2 SYNOPSIS

Title of the Study: A Phase 2 Randomized, Open-Label, Multicenter Study Comparing CO-101 with Gemcitabine as First-Line Therapy in Patients with Metastatic Pancreatic Adenocarcinoma	
Study Number: CO-101-001	
Study Drug: CO-101 (Gemcitabine elaidate)	
Investigators and Study Centres: This was a multicenter, multinational study conducted at 98 sites in Europe, Australia, and the Americas. The coordinating investigator in Europe and Australia was Tone Ikdahl M.D., Ph.D., Ullevål Cancer Centre, Oslo University Hospital, Ullevål, Oslo, Norway. The coordinating investigator for the Americas was Elizabeth Poplin M.D., Cancer Institute of New Jersey, New Brunswick, New Jersey, United States of America (USA).	
Publication (reference): N/A	
Date of First Patient Randomized: 04-Aug-2010 **Date of Last Patient Randomized:** 09- April-2012	**Phase:** Phase 2

Objectives:

Primary objective:

- To compare the efficacy of gemcitabine elaidate and gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) and low human equilibrative nucleoside transporter 1 (hENT1) expression.

Secondary objectives:

- To compare the efficacy of gemcitabine elaidate and gemcitabine in patients with mPDAC and known hENT1 status (all patients and high hENT1 expression).
- To compare the tolerability and toxicity of gemcitabine elaidate with gemcitabine.
- To compare changes in pain severity in patients receiving gemcitabine elaidate and gemcitabine.
- To compare changes in health status in patients receiving gemcitabine elaidate and gemcitabine.
- To perform sparse pharmacokinetic (PK) sampling in patients taking gemcitabine elaidate to contribute towards development of a population PK model of gemcitabine elaidate.
- To evaluate the clinical utility of the hENT1 diagnostic test.

Methodology: This open-label, randomized, controlled, multicenter Phase 2 study compared gemcitabine elaidate with gemcitabine as first-line therapy in patients with mPDAC. Eligible patients were randomized (1:1) to receive either gemcitabine elaidate or gemcitabine, which was infused intravenously over 30 ± 3 minutes, under medical supervision. Each cycle of gemcitabine elaidate was administered weekly for 3 of every 4 weeks (4^{th} week rest) at a dose of 1250 mg/m^2/day. The first cycle of gemcitabine comprised weekly administration of 1000 mg/m^2/day for 7 weeks (8^{th} week rest); subsequent cycles comprised weekly administration for 3 weeks every 4 weeks, in accordance with the manufacturer's labeling. Dosing was to be delayed or decreased according to the protocol-specified toxicity criteria. Dose escalation beyond the starting dose was allowed if patients tolerated the first cycle (8 weeks) of gemcitabine or first 2 cycles (8 weeks) of gemcitabine elaidate, according to the criteria defined in the protocol.
Protocol-specified treatment (PST) was continued until there was clinical tumor progression or unacceptable toxicity. The study was closed when the required number of events of death (80%

events) had been observed in patients with low hENT1 tumor expression.

Serial assessments for antitumor efficacy, adverse events, pain severity, and health status were performed in all patients. Tumor hENT1 status was determined after randomization but before the final efficacy analysis using predefined criteria to classify patients as hENT1 -high or -low so that the primary endpoint population (patients with low tumor hENT1 expression) could be identified prospectively.

Sparse blood sampling for population PK analyses was conducted in all patients treated with gemcitabine elaidate following implementation of amendment 1of the protocol. An optional specimen of blood was collected from consenting patients and banked centrally for future pharmacogenetic evaluation of polymorphisms relating to drug metabolism and tumor outcomes. RNA profiling was to be performed on tumor specimens and blood samples, and proteomics were also to be performed on serum/plasma. Central laboratories were used for hematology, serum chemistry, and carbohydrate antigen (CA) 19-9 testing, electrocardiogram (ECG) interpretation, and PK assay. Immunohistochemistry for hENT1 protein and scoring to assess hENT1 status (high or low) was performed centrally (Ventana Medical Systems Inc). Investigational centers interpreted tumor scans locally for the purpose of making treatment decisions and for final tumor response evaluation. Wherever possible, a tumor biopsy was to be taken from patients who relapsed prior to initiation of second-line therapy.

Adverse events (AEs) were assessed from the time of informed consent to 28 days after the last PST administration and all patients were followed indefinitely at approximately monthly intervals to determine survival status. Patients with stable disease (SD) or better continued to have tumor scans every 8 ± 1 week until tumor progression. After discontinuation of PST, second-line and subsequent specific anticancer therapy was used at the investigator's discretion, although patients randomized to gemcitabine could not cross over to receive gemcitabine elaidate. An independent data monitoring committee (IDMC) monitored the overall conduct of the study.

Number of Patients:

Planned:

360 (180 per arm)

Analyzed:

ITT Population - 367 randomized patients (182, gemcitabine elaidate; 185, gemcitabine)

Safety Population - 360 treated patients(179, gemcitabine elaidate; 181, gemcitabine)

Tumor Evaluable Population - 358 treated patients with known hENT1 status and measurable tumor at baseline (178, gemcitabine elaidate; 180, gemcitabine)

Diagnosis and Main Criteria for Inclusion/Exclusion:

Patients aged ≥ 18 years with histologically or cytologically confirmed metastatic pancreatic ductal adenocarcinoma; adequate hematological and biological function; Eastern Cooperative Oncology Group (ECOG) status of 0 or 1; and, an estimated life expectancy ≥ 12 weeks. Patients with symptomatic brain metastases and those who had received prior palliative therapy for pancreatic cancer were excluded, as were patients who had a radical pancreatic resection within 6 months, or an exploratory laparotomy palliative (e.g. bypass) surgery or other procedures (e.g. stent insertions) < 14 days prior to randomization.

Test Product, Dose and Mode of Administration, Lot Number:

Gemcitabine elaidate (15 mg/mL) was administered as a 30-minute intravenous infusion at a dose of 1250 mg/m^2/day on Days 1, 8, and 15 in a 4-week schedule. The lot numbers distributed and used were P000457, P001820, P001334, P002644, P002917, P004362, P103467, P100617, P002917, P903925.

Reference Therapy, Dose and Mode of Administration, Lot Number:

Gemcitabine was administered as a 30 ± 3-minute intravenous infusion at a dose of 1000 mg/m^2/day once weekly for 7 of the first 8 weeks, then on Days 1, 8, and 15 in a 4-week schedule. For sites outside of North America, gemcitabine was purchased by Clovis Oncology, labeled as investigational medicinal product and distributed for use. Sites in North America procured gemcitabine from commercial sources and prepared it for use according to the current prescribing information.

Duration of Treatment:

Protocol-specified treatment was continued until there was objective tumor progression or unacceptable toxicity.

Criteria for Evaluation:

Efficacy:

- Overall survival (OS)
- Objective response rate of tumor (ORR)
- Duration of response
- Progression-free survival (PFS)
- Pain severity using the worst score on the brief pain inventory (BPI) short form
- CA 19-9 level

Safety:

- AEs
- Hematology, clinical chemistry, and urinalysis
- Physical examination and vital signs
- Concomitant medications/procedures
- 12-lead ECGs
- ECOG performance status
- Dose modifications of PST

Other:

- Tumor hENT1 expression
- Health status using the European Quality of Life-5 Dimension (EQ-5D) instrument and European Quality Visual Analog Scale (EQ VAS)
- Pharmacogenomic profile and proteomics
- Blood sampling for population PK analysis (patients treated with gemcitabine elaidate only)

Statistical Methods:

All efficacy evaluations were conducted using the ITT population unless otherwise specified.

For the primary efficacy endpoint of OS, distributions between the gemcitabine elaidate and gemcitabine groups were compared among the subgroups of patients defined by hENT1 status in the following order: hENT1-low patients; all randomized patients; and hENT1-high patients. The ordered step-down procedure for multiple comparisons was used to control for the Type 1 error rate, with testing in subsequent subgroups only occurring if the p-value was < 0.05 in the previous subgroup. If OS was not statistically significant in one of the subgroups, statistical significance was not declared for the subsequent subgroups. Randomization was stratified by

ECOG PS and region. The stratified log rank test and stratified Cox proportional hazards test for a treatment effect were performed to account for these stratification factors, with the stratified log rank test considered the primary analysis for OS. Sensitivity analyses (censoring distribution, multivariate Cox proportional hazards model and length of follow-up for OS) were also performed for the primary efficacy endpoint of OS.

Secondary efficacy endpoints were also analyzed using the ordered step-down procedure, and unless otherwise specified, within each secondary endpoint, the three hENT1 subgroups defined for the primary endpoint were tested in the same order as listed above. Variables were analyzed in the following order: OS in all patients and patients with high hENT1 expression; objective response rate of tumor (ORR); time to progression (TTP) and PFS in patients with measurable/evaluable disease using RECIST (Version 1.1); CA 19-9 velocity and response rate; drug tolerability and toxicity using clinical AE monitoring, clinical laboratory testing, ECG outcomes and dose-modification of PST; change from baseline in pain severity measured by the worst pain on the BPI short form; change from baseline in health status measured by the EQ-5D instrument and EQ VAS; PK profiles for CO-1.01 correlated with ECG changes (especially QTc interval).

Safety endpoints included AEs, vital signs (including radial pulse, blood pressure and temperature), 12-lead ECGs and clinical laboratory evaluations (hematology, serum chemistry and urinalysis).

Summary of Results:

The demographics and baseline clinical characteristics of the hENT1-low subgroup are summarized in the table below:

Demographics and Baseline Characteristics in the hENT1-Low Subgroup (ITT Population)

Variable	Gemcitabine Elaidate (N=114)	Gemcitabine (N=118)	Total (N=232)
Age (years)			
Mean (SD)	62.8 (9.15)	59.8 (11.40)	61.3 (10.44)
Median (minimum–maximum)	64 (39, 86)	61 (26, 84)	62 (26, 86)
Age Categories			
≤ 50	11 (9.6)	26 (22.0)	37 (15.9)
51-60	30 (26.3)	30 (25.4)	60 (25.9)
61-70	53 (46.5)	41 (34.7)	94 (40.5)
71-80	17 (14.9)	19 (16.1)	36 (15.5)
81-90	3 (2.6)	2 (1.7)	5 (2.2)
Gender, N (%)			
Male	71 (62.3)	76 (64.4)	147 (63.4)
Female	43 (37.7)	42 (35.6)	85 (36.6)
Race, N (%)			
Asian	1 (0.9)	1 (0.8)	2 (0.9)
Black	1 (0.9)	0	1 (0.4)
White	97 (85.1)	109 (92.4)	206 (88.8)
Other	4 (3.5)	3 (2.5)	7 (3.0)
Missing	11 (9.6)	5 (4.2)	16 (6.9)

Demographics and Baseline Characteristics in the hENT1-Low Subgroup (ITT Population)			
Variable	**Gemcitabine Elaidate (N=114)**	**Gemcitabine (N=118)**	**Total (N=232)**
ECOG at Baseline, N (%)			
0	20 (17.5)	30 (25.4)	50 (21.6)
1	94 (82.5)	88 (74.6)	182 (78.4)
≥ 2	0	0	0
Months Since Pancreatic Cancer Diagnosis			
≤ 3	98 (86.0)	105 (89.0)	203 (87.5)
> 3-6	10 (8.8)	2 (1.7)	12 (5.2)
> 6-12	4 (3.5)	5 (4.2)	9 (3.9)
> 12-24	1 (0.9)	2 (1.7)	3 (1.3)
> 24	1 (0.9)	4 (3.4)	5 (2.2)
Number of Metastatic Sites			
1	29 (25.4)	36 (30.5)	65 (28.0)
2	47 (41.2)	46 (39.0)	93 (40.1)
3	25 (21.9)	20 (16.9)	45 (19.4)
4	8 (7.0)	14 (11.9)	22 (9.5)
≥ 5	5 (4.4)	2 (1.7)	7 (3.0)
Locations of Metastases			
Liver	98 (86.0)	105 (89.0)	203 (87.5)
Lymph Nodes	59 (51.8)	66 (55.9)	125 (53.9)
Peritoneum	28 (24.6)	21 (17.8)	49 (21.1)
Lungs	29 (25.4)	31 (26.3)	60 (25.9)
Brain	0	0	0
Kidney	3 (2.6)	2 (1.7)	5 (2.2)
Other	31 (27.2)	26 ((22.0)	57 (24.6)

Demographics and baseline clinical characteristics were balanced between treatment arms and consistent with that expected for patients with advanced PDAC.

Efficacy:

OS results in the hENT1-low subgroup are summarized in the table below.

Overall Survival in the hENT1-Low Subgroup (ITT Population)

Overall Survival	Gemcitabine Elaidate (N=114)	Gemcitabine (N=118)
OS (months)		
Median	5.7	6.1
Number (%) of Deaths	97/114 (85.1)	100/118 (84.7))
OS Probability (SE)		
6 Months	0.44 (0.05)	0.47 (0.05)
12 Months	0.19 (0.04)	0.17 (0.04)
18 Months	0.08 (0.03)	0.08 (0.03)
24 Months	N/A	N/A
Stratified Log-rank Test[a]	0.9732	
Stratified HR (gemcitabine elaidate vs. gemcitabine; 95% CI)[a]	0.994 (0.746, 1.326)	

KEY: CI = confidence interval; HR = hazard ratio; OS = overall survival; SE = standard error.

[a]Stratified by baseline ECOG PS (0 or 1) and geographic region (North America/Western Europe/Australia vs. Eastern Europe vs. South America).

The efficacy data were mature with approximately 85% of patients having a reported date of death. In the hENT1-low subgroup, there was no difference in OS between gemcitabine elaidate and gemcitabine (5.7 vs. 6.1 months, respectively; stratified HR (gemcitabine elaidate vs. gemcitabine; 95% CI): 0.994 (0.746, 1.326).

There was also no difference in OS between treatment groups in the All Patients Randomized Group and the hENT1-high subgroup. Furthermore, PFS and ORR comparisons were consistent with the OS outcomes.

The OS in patients treated with gemcitabine were similar in the hENT1-high vs. hENT1-low groups; median survival was 5.2 vs. 6.1 respectively; stratified HR (high vs. low; 95% CI) was 1.147 (0.809, 1.626).

In summary, these results indicate that in patients with metastatic pancreatic cancer: a prospectively defined robust tumor hENT1 cut-off level was not predictive of gemcitabine response; the efficacy of gemcitabine elaidate was no better than that of gemcitabine in patients with low tumor hENT1 expression.

Pharmacodynamic results

The planned exploratory analysis of the PK/PD relationship of gemcitabine elaidate was not conducted due to discontinuation of the clinical development program following analysis of the OS results in the hENT1-low subgroup.

Safety Results:

Overview of Treatment-Emergent Adverse Events (TEAEs)

An overview of TEAEs in the hENT1-low subgroup is summarized in the table below:

Overall Summary of Treatment-Emergent Adverse Events Reported in the hENT1-Low Subgroup (Safety Population), N (%)

	Gemcitabine Elaidate (N=112)	Gemcitabine (N=115)	Total (N=227)
Any TEAEs	110 (98.2)	112 (97.4)	222 (97.8)
Any TEAE of Grade ≥ 3	96 (85.7)	83 (72.2)	179 (78.9)
Grade 3	58 (51.8)	48 (41.7)	106 (46.7)
Grade 4	13 (11.6)	5 (4.3)	18 (7.9)
Grade 5 (death)	25 (22.3)	30 (26.1)	55 (24.2)
Treatment-related TEAE	98 (87.5)	91 (79.1)	189 (83.3)
SAE	53 (47.3)	52 (45.2)	105 (46.3)
Treatment-related SAE	11 (9.8)	12 (10.4)	23 (10.1)
TEAE resulting in study drug discontinuation	29 (25.9)	18 (15.7)	47 (20.7)
TEAEs leading to interruption of study drug	35 (31.3)	35 (30.4)	70 (30.8)
TEAEs leading to reduction or delay of study drug	69 (61.6)	65 (56.5)	134 (59.0)

The TEAEs reported in the hENT1-high subgroup and in the All Patients group were similar to those reported for the hENT1-low subgroup.

TEAEs (all CTCAE grades)

TEAEs reported by ≥ 10% patients in the hENT1-low subgroup are summarized in the table below.

Treatment-Emergent Adverse Events (all CTCAE grades) Reported in ≥ 10% Patients in the hENT1-Low Subgroup (Safety Population), N (%)

System Organ Class MedDRA Preferred Term	Gemcitabine Elaidate (N=112)	Gemcitabine (N=115)	Total (N=227)
At least 1 TEAE	110 (98.2)	112 (97.4)	222 (97.8)
Blood and Lymphatic System Disorders			
Anemia	45 (40.2)	48 (41.7)	93 (41.0)
Leukopenia	8 (7.1)	12 (10.4)	20 (8.8)
Neutropenia	33 (29.5)	33 (28.7)	66 (29.1)
Thrombocytopenia	36 (32.1)	42 (36.5)	78 (34.4)

Treatment-Emergent Adverse Events (all CTCAE grades) Reported in ≥ 10% Patients in the hENT1-Low Subgroup (Safety Population), N (%)

System Organ Class MedDRA Preferred Term	Gemcitabine Elaidate (N=112)	Gemcitabine (N=115)	Total (N=227)
Gastrointestinal Disorders			
Abdominal pain	18 (16.1)	17 (14.8)	35 (15.4)
Abdominal pain upper	10 (8.9)	17 (14.8)	27 (11.9)
Constipation	20 (17.9)	14 (12.2)	34 (15.0)
Diarrhea	23 (20.5)	21 (18.3)	44 (19.4)
Nausea	41 (36.6)	36 (31.3)	77 (33.9)
Vomiting	26 (23.2)	26 (22.6)	52 (22.9)
General Disorders and Administration Site Conditions			
Asthenia	31 (27.7)	27 (23.5)	58 (25.5)
Fatigue	25 (22.3)	30 (26.1)	55 (24.2)
Edema peripheral	18 (16.1)	22 (19.1)	40 (17.6)
Pyrexia	20 (17.9)	25 (21.7)	45 (19.8)
Hepatobiliary Disorders			
Hyperbilirubinaemia	8 (7.1)	12 (10.4)	20 (8.8)
Investigations			
Alanine aminotransferase increased	16 (14.3)	10 (8.7)	26 (11.5)
Aspartate aminotransferase increased	12 (10.7)	11 (9.6)	23 (10.1)
Metabolism and Nutrition Disorders			
Decreased Appetite	28 (25.0)	21 (18.3)	49 (21.6)
Neoplasms Benign, Malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma metastatic (disease progression)	22 (19.6)	28 (24.3)	50 (22.0)
Respiratory. Thoracic and Mediastinal Disorders			
Dyspnea	14 (12.5)	14 (12.2)	28 (12.3)

In the hENT1-low subgroup, the most frequently occurring TEAEs (all CTCAE grades) occurred in similar proportions across the treatment groups and were consistent with the safety profile expected for patients with advanced pancreatic cancer and treated with gemcitabine.

The TEAEs reported in the hENT1-high subgroup and in the All Patients group were comparable between treatment groups and similar to those reported for the hENT1-low subgroup.

Treatment-related TEAEs

Treatment-related TEAEs reported by ≥ 10% patients are summarized for the hENT1-low subgroup in the table below.

Treatment-Related Treatment-Emergent Adverse Events (all CTCAE grades) Reported in≥ 10% Patients in the hENT1-Low Subgroup (Safety Population), N (%)

System Organ Class MedDRA Preferred Term	**Gemcitabine Elaidate (N=112)**	**Gemcitabine (N=115)**	**Total (N=227)**
At least 1 treatment-related TEAE	98 (87.5)	91 (79.1)	189 (83.2)
Blood and Lymphatic System Disorders			
Anemia	33 (29.5)	42 (36.5)	75 (33.0)
Neutropenia	32 (28.6)	32 (27.8)	64 (28.2)
Thrombocytopenia	31 (27.7)	38 (33.0)	69 (30.4)
Gastrointestinal Disorders			
Diarrhea	14 (12.5)	12 (10.4)	26 (11.5)
Nausea	32 (28.6)	30 (26.1)	62 (27.3)
Vomiting	17 (15.2)	16 (13.9)	33 (14.5)
General Disorders and Administration Site Conditions			
Asthenia	18 (16.1)	14 (12.2)	32 (14.1)
Fatigue	16 (14.3)	26 (22.6)	42 (18.5)
Pyrexia	10 (8.9)	16 (13.9)	26 (11.5)

In the hENT1-low subgroup, the most frequently occurring treatment-related TEAEs (all CTCAE grades) occurred in similar proportions across the treatment groups, and the safety profile was consistent with that expected for gemcitabine and reported for gemcitabine elaidate in previous clinical trials. The most frequently occurring treatment-related TEAEs were disorders of the blood and lymphatic system (anemia, thrombocytopenia, neutropenia), the gastrointestinal system (diarrhea, nausea, vomiting) and general disorders (asthenia, fatigue, pyrexia).

The treatment-related TEAEs reported in the hENT1-high subgroup and in the All Patients group were comparable between treatment groups and similar to those reported for the hENT1-low subgroup.

TEAEs of NCI CTCAE toxicity ≥ Grade 3

TEAEs of NCI CTCAE toxicity ≥ Grade 3 are summarized for the hENT1-low subgroup in the table below.

Treatment-Emergent Adverse Events of NCI-CTCAE Toxicity ≥ Grade 3 Reported in ≥ 5% Patients in the hENT1-Low Subgroup (Safety Population), N (%)

System Organ Class MedDRA Preferred Term	**Gemcitabine Elaidate (N=112)**	**Gemcitabine (N=115)**	**Total (N=227)**
At least 1 grade 3 or higher TEAE	96 (85.7)	83 (72.2)	179 (78.9) *p=0.015*
Blood and Lymphatic System Disorders			
Anemia	13 (11.6)	13 (11.3)	26 (11.5)
Neutropenia	25 (22.3)	18 (15.7)	43 (18.9)
Thrombocytopenia	11 (9.8)	11 (9.6)	22 (9.7)
Gastrointestinal Disorders			
Abdominal pain	6 (5.4)	6 (5.2)	12 (5.3)
Vomiting	6 (5.4)	3 (2.6)	9 (4.0)
General Disorders and Administration Site Conditions			
Asthenia	6 (5.4)	11 (9.6)	17 (7.5)
Fatigue	7 (6.3)	7 (6.1)	14 (6.2)
Hepatobiliary Disorders			
Hyperbilirubinaemia	7 (6.3)	6 (5.2)	13 (5.7)
Investigations			
Alanine aminotransferase increased	7 (6.3)	4 (3.5)	11 (4.8)
Aspartate aminotransferase increased	6 (5.4)	4 (3.5)	10 (4.4)
Blood alkaline phosphatase	6 (5.4)	3 (2.6)	9 (4.0)
Neoplasms Benign, Malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma metastatic (disease progression)	21 (18.8)	27 (23.5)	48 (21.1)
Respiratory. Thoracic and Mediastinal Disorders			
Pulmonary embolism	4 (3.6)	6 (5.2)	10 (4.4)

The majority of TEAEs were CTCAE Grade 1 or Grade 2. The proportion of patients experiencing TEAEs ≥ CTCAE Grade 3 was higher for the gemcitabine elaidate treated group than the gemcitabine treated group (85.7% vs. 72.2% respectively, p=0.015), but this was not attributable to a particular adverse event or system organ class. As expected for cytotoxic therapeutics, the most frequently occurring toxicities ≥ Grade 3 were disorders of the blood and lymphatic system (anemia, thrombocytopenia, neutropenia) or events attributed to disease progression of the underlying pancreatic cancer.

The TEAEs ≥ CTCAE Grade 3 reported in the hENT1-high subgroup and in the All Patients group were comparable between treatment groups and similar to those reported for the hENT1-low subgroup.

TEAEs leading to study drug interruption, reduction or delay, or discontinuation

In the hENT1-low subgroup, TEAEs leading to study drug interruption were comparable between treatment arms and occurred in approximately 30% of patients. The main toxicities leading to study drug interruption were thrombocytopenia (7.0% of patients) and anemia (4.4% of patients).

TEAEs leading to reduction or delay of study drug were also comparable between treatment groups, occurring in approximately 59% of patients. The main toxicities leading to study drug reduction or delay were thrombocytopenia (25.1% of patients) and neutropenia (17.6% of patients).

In the hENT1-low subgroup, a slightly higher proportion of patients in the gemcitabine elaidate group discontinued study drug due to a TEAE compared with those in the gemcitabine group, but this difference was not statistically significant (25.9% vs. 15.7% respectively, p=0.071). The primary TEAE leading to study drug discontinuation was disease progression of the underlying pancreatic cancer (9.3% of patients in the hENT1-low subgroup), which occurred in a similar proportion of patients in each treatment arm.

TEAEs leading to study drug interruption, study drug reduction or delay, and study drug discontinuation in the hENT1-high subgroup and in the All Patients group were similar to those reported for the hENT1-low subgroup.

Treatment-emergent AEs that led to death

Treatment-emergent AEs that led to death are summarized for the hENT1-low subgroup in the table below.

Treatment-Emergent Adverse Events That Led to Death in the hENT1-Low Subgroup (Safety Population), N (%)

System Organ Class MedDRA Preferred Term	**Gemcitabine Elaidate (N=112)**	**Gemcitabine (N=115)**	**Total (N=227)**
At least 1 TEAE with an outcome of death	25 (22.3)	30 (26.1)	55 (24.2)
Cardiac Disorders			
Atrial fibrillation	0	1 (0.9)	1 (0.4)
Cardiac failure acute	1 (0.9)	0	1 (0.4)
Gastrointestinal Disorders			
Gastric hemorrhage	0	1 (0.9)	1 (0.4)
General Disorders and Administration Site Conditions			
Sudden cardiac death	1 (0.9)	0	1 (0.4)
Infections and Infestations			
Pneumonia	1 (0.9)	0	1 (0.4)
Sepsis	1 (0.9)	0	1 (0.4)
Neoplasms Benign, Malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma metastatic (disease progression)	19 (17.0)	26 (22.6)	45 (19.8)

Treatment-Emergent Adverse Events That Led to Death in the hENT1-Low Subgroup (Safety Population), N (%)			
System Organ Class MedDRA Preferred Term	**Gemcitabine Elaidate (N=112)**	**Gemcitabine (N=115)**	**Total (N=227)**
Nervous System Disorders			
Cerebrovascular accident	1 (0.9)	0	1 (0.4)
Renal and Urinary Disorders			
Renal failure	1 (0.9)	0	1 (0.4)
Renal failure acute	0	1 (0.9)	1 (0.4)
Respiratory. Thoracic and Mediastinal Disorders			
Chronic obstructive pulmonary disease	0	1 (0.9)	1 (0.4)
Pulmonary embolism	1 (0.9)	2 (1.7)	3 (1.3)
Respiratory failure	1 (0.9)	0	1 (0.4)

The primary TEAE leading to death was disease progression of the underlying pancreatic cancer, which occurred in 17% of patients treated with gemcitabine elaidate and 22.6% of those treated with gemcitabine. The TEAEs leading to death in the hENT1-high subgroup and in the All Patients group were similar to those reported for the hENT1-low subgroup.

Treatment-emergent SAEs

Treatment-emergent SAEs are summarized for the hENT1-low subgroup in the table below.

Treatment-Emergent SAEs Reported in ≥ 4 Patients in the hENT1-Low Subgroup (Safety Population), N (%)			
System Organ Class MedDRA Preferred Term	**Gemcitabine Elaidate (N=112)**	**Gemcitabine (N=115)**	**Total N=227**
At least 1 serious TEAE	53 (47.3)	52 (45.2)	105 (46.3)
Blood and Lymphatic System Disorders			
Anemia	5 (4.5)	1 (0.9)	6 (2.6)
Gastrointestinal Disorders			
Nausea	3 (2.7)	1 (0.9)	4 (1.8)
Vomiting	3 (2.7)	2 (1.7)	5 (2.2)
General Disorders and Administration Site Conditions			
Asthenia	2 (1.8)	2 (1.7)	4 (1.8)
Pyrexia	2 (1.8)	2 (1.7)	4 (1.8)
Hepatobiliary Disorders			
Cholangitis	2 (1.8)	3 (2.6)	4 (1.8)
Cholestasis	2 (1.8)	4 (3.5)	6 (2.6)

Treatment-Emergent SAEs Reported in ≥ 4 Patients in the hENT1-Low Subgroup (Safety Population), N (%)			
System Organ Class MedDRA Preferred Term	**Gemcitabine Elaidate (N=112)**	**Gemcitabine (N=115)**	**Total N=227**
Infections and Infestations			
Pneumonia	1 (0.9)	3 (2.6)	4 (1.8)
Metabolism and Nutrition Disorders			
Dehydration	4 (3.6)	2 (1.7)	6 (2.6)
Neoplasms Benign, Malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma metastatic	21 (18.8)	28 (24.3)	49 (21.6)
Respiratory. Thoracic and Mediastinal Disorders			
Pulmonary embolism	4 (3.6)	4 (3.5)	8 (3.5)
Vascular disorders			
Deep vein thrombosis	3 (2.7)	2 (1.7)	5 (2.2)

The treatment-emergent SAE profile was comparable across treatment groups. The primary TEAE leading to a categorisation of serious was disease progression of the underlying pancreatic cancer (21.6% of patients). The treatment-emergent SAEs in the hENT1-high subgroup and in the All Patients group were similar to those reported for the hENT1-low subgroup.

Treatment-Related Treatment-Emergent SAEs

Treatment-Related Treatment-Emergent SAEs are summarized for the hENT1-low subgroup in the table below.

Treatment-Related Treatment-Emergent SAEs Reported in Any Patient in the hENT1-Low Subgroup (Safety Population), N (%)			
System Organ Class MedDRA Preferred Term	**Gemcitabine Elaidate (N=112)**	**Gemcitabine (N=115)**	**Total N=227**
At least 1 serious treatment related TEAE	11 (9.8)	12 (10.4)	23 (10.1)
Blood and Lymphatic System Disorders			
Anemia	4 (3.6)	0	4 (1.8)
Leukopenia	1 (0.9)	0	1 (0.4)
Neutropenia	1 (0.9)	0	1 (0.4)
Thrombocytopenia	1 (0.9)	0	1 (0.4)
Gastrointestinal Disorders			
Gastric Hemorrhage	1 (0.9)	0	1 (0.4)
Nausea	1 (0.9)	1 (0.9)	2 (0.9)
Vomiting	1 (0.9)	2 (1.7)	3 (1.3)

Treatment-Related Treatment-Emergent SAEs Reported in Any Patient in the hENT1-Low Subgroup (Safety Population), N (%)			
System Organ Class MedDRA Preferred Term	**Gemcitabine Elaidate (N=112)**	**Gemcitabine (N=115)**	**Total N=227**
General Disorders and Administration Site Conditions			
Asthenia	1 (0.9)	2 (1.7)	3 (1.3)
Edema Peripheral	0	1 (0.9)	1 (0.4)
Pyrexia	1 (0.9)	2 (1.7)	3 (1.3)
Infections and Infestations			
Bronchopneumonia	0	1 (0.9)	1 (0.4)
Cellulitis	0	1 (0.9)	1 (0.4)
Enterococcal bacteraemia	0	1 (0.9)	1 (0.4)
Eschericia urinary tract infection	0	1 (0.9)	1 (0.4)
Viral upper respiratory tract infection	0	1 (0.9)	1 (0.4)
Investigations			
Hemoglobin decreased	1 (0.9)	0	1 (0.4)
Platelet count decreased	1 (0.9)	0	1 (0.4)
Metabolism and Nutrition Disorders			
Dehydration	0	2 (1.7)	2 (0.9)
Fluid retention	0	1 (0.9)	1 (0.4)
Renal and Urinary Disorders			
Acute pre-renal failure	0	1 (0.9)	1 (0.4)
Respiratory. Thoracic and Mediastinal Disorders			
Dyspnea	0	1 (0.9)	1 (0.4)
Epistaxis	1 (0.9)	0	1 (0.4)
Pneumothorax	0	1 (0.9)	1 (0.4)
Pulmonary embolism	1 (0.9)	0	1 (0.4)
Vascular disorders			
Venous thrombosis limb	1 (0.9)	0	1 (0.4)

In the hENT1-low subgroup, treatment-related treatment-emergent SAEs were comparable between treatment groups and occurred in 23 (10.1%) of all subjects. Anemia was the most frequent treatment-related treatment-emergent SAE, occurring in 4 patients, all in the gemcitabine elaidate arm (p=0.058)

The treatment-related treatment-emergent SAEs in the hENT1-high subgroup and in the All Patients group were similar to those reported for the hENT1-low subgroup.

Laboratory parameters

Hematological and clinical chemistry changes were similar across treatment groups within each patient group (hENT1-low, hENT1-high, All Patients).

Hematological and clinical chemistry Grade 3 and Grade 4 toxicities were similar across treatment groups in the All Patients group, and were consistent with the known laboratory abnormality profile of patients with advanced cancer and treatment with gemcitabine.

Other assessments

There were no notable differences across treatment groups or between patient groups in vital sign or ECG measurements

Conclusions:

The efficacy data were mature with approximately 85% of patients having a reported date of death. There was no difference in OS between gemcitabine elaidate and gemcitabine in patients with mPDAC and low tumor hENT1 expression, (median OS: 5.7 vs. 6.1 months, respectively; stratified HR (gemcitabine elaidate vs. gemcitabine; 95% CI): 0.994 [0.746, 1.326]). PFS and ORR analyses also concluded that there was no difference between the treatment arms in these patients. Efficacy outcomes were similar in the All Randomized patient population and in the patients with high tumor hENT1 expression.

The OS in patients treated with gemcitabine was similar in patients with high vs. low tumor hENT1 expression (median OS: 5.2 vs. 6.1 respectively; stratified HR (high vs. low; 95% CI): 1.147 [0.809, 1.626]). These results indicate that in patients with mPDAC a prospectively defined robust tumor hENT1 cut-off level was not predictive of gemcitabine response.

The clinical development program for gemcitabine elaidate was discontinued by the Sponsor following analysis of the efficacy results; therefore PK/PD analyses for gemcitabine elaidate were not conducted.

There were no meaningful differences between gemcitabine elaidate and gemcitabine in the safety profile of patients with low tumor hENT1 expression.

- The majority of TEAEs were CTCAE Grade 1 or Grade 2. The most frequently occurring toxicities ≥ Grade 3 were disorders of the blood and lymphatic system (anemia, thrombocytopenia, neutropenia) or events attributed to disease progression of the underlying pancreatic cancer.
- The most frequently occurring treatment-related TEAEs were disorders of the blood and lymphatic system (anemia, thrombocytopenia, neutropenia) and the gastrointestinal system (diarrhea, nausea and vomiting), and general disorders (asthenia, fatigue, pyrexia).
- Treatment-related treatment-emergent SAEs were comparable between treatment groups and occurred in approximately 10% of patients. Anemia was the most frequent treatment-related treatment-emergent SAE, occurring in 4 patients, all in the gemcitabine elaidate arm.
- TEAEs leading to study drug interruption were comparable between treatment arms and occurred in approximately 30% of patients. The main toxicities leading to study drug interruption were thrombocytopenia (7.0% of patients) and anemia (4.4% of patients).
- TEAEs leading to reduction or delay of study drug were also comparable between treatment groups, occurring in approximately 59% of patients. The main toxicities leading to study drug reduction or delay were thrombocytopenia (25.1% of patients) and neutropenia (17.6% of patients).
- A slightly higher proportion of patients in the gemcitabine elaidate group discontinued

study drug due to a TEAE compared with those in the gemcitabine group, but this difference was not statistically significant (25.9% vs. 15.7% respectively, p=0.071). The primary TEAE leading to study drug discontinuation was disease progression of the underlying pancreatic cancer (9.3% of patients), which occurred in a similar proportion of patients in each treatment arm

Laboratory abnormalities were similar between treatment groups.

In conclusion, the overall safety profile in patients with metastatic pancreatic adenocarcinoma and low tumor hENT1 expression was similar across treatment groups and consistent with that expected for gemcitabine, and with that reported for gemcitabine elaidate in previous clinical trials. Safety outcomes were similar in the All Patients population and in the patients with high tumor hENT1 expression.

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