Protocol Synopsis

Sponsor:	InnoPharmax Inc.
Investigational Product:	D07001-softgel capsules
Active Ingredient:	Gemcitabine hydrochloride
Protocol No.:	Inno-GO-03
Study Title:	Open-Label, Multicenter Study of D07001-Softgel Capsules (Oral Gemcitabine Hydrochloride) in Subjects with Unresectable, Metastatic or Locally Advanced Gastrointestinal Cancer in Dose-Escalation Phase and in Subjects with Advanced Biliary Tract Cancer Following Primary Chemotherapy or Combined Chemoradiotherapy in Dose-Expansion Phase
Phase of Development:	1b/2
Study Site(s):	The study will be conducted in Taiwan, Korea, and the United States of America (USA).
Indication(s):	Chemotherapy following primary chemotherapy or combined chemoradiotherapy (CCRT) for advanced biliary tract cancer (BTC) (cholangiocarcinoma or gallbladder cancer)
Objectives:	**Part 1: Dose-Escalation Phase (Phase 1b)** <u>Primary Objective</u> • To assess the safety and tolerability of increasing doses of D07001-softgel in patients with unresectable locally advanced or metastatic gastrointestinal (GI) cancer <u>Secondary Objectives</u> • To evaluate the pharmacokinetic (PK) profile of D07001-softgel <u>Exploratory Objectives</u> • To evaluate the preliminary data on the efficacy of increasing doses of D07001-softgel • To investigate the effect of increasing doses of D07001-softgel on additional parameters such as tumor markers • To investigate the relationship between the efficacy, safety, and PK of D07001-softgel and pharmacogenomic, pharmacoproteomic, and cellular markers, including the levels of immune cells, circulating endothelial progenitor cells and circulating tumor cells **Part 2: Dose-Expansion Phase (Phase 2)** <u>Primary Objectives</u> • To assess the safety and tolerability of D07001-softgel in patients who have achieved stable disease or better following

	first-line chemotherapy or CCRT for unresectable metastatic or locally advanced BTC Secondary Objectives • To assess the PK profile of D07001-softgel, including the effect of food Exploratory Objectives • To evaluate the efficacy of D07001-softgel, as assessed by progression-free survival (PFS), overall survival (OS), time-to-progression (TTP), and objective response rate (ORR; in patients with measurable disease at baseline only), in patients who have achieved stable disease or better following first-line chemotherapy or CCRT for unresectable metastatic or locally advanced BTC • To investigate the effect of D07001-softgel on tumor markers • To investigate the relationship between the efficacy, safety, and PK of D07001-softgel and pharmacogenomic, pharmacoproteomic, and cellular markers, including the levels of immune cells, circulating endothelial progenitor cells and circulating tumor cells
Study Design:	This open-label, multicenter study will be conducted in 2 parts: a dose-escalation phase (Part 1) and a dose-expansion phase (Part 2). In both Part 1 and Part 2, eligible patients will be assigned to receive oral D07001-softgel on Days 1, 3, 5, 8, 10, 12, 15, 17, and 19 of a 21-day cycle (9 doses per cycle). There will be no gap between the cycles, e.g., the second cycle will commence immediately on the next day after Day 21 of the first cycle (Day 22 overall). Dosing on 2 consecutive days will not be allowed; there will be at least 1 day between 2 doses. **Part 1: Dose-Escalation Phase (Phase 1b)** Part 1 of the study will follow a 3+3 dose-escalation scheme at predefined dose levels. There will be sequential cohorts of 3 to 6 patients each with increasing doses of 40 mg, 60 mg, 80 mg, 120 mg, and 160 mg per cohort. There will be no intra-patient dose escalation. Cycle 1 (21 days) is defined as the dose-limiting toxicity (DLT) assessment period. Each cohort will enroll 3 patients. If none of the 3 patients in the cohort experiences a DLT, the study may proceed with dose escalation to the next cohort. If 1 out of 3 patients experiences a DLT, 3 additional patients will be entered into that cohort for a total of 6 patients. If none of the 3 additional patients in that cohort experiences a DLT, then the next ascending dose cohort may proceed. Dose escalation to a subsequent cohort will only proceed after assessment of safety and tolerability data (and raw PK data, if available) of the preceding cohort at a review meeting of the Safety Board. If ≥2 patients in a 3-6 patient cohort experience a DLT during Cycle 1, the maximum tolerated dose

	(MTD) is considered to have been exceeded and no additional patients will be treated at the current or higher doses. In this case, the Safety Board may decide to evaluate an intermediate dose level 20 mg lower than the dose level at which ≥2 patients in a cohort experienced a DLT. If an MTD is not identified following dose escalation to 160 mg, the intermediate dose level of 140 mg may also be evaluated. If an intermediate dose level is evaluated, up to 6 additional patients will be enrolled at that dose level. Patients in Part 1 will continue treatment until withdrawal due to a DLT (Cycle 1 only), disease progression according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1), withdrawn consent, or when another treatment discontinuation criterion is met. PK samples will be obtained during Cycle 1. For Cycle 1 Day 1 and Day 15 visits, overnight fasting, except for water and medications is required. Preliminary efficacy data will be obtained in Part 1. Tumor assessments by RECIST v1.1 will be conducted every 6 weeks relative to the first dose of study medication for all patients until disease progression, death, or withdrawal of consent. Disease progression will be based on the Investigator's evaluation of tumor assessments. Patients who are discontinued from study drug for a reason other than disease progression, death, or withdrawal of consent are to continue tumor assessments on the same schedule. **Part 2: Dose-Expansion Phase (Phase 2)** The highest dose level of D07001-softgel tested at which <2 of 6 patients experience a DLT will be expanded in Part 2 of the study. In addition, because the highest dose level selected in Part 1 could lead to cumulative toxicity during treatment, the next lowest dose level below the highest evaluated in Part 1 at which <2 of 6 patients experienced a DLT will also be expanded for assessment in Part 2. If an MTD is not identified in Part 1 of the study, the 2 dose levels used in Part 2 will be 160 mg and 120 mg, or 160 mg and 140 mg if the intermediate dose of 140 mg has been evaluated in Part 1. In Part 2 of the study, eligible patients will be randomized in a 1:1 ratio to receive D07001-softgel in an open-label manner at 1 of the 2 dose levels selected for expansion. Twenty (20) patients will be enrolled to each dose-expansion cohort. Patients will be treated until withdrawal from treatment due to disease progression according to RECIST v1.1, withdrawn consent, or when another treatment discontinuation criterion is met. Patients who are discontinued from study drug for reasons other than disease progression or toxicity in the first 2 cycles of Part 2 will be replaced. As for Part 1, tumor assessments by RECIST v1.1 in Part 2 will be conducted every 6 weeks relative to the first dose of study

	medication for all patients until disease progression, death, or withdrawal of consent. Disease progression will be based on the Investigator's evaluation of tumor assessments. Patients who are discontinued from study drug for a reason other than disease progression, death, or withdrawal of consent are to continue tumor assessments on the same schedule. PK samples will be obtained during Cycle 1. For Cycle 1 Day 1 visit, overnight fasting, except for water and medications is required. In addition, for all patients in the higher dose-expansion cohort only, the PK of D07001-softgel will be evaluated after a high-fat breakfast or after overnight fasting. Patients will receive D07001-softgel on Cycle 1 Day 15 and Cycle 2 Day 1 in a high-fat fed or a fasting state. Patients will be randomized to the fed/fasted states in 1 of 2 sequences (Sequence 1: Cycle 1 Day 15 high fat, Cycle 2 Day 1 fasting; Sequence 2: Cycle 1 Day 15 fasting, Cycle 2 Day 1 high fat) with 10 patients per sequence in a cross-over design (20 patients overall). PK samples will be taken over a period of 48 hours post-dose for the food-effect evaluation in this dose-expansion cohort. Safety, tolerability, efficacy, and PK data will be compared between the 2 dose-expansion cohorts to support selection of a recommended D07001-softgel dose for further clinical development as chemotherapy following primary chemotherapy or CCRT for unresectable metastatic or locally advanced BTC. Patients in Part 1 and Part 2 who are continuing to derive clinical benefit from study drug at the time of study closure, as assessed by the Investigator, will be provided access to the study drug via a mechanism to be determined by the Sponsor.
Sample Size:	No formal sample size calculations have been performed. In Part 1 of the study, 3-6 patients will be enrolled to each of the predefined dose cohorts. If an intermediate dose level is to be investigated, another 3-6 patients will be enrolled to that cohort. In Part 2, 40 patients will be enrolled to receive D07001-softgel at the 2 dose levels selected in Part 1 (20 patients at each dose level).
Inclusion Criteria:	Patients will be entered into this study only if they meet all of the following criteria: 1. Provision of a signed and dated written Informed Consent Form (ICF) prior to any study-specific procedures 2. Male or female patients aged 18 years or older at screening (aged 20 years or older in Taiwan) 3. Histopathological or cytologic diagnosis of unresectable, metastatic or locally advanced GI cancer (Part 1) or unresectable metastatic or locally advanced BTC (cholangiocarcinoma or gallbladder cancer; Part 2) 4. Part 1 only: Refractory to or have relapsed from all standard therapies of advanced GI malignancy

	5. Part 2 only: a. Achieved stable disease or better, based on the Investigator's assessment, in response to first-line systemic therapy or CCRT, with continued stable disease or better based on imaging studies obtained as part of screening b. Completed first-line systemic therapy (with 2-8 cycles of chemotherapy with a gemcitabine-based regimen) or CCRT, based on the local standard of care and preferences in the participating countries Note: No more than 30% of patients enrolled in Part 2 will have received CCRT 6. No more than 60 days have elapsed between completion of the prior line of chemotherapy or CCRT and enrollment 7. Part 2 only: Patient has not received intervening systemic therapy since first-line treatment 8. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0-2 in Part 1 and 0-1 in Part 2 9. Life expectancy is >12 weeks 10. Adequate bone marrow function, demonstrated by: a. Absolute neutrophil count (ANC) ≥1,500 cell/mm^3 b. Platelet count ≥100,000 cells/mm^3 c. Hemoglobin ≥9 g/dL 11. Adequate liver function, demonstrated by: a. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 x upper limit of normal (ULN), or ≤5.0 x ULN in the case of liver metastases b. Total bilirubin ≤1.5 x ULN c. Albumin ≥3.0 g/dL d. International normalized ratio (INR) <1.5 12. Adequate renal function, demonstrated by: a. Serum creatinine ≤1.5 x ULN b. Creatinine clearance ≥ 60mL/min calculated by Cockcroft-Gault formula or directly measured with 24hr urine collection 13. If a woman of childbearing potential, the patient has a negative serum pregnancy test at screening and is not breastfeeding 14. If a woman of childbearing potential, patient must use a medically acceptable form of contraception as 2 barrier methods (e.g., combination of condom, diaphragm, or intrauterine device), hormonal contraception (estrogen or progesterone agents) or 1 barrier method in combination with spermicide. Birth control is required 1 month prior to screening, for the duration of their study participation, and for 1 month after the end of the study; female partners of male patients must adhere to the same birth control methods.

	15. Patient is willing to comply with protocol-required visit schedule and visit requirements
Exclusion Criteria:	Patients will not be entered into this study if they meet any of the following criteria: 1. Part 2 only: More than one prior chemotherapy regimen for unresectable metastatic or locally advanced BTC Note: prior radiation (with or without radiosensitizing doses of chemotherapy) or fluoropyrimidine chemotherapy are allowed as postsurgical adjuvant therapy. 2. Part 2 only: Received any systemic therapy (chemotherapy, biologics, immunotherapy, or investigational agents) for metastatic disease other than gemcitabine-based chemotherapy or CCRT for locally advanced BTC 3. Diagnosis of active malignancy (other than GI cancer [Part 1] or BTC [Part 2]) within the past 2 years, except nonmelanoma skin carcinoma and carcinoma-in-situ of uterine cervix treated with curative intent 4. Prior discontinuation of gemcitabine because of pulmonary or hepatic toxicity or hemolytic uremic syndrome (HUS) or hypersensitivity, allergic reaction, or intolerance 5. Any GI disorder which would significantly impede absorption of an oral agent 6. Known brain or leptomeningeal metastases 7. Surgery or radiation therapy within the past 28 days 8. Part 2 only: Evidence of disease progression, based on the Investigator's assessment, on the screening computed tomography (CT) scan or magnetic resonance imaging (MRI) scan 9. Any active disease or condition that would not permit compliance with the protocol 10. Residual toxicity from prior chemotherapy or CCRT that is Grade ≥2 (residual Grade 2 neuropathy and alopecia are permitted) 11. Clinically significant cardiovascular disease (e.g., uncontrolled hypertension, unstable angina, congestive heart failure, or New York Heart Association [NYHA] Grade 2 or greater), or uncontrolled serious cardiac arrhythmia 12. Patient has a history of drug or alcohol abuse within last year 13. Patient has documented cerebrovascular disease 14. Patient has a seizure disorder not controlled on medication (based on decision of Investigator) 15. Patient received an investigational agent within 28 days of enrollment 16. Patients with uncontrolled active viral, bacterial, or systemic

	fungal infection 17. Patient has known human immunodeficiency virus (HIV) infection 18. Patient has hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection in medical history. If positive results are not indicative of true active or chronic infection, the patient can enter the study after discussion and agreement between the Investigator and the Clinical Research Organization (CRO) Medical Monitor 19. Patient has received yellow fever vaccine or other live attenuated vaccine(s) within the 4 weeks prior to screening 20. Patient has any other serious medical condition that, in the Investigator's medical opinion, would preclude safe participation in, and compliance with, a clinical trial
Primary Endpoints and Secondary Endpoints:	**Part 1: Dose-Escalation Phase (Phase 1b)** <u>Primary Endpoint:</u> • The safety endpoints are: o DLTs o MTD o Hematology, serum chemistry, coagulation parameters, and urinalysis laboratory data changes o Adverse event (AE)/serious adverse event (SAE) incidence o Incidence of patients experiencing toxicity Grade ≥3 according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 o Physical examination result changes o Vital signs changes o Electrocardiogram (ECG) results (including PR, QRS, QT, QTc, and RR intervals) <u>Secondary Endpoints:</u> • PK parameters: maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the curve (AUC), elimination half-life ($t_{1/2\ el}$), apparent clearance (Cl/F), and apparent volume of distribution (Vz/F) <u>Exploratory Endpoints:</u> • The efficacy endpoints are: o PFS o OS o TTP o ORR (in patients with measurable disease at baseline only) • Tumor marker (cancer antigen [CA]-19-9, carcinoembryonic antigen [CEA]) levels at the times specified in the event schedule

	• Pharmacogenomic, pharmacoproteomic, and cellular analysis **Part 2: Dose-Expansion Phase (Phase 2)** Primary Endpoints: • The safety endpoints are: o Dose interruptions/modifications o Hematology, serum chemistry, coagulation parameters, and urinalysis laboratory data changes o AE/SAE incidence o Incidence of patients experiencing toxicity Grade ≥3 according to CTCAE v4.03 o Physical examination result changes o Vital signs changes o ECG results (including PR, QRS, QT, QTc, and RR intervals) Secondary Endpoints: • PK parameters: C_{max}, T_{max}, AUC, $t_{1/2\ el}$, Cl/F, and Vz/F Exploratory Endpoints: • The efficacy endpoints are: o PFS o OS o TTP o ORR (in patients with measurable disease at baseline only) • Tumor marker (CA-19-9, CEA) levels at the times specified in the event schedule • Pharmacogenomic, pharmacoproteomic, and cellular analysis
Drug Dosage/Cohorts:	**Part 1: Dose-Escalation Phase (Phase 1b)** Patients will receive D07001-softgel in the fasted state 3 times per week in 21-day cycles. Treatment will be administered in cohorts of 3-6 patients at dose levels of 40 mg, 60 mg, 80 mg, 120 mg, and 160 mg. Intermediate dose levels may be assessed in additional cohorts of 3-6 patients if considered necessary by the Safety Board. **Part 2: Dose-Expansion Phase (Phase 2)** Forty (40) patients will receive D07001-softgel in the fasted state 3 times per week in 21-day cycles at the 2 dose levels selected in Part 1 of the study (20 patients per dose-expansion cohort).
Route of Administration:	Oral
Study Duration:	The study duration for an individual patient is estimated to be a total of approximately 17 months, including approximately 8 months of treatment and an additional 9 months of follow up for survival.
Efficacy Assessment:	Tumor assessment will be made at screening using CT or MRI scans as measured by RECIST v1.1 guidelines. Patients will be assessed every 2 cycles (6 weeks) starting from 0-7 calendar days before the start of Cycle 3 until disease progression, death, or

	withdrawal of consent. The imaging technique (CT or MRI) used at screening should be used throughout the study. Patients will be considered evaluable for efficacy if they have at least 1 disease assessment on study. OS will be assessed by follow-up telephone contact every 6 weeks.
Pharmacokinetic Assessment:	In both Part 1 and 2 of the study, blood samples for PK will be collected at the following timepoints: • Cycle 1 Days 1 and 15: pre-dose (within 0.5 hour before study drug administration) and 0.25, 0.5, 1, 2, 4, 6, 8, 24, and 48 hours post-dose • Cycle 1 Day 8: pre-dose (within 0.5 hour before study drug administration) In Part 2 only, blood samples for the food-effect evaluation will be collected at the following timepoints: • Cycle 1 Day 15 and Cycle 2 Day 1: pre-dose (within 0.5 hour before study drug administration) and 0.25, 0.5, 1, 2, 4, 6, 8, 24, and 48 hours post-dose. PK Evaluations: for both Part 1 and 2, plasma samples will be analyzed for gemcitabine (dFdC) and difluorodeoxyuridine (dFdU) concentrations using validated liquid chromatography (LC)/mass spectrometry (MS)/MS assays; resulting data for each analyte will be used to calculate the following PK parameters: • dFdC and dFdU (Cycle 1 Days 1, 8, and 15): o $AUC_{(0-t)}$, $AUC_{(0-24)}$, $AUC_{(0-48)}$, $AUC_{(0-inf)}$, C_{max}, T_{max}, $t_{1/2\ el}$, $\%AUC_{extrapolated}$ • dFdC (Cycle 1 Days 1, 8, and 15): o Cl/F, Vz/F For Part 1 and 2, accumulation ratios for dFdC will be calculated for Day 15 relative to Day 1 for all AUC parameters and C_{max}. For Part 1 and the lower dose-expansion cohort in Part 2, the accumulation ratios for dFdU will be calculated for Day 15 relative to Day 1 for all AUC parameters and C_{max}, and the metabolic ratio will be calculated for dFdU for Days 1 and 15 for all AUC parameters. For the food-effect evaluation in the higher dose-expansion cohort in Part 2, bioequivalence of the fed and fasted states will be evaluated for $AUC_{(0-t)}$ and C_{max} (primary) and $AUC_{(0-inf)}$ (secondary), based on the 90% confidence interval (CI) within the predefined bioequivalence boundaries 0.8-1.25.
DLT and Safety Assessment:	Safety and tolerability will be assessed throughout treatment and the 30-day follow-up period. National Cancer Institute (NCI) CTCAE v4.03 will be used for grading toxicities. DLT definition: In Part 1 of the study, any of the following AEs occurring during Cycle 1 will be classified as DLTs, if there is a reasonable possibility that it is related to the study drug

	• Hematologic:
	  ○ Grade 4 neutropenia lasting >7 days
	  ○ Febrile neutropenia (defined as neutropenia Grade ≥3 and a body temp ≥38.3℃)
	  ○ Grade ≥3 neutropenic infection
	  ○ Grade 4 anemia
	  ○ Grade ≥3 thrombocytopenia with bleeding
	  ○ Grade 4 thrombocytopenia
	  ▪ any platelet count <10,000/μL
	  ▪ platelet count 10,000-25,000/μL for >5 days
	• Non-hematologic:
	  ○ Grade ≥3 toxicities that are considered clinically significant, except those that have not been maximally treated (e.g., nausea, vomiting, diarrhea*) or can be easily treated (e.g., electrolyte abnormalities).
	  [*Nausea, vomiting, and diarrhea: if Grade ≥3 toxicities persist for more than 48 h despite maximum treatment (loperamide, ondansetron, etc.), they will be considered dose limiting]
	• Delay by more than 7 days in receiving the next scheduled cycle due to persisting toxicities attributable to study drug.
	• Failure to deliver at least 6 of the planned 9 doses during Cycle 1 due to treatment-related toxicities.
	• Upon the second occurrence of a toxicity leading to a dose hold.
	Safety will be further assessed throughout the study by:
	• The incidence of AEs, SAEs, deaths on study, and dose modifications (dose reduction, interruption, or discontinuation of study drug)
	• The change from baseline in clinical laboratory test results, (hematology, serum chemistry, coagulation parameters, urinalysis), and tumor markers
	• Vital signs measurements
	• Physical examination findings
	• ECOG PS results
	• ECG findings (including PR, QRS, QT, QTc, and RR intervals)

Statistical Considerations:	**Analysis Sets** <u>Part 1</u> The following analysis sets will be defined for Part 1 of the study: • Enrolled Set (ENS): all patients who provided informed consent

	• Safety Analysis Set (SAF): all patients who received at least 1 dose of D07001-softgel • PK Analysis Set (PKS): all patients in the SAF with evaluable PK data, and who have no major protocol deviations considered to impact the analysis of the PK data <u>Part 2</u> The following analysis sets will be defined for Part 2 of the study: • ENS: all patients who provided informed consent • SAF: all patients who received at least 1 dose of study drug, classified by actual dose received • Modified Intent-to-Treat Set (mITT): all randomized patients who received at least 1 dose of study drug and with at least 1 post-baseline disease assessment Note: Patients who do not meet eligibility criteria prior to randomization but are still randomized into the study will be excluded from the mITT Set. • Per-Protocol Set: a subset of the mITT Set that excludes patients who have major protocol deviations • PKS: all patients in the SAF with evaluable PK data, and who have no major protocol deviations considered to impact the analysis of the PK data Data for patients in Part 1 and Part 2 will be analyzed separately. Data for Part 1 and Part 2 will be summarized using descriptive statistics (number of patients, mean, median, standard deviation (StD), minimum, and maximum) for continuous variables and using frequency and percentages for discrete variables. Unless otherwise specified, the baseline assessment will be the latest, valid pre-dose assessment available. Safety and PK analyses will be performed using descriptive statistics. Exploratory analyses for efficacy of each dose-expansion cohort in Part 2, time-to-event estimates and survival curves will be generated using Kaplan-Meier methodology for PFS and other survival outcomes.