Camostat in the Treatment of Painful Chronic Pancreatitis: The TACTIC Study. Gastroenterology 2024;166:658–666.e6.

In the above article, there was an error in the spelling of the first name of one of the co-authors. The name should read Shayan Irani, not Shayna Irani. The authors apologize for this error.