



CLINICAL STUDY PROTOCOL

Study Title: A Phase 2, Randomized, Double-blind Study of Gemcitabine and Nab-paclitaxel combined with Mometinib in Subjects with Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma Preceded by a Dose-finding, Lead-in Phase

Sponsor: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

IND Number: 120605

Indication: Previously untreated locally advanced or metastatic pancreatic ductal adenocarcinoma

Protocol ID: GS-US-370-1296

Clinical Program Manager: Name: PPD
Telephone: PPD

Gilead Medical Monitor: Name: Peter Lee, MD, PhD
Telephone: PPD

Protocol Version/Date: Original: 11 February 2014
Amendment 1: 14 March 2014

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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
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Study Title: A Phase 2, Randomized, Double-blind Study of Gemcitabine and Nab-paclitaxel combined with Momelotinib in Subjects with Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma Preceded by a Dose-finding, Lead-in Phase

IND Number: 120605

Study Centers Planned: Lead-in phase: Approximately 2-3 centers in the United States
Randomized treatment phase: Approximately 75 centers worldwide

Objectives: Primary Objectives:

- Lead-in phase: To evaluate the safety, pharmacokinetics, and define the maximum tolerated dose (MTD) of momelotinib (MMB) combined with gemcitabine/nab-paclitaxel (nab-P+G) in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma.
- Randomized treatment phase: To determine the efficacy of nab-P+G combined with either MMB administered at the MTD or placebo in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma as measured by improvement in overall survival (OS).

Secondary Objectives:

- Lead-in phase: To evaluate the efficacy of MMB combined with nab-P+G in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma.
- Randomized treatment phase:
 - To evaluate the efficacy of nab-P+G combined with either MMB or placebo as measured by improvement in progression free survival (PFS)
 - To evaluate the efficacy of nab-P+G combined with either MMB or placebo as measured by improvement in overall response rate (ORR)
 - To evaluate the safety and tolerability of nab-P+G combined with either MMB or placebo

Study Design:

Lead-in: An open-label, non-randomized phase with dose escalation as shown in the following table.

Dose Level	MMB	G	nab-P
-2	100 mg once daily	800 mg/m ²	100 mg/m ²
-1	100 mg once daily	1000 mg/m ²	100 mg/m ²
1*	100 mg once daily	1000 mg/m ²	125 mg/m ²
2	150 mg once daily	1000 mg/m ²	125 mg/m ²
3	200 mg once daily	1000 mg/m ²	125 mg/m ²
4	150 mg twice daily	1000 mg/m ²	125 mg/m ²
5	200 mg twice daily	1000 mg/m ²	125 mg/m ²

Dose Level	MMB	G	nab-P
2a	150 mg once daily	1000 mg/m ²	100 mg/m ²
3a	200 mg once daily	1000 mg/m ²	100 mg/m ²
4a	150 mg twice daily	1000 mg/m ²	100 mg/m ²
5a	200 mg twice daily	1000 mg/m ²	100 mg/m ²

*Starting dose

G: gemcitabine; MMB: momelotinib; nab-P: nab-paclitaxel

Three subjects will initially enroll into Dose Level 1. If no dose limiting toxicity (DLT) occurs in all 3 subjects during the first 28 days (Cycle 1) of treatment, 3 additional subjects will enroll into Dose Level 2. If 1 DLT occurs in any Dose Level, that Dose Level will be expanded to enroll 3 additional subjects. If a second DLT occurs within the same Dose Level after cohort expansion, the maximum tolerated dose (MTD) of nab-P+G combined with MMB has been exceeded. Dose escalation will continue from Dose Level 2 to 3 to 4 to 5 if no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects within each Dose Level.

If ≥ 2 DLTs occur in Dose Level 1, Dose Level -1 will open to enroll 3 additional subjects. If no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects of Dose Level -1, then Dose Level -1 will be the MTD of nab-P+G combined with MMB. If ≥ 2 DLTs occur in Dose Level -1, Dose Level -2 will open to enroll 3 additional subjects. If no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects of Dose Level -2, then Dose Level -2 will be the MTD of nab-P+G combined with MMB. If ≥ 2 DLTs occur at Dose Level -2, the study will discontinue permanently.

If ≥ 2 DLTs occur in Dose Level 2, 3, 4, or 5 then Dose Level 2a, 3a, 4a, or 5a will open, respectively. If no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects of Dose Level 2a, then Dose Level 3a will open to enroll 3 additional subjects. Dose escalation will continue from Dose Level 3a to 4a to 5a if no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects of each Dose Level. If ≥ 2 DLTs occur in either Dose Level 2a, 3a, 4a, or 5a, then Dose Level 1, 2, 3, or 4 will be the MTD of nab-P+G combined with MMB, respectively.

Please refer to [Appendix 5](#) for flow diagram of dose escalation.

Dose limiting toxicities are based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Dose limiting toxicities refer to toxicities experienced during the first 28 days (Cycle 1) of treatment that have been judged to be clinically significant and related to study treatment. A DLT is defined as:

- Grade 4 neutropenia lasting > 5 days. Subjects who develop Grade 4 neutropenia during the first 28 days of treatment must have a repeat assessment of their neutrophil count 5 days after the onset of Grade 4 neutropenia to assess for this DLT.
- Grade ≥ 3 neutropenia with fever (temperature $\geq 100.5^{\circ}$ F)
- Grade 4 thrombocytopenia
- Grade 3 or higher non-hematologic toxicity, excluding:
 - Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy
 - Grade 3 diarrhea with maximum duration of 48 hours on adequate medical therapy
 - Alopecia
- After the MTD is established by lead-in phase, the study will proceed to the randomized treatment phase.

Tumor biopsy will be performed at the time of the first restaging (at approximately week 8) in an optional substudy to investigate pharmacodynamic and mechanism of action biomarkers.

Randomized Treatment: The randomized, double-blind, placebo-controlled phase of the trial. A total of 300 eligible subjects will be randomized in a 1:1 manner (150 subjects per treatment group) to receive either MMB or placebo in combination with nab-P+G in 28-day cycles. Treatment assignment of this phase will be stratified by ECOG (0 vs. 1) and baseline c-reactive protein (CRP) plasma level (high vs. low).

CT or MRI scans will be performed every 8 weeks to evaluate response to treatment by Response Evaluation Criteria In Solid Tumor (RECIST) v1.1 criteria.

Tumor biopsy will be performed at the time of the first restaging (at approximately week 8) and/or at the time of progression in an optional first and/or second substudy to investigate pharmacodynamics, mechanism of action and resistance biomarkers.

Number of Subjects Planned:	Lead-in phase: 9 to 36 subjects Randomized treatment phase: approximately 300 subjects
Target Population:	Previously untreated metastatic pancreatic ductal adenocarcinoma
Duration of Treatment:	Each treatment cycle will be 28 days. Treatment will continue in the absence of disease progression, unacceptable toxicity, consent withdrawal, or subject's refusal of treatment.
Diagnosis and Eligibility Criteria:	Inclusion Criteria: <ol style="list-style-type: none">1) Age \geq 18 years old2) Initial diagnosis of metastatic pancreatic adenocarcinoma must have occurred \leq 6 weeks prior to randomization3) The presence of metastatic pancreatic adenocarcinoma plus 1 of the following:<ul style="list-style-type: none">• Histological diagnosis of pancreatic adenocarcinoma confirmed pathologically, OR• Pathologist confirmed histological/cytological diagnosis of adenocarcinoma consistent with pancreas origin in conjunction with either:<ul style="list-style-type: none">— The presence of a mass in the pancreas, OR— A history of resected pancreatic adenocarcinoma4) Measurable disease per RECIST v1.1

- 5) Adequate organ function defined as follows:
 - Hepatic: Total bilirubin < upper limit of normal (ULN); AST (SGOT) and ALT (SGPT) $\leq 3 \times$ upper limit of normal (ULN)
 - Hematological: Absolute neutrophil count (ANC) > 1500 cells/mm³, platelet > 100,000 cells/mm³, hemoglobin > 9 g/dL
 - Renal: Serum creatinine < ULN OR calculated creatinine clearance (CrCl) ≥ 60 ml/min as calculated by the Cockcroft-Gault method
- 6) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- 7) Negative serum pregnancy test for female subjects (unless surgically sterile or greater than two years postmenopausal)
- 8) Male and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in [Appendix 3](#)
- 9) Females who are nursing must agree to discontinue nursing before the first dose of investigational product (IP)
- 10) Able to comprehend and willing to sign the written informed consent form

(Diagnosis and
Eligibility Criteria
(Continued):

Exclusion Criteria:

- 1) Neoadjuvant or adjuvant chemotherapy or chemoradiotherapy for pancreatic adenocarcinoma
- 2) Currently or previously treated with biologic, small molecule, immunotherapy, chemotherapy, or other agents for metastatic pancreatic carcinoma
- 3) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active or chronic bleeding event within 4 weeks prior to first dose of IP, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician

- 4) History of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to randomization, adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 5 years
- 5) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy), within 28 days of first dose of IP
- 6) Minor surgical procedure(s) within 7 days of randomization or not yet recovered from prior minor surgery (placement of central venous access device, fine needle aspiration, or endoscopic biliary stent ≥ 1 day before randomization is acceptable)
- 7) Known positive status for human immunodeficiency virus (HIV)
- 8) Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier
- 9) Peripheral neuropathy \geq Grade 2
- 10) Known or suspected brain or central nervous system metastases
- 11) Diagnosis of pancreatic islet neoplasm, acinar cell carcinoma, non-adenocarcinoma (ie, lymphoma, sarcoma), adenocarcinoma originating from the biliary tree or cystadenocarcinoma
- 12) History of interstitial pneumonitis and/or require supplemental oxygen therapy
- 13) External biliary drain
- 14) Paracentesis or thoracentesis for malignant effusion within 14 days of randomization
- 15) Documented myocardial infarction or unstable/uncontrolled cardiac disease (ie, unstable angina, congestive heart failure [New York Heart Association > Class III]) within 6 months of randomization
- 16) Use of strong CYP3A4 inhibitors or strong CYP3A4 inducers within 1 week prior to the first dose of IP
- 17) Known hypersensitivity to MMB, gemcitabine and/or nab-paclitaxel, their metabolites, or formulation excipients

- 18) Uncontrolled hypertension (seated systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) at Screening
- 19) QTc interval > 450 msec, unless attributed to bundle branch block
- 20) Pregnant

Study Procedures/
Frequency:

Screening:

Screening will commence with obtaining the subject's signed informed consent and will occur up to 21 days prior to first dose of IP (MMB) for the lead-in phase or randomization for the randomized treatment phase. Screening procedures will include the following: medical history review, physical exam, vital signs, 12-lead ECG, ECOG performance status, prior/ concomitant medication review, blood collection for pregnancy test (females), laboratory assessment, adverse event (AE) assessment, and CT or MRI (scans obtained as part of standard medical practice up to 21 days during the screening period are acceptable).

Treatment Phase:

Lead-in: Each treatment cycle is 28 days. Subjects meeting eligibility will undergo 3 weekly visits each cycle. Beginning with Day 1 of Cycle 1, subjects will self-administer MMB orally once daily or twice daily in the morning and evening as per the dosing cohort they are assigned to. All subjects will also receive nab-P+G administered intravenously on Days 1, 8, and 15 of each cycle. Staging scan will be performed at baseline and approximately every 8 weeks thereafter.

After discontinuation of treatment, subjects will be followed for safety for 30 days and for survival approximately every 6 months for up to 5 years.

Randomized treatment: Each treatment cycle is 28 days. Subjects meeting eligibility will undergo 3 weekly visits each cycle. Beginning with Day 1 of Cycle 1, subjects will self-administer MMB or placebo. All subjects will also receive nab-P+G administered intravenously on Days 1, 8, and 15 of each cycle. Staging scan will be performed at baseline and approximately every 8 weeks thereafter.

After discontinuation of treatment, subjects will be followed for safety for 30 days and for survival approximately every 6 months for up to 5 years.

**Test Product, Dose,
and Mode of
Administration:**

MMB tablet will be self-administered orally once daily or twice daily in the morning and evening (dose frequency as instructed by clinical investigator), beginning on Day 1 of the study, and thereafter at approximately the same time each day until end of treatment.

Reference Therapy, Dose, and Mode of Administration:	Nab-paclitaxel intravenously over 30-40 minutes or as per institutional standard of care followed immediately by gemcitabine intravenously over 30 minutes or as per institutional standard of care on Days 1, 8, and 15. Cycle repeats every 28 days.
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Criteria for Evaluation:

Safety: The overall safety profile of each treatment group will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any adverse events (AEs) or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation of study drug.

Efficacy: Primary Endpoints:
Lead-in: Incidence of dose limiting toxicities (DLTs) as defined in Section 3.1
Randomized treatment: Overall survival (OS), defined as the interval from randomization to death from any cause
Secondary Endpoints:
Overall response rate (ORR) (complete response [CR] + partial response [PR]), assessed as per RECIST v1.1
Progression-free survival (PFS), defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause
Overall survival will also be the secondary endpoint for the lead-in phase
Exploratory endpoints are described in the body of the protocol

Pharmacokinetic: Pharmacokinetic (PK) blood samples will be collected at the timepoints specified in the protocol.

Pharmacodynamic and Exploratory Biomarkers:

PPD

Statistical Methods:**Analysis Methods**

The Intent-to-Treat (ITT) Analysis Set will be used in the analyses of the primary efficacy endpoint, OS. The ITT Analysis Set consists of all randomized subjects, with study treatment assignment designated according to initial randomization. A Safety Analysis Set consists of subjects in the ITT Analysis Set who received ≥ 1 dose of study drug, with study treatment designated according to the actual treatment received. Other analysis sets [per-protocol (PP) and PK/pharmacodynamic analysis sets] will be used for additional analyses as well.

Unless otherwise specified, data from the lead-in and randomized treatment parts will be summarized and analyzed separately.

Subject characteristics and study results will be described and summarized by treatment arm and assessment for the relevant analysis sets. Descriptive summaries will be prepared to show sample size, mean, standard deviation (StD), 95% confidence intervals (CIs) on the mean, median, minimum and maximum for continuous variables and counts, percentages and 95% CIs on the percentage for categorical variables.

For the primary efficacy analysis, the difference in OS between the treatment arms will be assessed in the ITT Analysis Set using Kaplan-Meier (KM) methods and the stratified log-rank test. Medians, ranges, the proportion of subjects who are surviving at 24 and 48 weeks from randomization (based on KM estimates), hazard ratios, and the corresponding 95% CIs (as calculated using a Cox proportional hazards regression model) will be presented.

Efficacy endpoints will be analyzed based on the ITT and PP Analysis Sets, with ITT Analysis Set as primary. Time-to-event efficacy endpoints will be analyzed in a similar manner as OS. Categorical endpoints will be compared using the Cochran-Mantel-Haenszel (CMH) test adjusted for stratification factors. Continuous endpoints will be assessed using analysis of covariance (ANCOVA) with treatment and stratification factors as factor and baseline value as covariate.

Based on the Safety Analysis Set, information regarding IP administration, IP compliance and safety variables will be described and summarized.

Using data from the PK and pharmacodynamic Analysis Sets, MMB plasma concentrations and pharmacodynamic markers will also be described and summarized.

Sample Size Calculation

Based on the historical data (MPACT trial in patients with metastatic pancreatic cancer), the median OS was 8.5 months in the nab-P+G group. Ruxolitinib Phase II RECAP trial (ruxolitinib or placebo in combination with capecitabine in patients with refractory metastatic pancreatic cancer) reported, in a pre-specified subgroup identified prospectively as most likely to benefit from JAK inhibitor treatment, a hazard ratio (HR) for OS of 0.47.

For the randomized treatment phase of the study, a total of 162 OS events need to be observed to detect a HR of 0.6 with 90% power at a 2-sided 0.05 significance level. Assuming an accrual rate of 20 subjects per month, median OS of 8.5 months in the control arm, and no lost-to-follow-up, a sample size of 150 subjects in each arm need to be enrolled to observe the 162 OS events. The expected study duration of observing 162 OS events in the randomized treatment phase is ~21 months. One interim analysis will be conducted when 81 OS events have been observed. An O'Brien-Fleming boundary will be applied to assess the efficacy at the interim analysis. The efficacy boundaries (p-value) for the interim and final analyses will be 0.003 and 0.049, respectively.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
ADME	absorption, distribution, metabolism, elimination
AE	adverse event
AKT	Protein Kinase B
ALT	alanine transaminase
AM	morning
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin
AST	aspartate transaminase
AUC	area under the plasma/serum/peripheral mononuclear cell concentration versus time curve
AUC _{0-last}	area under the concentration versus time curve from time 0 to the last quantifiable concentrations
AUC _{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0-last} + (C_{last}/\lambda_z)$
AUC _τ	area under the concentration versus time curve over the dosing interval
BCRP	breast cancer resistance protein
BSEP	bile salt export pump
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	complete blood count
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	confidence interval
C _{last}	last observed quantifiable plasma concentration of drug
CL/F	apparent oral clearance after administration of the drug: $CL/F = \text{Dose}/AUC_{inf}$ where “dose” is the dose of the drug
C _{max}	maximum observed serum/plasma concentration of drug
CMH	Cochran-Mantel-Haenszel
Conmed	concomitant medication
CR	complete response
CrCL	creatinine clearance
CRF	case report form(s)
CRO	contract (or clinical) research organization
CRP	c-reactive protein
CSR	clinical study report

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

CT	computed tomography/ computed axial tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DDI	drug-drug interaction
DLT	dose limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
EOT	end of treatment
eSAE	electronic serious adverse event
ET	essential thrombocythemia
EudraCT	European clinical trials database
EU	European Union
EQ-5D	EuroQoL-5D
FACT-Hep	Functional Assessment of Cancer Therapy – Hepatobiliary
FDA	(United States) Food and Drug Administration
G	gemcitabine
GCP	Good Clinical Practice (Guidelines)
GGT	gamma-glutamyl transpeptidase
GLP	good laboratory practice
GSi	Gilead Sciences, Inc.
H	hour
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HR	hazard ratio
IB	investigator's brochure
IC ₅₀	inhibitory concentration 50
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device(s)
IXRS	interactive voice/web response system
JAK	Janus Kinase
kg	kilogram
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LDH	lactate dehydrogenase
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
μM	micromole
msec	millisecond
MMB	momelotinib
MRD	maximum recommended dose
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N	number enrolled
nab-P	nab-paclitaxel
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OCT	organic cation transporter
OS	overall survival
ORR	overall response rate
PD	progressive disease
PE	physical exam
PFS	progression-free survival
P-gp	permeability glycoprotein
PI3K-AKT	phosphatidylinositol-3-kinase and protein kinase B
PK	pharmacokinetic
PP	Per-Protocol
PR	partial response
PRO	patient-reported outcome(s)
PT	prothrombin time
PTT	partial thromboplastin time
PTM	placebo to match
PV	polycythemia vera

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

QTc	corrected QT interval
RAF	rapidly accelerated fibrosarcoma
RBC	red blood cell
RECIST	Response Evaluation Criteria In Solid Tumor
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SADR	serious adverse drug reaction(s)
SAE	serious adverse event(s)
SAP	statistical analysis plan
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvate transaminase
SOP	standard operating procedure
STAT	Signal Transducer and Activator of Transcription
StD	standard deviation
sTNFR	soluble tumor necrosis factor receptor
SUSAR	suspected unexpected serious adverse reaction(s)
T _{1/2}	an estimate of the terminal elimination half-life of the drug in serum/plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T _{last}	the time (observed time point) of C _{last}
T _{max}	the time (observed time point) of C _{max}
TBK1	TANK-binding kinase 1
TTR	time to response
TYK2	tyrosine kinase 2
ULN	upper limit of normal
WBC	white blood cell
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the serum, plasma concentration of drug versus time curve
5-FU	5-fluorouracil

1. INTRODUCTION

1.1. Background

Pancreatic carcinoma is the fourth leading cause of cancer-related death and in 2013, an estimated 45,220 new cases of pancreatic carcinoma will be diagnosed in the United States (US), and an estimated 38,460 people will die from the disease {24651}. Overall prognosis of pancreatic carcinoma is poor, with surgical tumor resection being the only effective cure although only 10-15% of patients are candidates for surgical resection {27725}.

For those with metastatic disease, systemic therapy is the treatment of choice. Gemcitabine has been a preferred first-line monotherapy option for those with metastatic disease based on the finding that it is more effective than bolus 5-fluorouracil (5-FU) in palliating symptoms of advanced pancreatic cancer, with clinical benefit rates of 23.8% for gemcitabine versus 4.8% for 5-FU. Median survival was 4.4 months for 5-FU, and 5.7 months for gemcitabine {17153}.

In 2011, results from a Phase 1/2, single arm study of albumin-bound paclitaxel + gemcitabine (nab-P+G) in patients with advanced pancreatic cancer were published, revealing a response rate of 48%, overall survival of 12.2 months, and 1-year survival rate of 48% for the two-drug regimen {27728}. Data from a subsequent randomized Phase 3 study of nab-P+G compared to gemcitabine alone in patients with metastatic adenocarcinoma of the pancreas (MPACT trial) confirmed the survival improvement for the combination regimen, ie, 8.5 months for nab-P+G versus 6.7 months for gemcitabine alone ($p < 0.001$). Progression-free survival was 5.5 months for nab-P+G, versus 3.7 months for gemcitabine alone ($p < 0.001$). Survival rates were 35% and 22% for nab-P+G and gemcitabine alone at 1 year, respectively {27729}. Based on these results, the combination of nab-P+G was approved by the Food and Drug Administration (FDA) as first line therapy for metastatic pancreatic carcinoma. Another combination regimen that has also demonstrated improvement in PFS and OS in patients with metastatic pancreatic carcinoma is the 4-drug combination of oxaliplatin, irinotecan, leucovorin, and fluorouracil administered as per the FOLFIRINOX regimen {21890}.

1.2. Momelotinib (MMB)

1.2.1. General Information

MMB dihydrochloride (N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide, CYT387, GS-0387) is a novel, weakly basic, disubstituted pyrimidine compound with a molecular weight of 487.38 Da. The free base is poorly soluble in water. MMB is presented for clinical administration as a dihydrochloride monohydrate salt. The dihydrochloride monohydrate salt shows kinetic solubility in water at concentrations up to 60 mg/mL. MMB dihydrochloride is manufactured from a pyrimidine scaffold in a five-step process.

In cellular assays and in vitro, MMB was shown to be a potent and selective ATP-competitive small-molecule inhibitor of Janus kinase 1 (JAK1) and JAK2, and is active at low nanomolar concentrations. MMB demonstrates marked disease-modifying properties in ex vivo assays of human erythroid cells from polycythemia vera patients and in a transgenic mouse model of myeloproliferative neoplasm. Kinase profiling of MMB indicates the compound is broadly selective for JAK1 and JAK2 over other kinase enzymes, including the closely related JAK3 and tyrosine kinase 2 (TYK2). MMB displays potent in vitro inhibitory activity against cells dependent on JAK2.

For further information on MMB, refer to the current edition of the investigator's brochure (IB) for MMB.

1.2.2. Nonclinical Pharmacology and Toxicology

1.2.2.1. Absorption, Distribution, Metabolism, and Elimination (ADME)

Equivalent mean maximal plasma concentrations of MMB (~700 ng/mL) and comparable elimination half-lives (~1h) were observed in both fed and fasted animals, consistent with previous data. There was however a notable prolongation in absorption in fed dogs with a delayed T_{max} (3h fed vs. 1h fasted). Furthermore, the AUC following dosing to fed dogs was approximately double that seen in fasted animal studies suggesting that MMB systemic availability is markedly improved when the compound is administered postprandially.

Consistent with the moderate to high bioavailability seen in nonclinical species, MMB shows high permeability in vitro across human Caco-2 cell monolayers with low efflux potential. These results indicate that MMB is likely to have high permeability across the intestinal mucosa in humans and high oral absorption in vivo.

Data from plasma protein binding studies using rat and human plasma indicate that MMB binds extensively to rat plasma proteins (~ 97%) and moderately to human plasma proteins (87% to 92%). The mean human blood-to-plasma ratio was determined to be approximately 1.1, suggesting similar distribution between the cellular and plasma fractions of blood. The rat blood-to-plasma ratio ranged from 0.6 to 0.8 indicating a lesser partitioning into blood cells.

The systemic clearance of MMB was low in rats and significantly higher in dogs. The steady-state volume of distribution in both species substantially exceeded total body water. Following oral administration as the dihydrochloride salt, MMB showed high bioavailability in the rat (50%) and moderate bioavailability in the dog (20%). The PK parameters in both the rat and dog indicated that MMB was well absorbed. In the rat, less than 10% of an administered dose of MMB was recovered in the urine as parent compound suggesting that urinary excretion is a minor clearance route for the parent compound.

The distribution of MMB into brain tissue was assessed in Swiss outbred mice following intravenous administration (5 mg/kg). The brain-to-plasma ratio for MMB was determined to be 0.075 and 0.215 at 5 and 60 minutes following MMB administration, respectively, suggesting low permeability of MMB across the blood brain barrier.

Metabolite profiling has identified major putative metabolites from in vitro and in vivo studies. Metabolite M19 (GS-642112) was present in greater amounts in both rat (both dose levels) and dog plasma pools, than in the human plasma pool. Metabolites M15, M17, and M20 were present in greater amounts in the rat plasma pool (both dose levels), than in the human or dog plasma pools. Metabolite M21 (GS-644603) was present in human plasma at higher levels than that observed in rat plasma (20 mg/kg or 80 mg/kg doses, respectively). Metabolite M21 was not observed in the dog plasma. M8 was not observed in either the rat or dog plasma pools.

The ability of the major drug-metabolizing CYP450 enzymes (CYP1A2, 2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5) to metabolize MMB was assessed with recombinant human CYP450 enzymes (Supersomes™). These in vitro studies demonstrated that MMB is partially metabolized by CYP3A4 and aldehyde oxidase.

The potential of MMB to impair the metabolism of other agents by inhibition of major drug metabolizing enzymes has also been investigated. The half-maximal inhibitory concentration (IC₅₀) of MMB on the five CYP isoforms investigated (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was greater than 25 µM. MMB is therefore unlikely to mediate significant metabolic drug-drug interactions through inhibition of these isoforms in vivo. MMB was determined to have the potential to be an inhibitor of UGT1A1, a major human uridine diphosphate glucuronosyltransferase enzyme responsible for the glucuronidation of bilirubin, with an IC₅₀ of 0.3 µM but it is not clinically relevant as no clinically significant elevation of indirect (unconjugated) bilirubin has been reported in the Phase 1/2 CCL09101 study.

The potential of MMB to inhibit the major drug transporters was studied in cells in which the individual transporters were over expressed and determining were possible the MMB IC₅₀ for the transport of probe substrates. MMB did not significantly inhibit P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP mediated transport of probe substrates at 15 µM. MMB was determined to be an inhibitor of BCRP with an IC₅₀ of 2.9 µM.

1.2.2.2. Nonclinical Toxicology

Nonclinical safety pharmacology and toxicology studies have characterized the safety of MMB and included both repeat dose toxicology studies and in vitro genotoxicity studies. All pivotal toxicology studies, including the genotoxicity studies, were conducted in full compliance with GLP regulations (21 CFR 58). The scope of the nonclinical safety evaluation is consistent with guidance issued by the International Conference on Harmonisation (ICH).

The potential for MMB to induce hemodynamic or ECG effects was evaluated in male beagle dogs following a single oral dose of 5, 30 or 100 mg/kg. A marked decrease in mean arterial pressure and increase in heart rate was observed after a single dose of 100 mg/kg.

Toxicological findings were principally related to the pharmacological action of the compound, as indicated by hematological and organ weight changes related to lymphatic and bone marrow tissues. A dose-dependent decrease in body weight gain, correlated with a dose-dependent decrease in food consumption, was observed in all studies and considered significant at high-dose levels in all studies except the 13-week dog study. Following very high exposure levels in the rat 28-day study, some off-target reversible toxicity was observed that included changes in the kidney, gastrointestinal tract, heart, and liver, of which none were observed in the

rat 13-week study or the dog studies. Female reproductive changes were observed only at high doses in the rat 28-day study and were reversible. Dose-dependent testicular degeneration was observed in rats following 28 days or 13 weeks of repeated dosing. Recovery of testicular findings was dependent upon the cycle length of spermatogenesis with reversibility observed after a 10-week recovery period (13-week study) but not after a 28-day recovery period (28-day study). These changes were not observed above background levels in sexually mature dogs consistent with the role of JAK2 in maturation of the reproductive organs {24788}.

There were several effects observed that could not be readily attributed to JAK1 and JAK2 inhibition. This potential off-target toxicity was noted in the kidney, heart, and gastrointestinal tract of the rat, and gall bladder of the dog. All effects were reversible upon cessation of dosing.

In the 90-day oral rat toxicity study, based upon the significant loss of body weight at 80 mg/kg/day, the no observed adverse effect level (NOAEL) was determined as 20 mg/kg/day, with associated Day 91 AUC₀₋₂₄ values of 94,200 ng·h/mL in males and 102,000 ng h/mL in females. The C_{max} values in males and females on day 91 were 6720 and 7290 ng/mL, respectively.

In the 3-month dog study, the highest NOAEL was 60 mg/kg/day once daily. Associated AUC₀₋₁₂ values at the NOAEL on Day 91 were 4160 and 3220 ng·h/mL, respectively. The C_{max} values in males and females on day 91 were 1250 and 1150 ng/mL, respectively.

The plasma AUC_τ in patients from Study CCL09101 at 300 mg capsule was 4.3 µg h/mL. Therefore, the margin of exposure for the NOAEL in the 90-day toxicity studies to the steady state AUC NOAEL is 22 in the rat and 0.8 in the dogs.

An in vitro bacterial reverse mutation assay (Ames test), an in vitro mammalian cell gene mutation assay (chromosomal aberration test), and an in vivo rat bone marrow micronucleus assay were conducted with MMB. No evidence of mutagenicity or clastogenicity was observed indicating a low potential for MMB to cause genotoxicity.

Preliminary data from a dose range finding embryo-fetal developmental toxicity study in rats are available. MMB was orally administered to pregnant rats (7 to 8/group plus additional animals for TK evaluations) at 0 (vehicle), 4.3, 17, and 68 mg free base equivalents/kg/day (5, 20, 80 mg/kg/day dihydrochloride salt) from gestation days 6 through 17. Based on the preliminary data, no maternal adverse effects and no embryo fetal adverse events were observed at 4.3 mg/kg/day. Maternal toxicity was observed at 17 and 68 mg/kg/day. At these maternally toxic doses, MMB administration resulted in embryo fetal effects (increase in post implantation loss resulting in a reduced number of viable fetuses). No viable fetuses were obtained at 68 mg/kg/day. At 17 mg/kg/day, there was an increase in the percentage of litters with absent innominate artery. The toxicokinetic data is not yet available from this study. Based on the data from non-pregnant female rats, the mean systemic exposure (AUC₀₋₂₄) at the NOAEL is 4-fold higher than the systemic exposure observed in patients administered 300 mg MMB, the maximum recommended dose (MRD). The exposure of MMB in non-pregnant rats at 17 mg/kg/day, the current minimum effect level, is approximately 23 fold higher than the MRD.

A more detailed summary of findings from the studies in rats and dogs is available in the IB for MMB. Investigators should refer to this document prior to initiating therapy with MMB.

1.2.3. Clinical Trials of Momelotinib

As of November 2013, 4 clinical studies of MMB have been completed and 3 clinical studies are ongoing.

Completed Clinical Trials

- Study YM387-I-02, A Randomized, Open-Label, 4-Way Crossover Study to Evaluate the Relative Bioavailability of Single Oral Doses of CYT387 Capsule Formulation versus Tablet Formulation and a Food Effect in Healthy Adult Volunteers
- Study CCL09101, A Phase I/II, Open-Label, Dose-Escalation Study Evaluating the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Orally-Administered CYT387 in Primary Myelofibrosis or Post-Polycythemia Vera Myelofibrosis or Post-Essential Thrombocythemia Myelofibrosis
- Study GS-US-352-0102, A Phase 1 Study of a Novel Formulation of GS-0387 to Determine the Relative Bioavailability, Food Effect, and Interaction with Omeprazole in Healthy Volunteers
- Study GS-US-352-1149, A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism, and Excretion of Momelotinib

Ongoing Clinical Trials

- Study CCL09101E, A Phase II, Open-Label Extension Study Evaluating the Long Term Safety, Tolerability & Efficacy of Orally-Administered CYT387 in Primary Myelofibrosis or Post-Polycythemia Vera or Post-Essential Thrombocythemia Myelofibrosis
- Study YM387-II-02, A Phase I/II, Open-Label Study Evaluating Twice-Daily Administration of CYT387 in Primary Myelofibrosis or Post-Polycythemia Vera or Post-Essential Thrombocythemia Myelofibrosis
- Study GS-US-352-0101, A Phase 3, Randomized, Double-blind Active-controlled Study Evaluating Momelotinib vs. Ruxolitinib in Subjects with Primary Myelofibrosis (PMF) or Post-Polycythemia Vera or Post-Essential Thrombocythemia Myelofibrosis (Post-PV/ET MF)

1.3. Anticipated Risk

A recent clinical trial of the JAK2 inhibitor fedratinib (SAR302503) in myelofibrosis was halted due to reported cases of Wernicke's encephalopathy. Wernicke's encephalopathy has not been reported in clinical trials with MMB. Peripheral neuropathy, however, has been reported as an adverse event. To further understand the possible mechanism and/or contributing factors of peripheral neuropathy, thiamine status will be monitored during the treatment phase of this study.

1.4. Rationale for This Study

Signaling pathways that play an important role in pancreatic carcinoma cell growth and differentiation include the JAK-STAT pathway. In particular, STAT3 has been identified as a key oncogenic factor in a number of epithelial malignancies, with aberrant STAT3 activation shown to be a requirement for the survival of several types of human cancer cells, promoting the over-expression of genes that encode anti-apoptotic proteins, cell-cycle regulators, and angiogenic factors {27599}, {27604}. In normal pancreas, STAT3 is not vital for normal development but in the majority of pancreatic adenocarcinomas, there is constitutive activation of STAT3 {27727}. Mouse models that tested the impact of conditional inactivation of STAT3 in pancreatic ductal adenocarcinomas have demonstrated the requirement of STAT3 in multiple steps of pancreatic carcinoma pathogenesis including development of the earliest premalignant pancreatic lesions, acinar-to-ductal metaplasia, and formation of pancreatic intraepithelial neoplasia {27601}. Furthermore, exposure of pancreatic tumor cells to the JAK2 inhibitor AG490 was shown to significantly inhibit the expression of phosphorylated STAT3 with subsequent reduction in the invasion and adhesion potential of human pancreatic tumor cells along with decrease in the expression of cyclin D1, bcl-xL, and vascular endothelial growth factor mRNAs, followed by growth arrest {27605}, {27612}.

MMB, in addition to being a JAK inhibitor, also has inhibitory activity against TANK binding kinase 1 (TBK1). Mutations in KRAS, present in approximately 90% of pancreatic carcinomas, drive tumor growth by engaging multiple downstream mitogenic and pro-survival pathways including the RAF-MAPK and PI3K-AKT pathways {27602}. Utilizing systematic RNA interference to detect synthetic lethal partners of oncogenic KRAS, TBK1 was found to be selectively essential in cells that contain mutant KRAS. Upon suppression of TBK1, apoptosis was induced in human cancer cells that depended on oncogenic KRAS expression along with reduction in cell proliferation and colony formation, suggesting TBK1 pathway perturbation may represent a method of targeting oncogenic KRAS-driven cancers {27596}, {27726}.

In the clinical setting, benefits of JAK inhibition were reported in patients from the RECAP trial, a randomized, double blind, placebo-controlled study of capecitabine combined with either ruxolitinib (JAK1/2 inhibitor) or placebo in patients with recurrent or refractory metastatic pancreatic carcinoma. In a pre-specified subgroup analysis conducted in patients identified prospectively as being most likely to benefit from JAK inhibitor treatment, the hazard ratio for survival was 0.47 (p=0.005). Within this subgroup of patients, 6 months survival in the ruxolitinib arm was 42%, compared to 11% for placebo (Incyte Corporation press release 21 Aug 2013, <http://investor.incyte.com/phoenix.zhtml?c=69764&p=irol-newsArticle&ID=1848898&highlight=>).

In light of these findings, the safety and efficacy of MMB in combination with chemotherapy for patients with previously untreated metastatic pancreatic ductal adenocarcinoma will be investigated in this study. Based on dose/exposure-response of Study CCL09101 in myelofibrosis, the MMB starting dose of 100 mg once-daily has the potential to be efficacious. The highest escalated dose of 200 mg twice-daily is expected to provide longer duration of target inhibition.

1.5. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

Primary Objectives:

- Lead-in phase: To evaluate the safety, pharmacokinetics, and define the MTD of MMB combined with nab-P+G in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma.
- Randomized treatment phase: To determine the efficacy of nab-P+G combined with either MMB or placebo as first line therapy in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma as measured by improvement in overall survival (OS).

Secondary Objectives:

- Lead-in phase: To evaluate the efficacy of MMB combined with nab-P+G in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma.
- Randomized treatment phase:
 - To evaluate the efficacy of nab-P+G combined with either MMB or placebo as measured by improvement in PFS
 - To evaluate the efficacy of nab-P+G combined with either MMB or placebo as measured by improvement in ORR
 - To evaluate the safety and tolerability of nab-P+G combined with either MMB or placebo

Exploratory Objectives:

PPD

[REDACTED]

[REDACTED]

3. STUDY DESIGN

3.1. Study Design

There will be a screening period of up to 21 days to assess subject eligibility including confirmation of previously untreated metastatic pancreatic ductal adenocarcinoma. CT or MRI scans of the tumor will be required within 21 days of first dose of IP (MMB) for the lead-in phase or randomization for the randomized treatment phase to assess subject disease status prior to treatment. This study will consist of 2 sequential phases: Lead-in and Randomized treatment. The end of this trial is defined as the date of the last study contact of the last study subject.

Lead-in: The study will begin with an open-label, non-randomized, dose-finding phase to define the MTD of MMB in combination with nab-P+G in pancreatic adenocarcinoma patients. Dose escalation is shown in Table 3-1.

Table 3-1. Dose Escalation Scheme

Dose Level	MMB	G	nab-P
-2	100 mg once daily	800 mg/m ²	100 mg/m ²
-1	100 mg once daily	1000 mg/m ²	100 mg/m ²
1*	100 mg once daily	1000 mg/m ²	125 mg/m ²
2	150 mg once daily	1000 mg/m ²	125 mg/m ²
3	200 mg once daily	1000 mg/m ²	125 mg/m ²
4	150 mg twice daily	1000 mg/m ²	125 mg/m ²
5	200 mg twice daily	1000 mg/m ²	125 mg/m ²

Dose Level	MMB	G	nab-P
2a	150 mg once daily	1000 mg/m ²	100 mg/m ²
3a	200 mg once daily	1000 mg/m ²	100 mg/m ²
4a	150 mg twice daily	1000 mg/m ²	100 mg/m ²
5a	200 mg twice daily	1000 mg/m ²	100 mg/m ²

*Starting dose

G: gemcitabine; MMB: momelotinib; nab-P: nab-paclitaxel

Three subjects will initially enroll into Dose Level 1. If no DLT occurs in all 3 subjects within the first 28 days (Cycle 1) of treatment, 3 additional subjects will enroll into Dose Level 2.

If 1 DLT occurs in any Dose Level, that Dose Level will be expanded to enroll 3 additional subjects. If a second DLT occurs within the same Dose Level after cohort expansion to 6 subjects, the MTD of nab-P+G combined with MMB has been exceeded. Dose escalation will continue from Dose Level 2 to 3 to 4 to 5 if no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects within each Dose Level.

If ≥ 2 DLTs occur in Dose Level 1, Dose Level -1 will open to enroll 3 additional subjects. If no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects of Dose Level -1, then Dose Level -1 will be the MTD of nab-P+G combined with MMB. If ≥ 2 DLTs occur in Dose Level -1, Dose Level -2 will open to enroll 3 additional subjects. If no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects of Dose Level -2, then Dose Level -2 will be the MTD of nab-P+G combined with MMB. If ≥ 2 DLTs occur at Dose Level -2, the study will discontinue permanently.

If ≥ 2 DLTs occur in Dose Level 2, 3, 4, or 5 then Dose Level 2a, 3a, 4a, or 5a will open, respectively. If no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects of Dose Level 2a, then Dose Level 3a will open to enroll 3 additional subjects. Dose escalation will continue from Dose Level 3a to 4a to 5a if no DLT occurs in 3 subjects or < 2 DLTs occur in up to 6 subjects of each Dose Level. If ≥ 2 DLTs occur in either Dose Level 2a, 3a, 4a, or 5a, then Dose Level 1, 2, 3, or 4 will be the MTD of nab-P+G combined with MMB, respectively.

Please refer to [Appendix 5](#) for flow diagram of dose escalation.

Dose limiting toxicities are based on CTCAE version 4.03. Dose limiting toxicities refer to toxicities experienced during the first 28 days of treatment (Cycle 1) that have been judged to be clinically significant and related to study treatment. A DLT is defined as:

- Grade 4 neutropenia lasting > 5 days. Subjects who develop Grade 4 neutropenia during the first 28 days of treatment must have a repeat assessment of their neutrophil count 5 days after the onset of Grade 4 neutropenia to assess for this DLT.
- Grade ≥ 3 neutropenia with fever (temperature $\geq 100.5^\circ\text{F}$)
- Grade 4 thrombocytopenia
- Grade 3 or higher non-hematologic toxicity, excluding:
 - Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy
 - Grade 3 diarrhea with maximum duration of 48 hours on adequate medical therapy
 - Alopecia
- A treatment-emergent AE that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk
- Any treatment delay > 4 weeks that is due to study treatment-related adverse effects

After the MTD is established by the lead-in phase, the study will proceed to randomized treatment phase.

Randomized treatment: The randomized, double-blind, placebo-controlled phase of the trial. A total of 300 subjects will be randomized via interactive voice/web response system (IXRS) in a 1:1 manner (150 subjects per treatment group) to either MMB or placebo in combination with nab-P+G. Treatment assignment of this phase will be stratified by ECOG and plasma CRP level at diagnosis.

In both lead-in and randomized treatment phases, patient-reported outcomes (PRO), clinical, laboratory, and disease assessments will be completed at regular study visits as defined in [Appendix 2](#). Thiamine status will be tested at baseline and every 12 weeks until EOT. CT or MRI scans will be performed approximately every 8 weeks to evaluate response to treatment by RECIST v1.1 criteria.

3.2. Study Treatments

The IP in this study is MMB (and its matching placebo). MMB/placebo will be supplied by GSI. The formulation, packaging, and dosing regimens for the IP are further described in [Section 5](#).

3.3. Duration of Treatment

Subjects will continue study treatment until disease progression, unacceptable toxicity, consent withdrawal, or subject's refusal of treatment. There will be a screening period of up to 21 days of first dose of IP (MMB) for the lead-in phase or randomization for the randomized treatment phase. Following treatment, subjects will be followed for safety for 30 days and for survival approximately every 6 months for up to 5 years.

3.4. Discontinuation Criteria

The study may be discontinued at any time based on periodic reviews of safety and efficacy data by Gilead.

Subject discontinuation criteria are described in [Section 6.8](#).

3.5. Source Data

The subject identification number and randomization number captured by the interactive voice/web response system (IXRS), as well as the patient reported outcomes data captured on paper are considered source data.

3.6. Biomarker Testing

3.6.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response including efficacy and/or adverse events, as well as to increase knowledge and understanding of the biology of related diseases and possible companion diagnostics development. The specific analyses will include, but will not be limited to, the biomarkers and

assays listed below. Because biomarker science is a rapidly evolving area of investigation, and adverse events in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of the art knowledge. Biomarker samples may be used for potential assay development of companion diagnostics.

Biomarker samples will be collected from all subjects for pharmacodynamic testing and exploratory analysis.

Pharmacodynamic: The transcription factor STAT3 is directly phosphorylated by JAKs in response to cytokine stimulation. The levels of phosphorylated STAT3 and other phosphoproteins will be evaluated in samples before and after treatment with MMB. Modulation of biomarkers related to JAK activation and/or MMB activity may be evaluated to further elucidate the mechanism of action of MMB.

Exploratory analysis: PPD

PPD

Tumor Tissue

The following tissue samples will be collected for pharmacodynamic and exploratory biomarker analysis:

- Archival tumor tissue will be collected from all subjects. Tissue blocks will be used to prepare fresh slides.
- Tumor biopsy will be performed at the time of the first restaging (at approximately week 8) on consenting subjects of a substudy of the lead-in and randomized treatment phases.
- Tumor biopsy will be performed at the time of progression on consenting subjects of a second substudy of the randomized treatment phase.

Blood - Plasma

PPD

Pre-treatment CRP, IL-6 and soluble TNF receptor-alpha-2 levels will be quantitated in plasma samples from all subjects to assess their predictive value. Additional protein biomarkers related to JAK activation and MMB activity will also be explored.

Blood – RNA

PPD



Exploratory Predictive Biomarkers for Subgroup Analysis

PPD



3.6.2. Biomarker Samples for Optional Future Research

PPD



3.6.3. Biomarker Samples for Optional Research

PPD



4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

The number of subjects to be enrolled in lead-in phase will depend on the total number of dose levels that may be needed to determine the MTD and may range from 9 to 36 subjects. Once the MTD has been established, approximately 300 subjects will be enrolled into randomized treatment phase.

4.2. Inclusion Criteria

Subjects must meet *all* of the following inclusion criteria to be eligible for participation in this study.

- 1) Age \geq 18 years old
- 2) Initial diagnosis of metastatic pancreatic adenocarcinoma must have occurred \leq 6 weeks prior to randomization
- 3) The presence of metastatic pancreatic adenocarcinoma plus 1 of the following:
 - Histological diagnosis of pancreatic adenocarcinoma confirmed pathologically, OR
 - Pathologist confirmed histological/cytological diagnosis of adenocarcinoma consistent with pancreas origin in conjunction with either:
 - The presence of a mass in the pancreas, OR
 - A history of resected pancreatic adenocarcinoma
- 4) Measurable disease per RECIST v1.1
- 5) Adequate organ function defined as follows:
 - Hepatic: Total bilirubin $<$ ULN; AST (SGOT) and ALT (SGPT) \leq 3 x ULN
 - Hematological: ANC $>$ 1500 cells/mm³, platelet $>$ 100,000 cells/mm³, hemoglobin $>$ 9 g/dL
 - Renal: Serum creatinine $<$ ULN OR calculated CrCl of \geq 60 ml/min as calculated by the Cockcroft-Gault method
- 6) ECOG Performance Status of 0 or 1
- 7) Negative serum pregnancy test for female subjects (unless surgically sterile or greater than two years postmenopausal)

- 8) Male and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in [Appendix 3](#)
- 9) Females who are nursing must agree to discontinue nursing before the first dose of IP
- 10) Able to comprehend and willing to sign the written informed consent form

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study

- 1) Neoadjuvant or adjuvant chemotherapy or chemoradiotherapy for pancreatic adenocarcinoma
- 2) Currently or previously treated with biologic, small molecule, immunotherapy, chemotherapy, or other agents for metastatic pancreatic carcinoma
- 3) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active or chronic bleeding event within 4 weeks prior to first dose of IP, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician
- 4) History of a concurrent or second malignancy except for adequately treated local basal cell or squamous cell carcinoma of the skin, cervical carcinoma in situ, superficial bladder cancer, asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥ 1 year prior to randomization, adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for ≥ 5 years
- 5) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy), within 28 days of first dose of IP
- 6) Minor surgical procedure(s) within 7 days of randomization or not yet recovered from prior minor surgery (placement of central venous access device, fine needle aspiration, or endoscopic biliary stent ≥ 1 day before randomization is acceptable)
- 7) Known positive status for HIV
- 8) Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier
- 9) Peripheral neuropathy \geq Grade 2
- 10) Known or suspected brain or central nervous system metastases

- 11) Diagnosis of pancreatic islet neoplasm, acinar cell carcinoma, non-adenocarcinoma (ie, lymphoma, sarcoma), adenocarcinoma originating from the biliary tree or cystadenocarcinoma
- 12) History of interstitial pneumonitis and/or require supplemental oxygen therapy
- 13) External biliary drain
- 14) Paracentesis or thoracentesis for malignant effusion within 14 days of randomization
- 15) Documented myocardial infarction or unstable/uncontrolled cardiac disease (ie, unstable angina, congestive heart failure [New York Heart Association > Class II]) within 6 months of randomization
- 16) Use of strong CYP3A4 inhibitors or strong CYP3A4 inducers within 1 week prior to the first dose of IP
- 17) Known hypersensitivity to MMB, gemcitabine and/or nab-paclitaxel, their metabolites, or formulation excipients
- 18) Uncontrolled hypertension (seated systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) at Screening
- 19) QTc interval > 450 msec, unless attributed to bundle branch block
- 20) Pregnant

5. INVESTIGATIONAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

Subjects in the randomized treatment phase will be randomized via IXRS in a 1:1 manner to Treatment Arm 1 or 2.

- Treatment Arm 1: MMB once- or twice-daily (dose frequency as instructed by clinical investigator) + nab-P+G on Days 1, 8, 15, cycle repeats every 28 days
- Treatment Arm 2: Placebo once- or twice-daily (dose frequency as instructed by clinical investigator) + nab-P+G on Days 1, 8, 15, cycle repeats every 28 days

The randomization will be stratified by ECOG performance status (0 vs. 1) and baseline CRP plasma level (high vs. low).

5.2. Description and Handling of MMB

5.2.1. Formulation

5.2.1.1. MMB Tablets

MMB is supplied as GS-0387-01 Form II (dihydrochloride monohydrate) and is available as 100 mg, 150 mg, and 200 mg strength (as free base equivalent) tablets. The tablets contain excipients, microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, silicon dioxide, propyl gallate, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide and red iron oxide. MMB tablets, 100 mg and 150 mg, are plain round, film-coated, brown tablets and MMB tablets 200 mg, are plain, capsule-shaped, film-coated, brown tablets.

5.2.1.2. Placebo to Match MMB Tablets (MMB PTM)

MMB PTM tablets are identical in physical appearance to the 100 mg, 150 mg, and 200 mg MMB tablets. The MMB PTM tablet contains the following excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, yellow iron oxide and red iron oxide. MMB PTM tablets, 100 mg and 150 mg, are plain round, film-coated, brown tablets and MMB PTM tablets 200 mg, are plain, capsule-shaped, film-coated, brown tablets.

5.2.2. Packaging and Labeling

MMB and MMB PTM tablets are packaged in white, high-density polyethylene bottles. Each bottle contains tablets, a silica gel desiccant, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed, aluminum-faced liner.

All IP labels will meet all applicable requirements of the US FDA and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (February 2010) and/or other local regulations as applicable.

5.2.3. Storage and Handling

MMB should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

Until dispensed to the subjects, all IP bottles should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, the drug products should be stored in the containers in which they were supplied.

5.3. Dosage and Administration

5.3.1. MMB and Placebo

In the randomized treatment phase, subjects will self-administer MMB/placebo orally once- or twice-daily. After the first dose of MMB or placebo on study, subjects will be observed for 4 hours.

On the day of nab-P+G administration, MMB/placebo is to be administered prior to nab-P+G.

The date and time of administration will be recorded on the respective eCRF page and in the source document.

5.3.2. Nab-paclitaxel and Gemcitabine

Nab-paclitaxel will be administered intravenously over approximately 30-40 minutes or as per institutional standard of care on Days 1, 8, and 15 of each 28-day cycle. Gemcitabine will be administered intravenously over approximately 30 minutes or as per institutional standard of care on Days 1, 8, and 15 of each 28-day cycle. Administer gemcitabine immediately after completion of nab-paclitaxel infusion.

Body surface area used in calculating the doses of nab-paclitaxel and gemcitabine of each treatment cycle will be the same as the Day 1 value of that cycle, unless there is a > 10% change in weight or height of the subject in which case the body surface area will be re-calculated based on the new weight and height of that subject within a cycle.

Anti-emetic prophylaxis prior to chemotherapy administration is at investigator's discretion and institutional standard of care.

Dosing of nab-paclitaxel and gemcitabine will be documented in the subject eCRF.

5.4. Dose Adjustment of Nab-Paclitaxel and Gemcitabine

Table 5-1. Dose Reduction of Nab-Paclitaxel and Gemcitabine

Dose level	Nab-paclitaxel (mg/m ²)	Gemcitabine (mg/m ²)
Dose prior to reduction	125	1000
1 st dose reduction	100	800
2 nd dose reduction	75	600

Table 5-2. Dose Modification of Nab-Paclitaxel and Gemcitabine for Neutropenia and/or Thrombocytopenia at Start of a Cycle or Within a Cycle

Cycle Day	ANC (cells/mm ³)		Platelet count (cells/mm ³)	Nab-paclitaxel/gemcitabine
Day 1	< 1,500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1,000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses
Day 15	If Day 8 doses were reduced or given without modification:			
	500 to < 1,000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses
Day 15	If Day 8 doses were withheld:			
	≤ 1,000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1,000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses

If Day 1 nab-paclitaxel dose is 100 mg/m² and gemcitabine dose is 800 mg/m², only 1 dose level reduction is allowed on Day 15. Subjects with ANC 500 to < 1000 or platelet count 50,000 to < 75,000 on Day 15 will hold nab-paclitaxel and gemcitabine dosing.

Table 5-3. Dose Modification of Nab-Paclitaxel and Gemcitabine for Other Adverse Drug Reactions

Adverse drug reaction	Nab-paclitaxel	Gemcitabine
Febrile neutropenia (grade 3 or 4)	Withhold until fever resolves and ANC ≥ 1,500, resume at next lower dose level	
Peripheral neuropathy (grade 3 or 4)	Withhold until improves to ≤ Grade 1, resume at next lower dose level	No dose reduction
Cutaneous toxicity (Grade 2 or 3)	Reduce to next lower dose level, discontinue treatment if toxicity persists	
Gastrointestinal toxicity (Grade 3 mucositis or diarrhea)	Withhold until improves to ≤ Grade 1, resume at next lower dose level	

Pulmonary effects, sometimes severe (such as pulmonary edema, interstitial pneumonitis or adult respiratory distress syndrome) have been reported in association with gemcitabine therapy. The etiology of these effects is unknown. If such effects develop and a diagnosis of pneumonitis is made after ruling out infectious etiology, treatment with nab-paclitaxel and gemcitabine will be permanently discontinued. Early use of supportive care measure may help ameliorate the condition.

5.5. Dose Adjustment of MMB

Table 5-4. MMB Dose Reduction for Thrombocytopenia

Platelet count (cells/mm ³)	MMB dose prior to dose reduction				
	200 mg twice-daily	150 mg twice-daily	200 mg once-daily	150 mg once-daily	100 mg once-daily
≥ 50,000	No dose adjustment required				
≥ 25,000 to < 50,000	150 mg twice-daily	200 mg once-daily	150 mg once-daily	100 mg once-daily	Interrupt treatment
< 25,000	Interrupt treatment				

For restarting dose of MMB after dose interruption for thrombocytopenia, refer to [Table 5-5](#).

In the event of a Grade 3 or 4 hematologic (aside from Grade 3 thrombocytopenia) or non-hematologic toxicity that the investigator considers related to MMB and clinically significant, MMB will be interrupted for a maximum of 28 days until the toxicity resolves or returns to baseline level. Following resolution of the toxicity or the toxicity returns to baseline level, treatment may be restarted at a reduced dose as per [Table 5-5](#).

Table 5-5. Restarting Doses of MMB After Treatment Interruption

Dose at time of toxicity	Restarting dose level
200 mg twice-daily	150 mg twice-daily
150 mg twice-daily	200 mg once-daily
200 mg once-daily	150 mg once-daily
150 mg once-daily	100 mg once-daily
100 mg once-daily	100 mg once-daily

MMB may only be restarted after dose interruption if platelet count is $\geq 50,000$ (cells/mm³).

No dose reduction of MMB below 100 mg once-daily is allowed. If the Grade 3 or 4 hematologic (aside from Grade 3 thrombocytopenia) or non-hematologic toxicity considered by the investigator to be related to MMB recurs after dose reduction to 100 mg once-daily, MMB will be discontinued permanently.

5.6. Restricted/Prohibited Medications

During the course of the clinical trial, subjects are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria.

The following therapies are not permitted at any point during the trial beginning with C1D1 (if administered, the subject may be removed from the trial):

- Anti-cancer therapy, experimental or approved, other than nab-paclitaxel, gemcitabine, and MMB administered in this study

The following therapies are not permitted in the first 28 days (Cycle 1) of treatment in lead-in phase only:

- Growth factor, eg. Neupogen®, Neulasta®, erythropoiesis stimulating agent, thrombopoietin mimetics

The following restricted medications are only permitted under the circumstances given. Each concomitant medication must be individually assessed against all exclusion criteria. If in doubt the investigator should contact the Gilead medical monitor before enrolling a patient or allowing a new medication to be started.

- Anti-hypertensive therapy should not be taken on the day of the first MMB dose until 4 hours after MMB administration
- Strong CYP3A4 Inhibitors/Inducers
 - MMB is partially metabolized by CYP3A4. Co-administration of strong CYP3A4 inhibitors may increase MMB exposure and caution should be exercised upon co-administration as dose adjustment of MMB may be required. As such, strong CYP3A4 inhibitors (eg, boceprevir, clarithromycin, fluoxetine, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) may be used only with prior approval by Gilead.
 - Co-administration of strong CYP3A4 inducers may decrease MMB. Strong CYP3A4 inducers (eg, carbamazepine, efavirenz, nevirapine, phenytoin, rifampin, St. John's wort) may be used only with prior approval by Gilead.

5.7. Breast Cancer Resistance Protein (BCRP) Substrates

MMB was determined to be an inhibitor of BCRP with an IC_{50} of 2.9 μ M. There is a potential that BCRP substrates may have higher exposure when co-administered with MMB.

5.8. Accountability for MMB or Placebo

The investigator or designee (eg, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drugs during the study. This includes acknowledgement of receipt of each shipment of study drugs (quantity and condition) and tracking of study drugs assigned/utilized for subject dosing (eg, log). All unused study drugs dispensed to subjects must be returned to the site.

MMB/placebo accountability records will be provided to each study site to:

- Record the date received and quantity of study drug kits.
- Record the date, subject number, subject initials, the study drug kit number dispensed.
- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information.
- Dispensing records will include the initials of the person dispensing the study drug or supplies.

5.8.1. Investigational Medicinal Product Return or Disposal

The method of study drug return and destruction are described in Section [9.1.7](#).

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in [Appendix 2](#) and described in the text that follows. Additional information is provided in the study procedures manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

Subject eligibility will be established at the conclusion of the screening evaluations. The screening number and/or subject ID will be assigned for that individual subject by Gilead and/or the designated IXRS.

It is the responsibility of the investigator to ensure that each subject is eligible for the study before start of treatment in lead-in phase or before randomization in randomized treatment phase. A subject will be considered enrolled once he or she has started treatment in lead-in or has completed randomization in randomized treatment.

For randomized treatment phase of the study, subjects in both treatment arms will undergo all the same procedures. Details regarding randomization and treatment assignment are in [Section 5.1](#).

6.2. Description of Study Procedures

The sections below describe the individual study procedures outlined in subsequent sections and the schedule of assessments.

6.2.1. Informed Consent

All subjects must personally sign and date the institutional review board / independent ethics committee (IRB/IEC) approved informed consent form before any study procedures are performed. The following optional procedures will require separate subject consent either within the or on a separate main informed consent form, per IRB/IEC requirements:

- Biomarker Samples for Optional Future Research
- Biomarker Samples for Optional Research
- Tumor Biopsy Substudies

6.2.2. Medical History

A complete medical and surgical history will be obtained by the investigator or designee prior to enrollment and recorded on the electronic case report form (eCRF).

6.2.3. Prior/Concomitant Medications

All outpatient medications taken within the 3 months prior to screening and during the screening period will be obtained prior to enrollment and recorded on the eCRF. At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription, non-prescription medications, vitamins and minerals.

6.2.4. Physical Examination

At screening, a complete physical examination will be performed including height and weight. Height and weight should be collected with the subject standing without shoes. Physical examination findings during the screening period will either be reported as medical history or AEs based on the requirements in Section 7.

At subsequent study visits, the physical examination will be an interim examination to monitor for any changes, and will also include weight and assessment of disease-related clinical signs and symptoms.

6.2.5. Vital Signs

Vital signs will include pulse, systolic and diastolic blood pressure, and body temperature. Vital signs should be collected with the subject in a seated position for at least 5 minutes before taking any measurement.

6.2.6. Electrocardiogram

A single 12-lead electrocardiogram (ECG) will be collected at the applicable study visit per standard practice, and will be transferred to a central reader for analysis. The investigator will review all ECGs and retain the tracing with the source documents.

Following completion of a planned thorough QT study and a review of cardiovascular-related events, ECG monitoring may be discontinued in this study.

6.2.7. Laboratory Assessments

Screening laboratory samples should be obtained within 21 days prior to the first dose of IP (MMB) for the lead-in phase or randomization for the randomized treatment phase. Local laboratory CBC assessments may be collected as required for dose adjustments throughout the study. Local laboratory assessments resulting in a dose change will be reported on the eCRF.

The central laboratory will be responsible for chemistry, hematology, coagulation, urinalysis, and serum pregnancy testing per [Table 6-1](#) and storage of other study samples. Other tests listed in [Table 6-1](#) will be performed by Gilead or a designated laboratory. Urine pregnancy test will be performed by the site. Any sample collected per the Study Procedures Table ([Appendix 2](#)) may be analyzed for any tests necessary to ensure subject safety. Specific instructions for processing, labeling, and shipping samples will be provided in a central laboratory manual. The date and time of sample collection will be reported to the central laboratory.

Table 6-1. Analytes

Chemistry	Urinalysis	Hematology and Coagulation	Other Analytes
Albumin	Color and appearance	WBC	Serum beta hCG ^b
Alkaline phosphatase	Specific gravity	WBC differential	Hepatitis B surface antigen
ALT (SGPT)	pH	Basophil	Hepatitis B surface antibody
AST (SGOT)	Occult blood	Eosinophil	Hepatitis B core antibody
Amylase	Protein	Lymphocyte	Hepatitis C antibody
Bicarbonate	Glucose	Monocyte	Thiamine status ^d
BUN	Bilirubin	Neutrophil	MMB PK ^e
Calcium	Leukocyte esterase	Hemoglobin	MMB pharmacodynamic and exploratory biomarkers ^f
Chloride	Nitrite	Hematocrit	
Creatinine ^a	Urobilinogen	Platelet	
CRP	Ketones	ANC	
GGT	Microscopic ^c	PT/INR	
Glucose	Urine Pregnancy ^b	aPTT	
LDH			
Lipase			
Magnesium			
Phosphorus			
Potassium			
Sodium			
Total bilirubin			
Direct bilirubin			
Total protein			
Uric acid			
CA19-9			
CEA			

ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CEA=carcinoembryonic antigen; GGT = gamma-glutamyl transferase; hCG = human chorionic gonadotropin; LDH = lactate dehydrogenase; WBC = white blood cell

a Estimated creatinine clearance/glomerular filtration rate will be calculated based on the Cockcroft-Gault formula

b Females of child-bearing potential only. Serum pregnancy will be conducted at Screening. Urine pregnancy will be conducted pre-dose on Days 1 and 15 of each cycle

c Reflex testing based on other abnormalities

d Thiamine status may be analyzed directly in whole blood or other analyte(s)

e Section 6.2.7.1

f Section 3.6

6.2.7.1. MMB Pharmacokinetics and Pharmacodynamics (all subjects)

Intensive PK samples of MMB and metabolites (GS-644603 and GS-642112) will be collected from subjects in lead-in phase on Day 15 of Cycle 1 (pre-MMB dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-MMB dose); 24 hours post-MMB dose sampling will not be applicable in the twice-daily cohort.

Intensive pharmacodynamics samples will also be collected from subjects in lead-in phase on Day 15 of Cycle 1 (pre-MMB dose and at 1, 2, 4, 6, 8, 12, and 24 hours post-MMB dose); 24 hours post-MMB dose sampling will not be applicable in the twice-daily cohort.

Sparse PK and pharmacodynamics samples of MMB and metabolites (GS-644603 and GS-642112) will be collected for subjects in randomized treatment phase: trough samples on Day 1 of Cycles 2 and 3 at approximately 20 to 26 hours after the previous dose of MMB in the once-daily cohort, or at approximately 10 to 14 hours after the previous dose of MMB in the twice-daily cohort; pre-MMB dose samples on Day 1 of Cycles 4, 5, and 6.

The PK of nab-paclitaxel and gemcitabine may also be analyzed using these samples.

6.2.7.2. MMB Tumor Biopsy Substudies (optional, additional consent required)

PPD



6.2.8. Patient-Reported Outcomes Assessments (PRO)

PRO will be collected for a maximum of one year from randomization/baseline or until disease progression, whichever is earlier.

6.2.8.1. Functional Assessment of Cancer Therapy – Hepatobiliary (FACT-Hep)

The FACT-Hep is a 45-item self-report questionnaire developed to assess the quality of life of pancreatic carcinoma patients. It assesses symptoms and other health-related quality of life across four dimensions (physical, social/family, emotional and functional), as well as an 18-item disease-specific hepatobiliary cancer subscale.

6.2.8.2. EuroQol-5D (EQ-5D)

The EQ-5D is a general health quality of life self-report instrument that assesses five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels, ranging from no health problem, moderate health problem(s), and extreme health problem(s). It also includes a single visual analog scale for assessment of current general health.

6.2.9. Disease Assessments

6.2.9.1. Tumor Imaging (CT or MRI)

CT with contrast or MRI (for subjects who cannot tolerate CT contrast) will be obtained to document metastatic disease, identify target lesions as described in RECIST version 1.1, and to assess response and disease progression. Imaging of the chest and abdomen by CT scan with contrast or MRI will be performed at Screening, and every 8 weeks during the treatment period regardless of cycle number or dose interruption.

Scans taken as part of standard medical practice up to 21 days prior to first dose of IP (MMB) for the lead-in phase or randomization for the randomized treatment phase can be used for Screening. During the treatment phase, scans may be performed at time points other than every 8 weeks as clinically indicated to assess tumor progression.

For subjects who stop study treatment in the absence of disease progression (eg. experienced unexpected toxicity), scans should continue to be collected approximately every 8 weeks until disease progression or initiation of systemic anti-tumor therapy other than the study treatment, (whichever is earlier).

Scans will be transferred to a central reader for analysis. Repeat scans may be required if the original scan is not accepted by the central reader, which may occur if the scan is of poor quality. The same imaging procedure and specifications (eg, contrast agent, scanner, slice thickness, etc.) used to define measurable target and non-target lesions must be used throughout the study for each subject.

CT scans may not be performed at sites or in countries where additional radiology approval is required, unless that approval is sought and granted.

6.2.9.2. Treatment Response Assessment

Tumor burden will be characterized at baseline, and response assessments will be performed as per RECIST v1.1 at approximately every 8 weeks.

6.2.9.3. ECOG Performance Status

The ECOG performance status is an investigator assessment of the impact of the disease on the subject's activities of daily living. It is assessed on a 6-point scale as described in [Appendix 5](#).

6.3. Pretreatment Assessments

6.3.1. Screening Visit

The screening date will be defined as the date the subject signs the informed consent. Subjects will be screened within 21 days of first dose of IP (MMB) for the lead-in phase or randomization for the randomized treatment phase to determine eligibility for participation in the study. Screening laboratory results for pregnancy testing (females of child bearing potential), chemistry, hematology, coagulation and urinalysis should be obtained from central laboratory and meet all eligibility criteria in order for a subject to be enrolled. Subjects who do not enroll within the 21 day screening window will be screen failed. Re-screening is allowed.

The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history, including prior/concomitant medication review
- Complete physical examination including body weight and height
- Vital Signs
- Single 12-lead ECG
- ECOG performance status
- Laboratory assessments
 - Chemistry
 - Complete blood count (CBC) with differential
 - Coagulation
 - Hepatitis testing
 - Serum pregnancy test (females of child-bearing potential)
 - Urinalysis
- CT scan with contrast or MRI (scans taken as part of standard medical practice up to 21 days prior to first dose of IP (MMB) for the lead-in phase or randomization for the randomized treatment phase are acceptable)
- Record any adverse events (occurring after signing of the consent form)
- Complete/enter IXRS subject/visit information

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 21 days after screening for enrollment/randomization into the study.

From the time of obtaining informed consent through the first administration of IP, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See section 7 Adverse Events and Toxicity Management for additional details.

6.3.2. Subject Randomization

In randomized treatment phase a subject will be considered enrolled once the site has completed the IXRS randomization module. IXRS will be utilized to assign IP at the time of randomization. Details regarding randomization and treatment assignment are in Section 5.1.

The site will train the subject on the dosing schedule for the IP and the dosing diary at the time of dispensing. Baseline visit/Cycle 1 Day 1 (C1D1) may occur within 3 business days following randomization.

6.3.3. Baseline Visit / C1D1

Subjects who have met all eligibility criteria will return to the clinic on C1D1 to perform baseline assessments. C1D1 is defined as the date of the first dose of IP.

The following baseline assessments will be conducted prior to the first dose of MMB/placebo + nab-P+G:

- Physical examination, including weight
- Vital signs (pre- and post- first MMB dose on C1D1 every 2 hours for 4 hours)
- PROs
 - FACT-Hep
 - EQ-5D
- Single 12-lead ECG
- ECOG performance status
- Laboratory assessments and blood sampling (refer to [Appendix 2](#))
 - Chemistry
 - CBC with differential

- Coagulation
- Thiamine status
- MMB predictive biomarkers sampling
- MMB exploratory biomarkers: PPD
- MMB exploratory biomarkers: PPD
- Request archival tumor tissue specimen as applicable: Efforts to acquire tissue sample should begin on C1D1
- Urinalysis
- Urine pregnancy test, if applicable
- Record any adverse events
- Concomitant medications review
- IP accountability and dispensing as assigned by IXRS

6.4. Treatment Assessments

Each on-study visit will be scheduled relative to Day 1. Visits will follow the Study Procedures Table in [Appendix 2](#).

6.4.1. Days 1 of Subsequent Cycles, Days 8 and 15

On-study visits during the treatment period may be completed within a window of ± 3 business days. The following procedures will be completed pre-dose on Days 1, 8 and 15 of each cycle, unless otherwise specified:

- Physical examination, including weight (Days 1 only)
- Vital signs
- PROs (Days 1 only)
 - FACT-Hep
 - EQ-5D
- Single 12-lead ECG (approximately every 2 weeks for the first 3 cycles, then on Day 1 of each subsequent cycle)

- ECOG performance status
- Laboratory assessments and blood sampling (refer to [Appendix 2](#))
 - Chemistry
 - CBC with differential
 - MMB predictive biomarkers sampling (Day 1 of Cycle 2 only)
 - MMB 24-hour PK and pharmacodynamics (Day 15 of Cycle 1 in lead-in phase only)
 - MMB PK and pharmacodynamics (Days 1 of Cycle 2 to 6 in randomized phase only)
 - MMB exploratory biomarkers: **PPD** (Days 1 only, additional consent required)
 - Urinalysis (Days 1 only)
 - Urine pregnancy test (if applicable, Days 1 only)
- Record any adverse events
- Concomitant medications review
- Enter subject status/information (as applicable) into IXRS
- IP accountability and dispensing by IXRS (Days 1 only)

6.4.2. Every 8 Weeks

CT with contrast or MRI will be performed for tumor response assessment approximately every 8 weeks \pm 3 days regardless of cycle number or dose interruption. Same procedure will be used throughout study.

Tumor biopsy will also be performed after Cycle 2 at approximately week 8 and/or at disease progression for consented substudy subjects only. Tumor biopsy samples collected at approximately 2-4 hours after dose is preferred. For subjects whose MMB/placebo dose has been withheld, biopsy can happen anytime at week 8 and/or at disease progression.

6.4.3. Every 12 Weeks

The following laboratory assessments will be collected every 12 weeks:

- Coagulation
- Thiamine Status

6.4.4. End of Treatment (EOT) Visit

Subjects who discontinue the study treatment regardless of the reason must have EOT visit on the day of study treatment discontinuation with a window of ± 7 days and prior to initiating a new anti-cancer regimen. The following procedures will be conducted:

- Physical examination, including weight
- Vital signs (pre-dose only)
- PROs
 - FACT-Hep
 - EQ-5D
- Single 12-lead ECG
- ECOG performance status
- Laboratory assessments and blood sampling
 - Chemistry
 - CBC with differential
 - Coagulation
 - MMB exploratory biomarkers: PPD (in randomized phase only)
 - Urinalysis
 - Urine pregnancy test (if applicable)
- CT with contrast or MRI (± 3 days; use same procedure throughout study, not necessary if restaging scan was performed within the prior 8 weeks)
- Record any adverse events
- Concomitant medications review
- IP accountability

6.5. Unscheduled visits

Unscheduled visits may occur at any time during the study. Vital signs, laboratory assessments, ECG, and PE may be conducted at these visits.

6.6. Post-treatment Follow-up Assessments

After discontinuing treatment, subjects will complete the 30-day safety follow-up visit and will be contacted via phone call every 6 months for up to 5 years.

6.6.1. 30-Day Safety Follow-up Visit

The following procedures will be completed 30 days after the subject's last dose of IP, within a window of ± 7 days:

- Physical examination, including weight
- Vital signs
- PROs
 - FACT-Hep
 - EQ-5D
- ECOG performance status
- Laboratory assessments
 - Chemistry
 - CBC with differential
 - Coagulation
 - Urinalysis
- Concomitant medications review
- Record any adverse events (30 days post last dose of IP)

6.6.2. 5-Year Long Term Survival Follow-Up

Subjects will be contacted via phone call every 6 months for determination of long term survival status and record of any other anti-cancer therapy for up to 5 years after the last dose of IP.

Subjects who are not deceased by the time GSI has made the determination the study will be ended will receive a final follow-up phone call to assess survival status and communicate the Sponsor's decision. These subjects will be censored on the date the subject was last contacted.

The investigator will make every effort to contact the subject or a close relative or caretaker by phone to collect survival information. The investigator should show due diligence by documenting in the source documents steps taken to contact the subject i.e., dates of phone calls, registered letters, etc.

6.7. Withdrawal from Treatment, Procedures, and Study

6.7.1. Subjects' Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required treatment or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from the IP and must discuss with the subject the options for continuation of the scheduled procedures ([Appendix 2](#)) and collection of data, including endpoints and adverse events. The investigator must document the change to the Study Procedures Table ([Appendix 2](#)) and the level of follow-up that is agreed to by the subject (eg. in person, by phone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required treatment or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

6.7.2. Investigator or Sponsor Decision to Withdraw or Terminate Subjects' Participation Prior to Study Completion

The investigator and/or GSI can decide to withdraw a subject(s) from IP and/or other protocol-required treatment, protocol procedures, or the study as a whole at any time prior to study completion.

6.8. Criteria for Discontinuation from Treatment or Study

6.8.1. Criteria for Discontinuation from Treatment

The reason for discontinuation from treatment will be recorded on the EOT CRF. Study treatment may be discontinued for any of the following reasons:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree

- Toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Disease progression (based on investigator assessment of baseline and post-baseline scans as per RECIST v1.1)
- Subject request to discontinue treatment for any reason
- Subject noncompliance
- Initiation of systemic anti-neoplastic therapy other than treatments per protocol in the absence of progression
- Discontinuation of the study treatment at the request of GSI, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)
- Pregnancy during treatment; refer to [Appendix 3](#)

If a subject has discontinued the study treatment due to toxicity, he/she should not have withdrawal of consent recorded as the reason for discontinuation. Instead, the reason for discontinuation must be recorded as due to adverse drug reaction.

Every attempt should be made to keep the subject in the study and continue collecting CT or MRI scans for tumor assessment at every 8 weeks until disease progression or initiation of systemic anti-tumor therapy other than treatment per protocol. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. The subject will be asked to attend the post-treatment follow-up assessment visit above when discontinuing from the study.

6.8.2. Criteria for Discontinuation from Study

Subjects may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time.

As a general rule, if a subject discontinue study treatment and later is withdrawn from the study or completes the study follow-up, the reasons may include the following:

- Withdrawal of consent from study
- Lost to follow-up
- Death
- Investigator's decision to remove the subject from the study, in consultation with the Gilead Medical Monitor

- Discontinuation of the study at the request of GSI, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)
- Pregnancy during the study; refer to [Appendix 3](#)

6.9. Protocol Deviations

GSI's policy prohibits exemptions from protocol inclusion/exclusion criteria. In the event of a significant deviation related to gross non-compliance from the protocol or incidences that impose significant risk to subject safety, the investigator or designee must notify GSI and/or its designee immediately. The site will be required to document deviations in accordance with GSI's procedures and in accordance with the site's procedures and processes.

6.10. End of Study

End of study for a subject is defined as the date of the last study-related procedure or the date of death for an on-study subject.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section [7.7.1](#))
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A serious adverse event (SAE) or serious adverse drug reaction (SADR) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements. Examples of medically important events include:
 - Intensive treatment in an emergency room or at home for allergic bronchospasm
 - Blood dyscrasias or convulsions that do not result in hospitalization
 - Development of drug dependency or drug abuse

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

To maintain the integrity of the study, the following events that are assessed as unrelated to IP will not be considered as SAE:

- Progression of pancreatic carcinoma
- Death related to progression of pancreatic carcinoma

However, events of progression of pancreatic carcinoma and death related to progression of pancreatic carcinoma that are assessed by the investigator to be related to study drug will be considered as SAE and will be reported to regulatory agencies in an expedited fashion by GSI.

All events of progression of pancreatic carcinoma and death related to progression of pancreatic carcinoma, regardless of investigator assessment of relationship to IP, will be reported in the eCRFs and, as appropriate, in the final clinical study report and in any relevant aggregate safety reports.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, coagulation, and urinalysis) that require medical or surgical intervention or lead to IP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are

associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to IP therapy using clinical judgment and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the IP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 in study manual and available at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affect clinical status, and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead or CRO

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the CRF/eCRF database and GSI Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Investigators are not obligated to actively seek SAEs after the protocol defined 30-day follow up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IP, he/she should promptly document and report the event to Gilead DSPH.

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.
- At the time of study start, SAEs will be reported using a paper serious adverse event reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system. GSI will notify sites in writing and provide training and account information prior to implementing an eSAE system.

Serious Adverse Event Paper Reporting Process

All SAEs will be recorded on the serious adverse event report form and submitted by faxing or emailing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead DSPH.

Gilead DSPH: Fax: 1-650-522-5477
 E-mail: Safety_fc@gilead.com

Electronic Serious Adverse Event (eSAE) Reporting Process

Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours as described above.
- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, GSI may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, coagulation, and urinalysis) that require medical or surgical intervention or lead to IP interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE Version 4.03.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Toxicity Management

Dosing requirements for certain toxicities are specified in Section 5.3. The investigator may contact the Medical Monitor to review toxicities that are not directly discussed in the protocol.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in

question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows:
Email: Safety_FC@gilead.com or Fax: +1 (650) 522-5477.

Pregnancies of female partners of male study subjects exposed to MMB or other study drugs must also be reported and relevant information should be submitted to GSI DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com or Fax: +1 (650) 522-5477.

Refer to Appendix 3 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Emergency Unblinding

In the event of a medical emergency where breaking of the blind is being considered by the treating physician, the investigator may break the blind using the IVRS. It is recommended that the GSI Medical Monitor be contacted before the investigator breaks the blind. Please note that the treatment assignment should not be unblinded if unblinding will not affect the way the subject would be treated. In the event of a medical emergency, where breaking of the blind is required per the medical judgment of the investigator, the GSI Medical Monitor must be contacted as soon as possible after the unblinding. The unblinding must be clearly justified and explained by a comment in the source documentation, along with the date on which the code was broken and the identity of the person authorizing the unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

GSI DSPH may independently unblind cases for expedited reporting of SUSARs.

7.7.2.3. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IP and/or Gilead concomitant medications, but do not apply to non-GSI concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situation report form; however, for special situations that result in AEs due to a non-GSI concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 and the CRF/eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

The methods specified here pertain to the randomized treatment portion of the study. Similar descriptive methods will be used to characterize the data from subjects in the non-randomized lead-in phase of the study.

In general, count and percent of subjects will summarize categorical and ordinal data. Mean, standard deviation, minimum, quartiles, median, and maximum will summarize continuous data, Kaplan-Meier (KM) cross product method will summarize time-to-event data.

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are:

- Lead-in phase: To evaluate the safety, pharmacokinetics, and define the MTD of MMB combined with nab-P+G in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma
- Randomized treatment phase: To determine the efficacy of nab-P+G combined with either MMB or placebo in subjects with previously untreated metastatic pancreatic ductal adenocarcinoma as measured by improvement in overall survival (OS).

8.1.2. Primary Endpoint

Lead-in: Incidence of DLT as defined in Section 3.1.

Randomized treatment: Overall survival (OS), defined as the interval from randomization to death from any cause

8.1.3. Secondary Endpoint

Lead-in:

- Overall survival (OS) – defined as the interval from first dose date of IP in lead-in phase to death from any cause.
- Progression free survival (PFS) – defined as the interval from first dose date of IP in lead-in phase to the earlier of the first documentation of definitive disease progression or death from any cause; definitive disease progression is progression based on RECIST criteria v1.1. Data from survival, non-progressing subjects will be censored at the earliest of the time of initiation of anti-tumor therapy other than the study treatment or the last time that lack of definitive disease progression was objectively documented while on study.
- Overall response rate (ORR) - defined as the proportion of subjects who achieve a Complete Response (CR) or Partial Response (PR) as assessed by RECIST v1.1.

Randomized treatment: Progression free survival (PFS) and overall response rate (ORR).

- Progression free survival (PFS) – defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause; definitive disease progression is progression based on RECIST v1.1 criteria. Data from survival, non-progressing subjects will be censored at the earliest of the time of initiation of anti-tumor therapy other than the study treatment or the last time that lack of definitive disease progression was objectively documented while on study.
- Overall response rate (ORR) – defined as the proportion of subjects who achieve a Complete Response (CR) or Partial Response (PR) as assessed by RECIST v1.1.

8.1.4. Exploratory Endpoints

Exploratory endpoints for randomized treatment phase are:

PPD

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Intent-to-Treat (ITT) Analysis Set

The Intent-to-Treat (ITT) Analysis Set consists of all randomized subjects regardless of whether subjects receive any study drug. Following the ITT principle, subjects are analyzed according to the treatment they are assigned to at randomization.

The ITT Analysis Set will be used for demographic and baseline characteristics, medical and disease history, and efficacy analyses. The analysis of OS based on the ITT Analysis Set will be considered the primary analysis of the study. Subjects in the ITT Analysis Set will be considered the primary analysis of the study. Subjects in the ITT Analysis Set who do not have sufficient baseline or on-study tumor status information to be adequately assessed for response status will be included in the denominators in the calculation of response rates.

8.2.1.2. Per-Protocol (PP) Analysis Set

The Per-Protocol (PP) Analysis Set consists of all subjects in the ITT Analysis Set who meet the general criteria defining the target population for this study, are adherent to the protocol, compliant with study drug, and are evaluable for relevant efficacy endpoints. Study treatment assignment will be designated according to the actual treatment received. The specific classification of subjects to be excluded from the PP Analysis Set will be included in the statistical analysis plan (SAP) and finalized prior to database lock.

The PP Analysis Set will be used in sensitivity analyses of the primary and secondary endpoints as needed.

8.2.1.3. Safety Analysis Set

The Safety Analysis Set consists of subjects in the ITT Analysis Set who received ≥ 1 dose of study drug, with study treatment assignment designated according to the actual treatment received.

The Safety Analysis Set will be used in the analyses of safety variables, study treatment administration and compliance.

8.2.1.4. Pharmacodynamic and Pharmacokinetic (PK) Analysis Sets

The Pharmacodynamic and PK Analysis Sets consist of all subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

Unless otherwise specified, data from the lead-in and randomized treatment parts will be summarized and analyzed separately.

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation (StD), 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% CIs on the percentage. Unless otherwise indicated, 95% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by relevant treatment arm, analysis set, and timepoint. As appropriate, changes from baseline to each subsequent timepoint will be described and summarized by treatment arm. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized by treatment arm. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

The baseline value will be the last (most recent) pre-treatment value in safety analyses and the last (most recent) pre-randomization value for efficacy analyses. Subjects with discrepancies between the stratification factor values at randomization and the actual values as documented on data review will be categorized in the analyses according to the actual values. In the situation that there is insufficient information in a stratum (ie, if there are <6 subjects or there is no informative event in a stratum), that stratum will be pooled with the smallest adjacent stratum for stratified analyses; the smallest stratum is defined as that stratum having the fewest number of subjects or the fewest number of events in case the former is a tie and the adjacent stratum is defined as a stratum having one factor of the 2 at the same level. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

Unless otherwise specified, all analyses will be 2-sided at the 0.05 level of significance.

The following censoring conventions will be applied for time-to-event endpoints:

- OS: Data from surviving subjects will be censored at the last time that the subject was known to be alive.
- PFS and DOR: Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of anti-tumor therapy other than the study treatment or the last time that lack of definitive progression was objectively documented. Data from subjects who have disease progression or die after ≥ 2 consecutive missing tumor assessments or after the initiation of anti-tumor therapy other than the study treatment will be censored at the last time prior to the missing assessments that lack of definitive progression was objectively documented or at the time of initiation of anti-tumor therapy other than the study treatment, whichever is earlier. If a subject does not have a baseline tumor assessment, then the PFS time will be censored at the randomization date, regardless of whether or not definitive disease progression or death has been observed.

8.4. Demographic Data and Baseline Characteristics

Subject demographic and baseline characteristics will be listed and summarized by treatment arm for the ITT Analysis Set. Imbalances in subject characteristics may be compared using the Wilcoxon rank-sum test for continuous variables and the Fisher's exact test for categorical variables.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint for randomized treatment phase is OS as defined in Section 8.1.2. For the primary efficacy analysis, the difference in OS between the treatment arms will be assessed in the ITT Analysis Set using Kaplan-Meier (KM) methods and the stratified log-rank test adjusted for the stratification factors. Median, ranges, the proportion of subjects who are surviving at 24 and 48 weeks from randomization (based on KM estimates), hazard ratios and corresponding 95% CIs (as calculated using a Cox proportional hazards regression model) will be presented.

The following exploratory sensitivity analyses may be performed:

PPD

■

The Cox regression approach will be used to explore the influences of the stratification factors, other baseline characteristics, and treatment on OS.

8.5.2. Other Time-to-Event Endpoints

Differences between the treatment arms in PFS, TTR, and DOR will be assessed in the appropriate analysis set using Kaplan-Meier methods and stratified log-rank tests. Medians, quartiles, ranges, hazard ratios and corresponding 95% CIs will be presented.

A supportive Cox regression analysis of PFS in the ITT analysis set will be performed using the same methods as in the analysis of OS if a sufficient number of events occur.

8.5.3. Categorical Endpoints

Difference in ORR and other categorical endpoints between treatment arms will be compared using Cochran-Mantel-Haenszel (CMH) Chi-square tests for association between treatment and response, after adjusting for stratification factors. Subjects who do not have sufficient baseline or on-study assessment to characterize tumor response will be counted as non-responders. Odds ratio and the corresponding 95% CIs will be presented.

The potential influence of subject baseline characteristics and of treatment on response rates will be explored with logistic regression modeling.

8.5.4. Continuous Endpoints

Differences between treatment arms for continuous endpoints will be assessed using analysis of covariance (ANCOVA) with stratification factor and treatment as factors and baseline value as covariate. In these analyses, both changes from baseline to each subsequent time point and best overall on-study changes will be evaluated. Means and standard errors will be presented. Least-squares means and 95% CI will be presented.

8.5.5. Control of Type I Error Rate in Efficacy Analyses

In the efficacy analyses, the following procedures will be implemented to preserve the overall type I error rate across the primary and secondary endpoints of the study at a 2-sided significance level of 0.05.

The primary endpoint analysis will serve as the gatekeeper for the secondary endpoint analyses, ie, the primary efficacy hypothesis must be rejected at the 2-sided 0.05 significance level before the efficacy hypotheses for the secondary endpoints will be evaluated. If the primary hypothesis is rejected, the 2 secondary endpoints will be tested sequentially in the order listed (PFS, ORR), at the 2-sided 0.05 significance level. If a null hypothesis is not rejected, formal sequential testing will be stopped and only nominal significance will be cited for the remaining secondary endpoints.

Analyses and p-values will be reported for all of the efficacy endpoints, including the primary endpoints, the secondary endpoints, and all of the exploratory endpoints.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug (MMB or placebo) plus 30 days will be summarized by treatment group (according to the study drug received). Data for the pretreatment will be included in data listings.

8.6.1. Extent of Exposure

Descriptive information will be provided by treatment arm regarding the number of doses of study drug prescribed, the total number of doses taken, the percent of expected doses taken, the number of days of study drug, and the number and timing of prescribed dose modification and interruptions.

Compliance will be described by treatment arm in terms of the proportion of study drug actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed modification and interruptions).

8.6.2. Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs. A treatment-emergent AE is defined as an AE that occurs or worsens in the period from the first dose of IP to 30 days after the last dose of study drug (MMB or placebo).

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA <http://www.meddrasso.com>) with descriptions by System Organ Class, High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-0614_QuickReference_8.5x11.pdf), whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to the IP will be categorized as related or unrelated.

Treatment-emergent AEs will be summarized by treatment arm. Summary tables will be presented to show the number of subjects reporting treatment-emergent AEs by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent AEs within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. AE descriptions will be presented by decreasing frequency for a given System Organ Class and Preferred Term. Separate listings and summaries will be prepared for the following types of treatment emergent AEs:

- Study-drug-related AEs
- AEs that are Grade ≥ 3 in severity
- AEs leading to IP interruption and/or dose modification
- AEs leading to IP discontinuation
- SAEs

8.6.3. Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥ 1 grade in the period from the first dose of study drug (MMB or placebo) to 30 days after the last dose of study drug (MMB or placebo). If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment emergent.

Hematological, serum biochemistry, and urine data will be programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the central laboratory will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc.

Hematological and serum biochemistry and their changes from baseline will be summarized by treatment arm, by visit. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to the worst grade post-baseline. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline to the worst grade post baseline. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

8.7. Pharmacokinetic Analysis

The concentration data of MMB and metabolites (GS-644603 and GS-642112), will be summarized by nominal sampling time using descriptive statistics. PK parameters (C_{\max} , T_{\max} , C_{last} , T_{last} , C_{tau} , λ_z , AUC_{tau} , and $T_{1/2}$), if available, will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation (%), standard deviation, median, minimum, and maximum). Plasma concentrations over time will be plotted in semi-logarithmic and linear formats as mean \pm standard deviation, and median (Q1, Q3) if applicable.

8.8. Biomarker Analysis

8.8.1. Pharmacodynamic Analysis

The baseline level, and the modulation pattern of tumor tissue pSTAT3 upon treatment, including change over time from baseline level, will be evaluated. Descriptive statistics will be provided at each sampling time, by treatment arms. Repeated measurement mixed model analysis will be performed to assess mean change from baseline over time by treatment arms. This analysis will be limited to the randomized treatment phase substudy subjects providing a tumor biopsy tissue sample at Week 8.

8.8.2. Exploratory Biomarker Analysis

PPD



8.9. Sample Size

Based on the historical data (MPACT trial in patients with metastatic pancreatic cancer), the median OS was 8.5 months in the nab-P+G group. Ruxolitinib Phase 2 RECAP trial (ruxolitinib or placebo in combination with capecitabine in patients with refractory metastatic pancreatic cancer) reported, in a pre-specified subgroup identified prospectively as most likely to benefit from JAK inhibitor treatment, the hazard ratio (HR) for OS was 0.47.

For the randomized treatment phase of the study, a total of 162 OS events need to be observed to detect a HR of 0.6 with 90% power at a 2-sided 0.05 significance level. Assuming an accrual rate of 20 subjects per months, median OS of 8.5 months in the control arm, and no lost-to-follow-up, a sample size of 150 subjects in each arm need to be enrolled to observe the 162 OS events. The expected study duration of observing 162 OS events in the randomized treatment phase is ~21 months.

8.10. Interim Analysis

One formal interim analysis may be conducted after ~50% of the expected number of OS events have been observed. At a constant accrual rate of 20 subjects per month, the interim analysis is expected to take place when approximately 230 subjects have been accrued in the study. An O'Brien-Fleming boundary will be applied to assess the efficacy at the interim analysis. The efficacy boundaries (p-value) for the interim and final analyses will be 0.0031 and 0.049, respectively. Boundary-crossing probabilities for the study are provided in [Table 8-1](#).

Table 8-1. Boundary-Crossing Probabilities at Interim and Final Analyses Based on the Assumptions of the Study

Analysis	Expected Events n (%)	Boundary to Reject H ₀	Boundary-Crossing Probabilities at Each Analysis	
			Under H ₀	Under H ₁
Interim	81 (50%)	0.0031	0.0031	0.2525
Final	162 (100%)	0.0490	0.0469	0.6475

8.11. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of safety data on a regular and ongoing basis, and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The committee will convene and review the safety data from subjects in the lead-in before the initiation of randomized treatment phase, and from subjects in randomized treatment phase at approximately 6 months after the first subject is enrolled, and thereafter at intervals of approximately 6 months.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, “Responsibilities of Sponsors and Investigators,” 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with GSI, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator’s (and any subinvestigator’s) participation in the study. The investigator and subinvestigator agree to notify GSI of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB (for studies conducted in the United States) or IEC (for studies conducted outside of the United States). The investigator will not begin any study subject activities until approval from the IRB or IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB or IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by local requirements. The consent form will inform subjects about optional testing and sample retention, and their right to receive clinically relevant analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from GSI, including but not limited to the investigator brochure, this protocol, CRF/eCRF, the IP, and any other study information, remain the sole and exclusive property of GSI during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from GSI. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, eg, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled;
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (eg, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with GSI. The investigator must notify GSI before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, GSI must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and GSI to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal GSI staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, GSI will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Product Accountability and Return

GSI recommends that used and unused IP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IP disposal procedures and provide appropriate instruction for destruction of unused IP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by GSI QA, the site may destroy used (empty or partially empty) and unused IP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IP is destroyed on site, the investigator must maintain accurate records for all IP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IP. Upon study completion, copies of the IP accountability records must be filed at the site. Another copy will be returned to GSI.

The study monitor will review IP supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to GSI's appointed study monitors, to IRBs or IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by GSI. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency. GSI will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- the results of the study in their entirety have been publicly disclosed by or with the consent of GSI in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years
- The investigator will submit to GSI any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include GSI's confidential information (see Section 9.1.4).
- The investigator will comply with GSI's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, GSI will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the CRF/eCRF.

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of GSI may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the GSI Medical Monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or GSI access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, GSI and the investigator will assure that adequate consideration is given to the protection of the subjects' interests (see Section [6.7.2](#)).

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11. APPENDICES

- Appendix 1. Investigator Signature Page
- Appendix 2. Study Procedures Table
- Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and
Contraceptive Requirements
- Appendix 4. ECOG Performance Status
- Appendix 5. Dose-Escalation Flowchart- Lead-in Phase

Appendix 1. Investigator Signature Page

**GILEAD SCIENCES, INC.
333 LAKESIDE DR
FOSTER CITY, CA 94404**

STUDY ACKNOWLEDGEMENT

**A Phase 2, Randomized, Double-blind Study of Gemcitabine and Nab-paclitaxel combined
with Momelotinib in Subjects with Previously Untreated Metastatic Pancreatic Ductal
Adenocarcinoma Preceded by a Dose-finding, Lead-in Phase**

GS-US-370-1296, Protocol Amendment 1, 14 March 2014

This protocol has been approved by Gilead Sciences, Inc. The following signature documents
this approval.

Peter Lee
Name (Printed)
Medical Monitor

PPD
Signature

19 March, 2014
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary
details for me and my staff to conduct this study as described. I will conduct this study as
outlined herein and will make a reasonable effort to complete the study within the time
designated.

I will provide all study personnel under my supervision copies of the protocol and access to all
information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure
that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Study Phase	Screening	Randomization/ Baseline	Each Cycle (28 days +/- 3 business days)			Every 8 weeks	Every 12 weeks	EOT	30-day Safety Follow-up	5-year Long Term Survival Follow-up
Cycle Day	Screening	C1D1	1	8	15	N/A	N/A	N/A		
Window (day)	-21	-3	0	±3	±3	N/A	±3	±7	±7	N/A
General and Safety Assessments										
Informed Consent	X									
Medical and Medication History	X	X	X					X		
Physical Examination	X	X	X					X	X	
Vital Signs ¹	X	X	X	X	X			X	X	
12-lead ECG ²	X	X	X		X			X		
Adverse events/Concomitant medications ³	X	X	X	X	X			X	X	
IP Accountability and Dispensing		X	X					X		
IXRS Registration	X	X	X					X		
Overall Survival and Other Antitumor Therapy										X (Every 6 months)

1 C1D1 vital signs will be taken pre- and post-MMB/placebo dose every 2 hours for 4 hours; Vital signs will be taken pre-dose only at all subsequent visits

2 Approximately every 2 weeks for first 3 cycles, then on Day 1 of each subsequent cycle. Following completing of a planned thorough QT study and a review of cardiovascular-related events, ECG monitoring may be discontinued in this study

3 Adverse events will be assessed at pre- and post-MMB/placebo, nab-P+G dosing during applicable clinic visits. Subjects will also return to clinic at 30-day post last dose MMB/placebo or gemcitabine or nab-paclitaxel whichever is later, to assess AEs and SAEs

Study Phase	Screening	Randomization/ Baseline	Each Cycle (28 days +/- 3 business days)			Every 8 weeks	Every 12 weeks	EOT	30-day Safety Follow-up	5-year Long Term Survival Follow-up
Cycle Day	Screening	C1D1	1	8	15	N/A	N/A	N/A		
Window (day)	-21	-3	0	±3	±3	N/A	±3	±7	±7	N/A
Patient-Reported Outcomes										
FACT-Hep		X	X					X	X	
EQ-5D		X	X					X	X	
Laboratory Assessment										
CBC with differential	X	X	X	X	X			X	X	
Chemistry	X	X	X	X	X			X	X	
Coagulation	X	X					X	X	X	
Hepatitis B and C	X									
Thiamine status		X					X			
Urinalysis and Urine Chemistry	X	X	X					X	X	
Pregnancy Test ⁴	X	X	X					X		
MMB PK ⁵			X		X					
MMB pharmacodynamic ⁶			X		X					

- 4 If applicable (females of child bearing potential). Serum pregnancy will be conducted at Screening. Urine pregnancy will be conducted pre-dose on Days 1 of each cycle and at EOT
- 5 PK sampling to be performed at the following timepoints: Lead-in phase – Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-MMB dose on Day 15 of Cycle 1 (24 hour post-MMB dose sampling is not applicable in twice-daily dosing cohort); Randomized treatment phase – trough samples at approximately 20-26 hours post-MMB dose on Day 1 of Cycle 2 and 3 (or at 10-14 hours post-MMB dose in twice-daily dosing cohort), and pre-dose on Day 1 of Cycles 4, 5, and 6
- 6 Pharmacodynamic sampling to be performed at the following timepoints: Lead-in phase only – Pre-dose, 1, 2, 4, 6, 8, 12, and 24 hours post-MMB dose on Day 15 of Cycle 1 (24 hour post-MMB dose sampling is not applicable in twice-daily dosing cohort); Randomized treatment phase – trough samples at approximately 20-26 hours post-MMB dose on Day 1 of Cycle 2 and 3 (or at 10-14 hours post-MMB dose in twice-daily dosing cohort), and pre-dose on Day 1 of Cycles 4, 5, and 6

Study Phase	Screening	Randomization/ Baseline	Each Cycle (28 days +/- 3 business days)			Every 8 weeks	Every 12 weeks	EOT	30-day Safety Follow-up	5-year Long Term Survival Follow-up
Cycle Day	Screening	C1D1	1	8	15	N/A	N/A	N/A		
Window (day)	-21	-3	0	±3	±3	N/A	±3	±7	±7	N/A
MMB Predictive Biomarkers- hsCRP, IL-6, sTNFRa2		X	X ⁷							
MMB Exploratory Biomarkers- PPD (additional consent required) ⁸		X	X							
MMB Exploratory Biomarkers- PPD (randomized only) ⁹		X						X		
Biopsy tissue sample (additional consent required) ¹⁰						X				
Collect archival tumor tissue ¹¹		X								

7 Predictive biomarkers to be collected with EDTA tube on Day 1 of Cycle 1 and 2 in both lead-in and randomized treatment phases

8 Exploratory biomarkers to be collected in subset of patients (additional consent required) at the following timepoints in both lead-in and randomized treatment phases: PPD on Day 1 of each cycle

9 Exploratory biomarkers to be collected at the following timepoints in randomized treatment phase only: PPD on Day 1 of Cycle 1 and at EOT

10 Biopsy tissue sample to be collected in subset of patients (additional consent required) after completion of Cycle 2 at approximately week 8 in both lead-in and randomized treatment phases, and/or in a second subset of patients at disease progression in the randomized treatment phase only.

11 Archival tumor tissues block will be collected and shipped to central laboratory for sectioning after Day 1 of Cycle 1

Study Phase	Screening	Randomization/ Baseline	Each Cycle (28 days +/- 3 business days)			Every 8 weeks	Every 12 weeks	EOT	30-day Safety Follow-up	5-year Long Term Survival Follow-up
Cycle Day	Screening	C1D1	1	8	15	N/A	N/A	N/A		
Window (day)	-21	-3	0	±3	±3	N/A	±3	±7	±7	N/A
Disease Assessments										
ECOG Performance Status	X	X	X	X	X			X	X	
Treatment Response Assessment ¹²		X				X		X		
CT with contrast or MRI ¹³	X					X		X		

12 As per RECIST v1.1

13 Tumor evaluation by CT or MRI will be performed during screening and approximately every 8 weeks regardless of cycle number or dose interruption. Scans may be performed at other time points during the treatment phase as clinically indicated. Scan at EOT visit is not necessary if restaging scan is performed within the prior 8 weeks. For subjects who stop study treatment in the absence of disease progression (eg. experienced unexpected toxicity), scans should continue to be collected approximately every 8 weeks until disease progression or initiation of systemic anti-tumor therapy other than the study treatment (whichever is earlier). The same radiographic procedure to define measurable lesion(s) must be used throughout the study for each subject.

Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1. Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

The risks of treatment with momelotinib (MMB) during pregnancy have not been evaluated. Data available at this time suggest that this drug does not have a drug-drug interaction (DDI) with hormones used for contraception. Please refer to the latest version of the investigator's brochure for additional information.

Please refer to the regional prescribing information for information on the potential risks of treatment with gemcitabine and nab-paclitaxel.

2. Definition of Female of Childbearing Potential

For the purposes of this study, a female subject of childbearing potential is a woman who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes pubertal females regardless of whether or not she has had a menses (premenarchal, Tanner Stage 3) and perimenopausal women who have had a spontaneous menses in the last 12 months. A woman who has had a tubal sterilization is considered to be of childbearing potential.

- Women ≤ 54 years of age with amenorrhea of any duration will be considered to be of childbearing potential unless they have had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.
- Women > 54 years of age with cessation (for ≥ 12 months) of previously occurring menses due to ovarian failure will not be considered to be of childbearing potential.

3. Contraceptive Requirements

Male subjects and female subjects of childbearing potential who engage in intercourse must agree to utilize protocol specified methods of contraception from the screening/enrollment visit throughout the study period and for 30 days following the last dose of study drug MMB.

Female study subjects who are not heterosexually active must provide periodic confirmation of continued abstinence from heterosexual intercourse and regular pregnancy testing while taking MMB. The investigator will counsel subjects on the protocol specified method(s) for avoiding pregnancy in case the subject chooses to engage in heterosexual intercourse. See [Appendix Table 1](#) for the protocol specified contraceptive methods.

Female subjects of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline (Day 1) prior to receiving the first dose of study drug. Lactating females must discontinue nursing before IP administration.

Appendix Table 1 Protocol Specified Contraceptive Methods

Methods to Use by Themselves	Combination Methods	
	Hormone Methods (choose one and use with a barrier method)	Barrier Methods (use both OR choose one and use with a hormone method)
Intrauterine Devices (IUDs) <ul style="list-style-type: none"> Copper T 380A IUD LNg 20 IUD 	Estrogen and Progesterone <ul style="list-style-type: none"> Oral contraceptives Transdermal patch Vaginal ring Progesterone <ul style="list-style-type: none"> Injection Implant 	<ul style="list-style-type: none"> Diaphragm with spermicide OR Cervical cap with spermicide Male condom (with or without spermicide)
Tubal Sterilization	Partner's vasectomy must be used with a hormone or barrier method.	

The investigator will counsel all subjects on the most effective method(s) for avoiding pregnancy during the study.

4. Additional Requirements for Male Subjects

Male subjects must agree to use condoms during heterosexual intercourse and avoid sperm donation while enrolled in the study and for at least 90 days after administration of the last dose of IP.

5. Procedures to be Followed in the Event of Pregnancy

Subjects should be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. The investigator should report all pregnancies to the CRO Safety Department or Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy. The investigator should counsel the subject regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 4. ECOG Performance Status

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

Reference for ECOG {9480}

Appendix 5. Dose-Escalation Flowchart- Lead-in Phase



