CLINICAL STUDY PROTOCOL

Study Title:	A Phase 3, Randomized, Double-blind, Placebo-controlled 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	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	
IND Number:	120605	
EudraCT Number:	2014-004480-20	
ClinicalTrials.gov Identifier:	NCT02101021	
Indication:	Previously untreated metastatic pancreatic ductal adenocarcinoma	
Protocol ID:	GS-US-370-1296	
Clinical Trials Manager:	Name: Telephone:	PPD PPD
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Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3:	11 February 2014 14 March 2014 25 August 2014 16 July 2015

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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA, 94404

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IND Number:	120605
EudraCT Number:	2014-004480-20
ClinicalTrials.gov Identifier:	NCT02101021
Study Centers Planned:	Lead-in phase: Approximately 3-4 centers in the United States Randomized treatment phase: Approximately 150 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 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	150mg once daily	1000 mg/m^2	125 mg/m^2
3	200 mg once daily	1000 mg/m^2	125 mg/m^2
4	150mg twice daily	1000 mg/m^2	125 mg/m^2
5	200 mg twice daily	1000 mg/m^2	125 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 evaluable subjects or < 2 DLTs occur in 6 evaluable 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 evaluable subjects or < 2 DLTs occur in 6 evaluable 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 evaluable subjects or < 2 DLTs occur in 6 evaluable 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 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 ≥ 100.5 º 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 pharmacodynamics and mechanism of action biomarkers.

Randomized Treatment: The randomized, double-blind, placebo-controlled phase of the trial. A total of 400 eligible subjects with a modified Glasgow prognostic score (mGPS) of 1 or 2 will be randomized in a 1:1 manner (200 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 mGPS (1 vs. 2).

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: Up to 30 subjects Randomized treatment phase: approximately 400 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:** 1) Age ≥ 18 years old 2) 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 3) Measurable disease per RECIST v1.1 4) Adequate organ function defined as follows: • Hepatic: Total bilirubin ≤ 1.25 x upper limit of normal (ULN); AST (SGOT) and ALT (SGPT) ≤ 3 x ULN • Hematological: Absolute neutrophil count (ANC) > 1500 cells/mm^3, platelet > 100,000 cells/mm^3, hemoglobin > 9 g/dL • Renal: Serum creatinine < ULN OR calculated creatinine clearance (CrCl) ≥ 60 ml/min as calculated by the Cockroft-Gault method 5) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 6) mGPS of 1 or 2 at Screening (randomized phase only) 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

Exclusion Criteria:

1) Neoadjuvant or adjuvant chemotherapy or chemoradiotherapy for pancreatic adenocarcinoma
2) Investigational therapy within 21 days prior to first dose of IP
3) Currently or previously treated with biologic, small molecule, immunotherapy, chemotherapy, or other agents for metastatic pancreatic carcinoma
4) 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
5) 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 enrollment/randomization, or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to enrollment/randomization
6) 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
7) Minor surgical procedure(s) within 7 days of enrollment or not yet recovered from prior minor surgery (placement of central venous access device, fine needle aspiration, or endoscopic biliary stent ≥ 1 day before enrollment is acceptable)
8) Known positive status for human immunodeficiency virus (HIV)
9) Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier

10) Peripheral neuropathy ≥ Grade 2
11) Known or suspected brain or central nervous system metastases
12) Diagnosis of pancreatic islet neoplasm, acinar cell carcinoma, non-adenocarcinoma (ie, lymphoma, sarcoma), adenocarcinoma originating from the biliary tree or cystadenocarcinoma
13) History of interstitial pneumonitis and/or require supplemental oxygen therapy
14) External biliary drain
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 enrollment
16) Use of strong CYP3A4 inducers within 2 weeks 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) 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, 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 approximately every 8 weeks following C1D1.

	After discontinuation of treatment, subjects will be followed for safety for 30 days and for survival approximately every 3 months for up to 3 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 3 months for up to 3 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.
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:	<u>Primary Endpoints:</u> 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 <u>Secondary Endpoints:</u> 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 enrollment to the earlier of the first documentation of definitive disease progression or death from any cause

	Time to health-related quality of life (HRQoL) worsening, defined as the interval from randomization to a minimum of 8-point reduction in FACT-Hep total score or death from any cause, whichever is earlier. 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 time points specified in the protocol.
Pharmacodynamics 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/pharmacodynamics 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 (HR), 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 pharmacodynamics 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 subgroup of subjects with mGPS 1 or 2, the HR for OS was 0.60.

For the randomized treatment phase of the study, a total of 231 OS events need to be observed to detect a HR of 0.69 with 80% 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, 200 subjects in each arm need to be enrolled to observe the 231 OS events. The expected study duration of observing 231 OS events in the randomized treatment phase is ~24 months. A futility interim analysis will be performed when approximately 77 (33%) OS events have been observed in the study. A non-binding futility rule on OS will be implemented. Based upon the interim analysis result, the Data Monitoring Committee (DMC) may recommend stopping the study for futility if the observed HR for OS is ≥ 1.04. The conditional power of obtaining a statistically significant result at the final analysis given an observed HR of ≥ 1.04, assuming the current trend for future data, is $< 1\%$. Two efficacy interim analyses will be conducted when 77 (33%) and 154 (67%) 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 0.0002, 0.0120 and 0.0463, respectively.

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
AST	aspartate transaminase
AUC	area under the plasma/serum/peripheral mononuclear cell concentration versus time curve
$AUC_{0\text{-last}}$	area under the concentration verses 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 $AUC_{0\text{-last}} + (C_{last}/\lambda_z)$
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: $CL/F = Dose/AUC_{inf}$ 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
CT	computed tomography/ computed axial tomography scan
CTCAE	Common Terminology Criteria for Adverse Events

CYP450	cytochrome P450
ctDNA	circulating tumor DNA
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)
EOI	end of infusion
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
FSH	follicle stimulating hormone
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
HRQoL	health-related quality of life
hsCRP	high sensitivity c-reactive protein
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
IP	investigational product

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
mGPS	modified Glasgow prognostic score
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)
PTM	placebo to match
PV	polycythemia vera
RAF	rapidly accelerated fibrosarcoma
RBC	red blood cell
RECIST	Response Evaluation Criteria In Solid Tumor

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 (λz)
T_{last}	the time (observed time point) of Clast
T_{max}	the time (observed time point) of Cmax
TBK1	TANK-binding kinase 1
TTR	time to response
TYK2	tyrosine kinase 2
ULN	upper limit of normal
WBC	white blood cell
λz	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}. Maintenance therapy with sunitinib for those who do not demonstrate disease progression after 6 cycles of first line chemotherapy has also been explored, with preliminary encouraging results {28441}.

Desmoplasia is a prominent feature of pancreatic cancer, with most of the tumor mass consisting of activated fibroblast, immune cells, collagen, desmin, fibronectin, and hyaluronic acid {28438}, {28433}, {29553}. Components of this extracellular matrix form a barrier to impede active therapy from reaching cancer cells, and can interact with a complex network of cytokines and proteases to promote tumor proliferation and metastasis {28438}. Inflammation has been postulated to play a vital role in both the oncogenesis and progression of pancreatic cancer {28437},{28432}, with high levels of c-reactive protein (CRP), an acute phase protein and marker of inflammation, found to be associated with inferior cancer-specific survival {29788}, {28444}. Moreover, combination of hypoalbuminemia (< 35 g/L) and elevated CRP (> 10 mg/L), as in the Glasgow Prognostic Scoring system, provides additional prognostic information {29520}. The prognostic importance of CRP is further supported by a phase 2 study that tested the combination of ruxolitinib, a Janus kinase (JAK)1 and JAK2 inhibitor, with either capecitabine or placebo as

second line therapy in patients with metastatic pancreatic cancer (RECAP study). In the RECAP study, survival was favored in the pre-specified subgroup of patients with CRP > 13 mg/L who received ruxolitinib compared to those who received placebo, with a hazard ratio (HR) of 0.47 (95% CI: 0.26-0.85, p=0.01) {29522}.

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 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 feed 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 undergoes minor metabolism by CYP3A4 and is not a sensitive CYP3A4 substrate.

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 (IC_{50}) 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 IC_{50} 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 IC_{50} 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 IC_{50} 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. A 9-month oral toxicology study in dogs with a 10-week recovery period was conducted with MMB. The report is in progress, but upon review of the 9-month ophthalmic examination data, posterior subcapsular cataracts were observed in male and female dogs administered the high dose of 50 mg/kg/day free base equivalent. The mean systemic exposure, where cataracts were observed, was approximately twice the systemic exposure observed in patients.

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 $AUC_{0\text{-}24}$ 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 $AUC_{0\text{-}12}$ 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 (AUC_{0-24}) 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 April 2015, 10 clinical studies of MMB have been completed and 9 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-352-0108, A Phase I, Single-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of Momelotinib in Healthy Japanese and Caucasian Subjects.

- Study GS-US-352-1149, A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism, and Excretion of Momelotinib.

- Study GS-US-352-1150, A Phase I, Partially-Blinded, Randomized, Placebo- and Positive-Controlled Study to Evaluate the Effect of Momelotinib on the QT/QTc Interval in Healthy Subjects.

- Study GS-US-352-1151, A Phase I Study to Evaluate the Effect of Ritonavir and Rifampin on Momelotinib Pharmacokinetics and the Potential Effect of Momelotinib on CYP3A Enzymes and BCRP Transporters Using Probe Substrates.

- Study CCL09101E, A Phase II, Open-Label Extension Study Evaluating the Long Term Safety, Tolerability and 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-352-1153, A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of Momelotinib (MMB) in Subjects with Impaired Hepatic Function.

Ongoing Clinical Trials

- 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).

- Study GS-US-354-0101, A Phase 2, Open-label, Randomized Study to Evaluate the Safety and Efficacy of Momelotinib in Subjects with Polycythemia Vera or Essential Thrombocythemia.

- Study GS-US-352-1154, Open-label Study to Assess the Long-term Safety and Efficacy of Momelotinib in Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, Post-essential Thrombocythemia Myelofibrosis, Polycythemia Vera or Essential Thrombocythemia.

- Study GS-US-352-1214, A Phase 3, Randomized Study To Evaluate the Efficacy of Momelotinib Versus Best Available Therapy in Anemic or Thrombocytopenic Subjects with Primary Myelofibrosis, Post-polycythemia Vera Myelofibrosis, or Post-essential Thrombocythemia Myelofibrosis who were Treated with Ruxolitinib.

- Study GS-US-352-1152, A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of Momelotinib (MMB) in Subjects with Impaired Renal Function
- Study GS-US-370-1296, A Phase 3, Randomized, Double-blind, Placebo-controlled 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
- Study GS-US-370-1369, A Phase 1b Study Evaluating Momelotinib Combined with Capecitabine and Oxaliplatin in Subjects with Relapsed/Refractory Metastatic Pancreatic Ductal Adenocarcinoma
- Study GS-US-370-1297, A Phase 1b Parallel Cohort Study Evaluating the Efficacy and Safety of Momelotinib and Momelotinib Combined with Trametinib in Subjects with Metastatic KRAS-mutated Non-Small Cell Lung Cancer (NSCLC) Who Have Failed Platinum-Based Chemotherapy Preceded by a Dose-finding Lead-in Phase
- Study GS-US-370-1298, A Phase 1b Study of Erlotinib and Momelotinib for the Treatment of Epidermal Growth Factor Receptor (EGFR) Mutated EGFR Tyrosine Kinase Inhibitor (TKI) Naïve Metastatic Non-Small Cell Lung Cancer (NSCLC)

1.3. Other Relevant Clinical Information

A recent clinical trial of the JAK2 inhibitor fedratinib (SAR302503) in myelofibrosis was halted due to reported cases of Wernicke's encephalopathy. There has been one case of suspected Wernicke's encephalopathy reported in clinical trials with MMB in subjects with myelofibrosis. Peripheral neuropathy has also been reported as an adverse event. Based on these data, thiamine status will be monitored throughout the duration of the study treatment.

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}, {27786}.

Benefits of JAK inhibition in patients with pancreatic cancer is further supported by findings from the RECAP trial, which demonstrated a survival improvement for patients with high CRP or high mGPS (1 or 2) who received ruxolitinib treatment compared to those who received placebo {29522}. 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 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:

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

*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 evaluable subjects or < 2 DLTs occur in 6 evaluable 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 evaluable subjects or < 2 DLTs occur in 6 evaluable 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 evaluable subjects or < 2 DLTs occur in 6 evaluable 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 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 ≥ 100.5 ºF)
- 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 400 subjects will be randomized via interactive voice/web response system (IXRS) in a 1:1 manner (200 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 mGPS.

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. 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 Gilead Sciences, Inc. (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 3 months for up to 3 years.

3.4. 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 are considered source data.

3.5. Biomarker Testing

3.5.1. 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.

Specimens will be collected from all subjects. These samples will be used for the exploratory objectives outlined in this protocol and will be destroyed no later than 10 years after the end of study, unless a subject consents to the optional storage of samples for future research.

Pharmacodynamics: 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 (Tumor Tissue and Blood): PPD

Tumor Tissue

The following tissue samples will be collected for pharmacodynamics 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

Pre-treatment cytokine levels such as IL-6 and soluble TNF receptor-alpha-2 levels will be quantitated in blood samples from all subjects to assess their predictive value, and to monitor post-treatment to understand the effects of MMB. Additional protein biomarkers related to JAK activation and MMB activity will also be explored.

Circulating tumor DNA (ctDNA) isolated from plasma at several time points will be analyzed for disease monitoring, through ctDNA quantification and DNA sequencing of disease-specific markers such as mutant KRAS. Mutations relevant to resistance that develop on treatment may also be evaluated (U.S. subjects only at select sites).

3.5.2. Biomarker Samples for Optional Future Research

PPD

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

The number of subjects to be enrolled in the lead-in phase will depend on the total number of dose levels that may be needed to determine the MTD. Assuming maximum potential accrual, the planned enrollment for the lead-in phase is 30 evaluable subjects. However, additional subjects may be enrolled in order to ensure accrual of sufficient subjects who can be fully evaluated for DLT during the first 28 days of therapy. Thus, if a subject withdraws for administrative reasons or an eligibility criterion or if a protocol violation occurs that substantially impairs evaluation of safety and activity in a subject, another subject can be enrolled to complete accrual of the planned number of evaluable subjects for a dose level. Consideration will be given to whether the events leading to subject inevaluability may constitute a safety risk for further subject enrollment to the current or succeeding levels. The decision to accrue replacement subjects will be made by the GSI medical monitor working in collaboration with the investigators.

Once the MTD has been established, approximately 400 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 ≥ 18 years old

2) 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

3) Measurable disease per RECIST v1.1

4) Adequate organ function defined as follows:

- Hepatic: Total bilirubin ≤ 1.25 x ULN; AST (SGOT) and ALT (SGPT) ≤ 3 x ULN
- Hematological: ANC > 1500 cells/mm^3, platelet > 100,000 cells/mm^3, hemoglobin > 9 g/dL
- Renal: Serum creatinine < ULN OR calculated CrCl of ≥ 60 ml/min as calculated by the Cockroft-Gault method

5) ECOG Performance Status of 0 or1

6) mGPS of 1 or 2 at Screening (randomized phase only)

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) Investigational therapy within 21 days prior to first dose of IP

3) Currently or previously treated with biologic, small molecule, immunotherapy, chemotherapy, or other agents for metastatic pancreatic carcinoma

4) 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

5) 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 enrollment/randomization, or any other cancer that has been in complete remission without treatment for ≥ 5 years prior to enrollment/randomization

6) 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

7) Minor surgical procedure(s) within 7 days of enrollment or not yet recovered from prior minor surgery (placement of central venous access device, fine needle aspiration, or endoscopic biliary stent ≥ 1 day before enrollment is acceptable)

8) Known positive status for HIV

9) Chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C), or hepatitis B or C carrier

10) Peripheral neuropathy ≥ Grade 2

11) Known or suspected brain or central nervous system metastases

12) Diagnosis of pancreatic islet neoplasm, acinar cell carcinoma, non-adenocarcinoma (ie, lymphoma, sarcoma), adenocarcinoma originating from the biliary tree or cystadenocarcinoma

13) History of interstitial pneumonitis and/or require supplemental oxygen therapy

14) External biliary drain

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 enrollment

16) Use of strong CYP3A4 inducers within 2 weeks 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) 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) + standard doses of nab-P (125 mg/m^2) + G (1,000 mg/m^2) 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) + standard doses of nab-P (125 mg/m^2) + G (1,000 mg/m^2) on Days 1, 8, 15, cycle repeats every 28 days

The randomization will be stratified by ECOG performance status (0 vs. 1) and mGPS (1 vs. 2).

5.2. Description and Handling of Study Drug

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 round, film-coated, brown tablets and MMB tablets 200 mg, are 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 round, film-coated, brown tablets and MMB PTM tablets 200 mg, are capsule-shaped, film-coated, brown tablets.

5.2.1.3. Nab-Paclitaxel and Gemcitabine

Nab-paclitaxel (Abraxane®) and gemcitabine are commercially sourced for certain participating countries. Information regarding the formulation of commercially available nab-paclitaxel and gemcitabine can be found in the current Prescribing Information in the study pharmacy manual.

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.

Nab-paclitaxel (Abraxane®) and gemcitabine are commercially sourced and over-labeled for certain participating countries.

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 ºC (77 ºF); excursions are permitted between 15 ºC and 30 ºC (59 ºF and 86 ºF). Until dispense 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.

Nab-paclitaxel (Abraxane®) and gemcitabine are commercially sourced for certain participating countries. Information regarding the storage and handling of commercially available nab-paclitaxel and gemcitabine can be found in the current Prescribing Information.

5.3. Dosage and Administration

5.3.1. MMB and Placebo

The dose of MMB will be determined by the safety profile in the lead-in phase. Pharmacodynamics data from the lead-in phase may be used to support the dose selection. 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 of administration will be recorded on the respective eCRF page and in the source document. The time will be recorded on the eCRF for doses taken at a visit only.

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

Dose adjustment or discontinuation may be required based on emerging toxicities, and should follow the guidelines specified in this protocol and in the current Prescribing Information.

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
1st dose reduction	100	800
2nd 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/m^2 and gemcitabine dose is 800 mg/m^2, only 1 dose level reduction is allowed on Day 15. Subjects with ANC 500 to < 1,000 or platelet count 50,000 to < 75,000 on Day 15 will hold nab-paclitaxel and gemcitabine dosing.

Following resolution of the toxicity that led to dose reduction on Day 8 and/or 15 within a cycle, nab-paclitaxel and/or gemcitabine may be re-escalated on Day 1 of the subsequent cycle, at the investigator's discretion, to the doses prior to dose reduction.

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 MMB/placebo along with nab-paclitaxel and gemcitabine will be permanently discontinued. Early use of supportive care measure may help ameliorate the condition.

Acute infusion-related reactions are characterized by one or more of the following symptoms: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Given the possibility of extravasation with nab-paclitaxel infusion, it is advisable to closely monitor the infusion site for possible infiltration during administration. Limiting the infusion of nab-paclitaxel to 30 minutes, as directed, reduces the likelihood of infusion-related reactions.

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 ≥ 50,000 (cells/mm^3).

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 is 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 GSI 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 Inducers

  — MMB undergoes minor metabolism by CYP3A4 and is not a sensitive CYP3A4 substrate. Strong CYP3A4 inhibitor ritonavir resulted in clinically irrelevant increase in MMB exposure (C_{max} ~ 23% and AUC ~ 13%), thus MMB can be co-administered with CYP3A4 inhibitors.

  — Strong CYP3A4 inducers (eg, carbamazepine, phenytoin, St. John's wort) may decrease MMB exposure and may be used only with prior approval by GSI.

5.7. Breast Cancer Resistance Protein (BCRP) Substrates

In vitro, MMB was determined to be an inhibitor of BCRP. Results from a clinical drug-drug interaction study suggested that multiple doses of MMB at 200 mg increased the exposure (C_{max} and AUC) of rosuvastatin (a BCRP substrate) by approximately 3 fold. Plasma exposure of BCRP substrates may increase when administered with MMB. As such, where appropriate, dose modification or alternative medications as clinically appropriate may be considered when co-administered with MMB.

5.8. Organic Anion-Transporting Polypeptide (OATP) Inhibitors

MMB was determined to be a substrate of OATP1B1 and OATP1B3. A single dose of rifampin (potent inhibitor of OATP1B1 and OATP1B3) increased MMB C_{max} by ~40% and AUC_{inf} by ~56%. Care should be exercised when MMB is co-administered with OATP inhibitors.

Please refer to the investigator brochure of MMB and prescribing information of co-administered drugs for more details prior to administration.

5.9. Study Drug Accountability

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. Please refer to the study pharmacy manual for more information.

Study drug 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.

5.9.1. Study Drug 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 GSI 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
- Tumor Biopsy Substudies
- Optional Intensive PK Substudy

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 medications taken within 1 month 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 and non-prescription medications, vitamins and minerals.

6.2.4. Physical Examination

At Screening and End of Treatment visits, a complete physical examination will be performed including height (at Screening only) 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.

Beginning at C1D1, a modified physical examination will be performed to monitor for any changes, and will also include weight and assessment of disease-related clinical signs and symptoms. Baseline physical examination can be waived if it is conducted within 96 hours of C1D1.

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. Ophthalmic Assessments

Prior to enrollment, an ophthalmic exam will be performed to assess for cataracts and visual acuity. A repeat ophthalmic exam will be performed at Months 6, 12, and annually thereafter (± 28 days) while a subject remains on study treatment. All assessments will be performed in accordance with local standard practice.

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. If central laboratory results are not available, local laboratories may be used for dosing decision. Other tests listed in Table 6-1 will be performed by GSI 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 Alkaline phosphatase ALT (SGPT) AST (SGOT) Amylase Bicarbonate BUN Calcium Chloride Creatinine[a] Ferritin Serum iron GGT Glucose LDH Lipase Magnesium Phosphorus Potassium Sodium Total bilirubin Direct bilirubin Total protein Uric acid CA19-9 CEA	Color and appearance Specific gravity pH Occult blood Protein Glucose Bilirubin Leukocyte esterase Nitrite Urobilinogen Ketones Microscopic[c] Urine Pregnancy[b]	WBC WBC differential Basophil Eosinophil Lymphocyte Monocyte Neutrophil Hemoglobin Hematocrit Platelet ANC	Erythropoietin Serum beta hCG[b] hsCRP Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B core antibody Hepatitis C antibody Thiamine status[d] MMB PK[e] MMB pharmacodynamics and exploratory predictive biomarkers[f]

ANC = absolute neutrophil count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CEA=carcinoembryonic antigen; hsCRP = high-sensitivity c-reactive protein; 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 Cockroft-Gault formula
b Females of child-bearing potential only. Serum pregnancy will be conducted at Screening. Urine pregnancy will be conducted pre-dose on Day 1 of each cycle and at EOT
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 3.5

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.

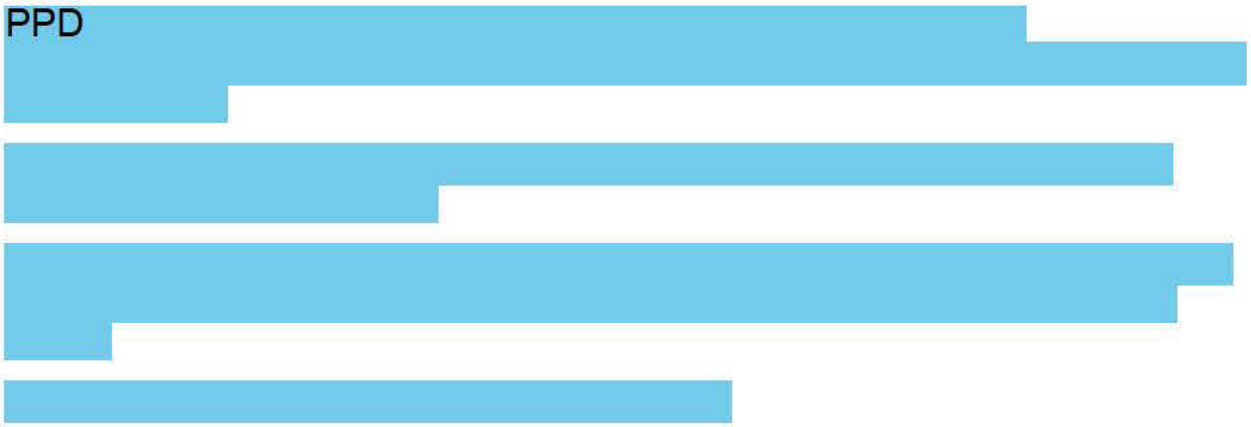
Intensive pharmacodynamics samples will also be collected from subjects in lead-in phase on Day 15 of Cycle 1 (pre-MMB dose and at 1, 2, 4, 6, 12, and 24 hours post-MMB dose); 24 hours post-MMB dose sampling will not be applicable in the twice-daily cohort.

Sparse PK 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 Pharmacokinetics Substudy (optional, additional consent required)

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



6.2.8. Patient-Reported Outcomes Assessments (PRO)

PRO assessments will be collected at Baseline (prior to enrollment/randomization) and throughout the duration of the study. See Appendix 2 for schedule of assessments.

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 with Gadolinium (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 vendor for collection and potential future analysis. 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 after Cycle 1 Day 1.

Per RECIST version 1.1, tumor markers are part of the evaluation of non-target lesions for complete response (CR), non-CR/non-progressive disease (PD) and PD. Tumor markers alone cannot be used to assess response, but could be used to confirm CR. Serum CA 19-9 level, collected +/- 14 days of a restaging radiographical study, will be the tumor marker used for assessment of CR, non-CR/non-PD, and PD as related to non-target lesion(s).

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. Baseline ECOG performance status can be waived if it is conducted within 96 hours of enrollment/randomization.

6.2.9.4. Modified Glasgow Prognostic Score (mGPS)

The mGPS is a well-studied, inflammation-based prognostic score that utilizes CRP and albumin levels as clinically useful markers of solid tumor behavior. Patients with serum CRP ≤ 10 mg/L are classified as mGPS 0 irrespective of their serum albumin levels, while patients with serum CRP > 10 mg/L are classified as either mGPS 1 or mGPS 2 according to their serum albumin levels (mGPS 1: albumin ≥ 35 g/L; mGPS 2: albumin < 35 g/L). The presence of systemic inflammation as measured by mGPS has been shown to correlate with poor outcome in patients with pancreatic cancer. It will be scored based on central laboratory results at Screening in the randomized phase.

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 days screening window will be screen failed. Re-screening is allowed (see Section 6.3.2).

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
- ECOG performance status
- Ophthalmic assessments (to be completed prior to enrollment)
- Laboratory assessments
  - Chemistry
  - Complete blood count (CBC) with differential and iron panel
  - Hepatitis testing

- hsCRP
- Serum pregnancy test (females of child-bearing potential)
- Urinalysis

- mGPS
- CT scan with contrast or MRI with Gadolinium (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.

Laboratory assessments may be repeated one time during the screening period for confirmation prior to registering the subject as a screen failure.

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. Re-Screening Criteria

Subjects who do not enroll or randomize within 21 days of screening will be screen failed.

Re-screening may be allowed. Subjects who are re-screened will be re-consented with new screening number. Assessments from the first screening attempt that fall within the specified timeframes (eg, CT scan within 21 days of enrollment/randomization) do not need to be repeated. GSI is to be informed prior to a subject re-screening.

6.3.3. Subject Randomization

In randomized treatment phase a subject will be considered enrolled once he/she receives the randomization ID in IXRS. IXRS will also 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.

6.3.4. Baseline Visit / C1D1

Subjects who have met all eligibility criteria will return to the clinic on C1D1 to perform baseline (C1D1 pre-dose) assessments. C1D1 may occur within 3 days following enrollment/randomization.

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

- PROs (to be completed prior to enrollment/randomization)
  - FACT-Hep
  - EQ-5D
- Physical examination, including weight
- ECOG performance status
- Vital signs (pre- and post- first MMB dose on C1D1 every 2 hours for 4 hours)
- Laboratory assessments and blood sampling (refer to Appendix 2)
  - Chemistry
  - CBC with differential and iron panel
  - Thiamine status
  - hsCRP
  - MMB predictive biomarkers sampling (ie, IL-6, sTNFRa2, erythropoietin)
  - ctDNA (U.S. subjects only)
  - 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

Baseline physical examination and ECOG performance status can be waived if both of these have been conducted within 96 hours of enrollment/randomization.

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

The following procedures will be completed pre-dose on Day 1 of each subsequent cycle ± 3 days, unless otherwise specified:

- PROs
  - FACT-Hep
  - EQ-5D
- Physical examination, including weight
- ECOG performance status
- Vital signs
- Laboratory assessments and blood sampling (refer to Appendix 2)
  - Chemistry
  - CBC with differential and iron panel
  - hsCRP (in Cycle 2 only)
  - MMB predictive biomarkers sampling (ie, IL-6, sTNFRa2, erythropoietin in Cycle 2 and every other subsequent cycle)
  - ctDNA in Cycles 2 and 3, and every other subsequent cycle (U.S. subjects only)
  - MMB PK (Cycles 2 to 6 in randomized phase only)
  - Urinalysis
  - Urine pregnancy test (if applicable)
- Record any adverse events
- Concomitant medications review

- Enter subject status/information into IXRS
- IP accountability and dispensing

6.4.2. Days 8 and 15 of All Cycles

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

- Vital signs
- Laboratory assessments and blood sampling (refer to Appendix 2)
  - Chemistry
  - CBC with differential
  - MMB 24-hour PK and pharmacodynamics (Day 15 of Cycle 1 in lead-in phase only)
- Record any adverse events
- Concomitant medications review
- Enter subject status/information into IXRS for nab-P+G dispensation

6.4.3. Every 8 Weeks

CT with contrast or MRI with Gadolinium will be performed for tumor response assessment approximately every 8 weeks ± 7 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.

6.4.4. Every 12 Weeks

The following laboratory assessment will be collected every 12 weeks ± 7 days:

- Thiamine Status

6.4.5. Every 6 Months

Ophthalmic assessments will be conducted to assess for presence or absence of cataracts and visual acuity at Months 6, 12, and annually thereafter until subject discontinues treatment with MMB. These assessments can be conducted within a window of ± 28 days.

6.4.6. End of Treatment (EOT) Visit

The following procedures will be conducted when a subject discontinues MMB with a window of ± 7 days and prior to initiating a new anti-cancer therapy:

- PROs
  - FACT-Hep
  - EQ-5D
- Complete physical examination including weight
- ECOG performance status
- Vital signs (pre-dose only)
- Laboratory assessments and blood sampling
  - Chemistry
  - CBC with differential
  - MMB predictive biomarkers sampling (ie, IL-6, sTNFRa2, erythropoietin)
  - ctDNA (U.S. subjects only)
  - Urinalysis
  - Urine pregnancy test (if applicable)
  - Thiamine Status
- CT with contrast or MRI with Gadolinium (± 7 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

- Enter subject status/information into IXRS
- IP accountability

6.5. Unscheduled visits

Unscheduled visits may occur at any time during the study. Vital signs, laboratory assessments, 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 3 months for up to 3 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:

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

6.6.2. 3-Year Long Term Survival Follow-Up

Subjects will be contacted via phone call every 3 months (± 28 days) for determination of long term survival status and record of any other anti-cancer therapy for up to 3 years after discontinuation of all study assessments (except for the FACT-Hep questionnaire). The FACT-Hep questionnaire will also be conducted via phone call every month after the EOT visit and for up to 1 year after entering long term survival follow-up.

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 ie, dates of phone calls, registered letters, etc.

6.7. Assessment for Premature Discontinuation from Study Treatment

If a subject discontinues study dosing (eg. as a result of an AE) prior to disease progression and/or initiation of new anti-cancer therapy, every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures, including disease assessments and the FACT-Hep questionnaire (see Section 6.8).

If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

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 despite maximum medical management, 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
- Death
- Investigator's decision, in consultation with the GSI Medical Monitor

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 event.

If a subject discontinues MMB, the subject can continue on gemcitabine + nab-paclitaxel and vice versa, at the discretion of the investigator, until disease progression or initiation of systemic anti-tumor therapy, whichever is earlier. EOT visit will occur after the discontinuation of MMB.

Every attempt should be made to keep the subject in the study to continue collecting CT or MRI scans for tumor assessment at every 8 weeks and conducting the FACT-Hep questionnaire via phone call every month 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 treatment.

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 or GSI at any time.

As a general rule, if a subject discontinues 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
- Discontinuation of the study at the request of GSI, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

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 (See Section 9.3.4).

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 sub-investigator 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 the study manual.

If a CTCAE term is not available for the AE/SAE, the severity will be graded using Grade 1 through Grade 5 as defined in the CTCAE definitions.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe (Grade 3) 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

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study IP, which must be reported to the CRF/eCRF database as instructed.

Serious Adverse Events

All SAEs, regardless of cause or relationship that occur after the subject first consents to participate in the study (e.g. 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 Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IP, regardless of causality, should also be reported.

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

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, e.g. 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

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

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.

Laboratory abnormalities (eg. thiamine deficiency) identified at Screening/Baseline and during study participation should be treated at the investigator's discretion.

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 Appendix 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 IXRS. 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.
- Pharmacokinetic parameters (C_{max}, C_{tau} and AUC_{tau}, if available) for MMB.

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).

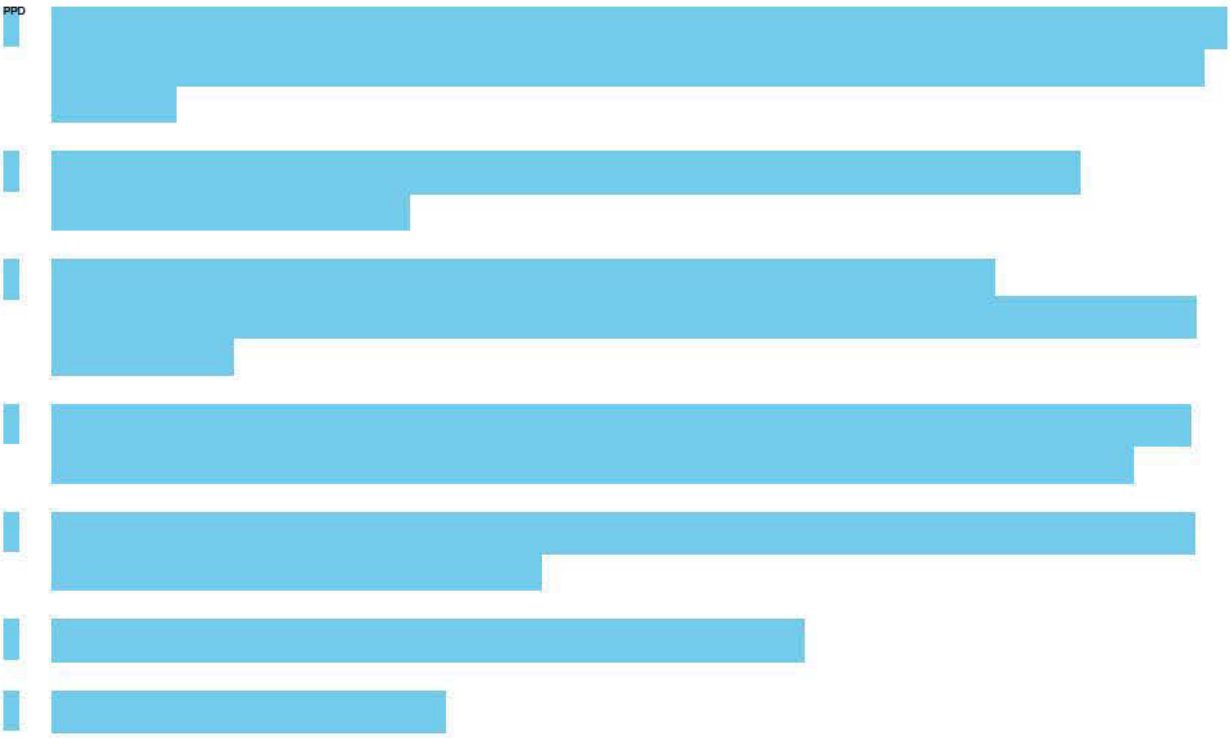
- Progression-free survival (PFS) – defined as the interval from randomization to the earlier of the first documentation of definitive disease progression or death from any cause; definitive disease progression is progression based on RECIST v1.1 criteria. Data from survival, non-progressing subjects 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.

- Time to HRQoL worsening – defined as the interval from randomization to a minimum of 8-point reduction in FACT-Hep total score or death from any cause, whichever is earlier.

8.1.4. Exploratory Endpoints

Exploratory endpoints for randomized treatment phase are:



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. Pharmacodynamics and Pharmacokinetic (PK) Analysis Sets

The Pharmacodynamics 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:

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, time to HRQoL worsening 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. Descriptive statistics will be provided for TTR.

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 3 secondary endpoints will be tested sequentially in the order listed (PFS, ORR, and time to HRQoL worsening), at the 2-sided 0.0316 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 study drug 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.meddramsso.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 study drug interruption and/or dose modification
- AEs leading to study drug 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

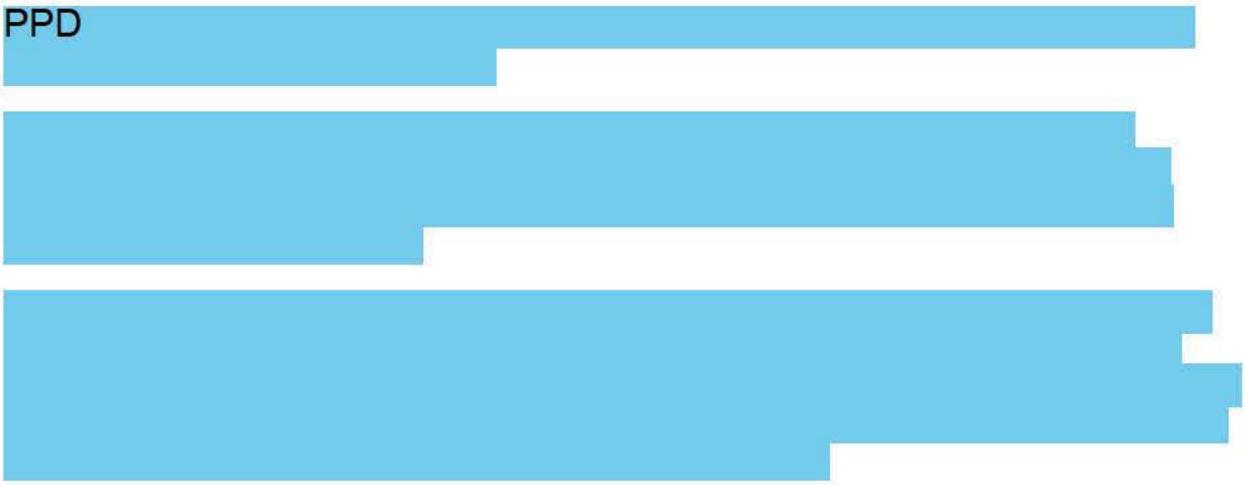
The concentration data of MMB and metabolites (GS-644603 and GS-642112), will be summarized by nominal sampling time using descriptive statistics. PK parameters (C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λ_z, $AUC_{tau,}$ and $T_{½}$), if available, will be listed and summarized using descriptive 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 ± standard deviation, and median (Q1, Q3) if applicable.

8.8. Biomarker Analysis

8.8.1. Pharmacodynamics Analysis

The baseline level, and the modulation of pSTAT3 upon treatment, including change over time from baseline level, will be evaluated. Descriptive statistics will be provided at each sampling time, by each dose level cohort in the lead-in phase. Spaghetti plots for each dose level and side-by-side boxplots comparing the dose levels at each time point will also be generated.

8.8.2. Exploratory Biomarker Analysis



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 subgroup of subjects with mGPS 1 or 2, a HR for OS of 0.60.

For the randomized treatment phase of the study, a total of 231 OS events need to be observed to detect a HR of 0.69 with 80% 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, 200 subjects in each arm need to be enrolled to observe the 231 OS events. The expected study duration to observe 231 OS events in the randomized treatment phase is anticipated to be ~24 months.

8.10. Interim Analysis

8.10.1. Futility Interim Analysis

A futility interim analysis will be performed when approximately 77 (33%) OS events have been observed in the study. A non-binding futility rule on OS will be implemented. Based upon the interim analysis result, the DMC may recommend early termination of the study for lack of efficacy if the observed HR for OS is ≥ 1.04, which has a 3.6% chance assuming the true HR is 0.69. The conditional power of obtaining a statistically significant result at the final analysis given an observed HR of ≥ 1.04, assuming the current trend for future data, is $< 1\%$.

8.10.2. Efficacy Interim Analysis

Two formal interim efficacy analyses may be conducted after approximately 77 (33%) and 154 (67%) OS events have been observed. At a constant accrual rate of 20 subjects per month, the interim analyses are expected to take place when approximately 242 and 363 subjects have

been accrued in the study, respectively. An O'Brien-Fleming boundary will be applied to assess the efficacy at the interim analyses. The efficacy boundaries (p-values) for the interim and final efficacy analyses will be 0.0002, 0.0120 and 0.0463, 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		Timing of Analysis (Since Randomization)	Number of Subjects Enrolled
			Under H_0	Under H_1		
Interim 1	77 (33%)	0.0002	0.0002	0.019	12.1 months	242
Interim 2	154 (67%)	0.0120	0.0119	0.399	18.1 months	363
Final	231 (100%)	0.0463	0.0379	0.382	23.9 months	400

The GS-US-370-1296 Study Team will remain blinded to treatment assignments throughout the trial until all subjects have completed the planned study visits or the study is terminated early and the database has been locked and unblinded.

8.11. Data Monitoring Committee

An external multidisciplinary Data Monitoring Committee (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 GSI 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 DMC will also review one futility and two efficacy interim analyses as described in Section 8.10. 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 intervals of approximately 3 months for the first 6 months after the first subject is enrolled, and approximately every 6 months afterwards.

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 GSI regarding future conduct of the study, including possible early study termination, GSI 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 within the agreed terms per the contract 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. Study Drug Accountability and Return

Used and unused IP supplies should be destroyed on site if the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by GSI. 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.

The study monitor will evaluate each study center's IP disposal procedures and provide appropriate instruction for destruction of unused IP supplies on site. The investigator must maintain accurate records for all IP destroyed at the site. 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.

If destruction of IP on site is not possible, the IP is to be returned to the shipping facility for eventual destruction. The monitor will provide further instructions for the return.

The study monitor will review IP supplies and associated records at study monitoring visits.

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 6.8). Should the primary objective of the trial not be met after primary analysis, Gilead will assess if further development of MMB in previously untreated metastatic pancreatic ductal adenocarcinoma is warranted and may determine to discontinue the trial. Subjects that remain on study may be considered for continued treatment with Gilead investigational product until disease progression, unacceptable toxicity, withdrawal of consent, or the Investigator or Sponsor deems treatment is no longer appropriate. Subjects will be reviewed for evidence of individual benefit by the investigator, and in consultation with the sponsor will ensure that the appropriate risk to benefit ratio is maintained for each subject. However, Gilead reserves the right, at its sole discretion, to determine whether to supply Gilead investigational product, and by what mechanism, after termination of the trial.

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Double-blind, Placebo-controlled 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 3, 16 July 2015

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

Peter Lee
Name (Printed)
Medical Monitor

PPD
Signature

2 July 2015
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 days)			Every 8 weeks	Every 12 weeks	Months 6, 12 & Annually Thereafter	EOT	30-day Safety Follow-up	3-year Long Term Survival Follow-up
Cycle Day	**Screening**	**C1D1**	**1**	**8**	**15**	**N/A**	**N/A**	**N/A**	**N/A**		
Window (day)	-21	-3*	±3	±3	±3	±7	±7	±28	±7	±7	±28
General and Safety Assessments											
Informed Consent	X										
Medical and Medication History	X										
Physical Examination	X	X[1]	X						X	X	
Vital Signs[2]	X	X	X	X	X				X	X	
Adverse events/Concomitant medications[3]	X	X	X	X	X				X	X	
Ophthalmic Assessments	X							X			
IXRS Registration	X	X	X						X		
IP Accountability and Dispensing		X	X						X		

* C1D1 must occur within 3 days following enrollment/randomization
1 Baseline physical examination may be waived if it is conducted within 96 hours of C1D1
2 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
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 days)			Every 8 weeks	Every 12 weeks	Months 6, 12 & Annually Thereafter	EOT	30-day Safety Follow-up	3-year Long Term Survival Follow-up
Cycle Day	**Screening**	**C1D1**	**1**	**8**	**15**	**N/A**	**N/A**	**N/A**	**N/A**		
Window (day)	-21	-3*	±3	±3	±3	±7	±7	±28	±7	±7	±28
Patient-Reported Outcomes											
FACT-Hep		X	X						X[4]	X	X[4]
EQ-5D		X	X						X	X	
Laboratory Assessment											
CBC with differential	X	X[5]	X[5]	X	X				X	X	
Chemistry	X	X	X	X	X				X	X	
Hepatitis B and C	X										
Thiamine status		X					X		X		
Urinalysis	X	X	X						X	X	
Pregnancy Test[6]	X	X	X						X		
MMB PK[7]			X		X						
MMB pharmacodynamics[8]					X						

4 FACT-Hep questionnaire will be conducted monthly via phone call monthly (± 7 days) after EOT visit, as well as for up to 1 year after entering long term survival follow-up
5 Iron panel (total iron and ferritin) will also be conducted on Day 1 of each cycle
6 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
7 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 on Day 1 of Cycles 2 and 3 at approximately 20-26 hours post-MMB dose (or at 10-14 hours post-MMB dose in twice-daily dosing cohort), and pre-MMB dose on Day 1 of Cycles 4, 5, and 6
8 Pharmacodynamics sampling to be performed at the following timepoints: Lead-in phase only – Pre-dose, 1, 2, 4, 6, 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)

Study Phase	Screening	Randomization/ Baseline	Each Cycle (28 days +/- 3 days)			Every 8 weeks	Every 12 weeks	Months 6, 12 & Annually Thereafter	EOT	30-day Safety Follow-up	3-year Long Term Survival Follow-up
Cycle Day	**Screening**	**C1D1**	**1**	**8**	**15**	**N/A**	**N/A**	**N/A**	**N/A**		
Window (day)	**-21**	**-3***	**±3**	**±3**	**±3**	**±7**	**±7**	**±28**	**±7**	**±7**	**±28**
Laboratory Assessment											
MMB Predictive Biomarkers-IL-6, sTNFRa2, erythropoietin		X	X[9]						X		
ctDNA (U.S. subjects only in the randomized phase)		X	X[10]						X		
hsCRP	X	X	X[11]								
Intensive PK (randomized phase; additional consent required)					X[12]						
Biopsy tissue sample (additional consent required)[13]						X					
Collect archival tumor tissue[14]		X									

9 Predictive biomarkers to be collected on Day 1 of Cycles 1, 2, and then Day 1 of every other subsequent cycle in lead-in and randomized treatment phases
10 ctDNA to be collected on Day 1 of Cycles 1-3 and then Day 1 of every other subsequent cycle for the U.S. subjects only in the randomized treatment phase
11 hsCRP to be collected on Day 1 of Cycles 1 and 2 in both lead-in and randomized treatment phases
12 Optional intensive PK sampling to be performed in subpopulation (additional consent required) on Day 15 of Cycle 1 at pre-MMB dose, at 1 hour post-MMB dose (prior to nab-P infusion), at End of Infusion (EOI) of nab-paclitaxel, and at 0.5, 1, 2, and 4 hours EOI of gemcitabine in the randomized treatment phase only.
13 Biopsy tissue sample to be collected in subset of subjects (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 subjects at disease progression in the randomized treatment phase only.
14 Archival tumor tissues block/slides 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 days)			Every 8 weeks	Every 12 weeks	Months 6, 12 & Annually Thereafter	EOT	30-day Safety Follow-up	3-year Long Term Survival Follow-up
Cycle Day	**Screening**	**C1D1**	**1**	**8**	**15**	**N/A**	**N/A**	**N/A**	**N/A**		
Window (day)	**-21**	**-3***	**±3**	**±3**	**±3**	**±7**	**±7**	**±28**	**±7**	**±7**	**±28**
Disease Assessments											
mGPS[15]	X										
ECOG Performance Status	X	X[16]	X						X	X	
Treatment Response Assessment[17]						X			X		
CT with contrast or MRI[18]	X					X			X		
Overall Survival and Other Antitumor Therapy											X (Every 3 months)

15 mGPS to be assessed at Screening in the randomized phase only
16 Baseline ECOG performance status may be waived if it is conducted within 96 hours of enrollment/randomization
17 As per RECIST v1.1
18 Tumor evaluation by CT or MRI with Gadolinium 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.

Nab-paclitaxel is suspected to cause serious birth defects when administered during pregnancy. Studies in animals have shown reproductive toxicity. In addition, studies of gemcitabine in animals have shown reproductive toxicity. Please refer to the regional prescribing information for more 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 non-menopausal woman who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes pubertal female 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.

A female subject may be considered menopausal in either of the following conditions:

- Surgical menopause: Appropriate medical documentation of prior complete bilateral oophorectomy (ie, surgical removal of the ovaries and occurring at the age at which the procedure was performed).

- Spontaneous menopause: Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified health care provider. The worldwide mean age of spontaneous menopause is 49.24 (SD 1.73) years.

A hormonal deficiency should be properly documented in the case of suspected spontaneous menopause as follows:

- If age $\geq$ 54 years and with the absence of normal menses: serum follicle stimulating hormone (FSH) level elevated to within the postmenopausal range based on the laboratory reference range where the hormonal assay is performed

- If age < 54 years and with the absence of normal menses: negative serum or urine human chorionic gonadotropin (hCG) with concurrently elevated serum FSH level in the postmenopausal range, depressed estradiol (E2) level in the postmenopausal range, and absent serum progesterone level, based on the laboratory reference ranges where the hormonal assays are performed.

3) Contraceptive Requirements

Male subjects of reproductive potential who engage in intercourse with females of childbearing potential must agree to utilize protocol specified methods of contraception from the Baseline/C1D1 visit throughout the study period and for 90 days from the last dose of MMB or 6 months from the last dose of nab-paclitaxel or gemcitabine (whichever is later).

Female subjects of childbearing potential who engage in intercourse must agree to utilize protocol specified methods of contraception from the Screening visit throughout the study period and for 30 days following the last dose of study drug.

Female subjects who are not heterosexually active must provide periodic confirmation of continued abstinence from heterosexual intercourse and regular pregnancy testing while taking MMB, nab-paclitaxel, and gemcitabine. 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. If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after microinsertion. Prior to verification, Essure is not considered a reliable form of contraception and the contraception methods described below must be used. Female subjects who utilize hormonal contraceptives as one of their birth control methods must have used the same method for at least 3 months before study dosing.

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

	Combination Methods	
Methods to Use by Themselves	**Hormone Methods** (choose one and use with a barrier method)	**Barrier Methods** (choose one and use with a hormone method)
Intrauterine Devices (IUDs) • Copper T 380A IUD • LNg 20 IUD **Tubal Sterilization**	**Estrogen and Progesterone** • Oral contraceptives • Transdermal patch • Vaginal ring **Progesterone** • Injection • Implant	• Diaphragm with spermicide OR • Cervical cap with spermicide • Male condom (with or without spermicide)
	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 MMB or for 6 months from the last dose of nab-paclitaxel or gemcitabine (whichever is later).

5) Procedures to be Followed in the Event of Pregnancy

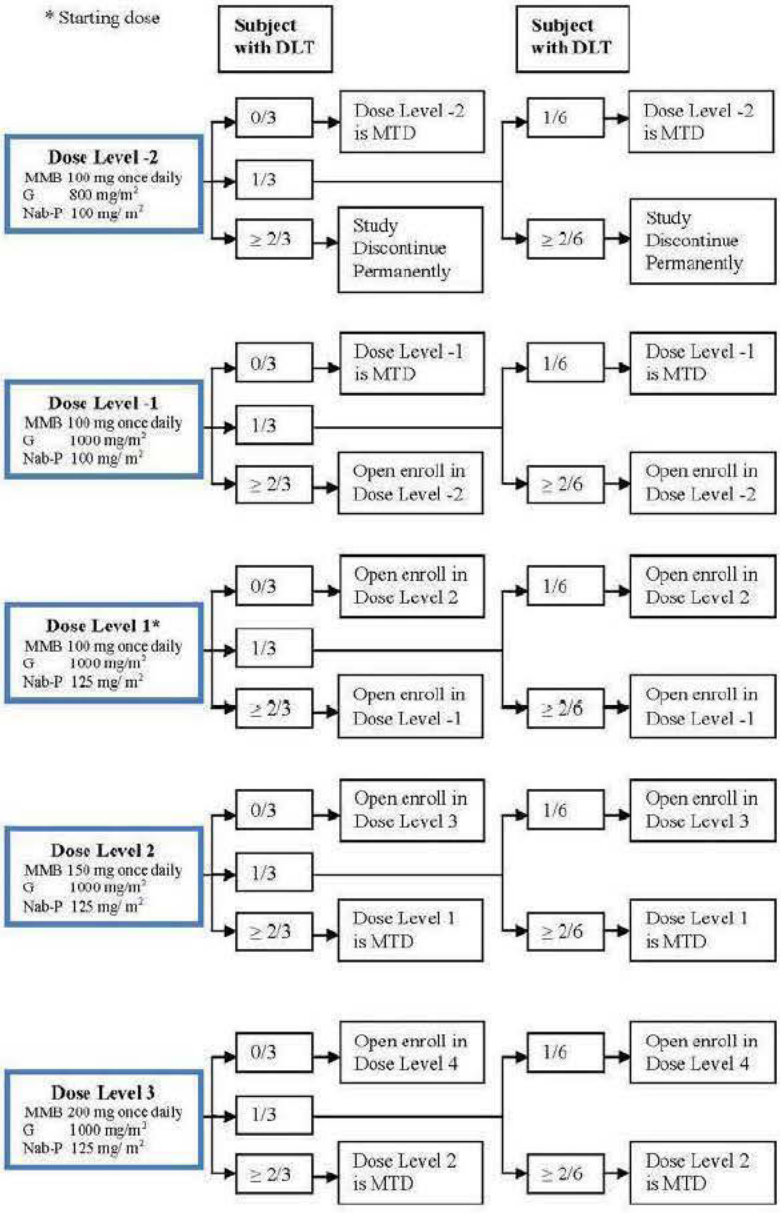
Subjects should be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. The investigator should report all pregnancies to the CRO Safety Department or GSI 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.

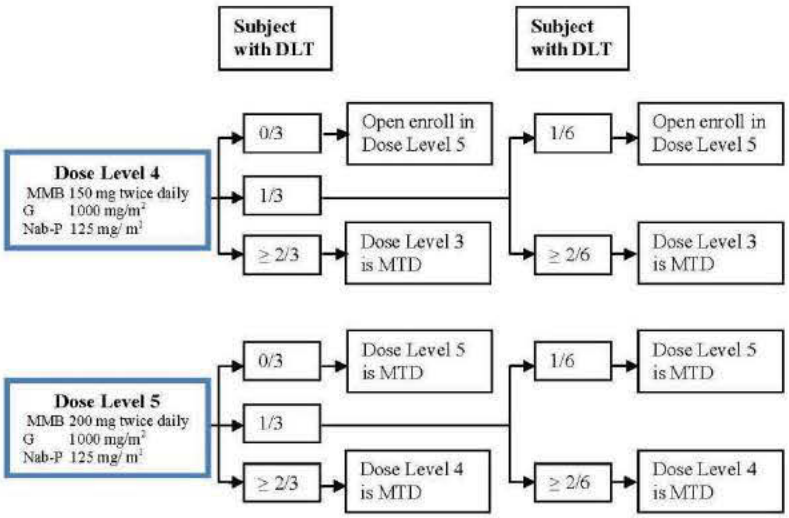
Appendix 4. ECOG Performance Status

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




Subject with DLT
Subject with DLT
Dose Level 4
MMB 150 mg twice daily
G 1000 mg/m²
Nab-P 125 mg/ m²
0/3
Open enroll in Dose Level 5
1/3
≥ 2/3
Dose Level 3 is MTD
1/6
Open enroll in Dose Level 5
≥ 2/6
Dose Level 3 is MTD
Dose Level 5
MMB 200 mg twice daily
G 1000 mg/m²
Nab-P 125 mg/ m²
0/3
Dose Level 5 is MTD
1/3
≥ 2/3
Dose Level 4 is MTD
1/6
Dose Level 5 is MTD
≥ 2/6
Dose Level 4 is MTD