Tyme, Inc.

CLINICAL STUDY PROTOCOL

Sponsor:	Tyme, Inc. 17 State St., 7th Floor New York, NY 10004
IND No.:	136891
Clinical Trials.gov Identifier:	NCT03512756
Indication:	Pancreas Cancer
Protocol ID:	Tyme-88-Panc
Tyme, Inc. Medical Monitor:	Name: [redacted] Phone: [redacted] Mobile: [redacted]
Clinical Research Organization (CRO) Medical Monitor:	Name: IQVIA Biotech: [redacted] Phone: [redacted] Mobile: [redacted]
Protocol Version/Date:	May 12, 2020 (Version 8)

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property or under control of Tyme, Inc., and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Tyme, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

PROTOCOL APPROVAL PAGE

Study Title:	A Randomized Phase 2/3 Multi-Center Study of SM-88 in Subjects with Pancreatic Cancer Whose Disease Has Progressed or Recurred
Protocol Number:	Tyme-88-Panc
Original Protocol Date of Issue:	February 15, 2018

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I, the undersigned, have read and approve this protocol and agree with its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practices, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.

Sponsor Signature: [redacted]

6/15/2020 | 16:57:26 PDT
(Date)

INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title: **A Randomized Phase 2/3 Multi-Center Study of SM-88 in Subjects with Pancreatic Cancer Whose Disease Has Progressed or Recurred**

Protocol Number: Tyme-88-Panc Version: May 12, 2020

By my signature, I

- Agree to comply with the conduct and terms of the study specified herein and with any other study procedures provided by the Sponsor, Tyme, Inc.
- Agree to comply with US Food and Drug Administration (FDA) regulations, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human subjects.
- Agree not to implement changes to the protocol without agreement from the Sponsor and prior written approval (where required) from the Institutional Review Board (IRB), except when necessary to eliminate an immediate hazard to the subjects.
- Agree to onsite monitoring of the case report forms (CRFs) and source documents by Tyme, Inc. or designee and to audit by Tyme, Inc. or designee and appropriate regulatory authorities, including, but not limited to, the FDA and IRB inspectors.
- Agree to supervise the conduct of the study and maintain responsibility for training and supervising all personnel who have been delegated responsibilities under my leadership. The protocol and other important study materials will be available to study staff throughout the conduct of the study.

_____ _____

Investigator's Signature Date

_____

Print Name

Table 1: Content Updates (Version 7 to 8)

Section	Page	Content Update
Synopsis	10-24	No. of Centers: Changed to 10 to 15
		Objectives: Part 1: Safety objectives included Part 2: Primary, safety, secondary safety, and additional secondary objectives included; PK/Safety objectives included
		Duration of Treatment: Language added on patients with a compromised immune system
		Study Procedures/Frequency: Clarification on sampling schemes and addition of 12-lead ECG collections in triplicate language, ECGs (single) and PK sampling.
		Screening period: Added language on compliance with all Study related activities; clarification language on consenting patients
		Inclusion Criteria: Updated information for Part 2 Added a sentence "A line of therapy is defined as either having prognosed on a line of treatment regimen or having received at least 2 months of a treatment regimen." Modified sentence: Of the two prior lines, subjects must have been exposed to a gemcitabine-based regimen for a prior line and a 5-FU-based regimen as a prior line of therapy. Investigational therapies as part of a prior line regimen are permitted. 1. Changed carcinoma to adenocarcinoma 3. Changed to Radiographically measurable disease of at least one site by CT scan (or magnetic resonance imaging, MRI, or PET/CT if allergic to CT contrast media). Imaging for baseline results must be obtained at most 14 days prior to Randomization. Changed first dose to randomization throughout. 8. Clarified language to at most 7 days prior to randomization 8b(i). Added prior to the screening laboratory assessment 8b(iii). Added or 24 hour urine-determined creatinine clearance ≥60 mL/min 8 (b)(iv). Deleted within 28 days of starting study
		Exclusion Criteria: Updated information for Part 2 Changed baseline to randomization throughout

Section	Page	Content Update
		1. 6. Changed Radiation to all measurable ~~target~~ lesions within 12 weeks of study baseline. 2. 7. Changed to No measurable lesions. 3. 8. Changed to "Current use, or any use within 14 days prior to Randomization, of a restricted medication (see Section 8.7), or subject requires any of these medications during treatment phase." 13/14. Added Note: testing is not required in the absence of clinical symptoms 15. Deleted component of regimen 4. 17. Subjects with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins; or a history of prior acute hepatotoxicity attributable to phenytoin. Moved: 5. 25. Subjects exhibiting idiosyncratic reactions to psoralen compounds. 6. 26. Subjects with a hypersensitivity to sirolimus. 7. 27. Changed to "Currently enrolled in, or have discontinued within 30 days of Randomization, from a clinical trial involving an investigational product or non-approved use of a drug or device." Modified: 22. Changed to "The second weight measure should be captured prior to randomization." 8. 23. Subjects who have a variety of factors influencing their ability to ingest and absorb oral drugs (such as unable to swallow, nausea, vomiting, chronic diarrhea and intestinal obstruction, etc.). 9. 24. Subjects with central nervous system metastasis, with the exception of subjects who have stable brain metastases as defined as off steroids and no CNS progression for 6 months after CNS treatment. 10. 34. Screening prolongation of QT/QTc interval [e.g., > 480 milliseconds (ms)] (CTCAE Grade 1) using Fredericia's QT correction formula.

Section	Page	Content Update
		11. 37. Presence of symptomatic or clinically significant ascites or pleural effusion, defined as requiring clinical intervention in the 30 days prior to consent. However, trace or small amount of physiologic fluid will not be excluded.
		Efficacy: Updated Secondary Endpoints: [redacted] Clarified language on efficacy and capecitabine; added language on investigative site
		PK: Updated language on the timing of meals; added language on ECGs
		Sample Size Justification: Overall survival (OS added)
Section 5.3 Additional Secondary Objectives of SM-88 vs the Control Arm	39	**Language update:** [redacted]
Section 6.2 Screening	40	Updated text and added a table to clarify screening Added language on Day 7 between randomization and start of first dose
Table 3	41	Added table
Section 6.3.1. Efficacy Assessment	44	• **Efficacy**: Updated Secondary Endpoints: [redacted] Clarified language on efficacy and capecitabine; added language on investigative site
Table 5	47	Table of events updated to include: • PK assessments in Day 1 cycle 1 and 2 (Part 2) • ECG language added Cycle 3 and 4 (Part 2) • ECG (triplicate) deleted • Food and drug diary added • Schedule of CTC collection and exploratory BM Footnotes c, g, h, j, k and o updated
Table 6	50	Table of events updated to include:

Section	Page	Content Update
		• Collection of exploratory biomarker added • CT scans added Footnotes f, h, m updated
Table 7	53	Table of events updated to include: • Collection of exploratory biomarker added • CT scans added [redacted] Footnotes f, h, m updated
Table 8	55	Sample collection updated: • CTC updated • CA19.9 updated [redacted] Footnotes f, h, m updated
Section 7.1 Inclusion Criteria	59	**Inclusion Criteria**: Updated information for Part 2 Added a sentence "A line of therapy is defined as either having prognosed on a line of treatment regimen or having received at least 2 months of a treatment regimen." Modified sentence: Of the two prior lines, subjects must have been exposed to a gemcitabine-based regimen for a prior line and a 5-FU-based regimen as a prior line of therapy. Investigational therapies as part of a prior line regimen are permitted. 1. Changed carcinoma to adenocarcinoma 3. Changed to Radiographically measurable disease of at least one site by CT scan (or magnetic resonance imaging, MRI, or PET/CT if allergic to CT contrast media). Imaging for baseline results must be obtained at most 14 days prior to Randomization. Changed first dose to randomization throughout. 8. Clarified language to at most 7 days prior to randomization 8b(i). Added prior to the screening laboratory assessment 8(b)(iii). Added or 24 hour urine-determinied creatinine clearance ≥60 mL/min

Section	Page	Content Update
		8 (b)(iv). Deleted within 28 days of starting study
Section 7.2 Exclusion Criteria	61	**Exclusion Criteria:** Updated information for Part 2 Changed baseline to randomization throughout 12. 6. Changed Radiation to all measurable ~~target~~ lesions within 12 weeks of study baseline. 13. 7. Changed to No measurable lesions. 14. 8 Changed to "Current use, or any use within 14 days prior to Randomization, of a restricted medication (see Section 8.7), or subject requires any of these medications during treatment phase." 13/14: Added Note: testing is not required in the absence of clinical symptoms 15. Deleted component of regimen 15. 17. Subjects with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins; or a history of prior acute hepatotoxicity attributable to phenytoin. Moved: 16. Subjects exhibiting idiosyncratic reactions to psoralen compounds. 17. Subjects with a hypersensitivity to sirolimus. 18. Changed to "Currently enrolled in, or have discontinued within 30 days of Randomization, from a clinical trial involving an investigational product or non-approved use of a drug or device." Modified: 22. Changed to "The second weight measure should be captured prior to randomization." 19. 23. Subjects who have a variety of factors influencing their ability to ingest and absorb oral drugs (such as unable to swallow, nausea, vomiting, chronic diarrhea and intestinal obstruction, etc.). 20. 24.Subjects with central nervous system metastasis, with the exception of subjects who have stable brain metastases as defined as off steroids and no CNS progression for 6 months after CNS treatment.

Section	Page	Content Update
		21. 34. Screening prolongation of QT/QTc interval [e.g., > 480 milliseconds (ms)] (CTCAE Grade 1) using Fredericia's QT correction formula. 37. Presence of symptomatic or clinically significant ascites or pleural effusion, defined as requiring clinical intervention in the 30 days prior to consent. However, trace or small amount of physiologic fluid will not be excluded.
Section 8.7 Randomization and Blinding	76	22. Randomized language changed to balance
Section 9 Assessment of Efficacy	78	Sections 9.1 and 9.2 updated Section 9.4 updated. Added PET/CT and clarified PK
Section 10 Pharmacokinetic Assessment	81	Part 1 updated, and Part 2 added along with discussion of sampling schemes
Section 11.1.4 Electrocardiogram	83	Language added to include ECGs will be performed at Screening, Day 1 of each cycle, pre-dose, and at approximately 2 hours post-dose and at subjects' Day 28 follow-up visit
Section 11.2.2 Relationship to Investigational Product or Study Procedures	87	Added language on non-related
Section 12 Statistics	90	Section 12.1 updated for Part 2. Section 12.2.1 added Evaluable 4-Cycle Population and updated Per-Protocol Population. Section 12.3.2 Part 2 primary objectives updated. Added sub-sections (Page 92): Key Secondary Objective, Additional Secondary Objectives, Exploratory Objectives. Section 12.3.3 Interim Analysis added.
Misc	--	Global: Minor changes for formatting and consistency

1. SYNOPSIS

Study Title	A Randomized Phase 2/3 Multi-Center Study of SM-88 in Subjects with Pancreatic Cancer Whose Disease Has Progressed or Recurred
Study Centers Planned	**Part 1 (completed):** Approximately 36 study centers in N. America will participate in this study. **Part 2:** Approximately 10 to 15 study centers in N. America will participate in this study.
Objectives	**Part 1:** Primary Objectives: [redacted] Secondary Objectives: [redacted]

Safety Objectives:

[redacted]

Part 2:

Primary Objective

To determine the OS of subjects treated with SM-88 used with methoxsalen, phenytoin, and sirolimus (MPS) versus the control arm (Physician's Choice).

Key Secondary Objective

- To report Investigator-determined PFS.

Additional Secondary Objectives

[redacted]

Exploratory Objectives

[redacted]

PK/Safety Objectives

[redacted]

Study Design	This is a two part, open-label, prospective, randomized, multi-center, Phase 2/3 trial in subjects with pancreatic cancer composed of the following parts: • **Part 1**: A total of 36 evaluable subjects will be randomized 1:1 between two doses of SM-88 460 mg/day (230 mg b.i.d) or 920 mg/day (460 mg b.i.d). The doses of the three conditioning agents - methoxsalen, phenytoin and sirolimus - will each maintain a consistent dose. • **Part 2**: The second part will consist of a subsequent expansion of the trial to further assess safety and efficacy of SM-88 containing the selected SM-88 RP2D from Part 1. A total of 250 subjects in the second part will be randomized 1:1 either to the SM-88 arm or Physician's Choice of therapy for the control arm.
Number of Subjects Planned	**Part 1:** • There are 36 evaluable subjects planned for enrollment in the first part. **Part 2:** • The second part of this clinical trial will expand the use of the selected SM-88 dose from the first part for up to an additional 125 subjects in addition to a Physician's Choice control arm with 125 subjects, for a maximum total trial size of 250 subjects. • For subjects who discontinue before they complete all planned study assessments, additional replacement subjects may be enrolled.
Target Population	Subjects will be ≥18 years of age with adequate organ function who have metastatic measurable pancreatic cancer. **Part 1:** • Subjects are eligible if they have histologically or cytologically confirmed adenocarcinoma of the pancreas with an ECOG score ≤ 2 and with documented progression or recurrence and have failed at least one line of prior systemic therapy. (This will be second line or beyond treatment for these subjects). **Part 2:** • Subjects are eligible if they have histologically or cytologically confirmed adenocarcinoma of the pancreas with an ECOG score ≤ 2 and have previously received two lines of prior systemic therapy. (This will be third line treatment for these subjects).
Duration of Treatment	For all subjects, treatment will continue until apparent PD (as defined in the protocol), unacceptable toxicity, or death. All subjects will be followed for OS until the end of this study, and possibly beyond their participation in the trial as approved by governing IRB.

	It is hypothesized that subjects may show clinical benefit prior to demonstrating traditional RECIST-based responses. Some subjects, particularly those with active immune systems, may even have tumor site inflammation that is visible on computed tomography (CT) imaging (i.e., pseudo-progression) at the first follow-up scan. Subjects with radiographic evidence of PD (per RECIST 1.1 in Part 1; per the Investigator in Part 2), but without clinical deterioration, may be considered for repeat confirmation scans before clinically significant PD is defined and study therapy is withdrawn. This decision should be balanced against the potential toxicity associated with continued treatment and alternative treatment options and must be discussed with and approved by the Medical Monitor. Continuation should be evaluated at least every 4 weeks after initial response assessment or sooner if clinical deterioration occurs. For all subjects randomized to the Physician's Choice control arm in Part 2, subjects will continue on study (with appropriate dose delay and/or modification if necessary) until disease progression, intolerable side effects or subject chooses to withdraw. **Treatment interruptions:** Any subject who experiences a DLT will have treatment discontinued until the toxicity is resolved to ≤ Grade 1 or returns to baseline level within 28 days, unless the toxicity requires permanent discontinuation as described by the protocol. **SM-88 used with MPS (Part 2 Only):** If SM-88 is considered to be associated with a DLT, the dose of SM-88 will be reduced by one capsule at each dose period to a total daily dose of 460 mg. If a subject has a second episode of any related or possibly drug-related DLT, SM-88 may be discontinued for up to 28 days while mitigating measures are attempted. If the DLT continues after restarting therapy, the subject will be removed from the study. If any of the methoxsalen, phenytoin, or sirolimus (MPS) is considered to be the component associated with a DLT, the individual component(s) may be discontinued for up to 28 days while mitigating measures are attempted (e.g., changing the timing of phenytoin to address phenytoin-related fatigue). This may be applied to any or all of the MPS components. If the DLT continues after restarting therapy, the subject will be removed from the study. **Control Arm (Part 2 Only):** In the case of Adverse Events or DLT in the control arm, refer to the prescribing information for dose modification or discontinuation.

Study Procedures/ Frequency	**<u>Screening Period</u>:** During the Screening Period, subjects will be evaluated for their eligibility to participate in the study and ability to comply with all study specified activities. Subjects must be consented within 8 weeks after their last dose of chemotherapy (last dose is the day of the last drug administration). Study agents must be administered within 12 weeks of the last dose of chemotherapy. All previous cancer treatment should be discontinued prior to starting study medications.
	[redacted]

Treatment Period:
Subjects will visit the clinic on Day 1 of each treatment cycle.

Treatment Cycles:

Part 1 and Part 2 SM-88 Arm:
Treatment cycles will begin on Day 1 and will be comprised of daily dosing with SM-88 used with MPS for 4 weeks with no break between treatment cycles for as long as there is no evidence of progression or safety concerns.

Control (Physician's Choice) Arm:

Capecitabine treatment cycles will begin on Day 1 and will be comprised of 1000 mg/m^2 orally twice a day, Days 1-14 on a 21-day cycle for as long as there is no evidence of progression.

Gemcitabine treatment cycles will begin on Day 1 and will be comprised of 1000 mg/m^2 IV on Days 1, 8, and 15 on a 28-day cycle for as long as there is no evidence of progression.

5-FU treatment cycles will begin on Day 1 and will be comprised of 2400 mg/m^2 continuous IV infusion over 46 hours on Days 1 and 15 on a 28-day cycle for as long as there is no evidence of progression.

Safety Assessments: [redacted]

Efficacy Assessments: [redacted]

	[redacted] **SM-88 used with MPS:** [redacted] Subjects in both parts of this study should be strongly encouraged to be on a low-carb diet. Inability to maintain a low-carb diet would not exclude subjects from participation in the trial. **Control (Physician's Choice) Arm:** Physician's Choice therapy will be administered for a total of 125 evaluable subjects until unacceptable toxicity, disease progression, or any of the treatment discontinuation criteria are met. **Post-Study Follow-up Period:** Twenty-eight (28) days after the last SM-88 dose or Physician's Choice therapy dose, subjects will be evaluated for safety at a follow-up study visit. Subjects will continue to be followed at 3-month intervals via review of the medical records, public social media, phone or in person for survival data.
Test Product, Dose, and Mode of Administration: SM-88 Treatment Arm	**Part 1:** • Subjects will be randomized to receive either 460 or 920 mg total daily dose of SM-88 used with MPS. • The low dose, SM-88(1) arm will receive: o SM-88 – one 230 mg capsule taken orally twice daily (460 mg total). o Methoxsalen – one 10 mg capsule taken orally once daily. o Phenytoin – one 50 mg tablet taken orally once daily. o Sirolimus – one 0.5 mg tablet taken orally once daily. • The high dose, SM-88(2) arm will receive: o SM-88 – two 230 mg capsules taken orally twice daily (920 mg daily). o Methoxsalen – one 10 mg capsule taken orally once daily.

	○ Phenytoin – one 50 mg tablet taken orally once daily. ○ Sirolimus – one 0.5 mg tablet taken orally once daily. **Part 2:** • Subjects will be randomized to either SM-88 used with MPS or Physician's Choice. • All subjects enrolled into Part 2 of the trial who are randomized to SM-88 used with MPS will receive: ○ SM-88 – two 230 mg capsules taken orally twice daily (total 920 mg daily). ○ Methoxsalen – one 10 mg capsule taken orally once daily. ○ Phenytoin – one 50 mg tablet taken orally once daily. ○ Sirolimus – one 0.5 mg tablet taken orally once daily. The four components of SM-88 used with MPS (SM-88, methoxsalen, phenytoin, and sirolimus) will be taken daily. It is best to take doses one hour before or two hours after meals, so as to ensure an empty stomach. They should be taken together consistently either in the morning or in the evening with a full glass of water – for example, before bedtime and upon waking up in the morning. A second dose of SM-88 will be taken 12 hours (+/- 4 hours) after the morning dose. Missed doses of any of the 4 agents will be omitted and skipped. Subjects who miss a dose of any of the 4 agents, for any reason, will omit that dose and take the next dose at the next regularly scheduled time point 12 hours (+/- 4 hours) after the missed dose was due. If the morning (AM) dose is missed, subjects will continue with the PM dose as scheduled and may take the adjunct medications (methoxsalen, phenytoin, and sirolimus) with their PM dose. If the PM dose is missed, subjects will skip that dose and resume dosing with the AM dose the following day.
Reference Therapy, Dose, and Mode of Administration	**Part 2 Only:** Investigator choice of the following therapies in the Control Arm: • **Capecitabine** (1000 mg/m^2 orally twice a day, Days 1-14 on a 21-day cycle) • **Gemcitabine** (1000 mg/m^2 IV on Days 1, 8, and 15 on a 28-day cycle) • **5-FU** (2400 mg/m^2 continuous IV infusion over 46 hours on Day 1 and 15 on a 28-day cycle)

Inclusion Criteria	Inclusion criteria include the following: **Part 1:** Biopsy-proven metastatic pancreatic adenocarcinoma with documented radiographic disease progression on or after one or more systemic therapies, including a gemcitabine-based chemotherapy regimen or any first line regimen as listed in *PANC G* National Comprehensive Cancer Network (NCCN) current guidelines. Chemotherapy given as part of prior chemo-radiation in the setting of non-metastatic pancreatic cancer does not count as a line of therapy. Chemotherapy given for at least 4 months as adjuvant after CR is considered as a first line therapy. **Part 2:** Biopsy-proven metastatic pancreatic adenocarcinoma on or after two prior lines of systemic therapy. A line of therapy is defined as either: having progressed on a treatment regimen, or having received at least 2 months of a treatment regimen. Chemotherapy given as part of prior chemo-radiation in the setting of non-metastatic pancreatic cancer does not count as a line of therapy unless metastases develop within 6 months of completing the chemo-sensitization. Chemotherapy given for at least 4 months as adjuvant after a CR to any therapy (e.g., surgery or radiation therapy) is also considered a first line therapy. Of the two prior lines, subjects must have been exposed to a gemcitabine-based regimen for a prior line and a 5-FU-based regimen as a prior line of therapy. Investigational therapies as part of a prior line regimen are permitted. 1. Subjects have received two (2) and not more than two (2) previous systemic regimens for the treatment of pancreatic adenocarcinoma. 2. Subjects must be eligible to receive one or more of the Physician's Choice options. 3. Radiographically measurable disease of at least one site by CT scan (or MRI or PET/CT, if allergic to CT contrast media). Imaging for baseline results must be obtained at most 14 days prior to Randomization. 4. Subjects must have completed any investigational cancer therapy at least 30 days prior to Randomization. 5. Subjects must have completed any other cancer therapy at least 14 days prior to Randomization, and recovered from major side effects of prior therapies or procedures. 6. ≥18 years of age. 7. ECOG PS ≤2. 8. Adequate organ function, defined as follows (lab results must be obtained at most 7 days prior to Randomization): a. All laboratory parameters ≤ Grade 2 NCI Common Terminology Criteria for Adverse Events (CTCAE) criteria. b. In addition:

	i. Hematologic: Platelets ≥ 100 x 10^9 g/dL; Absolute Neutrophil Count ≥ 1.5 x 10^9/L (without platelet transfusion or growth factors within the 7 days prior to the screening laboratory assessment). ii. Hepatic: aspartate transaminase/alanine transaminase ≤ 2.5 x upper limit of normal (ULN); total or conjugated bilirubin ≤ 1.5 x ULN, alkaline phosphatase (ALP) < 2.5 x ULN. iii. Renal: serum creatinine ≤ 1.5 x ULN and creatinine clearance ≥ 60 mL/min as calculated by the Cockroft-Gault method, or 24 hour urine-determined creatinine clearance ≥60 mL/min. iv. Coagulation: international normalized ratio (INR) ≤ 1.2. v. Albumin: ≥ 3.0 g/dL. 9. All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before Randomization, with the exception of alopecia and neurotoxicity (CTCAE Grade 1 or 2 permitted). 10. Able and willing to provide written informed consent to participate in this study. 11. Subject is willing and able to comply with the protocol for the duration of the study, including undergoing treatment and scheduled visits and examinations including follow-up. 12. Subjects must be able to swallow whole capsules. 13. Female subjects must either be of non-reproductive potential, not breast-feeding or must have a negative urine or serum pregnancy test within 28 days of Randomization, confirmed prior to treatment on Cycle 1 Day 1. 14. Subjects of fertile potential who engage in heterosexual intercourse with partners of childbearing potential must attest to the use of highly effective contraception while enrolled in the study and for at least 6 months following the last dose of study drug. Highly effective birth control methods include the following (the subject should choose 2 to be used with their partner): a. Oral, injectable, or implanted hormonal contraceptives. b. Condom with a spermicidal foam, gel, film, cream, or suppository. c. Occlusive cap (diaphragm or cervical/vault cap) with a spermicidal foam, gel, film, cream, or suppository. Or any one of the following: a. Intrauterine device. b. Intrauterine system (for example, progestin-releasing coil). c. Vasectomized male (as determined by the Investigator). d. Tubal ligation/sterilization (female).

Exclusion Criteria	Exclusion criteria are as follows: 1. Any screening laboratory, ECG, or other findings that, in the opinion of the Investigator, Medical Monitor or the Sponsor, indicate an unacceptable risk for the subject's participation in the study. 2. History or evidence of any clinically significant disorder, condition, or disease that, in the opinion of the Investigator or Medical Monitor, would pose a risk to the subject's safety or interfere with the study evaluations, procedures, or completion. Examples include: intercurrent illness such as active uncontrolled infection, active or chronic bleeding event within 28 days of Randomization, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements. 3. History of a concurrent or second malignancy, except for: adequately treated localized basal cell or squamous cell carcinoma of the skin, adequately treated superficial bladder cancer, adequately treated Stage 1 or 2 cancer currently in complete remission; or any other cancer that has been in complete remission for ≥ 5 years. 4. Subjects with MSI-H pancreatic cancer who have not previously received pembrolizumab. 5. Subjects with any known actionable mutation (e.g., BRCA mutation) who have not been treated with an approved drug for the mutation (the drug does not have to be approved for the indication). 6. Radiation to all measurable lesions within 12 weeks of study baseline. 7. No measurable lesions. 8. Current use, or any use within 14 days prior to Randomization, of a restricted medication (see Section 8.7), or subject requires any of these medications during treatment phase. 9. Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (i.e., larger than that required for placement of central venous access, percutaneous feeding tube, or biopsy) within 28 days of the first dose of study drug. 10. Minor surgical procedures within 7 days of Randomization, or not yet recovered from any prior surgery. 11. Any dysphagia, odynophagia, esophageal dysmotility or stricture, known gastrointestinal (GI) malabsorption syndrome, or intractable diarrhea that may significantly alter the absorption of any of the components of SM-88 used with MPS, e.g., cirrhosis. 12. Known human immunodeficiency (HIV) virus infection. Note: HIV testing is not required in the absence of clinical suspicion. 13. Known hepatitis B surface antigen (HBsAg) positive. Note: testing is not required in the absence of clinical suspicion. 14. Known hepatitis C (HCV) viral RNA present. Note: testing is not required in the absence of clinical suspicion.

	15. Have previously been enrolled in this study or any other study investigating SM-88 or have previously received any SM-88, methoxsalen, phenytoin, or sirolimus in a clinical trial. 16. History of any known drug allergies to any study medication. 17. Subjects with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins; or a history of prior acute hepatotoxicity attributable to phenytoin. 18. Subjects exhibiting idiosyncratic reactions to psoralen compounds. 19. Subjects with a hypersensitivity to sirolimus. 20. Currently enrolled in, or have discontinued within 30 days of Randomization, from a clinical trial involving an investigational product or non-approved use of a drug or device. 21. Subjects must not have any clinically significant and uncontrolled major medical condition(s) including, but not limited to: uncontrolled nausea/vomiting/diarrhea; active uncontrolled infection; symptomatic congestive heart failure (New York Heart Association [NYHA] class ≥ II); unstable angina pectoris or cardiac arrhythmia; psychiatric illness/social situation that would limit compliance with study requirements. 22. >5% weight loss at any time during the 28 days prior to consent, or >5% change in weight from consent (Screening) to Randomization (must be at least 1 week apart). This second weight measure should be captured prior to Randomization. 23. Subjects who have a variety of factors influencing their ability to ingest and absorb oral drugs (such as unable to swallow, nausea, vomiting, chronic diarrhea and intestinal obstruction, etc.). 24. Subjects with central nervous system metastasis, with the exception of subjects who have stable brain metastases as defined as off steroids and no CNS progression for 6 months after CNS treatment. 25. Pregnant or lactating women. 26. Substance abuse that cannot be ended, or subjects with mental disorders that will prevent compliance or evaluation including uncontrolled schizophrenia, uncontrolled depression or other uncontrolled disorders. 27. Subjects with a history of the light sensitive diseases for which methoxsalen would be contraindicated. Diseases associated with photosensitivity include: lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum, and albinism. 28. Subjects treated, or anticipated to be treated, with delavirdine (due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors caused by phenytoin). 29. Subjects with cutaneous melanoma or invasive squamous cell carcinomas or a history thereof, except for those in complete

	remission for ≥5 years (due to contraindication for use of methoxsalen). 30. Subjects with prior organ transplant or being treated, or anticipated to be treated, with cyclosporine (because long-term administration of the combination of cyclosporine and sirolimus is associated with deterioration of renal function). 31. Subjects with a seizure disorder that is not well controlled or who have required a change in seizure medications within 60 days of Randomization. 32. Subjects treated, or anticipated to be treated, with a calcineurin inhibitor (because concomitant use of sirolimus and a calcineurin inhibitor increases the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy [HUS/TTP/TMA]). 33. Subjects with interstitial lung disease (ILD) [including pneumonitis, bronchiolitis obliterans organizing pneumonia (BOOP), and pulmonary fibrosis]. 34. Screening prolongation of QT/QTc interval [e.g., > 480 milliseconds (ms)] (CTCAE Grade 1) using Fredericia's QT correction formula. 35. A family history of Long QT Syndrome or Torsades de Pointes. 36. Clinically significant cataracts or aphakia. 37. Presence of symptomatic or clinically significant ascites or pleural effusion, defined as requiring clinical intervention in the 30 days prior to consent. However, trace or small amount of physiologic fluid will not be excluded.
Criteria for Evaluation: Safety	Safety will be evaluated by recording adverse events (AEs), clinical laboratory results, physical examinations, vital signs, and ECGs.
Efficacy	**Part 1:** [redacted] **Part 2:** Efficacy of SM-88 used with MPS will be measured by OS; Investigator-determined PFS; [redacted]

	[redacted]
PK	**Part 1:** [redacted] **Part 2:** [redacted]
Statistical Methods: Sample Size Justification	**Part 1:** The trial will accrue 36 evaluable subjects during Part 1, in order to have sufficient subjects to determine which of the two doses will move forward into the expansion cohort of Part 2. The primary objective for Part 1 of this trial is to determine the ORR (between the included doses) based on the independent blinded third party review of radiologic imaging (i.e., diagnostic, contrast enhanced, CT) using RECIST 1.1 criteria as the endpoint. **Part 2:** Part 2 of the trial was amended to become a Phase 2/3, two-arm study with SM-88 used with MPS versus a Physician's Choice control. Part 2 of the trial will accrue 250 subjects, with 125 in each arm. The primary endpoint is the time from Randomization to death from any cause (Overall Survival; OS). It is estimated that the control group will have a median survival time of 3 months, based on reports in the literature. The statistical plan developed assumes a hazard ratio of 0.667, which assumes a 3-month median OS for the control arm and hence a 4.5-month median OS for the SM-88 arm. In order to have 80% power, using a two-sided log-rank test with a significance level 0.025, 125 subjects in each arm will be enrolled. An interim efficacy analysis is planned when 75% of events are reached. This could result in early stopping of the trial for efficacy. To account for dropouts of subjects who withdraw for reasons other than any of the outcomes (death, PD or toxicity), additional subjects may be enrolled to ensure an adequate number of subjects who have received at least one dose of the study treatment (the primary study per protocol

Safety	cohort). The total number of subjects consented will depend on the number of subjects receiving study treatment. All relevant safety data will be listed, summarized and reviewed after each subject completes each treatment cycle or after a subject has discontinued from the study.
Efficacy	• The efficacy of SM-88 used with MPS will be established using the primary endpoint of OS, compared by the log-rank test, stratified by randomization stratification factors (investigative site factors, Physician's Choice and ECOG (0-1 vs. 2). A Kaplan-Meier plot, and quartile estimates with 2-sided 95% confidence intervals (CIs) will also be presented. • Disease progression will be assessed according to study-specified end points. The response rate will be estimated with 95% exact 2-sided CIs. PFS will be summarized by using a log-rank test, Kaplan-Meier plot, and quartile estimates with 2-sided 95% CIs.
PK	PK data will be summarized by treatment using descriptive statistics.

This study will be conducted in accordance with the guidelines of Good Clinical Practices including archiving of essential documents.

TABLE OF CONTENTS

CLINICAL STUDY PROTOCOL 1
PROTOCOL APPROVAL PAGE 1
INVESTIGATOR PROTOCOL AGREEMENT 3
1. SYNOPSIS 10
LIST OF TABLES 29
2. LIST OF ABBREVIATIONS 30
3. INTRODUCTION 33
3.1. SM-88 Background 33
3.2. Safety of SM-88 Used with MPS 35
3.3. SM-88 Supportive Clinical Data 36
3.4. Effect of Food on SM-88 37
4. OBJECTIVES - *PART 1* 38
4.1. Primary Objective 38
4.2. Secondary Objectives 38
4.3. Safety Objectives 38
5. OBJECTIVES - *PART 2* 39
5.1. Primary Objective 39
5.2. Key Secondary Objective 39
5.3. Additional Secondary Objectives 39
5.4. Exploratory Objectives 39
5.5. PK/Safety Objectives 39
6. SUBJECT INVESTIGATIONAL PLAN 40
6.1. Overall Study Design 40
6.2. Screening Period (Part 1 and Part 2) 40
6.3. Efficacy Assessments 44
6.4. Safety Assessments 45
[redacted]
6.4.2. Post-Study Follow-up Period 46
7. SELECTION AND WITHDRAWAL OF SUBJECTS 62
7.1. Inclusion Criteria 62

7.2. Exclusion Criteria 65
7.3. Criteria for Subject Withdrawal....67
7.4. Criteria for Study Site Discontinuation 68
7.5. Criteria for Study Discontinuation....68
8. TREATMENT 69
8.1. Treatments Administered....69
8.2. SM-88 used with MPS....69
8.2.1. Control Arm (Physician's Choice) 70
8.3. Adverse Events 70
8.3.1. SM-88 used with MPS....70
8.3.2. Control Arm (Physician's Choice) 74
8.4. Dose Interruption / Discontinuation of SM-88 used with MPS 74
8.4.1. Permanent discontinuation of SM-88 used with MPS....75
8.4.2. Dose interruption of SM-88 and MPS from drug-related, or possibly related DLTs 75
8.4.3. Risk Mitigation/Discontinuation of MPS components of SM-88 used with MPS 77
8.5. Dose Interruption / Discontinuation of Control Arm (Physician's Choice) Therapy 78
8.6. Description and Handling of Product 78
8.6.1. SM-88 used with MPS....78
8.6.2. Part 2: Control Arm (Physician's Choice)....79
8.7. Randomization and Blinding 80
8.8. Concomitant Medications....80
8.9. Treatment Compliance....81
9. ASSESSMENT OF EFFICACY 82
9.1. Overall Survival (OS)....82
9.2. Progression-Free Survival (PFS) 82
[redacted]
10. PHARMACOKINETIC ASSESSMENT 85

11. ASSESSMENT OF SAFETY 87
11.1. Safety Parameters 87
11.1.1. Demographics and History 87
11.1.2. Vital Signs 87
11.1.3. Physical Examination 87
11.1.4. Electrocardiogram 87
11.1.5. Safety Laboratory Assessments 87
11.1.6. Ophthalmologic Exam (only required for those subjects enrolled in Part 1) 88
11.2. Adverse Events (AE) 90
11.2.1. Definition of Adverse Events 90
11.2.2. Relationship to Investigational Product or Study Procedures 91
11.2.3. Assessment of Severity 92
11.2.4. Reporting Adverse Events 92
12. STATISTICS 94
12.1. Hypotheses 94
12.2. Analysis Considerations 96
12.2.1. Analysis Populations 96
12.2.2. Exploratory Combined Population 97
12.2.3. Initial Analysis 97
12.3. Final Analysis 98
12.3.1. Safety Analysis 98
12.3.2. Efficacy Analyses 98
12.3.3. Interim Analysis 101
12.3.4. Pharmacokinetic Analyses 102
13. RESPONSIBILITIES 103
13.1. Investigator Responsibilities 103
13.1.1. Good Clinical Practice 103
13.1.2. Institutional Review Board Approval 103
13.1.3. Informed Consent 104
13.1.4. Treatment Withdrawal 104
13.1.5. Withdrawal of Consent 104
13.1.6. Confidentiality 105

13.1.7. Study Files and Retention of Records 105
13.1.8. Case Report Forms 106
13.1.9. Drug Accountability 106
13.1.10. Audits and Inspections 107
13.1.11. Protocol Compliance 107
13.2. Sponsor Responsibilities 107
13.2.1. Protocol Modifications 107
13.2.2. Study Report, Presentations and Publications 107
13.2.3. Data and Safety Monitoring 108
13.3. Joint Investigator/Sponsor Responsibilities 108
13.3.1. Access to Information for Monitoring 108
13.3.2. Access to Information for Auditing or Inspection 108
13.3.3. Study Discontinuation 108
14. APPENDIX A: SM-88 MOA 109
15. APPENDIX B: DETAILED DESCRIPTIONS OF ADVERSE EVENTS 112
16. LIST OF REFERENCES 123

LIST OF TABLES

Table 1: Content Updates (Version 7 to 8) 4
Table 2: List of Abbreviations 30
Table 3. Activities Performed During Screening Period 41
Table 4: Recommended Dose Modifications for SM-88 in Part 2 43
Table 5: Part 1 - SM-88 used with MPS Time and Events Schedule 47
Table 6: Part 2 - SM-88 used with MPS Time and Events Schedule 50
Table 7: Control Arm - Capecitabine Time and Events Schedule 53
Table 8: Control Arm - 5-FU Time and Events Schedule 56
Table 9: Control Arm - Gemcitabine Time and Events Schedule 59
Table 10: Adverse Events Possibly Associated with SM-88 71
Table 11: Adverse Events Associated with Sirolimus 72
Table 12: Adverse Events Associated with Methoxsalen 73
Table 13: Adverse Events Associated with Phenytoin 74
Table 14: Permanent Discontinuation Criteria for SM-88 used with MPS 75
Table 15: Dose-Limiting Toxicities Criteria for SM-88 used with MPS 77
Table 16: Drug Dispensing Guidelines 79
Table 17: Safety Laboratory Analytes 89
Table 18: Grading of Adverse Event Severity 92

2. LIST OF ABBREVIATIONS

Table 2: List of Abbreviations

Abbreviation or Specialist Term	Definition
ACE	Angiotensin-converting enzyme
AE	Adverse event
$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the plasma concentration-time curve from time 0 up to time "t"
AUC_{tau}	Area under the plasma concentration-time curve between dose administrations
BICR	Blinded independent central review
b.i.d	Bis in die (or dosing twice a day)
BOOP	Bronchiolitis obliterans organizing pneumonia
CA-19.9	Tumor marker used primarily in management of pancreatic cancer
CBR	Clinical Benefit Rate
CI	Confidence interval
CL/F	Oral clearance
C_{max}	Maximum observed plasma concentration
CNI	Calcineurin Inhibitor
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DRESS	Drug reaction with eosinophilia and systemic symptoms
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
[redacted]	

Abbreviation or Specialist Term	Definition
[redacted]	
Evaluable subject	A subject who has received at least 1 full cycle of therapies
FDA	United States Food and Drug Administration
GCP	Good Clinical Practices
GI	Gastrointestinal
H	Hypothesis
ICH	International Conference on Harmonization
ILD	Interstitial lung disease
INR	International normalized ratio
IRB	Institutional Review Board
LAT1	L-type amino acid transporter 1
LDH	Lactate dehydrogenase
MPS	Methoxsalen, phenytoin, and sirolimus
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NLR	Neutrophil:lymphocyte ratio
NOAEL	No-observed-adverse-effect-level
O_2	Oxygen
ORR	Overall Response Rate
OS	Overall Survival
OU	Oculus uterque (both eyes)
PABA	p-Aminobenzoic acid
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PR	Partial response
PRO	Patient-reported outcome

Abbreviation or Specialist Term	Definition
PS	Performance Status
q.d.	Quadue die (or dosing once a day)
RD	Recurrent disease
RECIST	Response Evaluation Criteria in Solid Tumors
ROS	Reactive oxygen species
RP2D	Recommended Phase II Dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SJS	Stevens-Johnson Syndrome
SM-88	D,L-alpha-metyrosine (racemetyrosine)
SM-88 used with MPS	SM-88 (D,L-alpha-metyrosine), methoxsalen, phenytoin, and sirolimus
SM-88 used with M2PS	SM-88 (D,L-alpha-metyrosine), melanin and melanotan 2, phenytoin, and sirolimus
SUV	Standardized uptake value
$t_{½}$	Apparent terminal phase half-life
T_{max}	Time to C_{max}
TEN	Toxic epidermal necrolysis
ULN	Upper limit of normal
UV	Ultraviolet
UVA	Ultraviolet A
Vz/F	Apparent volume of distribution
K_z	Apparent terminal phase elimination rate constant

3. INTRODUCTION

Approximately 53,070 people develop exocrine pancreatic cancer each year in the United States. Due to its typically aggressive growth profile and late-stage presentation of symptoms, one-year mortality is 80% (American Cancer Society) with few effective treatment alternatives. Surgical resection offers the best chance of cure. However, only 9% of subjects are diagnosed at the localized stage, causing the majority of pancreatic cancer cases to be unresectable (Siegel et al., 2016).

First-line systemic therapies are typically gemcitabine-based or fluorouracil/leucovorin-based combination regimens. Despite high toxicity levels, with the majority of subjects experiencing Grade 3 or greater adverse events, most progress within the first six months of treatment (Conroy et al., 2011; Von Hoff et al., 2013). The optimal second-line regimen has not been established. A limited amount of data suggests that second-line therapy may affect survival, and it is reasonable to consider further chemotherapy in subjects who maintain a good Performance Status (PS). A recently approved therapy using nanoliposomal irinotecan plus fluorouracil and folinic acid in the second-line setting demonstrated median OS of 6.1 months and only a 7.7% response rate (Wang-Gilliam et al., 2016), showing the need for additional therapeutic options. Equally distressing, the small increases in responses and progression-free survival (PFS) come with high levels of toxicity and loss of quality of life.

In the past, cytotoxic chemotherapy agents were developed without cancer-specific targets. More recently, approved targeted agents with novel mechanisms of action, have been shown to provide clinical benefit, without the same dose-limiting toxicity associated with cytotoxic drugs. Unfortunately, by their very definition, these agents are useful only in small numbers of selected subjects. Thus, there is a need for more effective, less toxic, and broadly applicable anti-cancer agents (Gatenby et al., 2009; Kohner et al. 2015).

3.1. SM-88 Background

Many studies have affirmed the role of oxidative stress in carcinogenesis (Moriya et al., 2001; Wiseman and Halliwell, 1996). Cells are exposed to various exogenous to endogenous (intracellular) sources of oxidative stress primarily produced by reactive oxygen metabolism, immune responses, and inflammation. The outcome of these processes is the production of reactive oxygen/nitrogen species (reactive oxygen species [ROS]/reactive nitrogen species) interacting and damaging cellular DNA that can lead to mutations, genomic instability (pre-cancerous state), and eventually to malignant transformations (cancerous state). These changes are also proposed as a therapeutic mechanism for targeted cell death (Kryston et al., 2011; Epstein et al., 2014; Akladios et al., 2015).

Natural tyrosine undergoes rapid renal clearance and published literature highlights the preferential uptake by cancer cells in comparison to normal healthy cells (Fuchs and Bode, 2005). The normal conversion of cellular phenylalanine to tyrosine and specific transport of tyrosine would suggest limited uptake of this product in environments where tumor cells are not present. One example of tyrosine's selectivity is the radiolabeled tyrosine derivative, ^{18}F-

Fluoroethyl-L-Tyrosine, that has been extensively studied as a diagnostic agent in positron emission tomography (PET) imaging of cancer (Hutterer et al., 2017).

SM-88 (D,L-alpha-metyrosine, racemetyrosine) is a novel dysfunctional modified amino acid. SM-88 is used with low doses (lower than doses used for approved indications) of three repurposed agents, methoxsalen, phenytoin, and sirolimus (hereafter, referred to as MPS). In 2019, SM-88 was granted the USAN certified name of *racemetyrosine*. SM-88 used with MPS, leverages the known altered metabolism of cancer (also known as the Warburg effect) to enhance and target the delivery of its amino acid and oxidizing reactive lipid species to the cancer (Lynch et al., 2000; Shigemitsu et al., 1999; Hara et al., 1998; May and Buse, 1989; Mortimer et al., 1987; Wiriyasermkul et al., 2012; Wei et al., 2016). SM-88 is believed to disrupt cancer cell protein synthesis processes and cause a breakdown of the cancer cells' regulatory proteins. The MPS components are used to create an environment which: 1) increases absorption of SM-88 into the tumor environment through increased cellular ketosis (sirolimus); sirolimus at these doses is reported to affect serum and intra-cellular glucose in the desired manner, i.e. increases the cancer cells' dependency on amino acids and lipids for biomass and energy, 2) increase the production of reactive lipid species (phenytoin), and 3) enhance the effect of oxidative stress selectively inside the cancer cell (methoxsalen). Cancer cells exist in a highly oxidative intracellular environment due to the Warburg effect and related metabolic changes, and this combination of agents is intended to accentuate the intensity of that ROS stress leading to apoptosis. A further discussion of the mechanism of action for SM-88 used with MPS is included in APPENDIX A: SM-88 MOA.

The three repurposed agents, methoxsalen, phenytoin and sirolimus, are intended to adjust the tumor microenvironment for increased overall effectiveness of the denatured amino acid (SM-88), rather than for their indicated/approved uses. Thus, these three agents are administered in lower doses than for their approved uses. The safety information for these three agents is taken from their respective Reference Listed Drug packaging inserts and prescribing information. Sirolimus is an approved immunomodulator used for prophylaxis of organ rejection in renal transplantation (Rapamune®; Package Insert, 2018). The current recommended dose of sirolimus is 2 to 5 mg/day with a 6 to 15 mg loading dose, higher than the 0.5 mg/day dose to be studied in this trial. Methoxsalen is approved for the treatment of psoriasis, eczema, vitiligo, and some cutaneous lymphomas when simultaneously exposing the skin to ultraviolet A (UVA) light (PUVA therapy) (Oxsorlan Ultra® Package Insert, 2015). The current recommended dose of methoxsalen for these indications is 20 to 70 mg/day, higher than the 10 mg/day dose to be studied in this trial. Phenytoin is currently approved as an anti-seizure medication (Dilantin® Package Insert, 2017). The current recommended dose of phenytoin in the management of seizure disorders is 300 to 600 mg/day, higher than the planned 50 mg/day dose to be studied in this trial.

D,L-alpha-metyrosine (racemetyrosine, SM-88) is the racemic mixture of alpha-metyrosine. A related drug, L-alpha-metyrosine (Demser®), is approved for the treatment of pheochromocytoma (Demser® Package Insert, 2015). The approved dose of L-metyrosine is 1000 to 4000 mg/day.

3.2. Safety of SM-88 Used with MPS

In Part 1 of this study (Tyme-88-Panc), there have been two reported cases of possibly drug related/related serious adverse event (Grade ≥ 3), arthralgia and hypotension, both occurring in one subject. To date, SM-88 at doses of up to 920 mg/day has not been associated with a dose-limiting toxicity. In pre-clinical toxicity studies, as reported at ESMO 2016, the no-observed-adverse-effect-level (NOAEL) has been found to be at doses greater or equal to approximately ten times the human-equivalent doses of SM-88's baseline dose in this clinical trial, i.e. 460 mg/day (Sokol G et al., 2016).

In an open-label, pilot study (Hoffman et al., 2013a; Hoffman et al., 2013b), a similar SM-88 based therapy (referred to as SM-88 used with M2PS) was administered to subjects with progressive metastatic cancer. In this study, SM-88 used with M2PS was comprised of an oral regimen of 225 mg SM-88, 50 µg melanin, 15 mg phenytoin, and 0.2 mg sirolimus, and a subcutaneous regimen of 5 mg SM-88, and the other containing 10 µg melanotan II, 2 mg phenytoin, and 0.05 mg sirolimus. There were no drug-related Grade 3 or 4 AEs, and 17% (5/30) of subjects reported drug-related Grade 2 AEs. No subject was withdrawn from the study or discontinued from treatment due to an AE, and no subject had a dose reduction or interruption of study drug administration due to an AE. All subjects experienced hyperpigmentation (97% Grade 1), which was an expected event as hyperpigmentation is associated with the use of melanin. Thirteen percent (13%) of subjects (4/30) experienced a Grade 2 transient fatigue at the initiation of therapy, which generally resolved within the first two weeks, and 3% (1/30) experienced Grade 2 pain. There were no other Grade 2 or above AEs. In addition, average Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) scores decreased from 1.6 at baseline to 0.6 after six weeks of treatment.

In another clinical trial (Tyme 2016b), SM-88 used with MPS was studied in an asymptomatic prostate cancer population, with SM-88 used with MPS administered daily over a six-month period (NCT02796898). Preliminary results showed no reported serious adverse events over 85 months of cumulative subject experience as presented at ASCO GU in 2018 and elsewhere (Roach M et al., 2018; Del Priore et al., 2017a; Del Priore et al., 2017b; Del Priore et al., 2017c). SM-88 dosing in this ongoing study was also increased from the original pilot study referenced above during a dose ranging portion, from 230 mg/day (q.d. dosing) to 460 mg/day (230 mg b.i.d). Dosing of sirolimus (0.5 mg/day) and phenytoin (50 mg/day) was consistent between both studies. 10 mg/day of methoxsalen was substituted for currently unavailable same class components in the pilot study (melanin and melanotan II), without a change in observed tolerability or therapeutic effects. There were Grade 2 and 3 events that in the opinion of the Investigator were not drug related. In the same trial, one subject experienced a Grade 3 adverse event (hyperkalemia) and two subjects experienced Grade 2 adverse events (urinary tract infection, phimosis and gouty arthritis) that were reported as non-drug related (Del Priore et al., 2017c).

There were no ocular toxicities reported in the Tyme 2016b trial. In addition, as reported at the European Society of Medical Oncology in Barcelona in July 2019, no ocular toxicities have yet been documented in Part 1 of this Tyme-88-Panc trial. Therefore, although required for Part 1 of the trial, the requirements for ophthalmological exams has been removed from Part 2 of this trial.

3.3. SM-88 Supportive Clinical Data

In the pilot study of SM-88 used with M2PS (see description above) in 30 subjects with a variety of progressive, metastatic cancer types, results were supportive of a therapeutic effect (Hoffman et al., 2013a; Hoffman et al., 2013b, Stega et al 2019). The median PFS overall was 14.7 months. The clinical benefit rate (CR + PR + stable disease [SD], as per Response Evaluation Criteria for Solid Tumors [RECIST] 1.1) was 90% (27/30), consisting of four complete responses (CRs), six PRs and 17 SDs (Stega et al 2019). In this trial, SM-88 used with M2PS was associated with a >2x increase ($p<0.05$) in PFS compared to the PFS immediately preceding the use of SM-88 used with M2PS (penultimate PFS). As discussed above, there were no reported significant toxicities (Grade ≥ 3) associated with the drug regimen (Hoffman et al., 2013b; Hoffman et al., 2014; Sokol et al., 2016). These clinical experiences have been updated, collated and published in conjunction with ASCO 2017 (Hoffman et al., 2017a; Hoffman et al., 2017b). In both of these updated reports, the safety and clinical results were consistent with the initial publications.

Eleven subjects with pancreatic cancer were identified following a case review of subjects treated with SM-88 used with M2PS in the pilot study and compassionate use program (presented at ASCO GI 2018) (Hoffman et al., 2017b). The average age was 63.2 (44-81), 36.4% (4/11) were female. Prior treatment included surgery only (n = 3), chemo only (n = 4), multi-modality therapy (n = 2), and unknown or none (n = 2). Duration of treatment ranged from 3-57 weeks (mean = 28.5). Overall reduction in tumor size was seen in 27.3% (3/11) including one CR with PFS of at least 6 months duration, and 2 PRs with one known PFS of 15 weeks. 72.7% (8/11) maintained SD for 6-61 weeks. One subject had an OS of 23.3 months with no further treatment, and one had an OS of 43.2 months. All subjects developed hyperpigmentation during treatment. Overall, the tolerability of SM-88 used with M2PS appeared acceptable. No serious or unexpected adverse events related to SM-88 were reported. Additional benefits have been documented, including: 1-3 points improvement in ECOG PS, 1-5 point mean improvement on European Organization for Research and Treatment of Cancer (EORTC) questionnaire (scale 1-7), weight gain (1-5 lbs.), and reduction in pain levels (1-9 points/10 scale) with cessation of all analgesics by the end of Cycle 1 in 36% (4/11).

In 2018, Tyme reported additional clinical data regarding SM-88. There was no indication of cross-resistance based on prior treatments, metastatic site, or other poor prognosis indicators in subjects enrolled in a pilot study and Compassionate Use program (Zhu et al., 2018a). Further, SM-88 reported no Grade 3 or 4 AEs with a modified RECIST 1.1 response rate of 41% across a range of breast cancer subsets (Zhu et al., 2018b). In an update of SM-88 in non-metastatic prostate cancer (Phase 1b/2 results), subjects treated with SM-88 used with MPS continued to report no drug related Grade 2, 3, or 4 AEs, and 92% of subjects maintained radiographic PFS at a median of 12 months from PSA recurrence. This paralleled the reduction in subjects' circulating tumor cells (CTCs) (Chen et al., 2018). Previously seen hyperpigmentation with SM-88 used with M2PS was not observed in subjects treated with SM-88 used with MPS (the regimen used in the non-metastatic prostate cancer Phase 1b/2 study). The potential correlation of SM-88 efficacy with cutaneous biomarkers may be explored in the future. Lastly, a retrospective review of PET-based standardized uptake value (SUV) results appeared to be consistent with the hypothesized metabolic mechanism of action (Bonta et al., 2018).

Based on the preliminary clinical experience with SM-88 used with M2PS, together with the similarity to SM-88 used with MPS, the Sponsor is proposing a path forward to study SM-88 used with MPS in clinical situations where optimal treatments have not been established, including late-stage, pancreatic cancer. Given the continued unmet medical need in subjects with pancreatic cancer, and the suggestion of possible benefit along with acceptable safety findings to date with SM-88, we believe the initiation of this larger, prospective, randomized clinical trial is justified.

3.4. Effect of Food on SM-88

An open-label study (Study Y101) was conducted in 16 healthy volunteers to assess the effect of food on the pharmacokinetic (PK) profile of SM-88 (administered as a single agent). In this study, subjects received a single 300 mg dose of SM-88 under fasting or fed (high-fat, high-calorie breakfast) in a randomized crossover fashion. When administered in the presence of a high-fat, high-calorie diet, the C_{max} and AUC of SM-88 increased by approximately 80%. Overall, SM-88 was safe and well tolerated in this study. To date, the safety profile of SM-88 has only been assessed in subjects treated under fasting conditions. In the present study, it is recommended that SM-88 doses be taken one hour before or two hours after meals, so as to ensure an empty stomach.

4. OBJECTIVES - *PART 1*

4.1. Primary Objective

[redacted]

4.2. Secondary Objectives

[redacted]

4.3. Safety Objectives

[redacted]

5. OBJECTIVES - *PART 2*

5.1. Primary Objective

To determine the OS of subjects treated with SM-88 used with methoxsalen, phenytoin, and sirolimus (MPS) versus the control arm (Physician's Choice).

5.2. Key Secondary Objective

- To report Investigator-determined PFS.

5.3. Additional Secondary Objectives

[redacted]

5.4. Exploratory Objectives

[redacted]

5.5. PK/Safety Objectives

[redacted]

6. SUBJECT INVESTIGATIONAL PLAN

6.1. Overall Study Design

This is a two part, open-label, prospective, randomized, multi-center trial of SM-88 used with MPS in subjects with pancreatic cancer. The first part will be used to determine which dose of SM-88 will be selected for further study (RP2D), and the second part will consist of an expansion cohort of subjects at this selected dose, randomized against Physician's Choice therapies. For Part 1, subjects have completed therapy and RP2D has been determined. Follow up on OS of subjects enrolled in Part 1 is continuing.

6.2. Screening Period (Part 1 and Part 2)

During the screening period, subjects will be evaluated for their eligibility to participate in the study. Subjects must be consented within 8 weeks after their last dose of chemotherapy (last dose is the day of the last drug administration). Study agents must be administered within 12 weeks of the last dose of chemotherapy. A subject does not have to be within 12 weeks of the last dose of chemotherapy if they have had a CR on their immediately preceding systemic therapy; however, consent must occur within 8 weeks of their first detectable recurrence, and study agent must be administered within 12 weeks of their first detectable recurrence. For instance, if a patient subject has a CR after systemic therapy, but recurs 6 months later, they are eligible to start this trial.

Whenever possible, Randomization and start of the first dose of study treatment (i.e., Cycle 1 Day 1, C1D1) should occur on the same date. Planning for Physician's Choice selection should begin at informed consent, so C1D1 can occur at Randomization to the assigned study arm. If needed, there may be, at most, 7 days between the date of Randomization and start of the first dose of study treatment (i.e., Cycle 1 Day 1).

Imaging and lab results must be assessed, at most, 14 days prior to a subject's first dose of study treatment (i.e., Cycle 1 Day 1). A subject's weight change, as described in the Exclusion Criteria, should be assessed just before Randomization.

All previous anti-neoplastic treatment should be discontinued for the experimental groups prior to starting study medications.

Activities to be carried out during this screening period and their corresponding timeframes are summarized in the table below. Results of screening labs, images, and weight change measures should be gathered prior to Randomization, as detailed below.

Table 3. Activities Performed During Screening Period

PRE-INFORMED CONSENT ACTIVITIES	TIME TO INFORMED CONSENT	TIME TO RANDOMIZATION	TIME TO FIRST DOSE OF STUDY DRUG (C1D1)
Last dose of any investigational therapy*	≤ 8 weeks	≥ 30 days	≥ 30 days (because Randomization occurs before C1D1)
Last dose of any other therapy*	≤ 8 weeks	≥ 14 days	≥ 14 days (because Randomization occurs before C1D1)
POST-INFORMED CONSENT ACTIVITIES	**TIME TO INFORMED CONSENT**	**TIME TO RANDOMIZATION**	**TIME TO FIRST DOSE OF STUDY DRUG (C1D1)**
Labs	N/A	≤ 7 days, but prior to Randomization confirmation	≤ 14 days
Imaging	N/A	≤ 14 days, but prior to Randomization confirmation	≤ 21 days
Weight**	N/A	Prior to Randomization confirmation	Prior to Randomization confirmation
Randomization	N/A	0	≤ 7 days

* A subject does not have to be within 12 weeks of the last dose of chemotherapy if they have had a CR on their immediately preceding systemic therapy; however, consent must occur within 8 weeks of their first detectable recurrence, and study agent must be administered within 12 weeks of their first detectable recurrence.
** A subject's weight change, as described in the Exclusion Criteria, should be assessed based on information from the 28 days prior to consent, or measured from consent (Screening) to Randomization (must be at least 1 week apart). If weight is measured in the Screening period between consent and Randomization, the second measure should be captured prior to Randomization.

6.3 Treatment Period (Part 1 and Part 2)

Subjects will visit the clinic on Day 1 of each treatment cycle. Given the treatment period completion of Part 1, Part 2 is presented below.

Treatment Cycles:

- SM-88 used with MPS
- Physician's Choice

Treatment cycles will begin on Day 1 and will be comprised of Physician's Choice options, or daily dosing with SM-88 used with MPS for 4 weeks with no break between treatment cycles for as long as there is no evidence of clinical progression and/or dose limiting toxicity (DLT).

Subjects will be enrolled in Part 2 of this trial as long as there are no DLTs or PDs, unacceptable toxicities, disease progressions, any treatment discontinuation criteria or death as defined in the protocol.

Dose Modifications (SM-88 used with MPS):

Part 1:

To support the study design, based on preclinical data and the Sponsor's previous clinical experience, there is no clear dose limiting toxicity (DLT) or established maximum tolerated dose (MTD). The 2-dose design stage of this part of the trial may provide useful information on both DLT and maximum tolerated dose (MTD). However, in Part 1, until more data is available to make a more informed decision, our understanding of potential toxicity supports having the dosing be as simple as possible, hence the current study design. There is also precedent for similar dose adjustments. For instance, liposomal doxorubicin palmar plantar erythrodysesthesia is often treated with dose delay and not dose reduction.

Additionally, based on past and ongoing clinical activity (Roach et al., 2018), persistent toxicity associated with SM-88 used with MPS is unexpected. The Part 1 randomized block design of 6 (3 low dose, 3 high dose) ensures that no more than 3 subjects will be treated at the higher dose in any one block. From our preclinical profile, there was no NOAEL, and ongoing and previous clinical experience is also consistent with no DLT or MTD near the trial doses. Taking a treatment holiday and then restarting at the same dose may allow evaluation of whether observed AEs are drug-related or disease-related.

For subjects experiencing a DLT in this trial, the dose of SM-88 will remain the same if treatment is reinitiated. For reinitiation in the SM-88(1) group (the lower dose cohort), SM-88 will remain one capsule b.i.d. For SM-88(2) (the higher dose cohort), SM-88 will remain the same if treatment is reinitiated (two capsules in the AM and 2 capsules in the PM). If a subject has a second episode of any related or possibly drug-related DLT, the subject should be removed from the study (refer to Table 4).

If any of the methoxsalen, phenytoin or sirolimus (MPS) is considered to be the component associated with a DLT and further administration of that component is contraindicated, it will be noted in the record and the subject removed from the trial after consultation with the Medical Monitor.

Part 2:

The RP2D of 920 mg/day administered as two 230 mg capsules, every 12 hours, allows for dose reduction. For subjects experiencing a DLT in Part 2 of the trial for the first time, the dose of SM-88 will be reduced by one capsule at each dose period to a total daily dose of 460 mg. If the subject has a second episode of any related or possibly drug-related DLT, SM-88 may be discontinued for up to 28 days while mitigating measures are attempted. If after restarting therapy the DLT continues, the subject will be removed from study (Table 4) (refer to Table 13).

If any of the methoxsalen, phenytoin, or sirolimus is considered to be the component associated with a DLT, the individual component(s) may be discontinued for up to 28 days while mitigating measures are attempted (e.g., changing the timing of phenytoin to address phenytoin-related fatigue, if experienced). This may be applied to any or all of the MPS components. If the DLT continues for more than 28 days, the subject will be removed from the study.

Table 4: Recommended Dose Modifications for SM-88 in Part 2

Dose Limiting Toxicity (DLT)	Current Dose	Dose Adjustment for Next Treatment
1st DLT	460 mg BID	Decrease dose to 230 mg BID
2nd DLT	230 mg BID	Discontinue study treatment for up to 28 days and attempt mitigation
3rd DLT (after restarting therapy)	230 mg BID	Remove subject from study

Dose Modifications (Control Arm: Physician's Choice):

Capecitabine
The recommended dose of capecitabine is 1000 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2000 mg/m^2 total daily dose). The recommended treatment schedule is as follows:

- Dosing for 2 weeks followed by a 1-week rest period, given as 3-week cycles.

Follow capecitabine package insert for dose modification guidelines. Dose modifications may be instituted at the start of treatment with capecitabine. Dose modifications must be noted in the EDC.

Gemcitabine
The recommended dosage of gemcitabine is 1000 mg/m^2 intravenously over 30 minutes. The recommended treatment schedule is as follows:

- Weekly dosing on Days 1, 8, and 15 of each 28-day cycle.

Follow gemcitabine package insert for dose modification guidelines. Dose modifications may be instituted at the start of treatment with gemcitabine. Dose modifications must be noted in the EDC.

5-FU
The recommended dosage of 5-FU is 2400 mg/m^2 continuous IV infusion over 46 hours. The recommended treatment schedule is as follows:

- Dosing on Days 1 and 15 of a 28-day cycle.

Follow 5-FU package insert for dose modification guidelines. Dose modifications may be instituted at the start of treatment with 5-FU. Dose modifications must be noted in the EDC.

6.3. Efficacy Assessments

Part 1

Efficacy Assessments: [redacted] Magnetic resonance imaging (MRI) or PET/CT may also be used as adjunctive imaging where brain lesions are present, provided that requirements for the endpoints used to meet the objectives are also met, e.g., measurable lesions.

Part 2

Efficacy Assessments: [redacted] Although subjects randomized to capecitabine will be on a 21-day treatment cycle, imaging for these subjects will be performed on the same schedule, based on a 28-day cycle, as the other arms. CT is the preferred primary imaging modality. Preferred CT technique includes enhanced, diagnostic quality CT with oral and IV contrast. MRI or PET/CT may also be used as adjunctive imaging where brain lesions are present, provided that requirements for the endpoints used to meet the objectives are also met, e.g., measurable lesions.

Some subjects, particularly those with active immune systems, may even have tumor site inflammation that is visible on CT imaging (i.e., pseudo-progression) at the first follow-up scan. Subjects with radiographic evidence of PD, but without clinical deterioration, may be considered for repeat confirmation scans before clinically significant PD is defined and study therapy is withdrawn. This decision should be balanced against the potential toxicity associated with continued treatment and alternative treatment options and must be discussed with and approved by the Medical Monitor. Continuation should be evaluated at least every 4 weeks after initial response assessment or sooner if clinical deterioration occurs.

All subjects will be followed for PFS and OS until the end of this study, and possibly beyond their participation in the trial, as approved by the local Institutional Review Board (IRB).

Subjects will also participate in mobile device-controlled actigraphy monitoring.

6.4. Safety Assessments

Parts 1 and 2

Safety Assessments: Routine safety evaluations, including clinical laboratory tests, physical examinations and vital signs will be conducted Day 1 of each treatment cycle, or more often if clinically indicated. ECGs will be performed at Screening, Day 1 of each cycle, pre-dose and at approximately 2 hours post-dose and at subjects' Day 28 follow-up visit. In Part 1, ophthalmologic examinations (as described in Section 11.1.6) will be conducted yearly while on study, i.e., after 12 months of investigational agent (+/- 1 month); this is not a requirement for Part 2. In addition to PK measurements, SM-88, methoxsalen, phenytoin and sirolimus levels will be tested monthly in all subjects independent of renal and hepatic functional status.

DLTs will be defined as an adverse event that meets the listed criteria and that is at least possibly related to any component of the study treatment (SM-88, methoxsalen, phenytoin, sirolimus or Physician's Choice) (Table 15).

In addition, there are certain serious adverse events related to specific components of SM-88 used with MPS that must be assessed (See Section 11.2). In Part 1, if these adverse events are observed, the subject will permanently discontinue SM-88 used with MPS and be monitored accordingly. In Part 2, a dose reduction of SM-88 is allowed.

6.4.1.1. Cohort Expansion

In Part 2, it is anticipated that a sufficient number of subjects will be enrolled to obtain 125 evaluable subjects who have completed at least one cycle of therapy at the RP2D dose level of SM-88, and 125 subjects in the Physician's Choice control group. However, should a biomarker indictor emerge, an additional cohort may be proposed.

6.4.2. Post-Study Follow-up Period

Twenty-eight (28) days after (at a follow-up study visit) the last SM-88 or Physician's Choice therapy dose, subjects will be evaluated for safety and other outcome measures obtained in the course of usual clinical care. Subjects will continue to be followed at 3-month intervals via review of medical records, public social media, phone or in person contact for survival data.

Table 5: Part 1 - SM-88 used with MPS Time and Events Schedule

Visit Description	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Follow-Up Visit	Annual	Survival Follow-up
Day (± 2 days)	-14 to -1	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	28 Day post Discontinuation of Treatment (± 2 days)	(±) 30 days)	Every 3-months (±7 days)
Informed consent	X															
Medical history	X															
Cancer history	X															
Hematology [a]	X[a]	X[a]		X[a]		X[a]		X[a]		X[a]		X[a]		X[a]		
Clinical chemistry [b]	X[b]	X[b]		X[b]		X[b]		X[b]		X[b]		X[b]		X[b]		
Urinalysis [c]	X[c]	X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		
Cholesterol and blood lipids [d]	X[d]	X[d]		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]		
CTC count	X	X		X		X		X		X		X		X		
PK's [e]		X[e]		X[e]												
Phenytoin, and sirolimus levels [f]		X[f]		X[f]		X[f]		X[f]		X[f]		X[f]		X[f]		
SM-88 and methoxsalen levels [g]		X[g]		X[g]		X[g]		X[g]		X[g]		X[g]		X[g]		
Other laboratory tests [h]	X[h]	X[h]		X[h]		X[h]		X[h]		X[h]		X[h]				
PET/CT scans [I]	X[i]				X[i]				X[i]				X[i]			
Physical exam [j]	X[j]	X[j]		X[j]		X[j]		X[j]		X[j]		X[j]		X[j]		
Vital signs [k]	X[k]	X[k]		X[k]		X[k]		X[k]		X[k]		X[k]		X[k]		
ECG [l]	X[l]	X[l]		X[l]		X[l]		X[l]		X[l]		X[l]		X[l]		
Ophthalmologic examination [m]															X[m]	
Concomitant meds	X	X		X		X		X		X		X		X		
CA-19.9	X	X		X		X		X		X		X		X		
Other efficacy labs [n]	X[n]	X[n]		X[n]		X[n]		X[n]		X[n]		X[n]		X[n]		

ECOG PS	X	X		X		X		X		X		X		X		
[redacted]																
Adverse events [o]	X[o]	X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		X[o]		
Dispense SM-88, methoxsalen, phenytoin and sirolimus[p]		X[p]		X[p]		X[p]		X[p]		X[p]		X[p]				
SM-88 pill count		X		X		X		X		X		X				
Survival Data [q]																X[q]

Time and Events Schedules (Continued) Abbreviations: CT = computed tomography; CTC = circulating tumor cell; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group Performance Status; [redacted] ET = early termination; eval = evaluation; LDH = lactate dehydrogenase; meds = medications; MRI = magnetic resonance imaging; NLR = neutrophil:lymphocyte ratio; PK = pharmacokinetic.

[a] Hematology with differential- Erythrocyte count, Hematocrit, Absolute reticulocyte count, Mean cell volume, Mean cell hemoglobin, Mean cell hemoglobin concentration, Leukocytes, Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils, Platelets

[b] Chemistry - Sodium, Potassium, Chloride, Glucose, Blood urea nitrogen, Creatinine, Alanine aminotransferase, Aspartate aminotransferase, Total bilirubin, Total protein, Albumin, Calcium, Magnesium, Phosphate, Total cholesterol, LDL, HDL and triglycerides

[c] Urinalysis - Color, Specific gravity, pH, Protein, Glucose, Ketones, Blood, Bilirubin, Leukocyte Esterase, Nitrites

[d] Total Cholesterol, LDL, HDL, and triglycerides should be monitored in subjects on Day 1 of each cycle if not included in standard "Chemistry". Subjects administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

[e] Will be drawn on Day 1 of Cycle 1 and Cycle 2 (± 4 days) at Pre-Dose, 0.5, 1, 2, 4 and 6 hours Post-Dose. All PK draws will have a window of ± 15 minutes.

[f] In addition to the PK testing, measurements of phenytoin and sirolimus levels will be conducted on Day 1 of all cycles in all subjects. These samples will be assayed at the local lab for all cycles.

[g] In addition to the PK testing, measurements of SM-88 and unbound methoxsalen levels will be conducted on Day 1 of all cycles in all subjects. These samples will be assayed at the central lab for all cycles.

[h] Other laboratory tests at screening include INR, HIV, Hep B, Hep C and Pregnancy Test.

[i] CT Scans are required should be conducted on Day 28 every other cycle after Baseline/Screening, i.e. Day 28 of Cycles 2, 4, 6 (± 5 day window). The elected imaging modality may be supplemented by alternative modalities as clinically indicated. If regional MRI was used to determine local progression for eligibility, then CT must also be performed at baseline and every other cycle. If results of a CT scan performed as a part of standard medical practice within 4 weeks of baseline are available, then an additional baseline scan will not be required. Sites are to perform the Imaging according to the Tyme-88-Panc Imaging Manual. Diagnostic quality CT is for RECIST.

[j] A complete physical examination will be performed at screening and at the End of Treatment Visit. An abbreviated physical examination to monitor for changes will be performed at all other visits indicated. Body weight should be measured at each physical examination. Inquiry about suicidal thoughts or behavior and emergency or worsening depression or unusual changes of mood and behaviors should be assessed at each treatment visit. Height should be measured at screening. As part of a complete physical exam, dermatologic evaluation will be conducted at each visit for the development of rash and potential sign of Stevens Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN). Subjects with a history of basal cell carcinoma will be regularly observed for potential new lesions.

k Vital signs will include blood pressure, respiratory rate, pulse, oxygen saturation, and temperature.

l All scheduled ECGs will be performed before any blood draws scheduled for the same time point. Subjects should be resting quietly and free of distraction for 10 minutes prior to ECG collection. The Investigator or a qualified designee will review all ECGs. The time of the previous study drug administration will be recorded. ECGs will be performed at Screening, Cycle 1 and Cycle 2 pre-dose and at approximately 2 hours post-dose and at subjects Day 28 Follow-up visit.

m Window of ± 30 days for this annual ophthalmologic evaluation. Data to be collected for the Ophthalmology exam will include the following: Record oculus uterque (OU) at baseline and q 12 mo:

a. Acuity best corrected

b. Acuity Uncorrected

c. Correction factor/RX

d. Cataracts present? If subject has cataracts, they should be graded per clinician SOC, who must use the same methodology of grading for follow-up evaluations.

e. Retina evaluation - normal, or not [if not, describe per clinician SOC; must use same for follow-up evaluation]

[n] Other efficacy labs include CEA, LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, urine N-telopeptide, hemoglobin, WBC, ANC, leptin, and NLR.

[o] Screen for symptoms of progressive multifocal leukoencephalopathy (PML), hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Consult a neurologist as clinically indicated

[p] SM-88 will be dispensed monthly for all cycles. SM-88 should be taken twice daily at approximately the same time each day with approximately 240 mL water to minimize GI disturbance. Doses are to be provided at least two-hours after meals and at least one-hour before. Dosing should be 8-12 hours apart and planned to minimize food consumption after dosing periods.

[q] Survival data to be collected every 3 months either by in person visits to the site or via telephone.

Table 6: Part 2 - SM-88 used with MPS Time and Events Schedule

Visit Description	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6+		Follow-Up Visit	Survival Follow-up
Day (± 2 days)	-14 to -1 days	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	Day 1	Day 28	28 Day Post Discontinuation of Treatment (± 2 days)	Every 3-months (±7 days)
Informed consent	X														
Medical history	X														
Cancer history	X														
Hematology [a]	X[a]	X[a]		X[a]		X[a]		X[a]		X[a]		X[a]		X[a]	
Clinical chemistry [b]	X[b]	X[b]		X[b]		X[b]		X[b]		X[b]		X[b]		X[b]	
Urinalysis [c]	X[c]	X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]	
Cholesterol and blood lipids [d]	X[d]	X[d]		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]	
CTC collection and exploratory biomarker analysis/sample banking		X		X		X		X		X		X		X	
Phenytoin and sirolimus levels [e]		X[e]		X[e]		X[e]		X[e]		X[e]		X[e]		X[e]	
SM-88 and methoxsalen levels [f]		X[f]		X[f]		X[f]		X[f]		X[f]		X[f]		X[f]	
Pharmacokinetics (PK) sampling		X		X											
Other laboratory tests [g]	X[g]														
CT scans [h]	X[h]				X[h]				X[h]				X[h]		
Physical exam [i]	X[i]	X[i]		X[i]		X[i]		X[i]		X[i]		X[i]		X[i]	
Vital signs [j]	X[j]	X[j]		X[j]		X[j]		X[j]		X[j]		X[j]		X[j]	
ECG - single [k]	X					X		X		X		X		X	
ECG - triplicate [k]		X[k]		X[k]											
Concomitant meds	X	X		X		X		X		X		X		X	
CA-19.9	X	X		X		X		X		X		X		X	
Other efficacy labs [l]	X[l]	X[l]		X[l]		X[l]		X[l]		X[l]		X[l]		X[l]	

ECOG PS	X	X		X		X		X		X		X		X	
[redacted]															
Wearable device (Fitbit)	Continuous daily wear beginning C1D1 until completion of follow-up visit														
Adverse events [m]	X[m]	X[m]		X[m]		X[m]		X[m]		X[m]		X[m]		X[m]	
Dispense SM-88, methoxsalen, phenytoin and sirolimus[n]		X[n]		X[n]		X[n]		X[n]		X[n]		X[n]			
SM-88 pill count		X		X		X		X		X		X			
Survival data [p]															X[p]
Food and drug diary		Daily documentation of study drug dose and meal times for SM-88 subjects, beginning on C1D1													

Time and Events Schedules (Continued) Abbreviations: CT = computed tomography; CTC = circulating tumor cell; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group Performance Status; [redacted] ET = early termination; eval = evaluation; LDH = lactate dehydrogenase; meds = medications; MRI = magnetic resonance imaging; NLR = neutrophil:lymphocyte ratio; PK = pharmacokinetic.

[a] Hematology with differential: Erythrocyte count, Hematocrit, Absolute reticulocyte count, Mean cell volume, Mean cell hemoglobin, Mean cell hemoglobin concentration, Leukocytes, Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils, Platelets

[b] Chemistry: Sodium, Potassium, Chloride, Glucose, Blood urea nitrogen, Creatinine, Alanine aminotransferase, Aspartate aminotransferase, Total bilirubin, Total protein, Albumin, Calcium, Magnesium, Phosphate, Total cholesterol, LDL, HDL and triglycerides

[c] Urinalysis: Color, Specific gravity, pH, Protein, Glucose, Ketones, Blood, Bilirubin, Leukocyte Esterase, Nitrites

[d] Total Cholesterol, LDL, HDL, and triglycerides should be monitored in subjects on Day 1 of each cycle if not included in standard "Chemistry." Subjects administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

[e] Measurements of phenytoin and sirolimus levels will be conducted on Day 1 of all cycles in all subjects. These samples will be assayed at the central lab for samples from Cycles 1 and 2, and the local lab for all subsequent cycles. In addition to the PK testing, measurements of SM-88 and unbound methoxsalen levels will be conducted on Day 1 of all cycles in all subjects. These samples will be assayed at the central lab for all cycles.

[f] In addition to the PK testing, measurements of SM-88 and unbound methoxsalen levels will be conducted on Day 1 of all cycles in all subjects. These samples will be assayed at the central lab for all cycles.

[g] Other laboratory tests at screening include: serum cortisol, INR, HIV, Hep B, Hep C and Pregnancy Test. For HIV, Hep B and Hep C, testing is not required in the absence of clinical suspicion.

[h] CT scans are required and should be conducted on Day 28 of every other (even-numbered) cycle after Baseline/Screening, i.e., Day 28 of Cycles 2, 4, 6 (± 5 day window). For all cycles beyond Cycle 6, this same measurement pattern should be continued (i.e., Day 28 of Cycles 8, 10, 12 (± 5 day window). The elected imaging modality may be supplemented by alternative modalities as clinically indicated. If regional MRI was used to determine local progression for eligibility, then CT (or PET/CT) must also be performed at baseline and every other cycle. If results of a CT scan performed as a part of standard medical practice within 14 days of Randomization are available, then an

additional baseline scan will not be required. Sites are to perform the Imaging according to the Tyme-88-Panc Imaging Manual. Preferred CT technique includes enhanced, diagnostic quality CT with oral and IV contrast.

[i] A complete physical examination will be performed at screening and at the end of treatment visits. An abbreviated physical examination to monitor for changes will be performed at all other visits indicated. Body weight should be measured at each physical examination. Inquiry about suicidal thoughts or behavior and emergency or worsening depression or unusual changes of mood and behaviors should be assessed at each treatment visit. Height should be measured at screening. As part of a complete physical exam, dermatologic evaluation will be conducted at each visit for the development of rash and potential sign of SJS/TEN. Subjects with a history of basal cell carcinoma will be regularly observed for potential new lesions.

[j] Vital signs will include blood pressure, respiratory rate, pulse, oxygen saturation, weight and temperature.

[k] For the SM-88 used with MPS arm, ECGs that are time-matched to PK sample collections (Day 1 of Cycles 1 and 2) will be collected in triplicate. ECGs will be performed before any blood draws scheduled for the same time point. Subjects should be resting quietly and free of distraction for 10 minutes prior to any ECG collection. The Investigator or a qualified designee will review all ECGs. The time of the previous study drug administration will be recorded. ECGs will be performed at Screening (single), Day 1 of Cycles 1 and 2 (in triplicate, for time-matched to PK sample collection for subjects in SM-88 arm), and at subjects' Day 28 follow-up visit (single).

[l] Other efficacy labs include: CEA, LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, hemoglobin, WBC, ANC, leptin, and NLR.

[m] Screen for symptoms of PML, hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Consult a neurologist as clinically indicated.

[n] SM-88 will be dispensed monthly for all cycles. SM-88 should be taken twice daily at approximately the same time each day with approximately 240 mL water to minimize GI disturbance. Doses are to be provided at least two-hours after meals and at least one-hour before. Dosing should be 8-16 hours apart and planned to minimize food consumption after dosing periods.

[o] Survival data to be collected every 3 months by review of medical records, public social media, phone or in person contact.

Table 7: Control Arm - Capecitabine Time and Events Schedule

Visit Description	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6+		Follow-Up Visit	Survival Follow-up
Day (± 2 days)	-14 to -1 days	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21	Day 1	Day 21	28 Day Post-Discontinuation of Treatment (± 2 days)	Every 3-months (±7 days)
Informed consent	X														
Medical history	X														
Cancer history	X														
Hematology [a]	X[a]	X[a]		X[a]		X[a]		X[a]		X[a]		X[a]		X[a]	
Clinical chemistry [b]	X[b]	X[b]		X[b]		X[b]		X[b]		X[b]		X[b]		X[b]	
Urinalysis [c]	X[c]	X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]	
Cholesterol and blood lipids [d]	X[d]	X[d]		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]	
CTC collection and exploratory biomarker analysis/sample banking		X		X		X		X		X		X		X	
Other laboratory tests [e]	X[e]														
CT scans [f]	X[f]				X[f] (Day 28)				X[f] (Day 28)				X[f] (Day 28)		
Physical exam [g]	X[g]	X[g]		X[g]		X[g]		X[g]		X[g]		X[g]		X[g]	
Vital signs [h]	X[h]	X[h]		X[h]		X[h]		X[h]		X[h]		X[h]		X[h]	
ECG - single [i]	X[i]													X[i]	
Concomitant meds	X	X		X		X		X		X		X		X	
CA-19.9	X	X		X		X		X		X		X		X	
Other efficacy labs [j]	X[j]	X[j]		X[j]		X[j]		X[j]		X[j]		X[j]		X[j]	
~~**Blood draw for exploratory biomarker analysis/sample banking**~~		~~X~~		~~X~~				~~X~~							

ECOG PS	X	X		X		X		X		X		X		X	
[redacted]															
Wearable device (Fitbit)	Continuous daily wear beginning C1D1 until completion of follow-up visit														
Adverse events [k]	X[k]	X[k]		X[k]		X[k]		X[k]		X[k]		X[k]		X[k]	
Dispense capecitabine [l]		X[l]		X[l]		X[l]		X[l]		X[l]		X[l]			
Survival data [m]															X[m]

Time and Events Schedules (Continued) Abbreviations: CT = computed tomography; CTC = circulating tumor cell; ECG = electrocardiogram; [redacted]; ET = early termination; eval = evaluation; LDH = lactate dehydrogenase; meds = medications; MRI = magnetic resonance imaging; NLR = neutrophil:lymphocyte ratio; PK = pharmacokinetic.

[a] Hematology with differential: Erythrocyte count, Hematocrit, Absolute reticulocyte count, Mean cell volume, Mean cell hemoglobin, Mean cell hemoglobin concentration, Leukocytes, Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils, Platelets

[b] Chemistry: Sodium, Potassium, Chloride, Glucose, Blood urea nitrogen, Creatinine, Alanine aminotransferase, Aspartate aminotransferase, Total bilirubin, Total protein, Albumin, Calcium, Magnesium, Phosphate, Total cholesterol, LDL, HDL and triglycerides

[c] Urinalysis: Color, Specific gravity, pH, Protein, Glucose, Ketones, Blood, Bilirubin, Leukocyte Esterase, Nitrites

[d] Total Cholesterol, LDL, HDL, and triglycerides should be monitored in subjects on Day 1 of each cycle if not included in standard "Chemistry". Subjects administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

[e] Other laboratory tests at screening include cortisol, INR, HIV, Hep B, Hep C and Pregnancy Test.

[f] CT scans are required and should be conducted on Day 28 of every other (even-numbered) cycle after Baseline/Screening, i.e., Day 28 of Cycles 2, 4, 6 (± 5 day window). For all cycles beyond Cycle 6, this same measurement pattern should be continued (i.e., Day 28 of Cycles 8, 10, 12 (± 5 day window). The elected imaging modality may be supplemented by alternative modalities as clinically indicated. If regional MRI was used to determine local progression for eligibility, then CT (or PET/CT) must also be performed at baseline and every other cycle. If results of a CT scan performed as a part of standard medical practice within 7 days of Randomization are available, then an additional baseline scan will not be required. Sites are to perform the Imaging according to the Tyme-88-Panc Imaging Manual.

[g] A complete physical examination will be performed at screening and at the End of Treatment Visit. An abbreviated physical examination to monitor for changes will be performed at all other visits indicated. Body weight should be measured at each physical examination. Inquiry about suicidal thoughts or behavior and emergency or worsening depression or unusual changes of mood and behaviors should be assessed at each treatment visit. Height should be measured at screening. As part of a complete physical exam, dermatologic evaluation will be conducted at each visit for the development of rash and potential sign of SJS/TEN. Subjects with a history of basal cell carcinoma will be regularly observed for potential new lesions.

[h] Vital signs will include blood pressure, respiratory rate, pulse, oxygen saturation, weight and temperature.

[i] All scheduled ECGs will be performed before any blood draws scheduled for the same time point. Subjects should be resting quietly and free of distraction for 10 minutes prior to ECG collection. The Investigator or a qualified designee will review all ECGs. ECGs will be performed only at baseline and follow-up visit.

[j] Other efficacy labs include: CEA, LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, hemoglobin, WBC, ANC, leptin, and NLR.

[k] Screen for symptoms of PML, hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Consult a neurologist as clinically indicated.

[l] Control arm treatment will be administered as follows: capecitabine (1000 mg/m^2 orally twice a day, Days 1-14 on a 21-day cycle).

[m] Survival data to be collected every 3 months by review of medical records, public social media, phone or in person contact.

Table 8: Control Arm - 5-FU Time and Events Schedule

Visit Description	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6+		Follow-Up Visit	Survival Follow-up
Day (± 2 days)	-14 to -1 days	Day 1 and Day 15	Day 28	Day 1 and Day 15	Day 28	Day 1 and Day 15	Day 28	Day 1 and Day 15	Day 28	Day 1 and Day 15	Day 28	Day 1 and Day 15	Day 28	28 Day Post-Discontinuation of Treatment (± 2 days)	Every 3-months (±7 days)
Informed consent	X														
Medical history	X														
Cancer history	X														
Hematology [a]	X[a]	X[a]		X[a]		X[a]		X[a]		X[a]		X[a]		X[a]	
Clinical chemistry [b]	X[b]	X[b]		X[b]		X[b]		X[b]		X[b]		X[b]		X[b]	
Urinalysis [c]	X[c]	X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]	
Cholesterol and blood lipids [d]	X[d]	X[d]		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]	
CTC collection and exploratory biomarker analysis/sample banking		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X	
Other laboratory tests [e]	X[e]														
CT scans [f]	X[f]				X[f]				X[f]				X[f]		
Physical exam [g]	X[g]	X[g]		X[g]		X[g]		X[g]		X[g]		X[g]		X[g]	
Vital signs [h]	X[h]	X[h]		X[h]		X[h]		X[h]		X[h]		X[h]		X[h]	
ECG - single [i]	X[i]													X[i]	
Concomitant meds	X	X		X		X		X		X		X		X	
CA-19.9	X	X		X		X		X		X		X		X	
Other efficacy labs [j]	X[j]	X[j]		X[j]		X[j]		X[j]		X[j]		X[j]		X[j]	
ECOG PS	X	X		X		X		X		X		X		X	
[redacted]															

[redacted]

Wearable device (Fitbit)	Continuous daily wear beginning C1D1 until completion of follow-up visit													
Adverse events [k]	X[k]	X[k]		X[k]		X[k]		X[k]		X[k]		X[k]		X[k]	
Dispense 5-FU [l]		X[l]		X[l]		X[l]		X[l]		X[l]		X[l]			
Survival data [m]															X[m]

Time and Events Schedules (Continued) Abbreviations: CT = computed tomography; CTC = circulating tumor cell; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group Performance Status; [redacted]; ET = early termination; eval = evaluation; LDH = lactate dehydrogenase; meds = medications; MRI = magnetic resonance imaging; NLR = neutrophil:lymphocyte ratio; PK = pharmacokinetic.

[a] Hematology with differential: Erythrocyte count, Hematocrit, Absolute reticulocyte count, Mean cell volume, Mean cell hemoglobin, Mean cell hemoglobin concentration, Leukocytes, Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils, Platelets

[b] Chemistry: Sodium, Potassium, Chloride, Glucose, Blood urea nitrogen, Creatinine, Alanine aminotransferase, Aspartate aminotransferase, Total bilirubin, Total protein, Albumin, Calcium, Magnesium, Phosphate, Total cholesterol, LDL, HDL and triglycerides

[c] Urinalysis: Color, Specific gravity, pH, Protein, Glucose, Ketones, Blood, Bilirubin, Leukocyte Esterase, Nitrites

[d] Total Cholesterol, LDL, HDL, and triglycerides should be monitored in subjects on Day 1 of each cycle if not included in standard "Chemistry". Subjects administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

[e] Other laboratory tests at screening include cortisol, INR, HIV, Hep B, Hep C and Pregnancy Test.

[f] CT scans are required and should be conducted on Day 28 of every other (even-numbered) cycle after Baseline/Screening, i.e., Day 28 of Cycles 2, 4, 6 (± 5 day window). For all cycles beyond Cycle 6, this same measurement pattern should be continued (i.e., Day 28 of Cycles 8, 10, 12 (± 5 day window). The elected imaging modality may be supplemented by alternative modalities as clinically indicated. If regional MRI was used to determine local progression for eligibility, then CT (or PET/CT) must also be performed at baseline and every other cycle. If results of a CT scan performed as a part of standard medical practice within 7 days of Randomization are available, then an additional baseline scan will not be required. Sites are to perform the Imaging according to the Tyme-88-Panc Imaging Manual.

[g] A complete physical examination will be performed at screening and at the End of Treatment Visit. An abbreviated physical examination to monitor for changes will be performed at all other visits indicated. Body weight should be measured at each physical examination. Inquiry about suicidal thoughts or behavior and emergency or worsening depression or unusual changes of mood and behaviors should be assessed at each treatment visit. Height should be measured at screening. As part of a complete physical exam, dermatologic evaluation will be conducted at each visit for the development of rash and potential sign of SJS/TEN. Subjects with a history of basal cell carcinoma will be regularly observed for potential new lesions.

[h] Vital signs will include blood pressure, respiratory rate, pulse, oxygen saturation, weight and temperature.

[i] All scheduled ECGs will be performed before any blood draws scheduled for the same time point. Subjects should be resting quietly and free of distraction for 10 minutes prior to ECG collection. The Investigator or a qualified designee will review all ECGs. ECGs will be performed only at baseline and follow-up visit.

[j] Other efficacy labs include: CEA, LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, hemoglobin, WBC, ANC, leptin, and NLR.

[k] Screen for symptoms of PML, hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Consult a neurologist as clinically indicated

[l] Control arm treatment will be administered as follows: 5-FU (2400 mg/m^2 continuous IV infusion over 46 hours on Days 1 and 15 on a 28-day cycle).

[m] Survival data to be collected every 3 months by review of medical records, public social media, phone or in person contact.

Table 9: Control Arm - Gemcitabine Time and Events Schedule

Visit Description	Screening	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6+		Follow-Up Visit	Survival Follow-up
Day (± 2 days)	-14 to -1 days	Days 1, 8 and 15	Day 28	Days 1, 8 and 15	Day 28	Days 1, 8 and 15	Day 28	Days 1, 8 and 15	Day 28	Days 1, 8 and 15	Day 28	Days 1, 8 and 15	Day 28	28 Day Post-Discontinuation of Treatment (± 2 days)	Every 3-months (±7 days)
Informed consent	X														
Medical history	X														
Cancer history	X														
Hematology [a]	X[a]	X[a]		X[a]		X[a]		X[a]		X[a]		X[a]		X[a]	
Clinical chemistry [b]	X[b]	X[b]		X[b]		X[b]		X[b]		X[b]		X[b]		X[b]	
Urinalysis [c]	X[c]	X[c]		X[c]		X[c]		X[c]		X[c]		X[c]		X[c]	
Cholesterol and blood lipids [d]	X[d]	X[d]		X[d]		X[d]		X[d]		X[d]		X[d]		X[d]	
CTC collection and exploratory biomarker analysis/sample banking		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X	
Other laboratory tests [e]	X[e]														
CT scans [f]	X[f]				X[f]				X[f]				X[f]		
Physical exam [g]	X[g]	X[g]		X[g]		X[g]		X[g]		X[g]		X[g]		X[g]	
Vital signs [h]	X[h]	X[h]		X[h]		X[h]		X[h]		X[h]		X[h]		X[h]	
ECG - single [i]	X[i]													X[i]	
Concomitant meds	X	X		X		X		X		X		X		X	
CA-19.9	X	X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X (Day 1 only)		X	
Other efficacy labs [j]	X[j]	X[j] (CEA Day 1 only)		X[j] (CEA Day 1 only)		X[j] (CEA Day 1 only)		X[j] (CEA Day 1 only)		X[j] (CEA Day 1 only)		X[j] (CEA Day 1 only)		X[j]	
ECOG PS	X	X		X		X		X		X		X		X	

[redacted]

Wearable device (Fitbit)	Continuous daily wear beginning C1D1 until completion of follow-up visit													
Adverse events [k]	X[k]	X[k]		X[k]		X[k]		X[k]		X[k]		X[k]		X[k]	
Dispense gemcitabine[l]		X[l]		X[l]		X[l]		X[l]		X[l]		X[l]			
Survival data [m]															X[m]

Time and Events Schedules (Continued) Abbreviations: CT = computed tomography; CTC = circulating tumor cell; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group Performance Status; [redacted] ET = early termination; eval = evaluation; LDH = lactate dehydrogenase; meds = medications; MRI = magnetic resonance imaging; NLR = neutrophil:lymphocyte ratio; PK = pharmacokinetic.

[a] Hematology with differential: Erythrocyte count, Hematocrit, Absolute reticulocyte count, Mean cell volume, Mean cell hemoglobin, Mean cell hemoglobin concentration, Leukocytes, Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils, Platelets

[b] Chemistry: Sodium, Potassium, Chloride, Glucose, Blood urea nitrogen, Creatinine, Alanine aminotransferase, Aspartate aminotransferase, Total bilirubin, Total protein, Albumin, Calcium, Magnesium, Phosphate, Total cholesterol, LDL, HDL and triglycerides

[c] Urinalysis: Color, Specific gravity, pH, Protein, Glucose, Ketones, Blood, Bilirubin, Leukocyte Esterase, Nitrites

[d] Total Cholesterol, LDL, HDL, and triglycerides should be monitored in subjects on Day 1 of each cycle if not included in standard "Chemistry". Subjects administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

[e] Other laboratory tests at screening include cortisol, INR, HIV, Hep B, Hep C and Pregnancy Test.

[f] CT scans are required and should be conducted on Day 28 of every other (even-numbered) cycle after Baseline/Screening, i.e., Day 28 of Cycles 2, 4, 6 (± 5 day window). For all cycles beyond Cycle 6, this same measurement pattern should be continued (i.e., Day 28 of Cycles 8, 10, 12 (± 5 day window). The elected imaging modality may be supplemented by alternative modalities as clinically indicated. If regional MRI was used to determine local progression for eligibility, then CT (or PET/CT) must also be performed at baseline and every other cycle. If results of a CT scan performed as a part of standard medical practice within 7 days of Randomization are available, then an additional baseline scan will not be required. Sites are to perform the Imaging according to the Tyme-88-Panc Imaging Manual

[g] A complete physical examination will be performed at screening and at the End of Treatment Visit. An abbreviated physical examination to monitor for changes will be performed at all other visits indicated. Body weight should be measured at each physical examination. Inquiry about suicidal thoughts or behavior and emergency or worsening depression or unusual changes of mood and behaviors should be assessed at each treatment visit. Height should be measured at screening. As part of a complete physical exam, dermatologic evaluation will be conducted at each visit for the development of rash and potential sign of SJS/TEN. Subjects with a history of basal cell carcinoma will be regularly observed for potential new lesions.

[h] Vital signs will include blood pressure, respiratory rate, pulse, oxygen saturation, weight and temperature.

[i] All scheduled ECGs will be performed before any blood draws scheduled for the same time point. Subjects should be resting quietly and free of distraction for 10 minutes prior to ECG collection. The Investigator or a qualified designee will review all ECGs. ECGs will be performed only at baseline and at follow-up visit.

[j] Other efficacy labs include: CEA, LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, hemoglobin, WBC, ANC, leptin, and NLR.

[k] Screen for symptoms of PML, hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Consult a neurologist as clinically indicated.

[l] Control arm treatment will be administered as follows: gemcitabine (1000 mg/m^2 IV on Days 1, 8, and 15 on a 28-day cycle).

[m] Survival data to be collected every 3 months by review of medical records, public social media, phone or in person contact.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Inclusion Criteria

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

1.

Part 1:

Biopsy-proven metastatic pancreatic adenocarcinoma with documented radiographic disease progression on or after one or more systemic therapies, including a gemcitabine-based chemotherapy regimen or any first line regimen as listed in *PANC G* National Comprehensive Cancer Network (NCCN) current guidelines. Chemotherapy given as part of prior chemo-radiation in the setting of non-metastatic pancreatic cancer does not count as a line of therapy. Chemotherapy given for at least 4 months as adjuvant after CR is considered as a first line therapy.

Part 2:

Biopsy-proven metastatic pancreatic adenocarcinoma on or after two prior lines of systemic therapy. A line of therapy is defined as either: having progressed on a treatment regimen, or having received at least 2 months of a treatment regimen. Chemotherapy given as part of prior chemo-radiation in the setting of non-metastatic pancreatic cancer does not count as a line of therapy unless metastases develop within 6 months of completing the chemo-sensitization. Chemotherapy given for at least 4 months as adjuvant after a CR to any therapy (e.g., surgery or radiation therapy) is also considered a first line therapy. Of the two prior lines, subjects must have been exposed to a gemcitabine-based regimen for a prior line and a 5-FU-based regimen as a prior line of therapy. Investigational therapies as part of a prior line regimen are permitted.

1. Subjects have received two (2) and not more than two (2) previous systemic regimens for the treatment of pancreatic adenocarcinoma.
2. Subjects must be eligible to receive one or more of the Physician's Choice options.
3. Radiographically measurable disease of at least one site by CT scan (or MRI or PET/CT, if allergic to CT contrast media). Imaging for baseline results must be obtained at most 14 days prior to Randomization.
4. Subjects must have completed any investigational cancer therapy at least 30 days prior to Randomization.
5. Subjects must have completed any other cancer therapy at least 14 days prior to Randomization, and recovered from major side effects of prior therapies or procedures.
6. ≥18 years of age.
7. ECOG PS ≤2.

8. Adequate organ function, defined as follows (lab results must be obtained at most 7 days prior to Randomization):
    a. All laboratory parameters ≤ Grade 2 NCI Common Terminology Criteria for Adverse Events (CTCAE) criteria.
    b. In addition:
        i. Hematologic: Platelets ≥ 100 x 10^9 g/dL; Absolute Neutrophil Count ≥ 1.5 x 10^9/L (without platelet transfusion or growth factors within the 7 days prior to the screening laboratory assessment).
        ii. Hepatic: aspartate transaminase/alanine transaminase ≤ 2.5 x upper limit of normal (ULN); total or conjugated bilirubin ≤ 1.5 x ULN, alkaline phosphatase (ALP) < 2.5 x ULN, or 24 hour urine-determined creatinine clearance ≥60 mL/min
        iii. Renal: serum creatinine ≤ 1.5 x ULN and creatinine clearance ≥ 60 mL/min as calculated by the Cockroft-Gault method, or 24 hour urine-determined creatinine clearance ≥ 60 mL/min.
        iv. Coagulation: international normalized ratio (INR) ≤ 1.2.
        v. Albumin: ≥ 3.0 g/dL.
9. All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before Randomization, with the exception of alopecia and neurotoxicity (CTCAE Grade 1 or 2 permitted).
10. Able and willing to provide written informed consent to participate in this study.
11. Subject is willing and able to comply with the protocol for the duration of the study, including undergoing treatment and scheduled visits and examinations including follow-up.
12. Subjects must be able to swallow whole capsules.
13. Female subjects must either be of non-reproductive potential, not breast-feeding or must have a negative urine or serum pregnancy test within 28 days of Randomization, confirmed prior to treatment on Cycle 1 Day 1.
14. Subjects of fertile potential who engage in heterosexual intercourse with partners of childbearing potential must attest to the use of highly effective contraception while enrolled in the study and for at least 6 months following the last dose of study drug. Highly effective birth control methods include the following (the subject should choose 2 to be used with their partner):
    a. Oral, injectable, or implanted hormonal contraceptives.
    b. Condom with a spermicidal foam, gel, film, cream, or suppository.
    c. Occlusive cap (diaphragm or cervical/vault cap) with a spermicidal foam, gel, film, cream, or suppository.

Or any one of the following:

a. Intrauterine device.

b. Intrauterine system (for example, progestin-releasing coil).

c. Vasectomized male (as determined by the Investigator).

d. Tubal ligation/sterilization (female).

7.2. Exclusion Criteria

Exclusion criteria are as follows (subjects who meet any of the following exclusion criteria may not be enrolled in this study):

1. Any screening laboratory, ECG, or other findings that, in the opinion of the Investigator, Medical Monitor or the Sponsor, indicate an unacceptable risk for the subject's participation in the study.
2. History or evidence of any clinically significant disorder, condition, or disease that, in the opinion of the Investigator or Medical Monitor would pose a risk to the subject's safety or interfere with the study evaluations, procedures, or completion. Examples include: intercurrent illness such as active uncontrolled infection, active or chronic bleeding event within 28 days of Randomization, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements.
3. History of a concurrent or second malignancy, except for: adequately treated localized basal cell or squamous cell carcinoma of the skin, adequately treated superficial bladder cancer, adequately treated Stage 1 or 2 cancer currently in complete remission; or any other cancer that has been in complete remission for ≥ 5 years.
4. Subjects with MSI-H pancreatic cancer who have not previously received pembrolizumab.
5. Subjects with any known actionable mutation (e.g., BRCA mutation) who have not been treated with an approved drug for the mutation (the drug does not have to be approved for the indication).
6. Radiation to all measurable lesions within 12 weeks of study baseline.
7. No measurable lesions.
8. Current use, or any use within 14 days prior to Randomization, of a restricted medication (see Section 8.7), or subject requires any of these medications during treatment phase.
9. Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (i.e., larger than that required for placement of central venous access, percutaneous feeding tube, or biopsy) within 28 days of the first dose of study drug.
10. Minor surgical procedures within 7 days of Randomization, or not yet recovered from any prior surgery.
11. Any dysphagia, odynophagia, esophageal dysmotility or stricture, known gastrointestinal (GI) malabsorption syndrome, or intractable diarrhea that may significantly alter the absorption of any of the components of SM-88 used with MPS, e.g., cirrhosis.
12. Known human immunodeficiency (HIV) virus infection. Note: HIV testing is not required in the absence of clinical suspicion.
13. Known hepatitis B surface antigen (HBsAg) positive. Note: testing is not required in the absence of clinical suspicion.
14. Known hepatitis C (HCV) viral RNA present. Note: testing is not required in the absence of clinical suspicion.
15. Have previously been enrolled in this study or any other study investigating SM-

88 or have previously received any SM-88, methoxsalen, phenytoin, or sirolimus in a clinical trial.

16. History of any known drug allergies to any study medication.
17. Subjects with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins; or a history of prior acute hepatotoxicity attributable to phenytoin.
18. Subjects exhibiting idiosyncratic reactions to psoralen compounds.
19. Subjects with a hypersensitivity to sirolimus.
20. Currently enrolled in, or have discontinued within 30 days of Randomization, from a clinical trial involving an investigational product or non-approved use of a drug or device.
21. Subjects must not have any clinically significant and uncontrolled major medical condition(s) including, but not limited to: uncontrolled nausea/vomiting/diarrhea; active uncontrolled infection; symptomatic congestive heart failure (New York Heart Association [NYHA] class ≥ II); unstable angina pectoris or cardiac arrhythmia; psychiatric illness/social situation that would limit compliance with study requirements.
22. >5% weight loss at any time during the 28 days prior to consent, or >5% change in weight from consent (Screening) to Randomization (must be at least 1 week apart). This second weight measure should be captured prior to Randomization.
23. Subjects who have a variety of factors influencing their ability to ingest and absorb oral drugs (such as unable to swallow, nausea, vomiting, chronic diarrhea and intestinal obstruction, etc.).
24. Subjects with central nervous system metastasis, with the exception of subjects who have stable brain metastases as defined as off steroids and no CNS progression for 6 months after CNS treatment.
25. Pregnant or lactating women.
26. Substance abuse that cannot be ended, or subjects with mental disorders that will prevent compliance or evaluation including uncontrolled schizophrenia, uncontrolled depression or other uncontrolled disorders.
27. Subjects with a history of the light sensitive diseases for which methoxsalen would be contraindicated. Diseases associated with photosensitivity include: lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum, and albinism.
28. Subjects treated, or anticipated to be treated, with delavirdine (due to potential for loss of virologic response and possible resistance to delavirdine or to the class of non-nucleoside reverse transcriptase inhibitors caused by phenytoin).
29. Subjects with cutaneous melanoma or invasive squamous cell carcinomas or history thereof, except for those in complete remission for ≥5 years (due to contraindication for use of methoxsalen).
30. Subjects with prior organ transplant or being treated, or anticipated to be treated, with cyclosporine (because long-term administration of the combination of cyclosporine and sirolimus is associated with deterioration of renal function).
31. Subjects with a seizure disorder that is not well controlled or who have required a change in seizure medications within 60 days of Randomization.
32. Subjects treated, or anticipated to be treated, with a calcineurin inhibitor (because

concomitant use of sirolimus and a calcineurin inhibitor increases the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy [HUS/TTP/TMA]).
33. Subjects with interstitial lung disease (ILD) [including pneumonitis, bronchiolitis obliterans organizing pneumonia (BOOP), and pulmonary fibrosis].
34. Screening prolongation of QT/QTc interval [e.g., > 480 milliseconds (ms)] (CTCAE Grade 1) using Fredericia's QT correction formula.
35. A family history of Long QT Syndrome or Torsades de Pointes.
36. Clinically significant cataracts or aphakia.
37. Presence of symptomatic or clinically significant ascites or pleural effusion, defined as requiring clinical intervention in the 30 days prior to consent. However, trace or small amount of physiologic fluid will not be excluded.

7.3. Criteria for Subject Withdrawal

The criteria for enrollment must be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, the Investigator must contact the Tyme, Inc. Medical Monitor (see cover page) to discuss whether the subject should be discontinued from the study drug.

Subjects may choose to discontinue study treatment or withdraw from the study for any reason at any time, and the reason for early withdrawal will be documented.

In addition, subjects must be permanently discontinued from the study if any of the following occur:

- Documented disease progression as detailed below
- Occurrence of rare, but serious adverse events as listed in Section 8.2
- Investigator decision for subject welfare
- Medically necessary in the opinion of the Investigator or Sponsor
- Uncontrolled intercurrent illness as defined by the Principal Investigator
- Non-compliance

It is hypothesized that subjects may show clinical benefit and reduced SUV prior to demonstrating traditional RECIST-based responses. Some subjects may even have tumor site inflammation that is visible on CT imaging (i.e., pseudo-progression) at the first follow-up scan.

Subjects with radiographic evidence of PD, but without clinical deterioration, may be considered for repeat confirmation scans before clinically significant PD is defined and study therapy is withdrawn. This decision should be balanced against the potential toxicity associated with continued treatment and alternative treatment options and must be discussed with and approved by the Medical Monitor. Continuation should be evaluated at least every 4 weeks after initial response assessment or sooner if clinical deterioration occurs.

Subjects who discontinue the study early will have early termination procedures and follow-up performed as shown in the study Time and Events Schedule.

7.4. Criteria for Study Site Discontinuation

Study site participation may be discontinued if Tyme, Inc., the Investigator, or the IRB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practices (GCP).

7.5. Criteria for Study Discontinuation

This study will be discontinued if Tyme, Inc. judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable, laws, regulations, and GCP. At the end of Part 1 of this clinical trial, when 36 subjects have completed at least 1 cycle of the therapy and are evaluable for safety, if greater than one-third of enrolled subjects experience Grade 3-4 AEs at least possibly related to SM-88 used with MPS, enrollment may be paused, and the study data will be reviewed to determine whether alternate dose levels or treatment schedules should be evaluated. This assessment will take place again when all subjects have completed at least 1 cycle of therapy. Other assessments will be conducted by the Data Safety Monitoring Board (DSMB) according to its charter.

8. TREATMENT

8.1. Treatments Administered

In Part 1, subjects are treated with SM-88 used with MPS. In Part 2, subjects are randomized to either the SM-88 used with MPS or control arm (Physician's Choice).

8.2. SM-88 used with MPS

The regimen consists of SM-88 and three conditioning agents:

- SM-88 – 460 mg/day (230 mg b.i.d) or 920 mg/day (460mg b.i.d) as randomly assigned
- Methoxsalen – 10 mg capsules q.d.
- Phenytoin – 50 mg tablets q.d.
- Sirolimus – 0.5 mg tablets q.d.

SM-88 and MPS will be taken daily. It is best to take doses one hour before or two hours after meals, so as to ensure an empty stomach. They should be taken together consistently either in the morning or in the evening with a full glass of water – for example, before bedtime and upon waking up in the morning.

A second dose of SM-88 will be taken 12 hours (+/- 4 hours) after the morning dose.

Missed doses of any of the 4 agents will be omitted and skipped. Subjects who miss a dose of any of the 4 agents, for any reason, will omit that dose and take the next dose at the next regularly scheduled time point 12 hours (+/- 4 hours) after the missed dose was due. If the morning (AM) dose is missed, subjects will continue with the PM dose as scheduled and may take the adjunct medications (methoxsalen, phenytoin, and sirolimus) with their PM dose. If the PM dose is missed, subjects will skip that dose and resume dosing with the AM dose the following day.

Part 1

The low dose, SM-88(1) arm will receive:

- SM-88 – one 230 mg capsules taken orally twice daily (460 mg total).
- Methoxsalen – one 10 mg capsule taken orally once daily.
- Phenytoin – one 50 mg tablet taken orally once daily.
- Sirolimus – one 0.5 mg tablet taken orally once daily.

The high dose, SM-88(2) arm will receive:

- SM-88 – two 230 mg capsules taken orally twice daily (920 mg daily).
- Methoxsalen – one 10 mg capsule taken orally once daily.
- Phenytoin – one 50 mg tablet taken orally once daily.
- Sirolimus – one 0.5 mg tablet taken orally once daily.

Part 2

All subjects enrolled into Part 2 who are randomized to SM-88 used with MPS will receive:

- SM-88 – two 230 mg capsules taken orally twice daily (total 920 mg daily).
- Methoxsalen – one 10 mg capsule taken orally once daily.
- Phenytoin – one 50 mg tablet taken orally once daily.
- Sirolimus – one 0.5 mg tablet taken orally once daily.

8.2.1. Control Arm (Physician's Choice)

All subjects enrolled into Part 2 who are randomized to the control arm (Physician's Choice) will receive a choice of the following therapies:

- **Capecitabine** (1000 mg/m^2 orally twice a day, Days 1-14 on a 21-day cycle)
- **Gemcitabine** (1000 mg/m^2 IV on Days 1, 8, and 15 on a 28-day cycle)
- **5-FU** (2400 mg/m^2 continuous IV infusion over 46 hours on Day 1 and 15 on a 28-day cycle)

8.3. Adverse Events

8.3.1. SM-88 used with MPS

There are known rare but potentially serious adverse events associated with SM-88 and MPS components. While doses of the approved drug components in this regimen are lower than their respective FDA-approved doses, the risks of these drugs when used together is not known and therefore, it is important that subjects are observed for these events.

Below are warnings and common adverse events associated with SM-88 and MPS components that may be relevant to this trial's enrollment criteria. Refer to APPENDIX B: DETAILED DESCRIPTIONS OF ADVERSE EVENTS for a more detailed description of these warnings.

Please note, with respect to Table 10, the list of possible adverse events and risks of SM-88 is based upon initial clinical testing of SM-88 used with MPS, as well as findings reported with the use of a similar product, DEMSER® (L-alpha-metyrosine). The mechanism of action of DEMSER® is believed to be similar to SM-88.

Table 10: Adverse Events Possibly Associated with SM-88

D,L-Alpha-Metyrosine		
Severe Warnings (Black Box)	Warning/Precautions*	Most Common Adverse Reactions*
(N/A)	• Maintain Fluid Volume During and After Surgery • Life-threatening arrhythmias may occur during anesthesia and surgery and may require treatment with a beta-blocker or lidocaine • Intraoperative Effects such as hypertensive crises or arrhythmias • Interaction with Alcohol and sedative effects of alcohol and other CNS depressants • Metyrosine Crystalluria • Caution engaging in activities requiring mental alertness and motor coordination • Hypotension • Arthralgia • Pregnancy Category C	• Sedation can be moderate to severe, especially immediately after initiating therapy • Drooling • Speech Difficulty • Trismus • Frank Parkinsonism • Depression • Hallucination • Disorientation • Confusion • Bloating and flatulence • Loss of skin color • Hot flashes • Diarrhea

*Based on USPI for L-alpha-metyrosine

Table 11: Adverse Events Associated with Sirolimus

Severe Warnings (Black Box)	Warning/Precautions	Most Common Adverse Reactions
• Increased susceptibility to infection and the possible development of lymphoma and other malignancies may result from immunosuppression • The safety and efficacy of Sirolimus as immune suppressive therapy have not been established in liver or lung transplant subjects, and therefore, such use is not recommended • Liver Transplantation – Excess mortality, graft loss, and hepatic artery thrombosis • Lung Transplantation – Bronchial anastomotic dehiscence	• Increased susceptibility to infection and the possible development of lymphoma • Hypersensitivity Reactions • Angioedema • Fluid Accumulation and Impairment of Wound Healing • Hyperlipidemia • Decline in Renal Function • Proteinuria • Latent Viral Infections • Interstitial Lung Disease/Non-Infectious Pneumonitis • *De Novo* Use Without Cyclosporine • Increased Risk of Calcineurin Inhibitor-Induced Hemolytic Uremic Syndrome/Thrombotic • Thrombocytopenic Purpura/Thrombotic Microangiopathy • Antimicrobial Prophylaxis • Embryo-Fetal Toxicity • Skin Cancer Events Interaction with Strong Inhibitors and Inducers of CYP3A4 and/or P-glycoprotein	• Sirolimus used in clinical studies for organ rejection prophylaxis and LAM: o Peripheral Edema o Hypertriglyceridemia o Hypertension o Hypercholesterolemia o Creatinine Increased o Constipation o Abdominal Pain o Diarrhea o Headache o Fever o Urinary Tract Infection o Anemia o Nausea o Arthralgia, Pain o Thrombocytopenia o Stomatitis o Nasopharyngitis o Acne o Chest Pain o Upper Respiratory Tract Infection o Dizziness o Myalgia

Table 12: Adverse Events Associated with Methoxsalen

Methoxsalen		
Severe Warnings (Black Box)	Warning/Precautions	Most Common Adverse Reactions
• Methoxsalen is a potent drug • Methoxsalen with UV radiation should be used only by physicians who have special competence in the diagnosis and treatment of psoriasis and who have special training and experience in photochemotherapy • Use of Psoralen and ultraviolent radiation therapy should be under constant supervision of such a physician • For the treatment of subjects with psoriasis, photochemotherapy should be restricted to subjects with severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, and only when the diagnosis is certain • Possibilities of ocular damage, aging of the skin, and skin cancer (including melanoma); the subject should be fully informed by the physician of the risks inherent in this therapy	• Skin Burning from UVA or sunlight can result if the recommended dosage of the drug is exceeded • Carcinogenicity in animal and human studies • Cataractogenicity • Actinic Degeneration • Basal Cell Carcinomas • Hepatic Diseases and drug exposure • Elderly Subjects with pre-existing history of cataracts, kidney and/or liver dysfunction, or skin cancer • Risks with concomitant photosensitizing agents • Do not sunbathe during the 24 hours prior to or after methoxsalen ingestion and wear UV exposure UVA-absorbing wrap-around sunglasses for 24 hours after methoxsalen ingestion	• Nausea • Pruritus • Erythema

Table 13: Adverse Events Associated with Phenytoin

Phenytoin		
Severe Warnings (Black Box)	Warning/Precautions	Most Common Adverse Reactions
(None in USPI)	• Withdrawal Precipitated Seizure: May precipitate status epilepticus • Potential increase in suicidal behavior and Ideation • Serious Dermatological Reactions, including SJS/TEN • Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan Hypersensitivity: phenytoin hypersensitivity • Hepatic Injury • Hematopoietic Complications	• Nervous System Reactions: o Nystagmus o Ataxia o Slurred Speech o Decreased Coordination o Somnolence o Mental Confusion

8.3.2. Control Arm (Physician's Choice)

There are known serious adverse events associated with each of the Physician's Choice therapies. Refer to the prescribing information for a more detailed description of these warnings (APPENDIX B: DETAILED DESCRIPTIONS OF ADVERSE EVENTS).

8.4. Dose Interruption / Discontinuation of SM-88 used with MPS

SM-88 used with MPS consists of four drugs (see Section 8.1), three of which are FDA-approved therapies which are dosed below their typically prescribed doses. There has only been one drug-related serious adverse event associated with SM-88 used with MPS in over 100 treated cancer subjects to date; the subject that experienced a drug-related SAE remains on treatment and has demonstrated response to therapy. However, the safety profile of SM-88 used with MPS has not been fully established. Rare, but potentially life-threatening adverse events have been associated with the other three approved drug components. Subjects enrolled in this clinical trial of SM-88 used with MPS will be observed for adverse events (outlined in Section 8.2) that are deemed at least possibly related to therapy. Below are instructions with regard to stopping SM-88 used with MPS in response to drug-related adverse events. If a subject has a dose interruption of greater than 28 days, they must be permanently discontinued from the study.

8.4.1. Permanent discontinuation of SM-88 used with MPS

Subjects must permanently discontinue SM-88 used with MPS and be removed from the study if any of the adverse events described in Table 13 are observed and deemed related, or possibly related, to study therapy. Treatment with SM-88 cannot be continued without MPS. Subjects are to follow early termination procedures and follow-up must be performed as shown in the study Time and Events Schedule.

Table 14: Permanent Discontinuation Criteria for SM-88 used with MPS

General	CTCAE Any possible drug-related Grade 4 event
Immune system disorders	CTCAE Grade ≥3 Allergic reaction (drug-related)
Blood and lymphatic system disorders	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) / Eosinophilia, leukocytosis, Hepatobiliary disorders
Skin and subcutaneous tissue disorders	Stevens–Johnson syndrome (SJS) / Toxic epidermal necrolysis (TEN)
	CTCAE Grade ≥ 3 Erythema multiforme
Psychiatric disorders	Any increase in suicidal ideation from baseline

8.4.2. Dose interruption of SM-88 and MPS from drug-related, or possibly related DLTs

For Part 1:

With the exception of the previously listed events in Table 13 that require permanent discontinuation of SM-88, for subjects who experience one of the following DLTs, the dosing of SM-88 must immediately be stopped until the toxicity has resolved to ≤ Grade 1 or returns to baseline level within 28 days from the DLT event.

- If the drug-related DLT is not resolved to ≤ Grade 1 within 28 days, the subject must permanently discontinue SM-88 and must be removed from study and to follow early termination procedures with follow-up performed as shown in the study schedule.
- Re-initiation of SM-88 can only occur after consultation with the Medical Monitor.
- Subjects are to receive all components of SM-88 used with MPS at the same doses as prior to withholding of treatment, as described in Section 8.1.

- If a subject has a second episode of a related or possibly drug-related DLT, the subject must permanently discontinue SM-88 and must be removed from study and to follow early termination procedures with follow-up performed as shown in the study schedule.
- Supportive care should be implemented for all AE toxicities.

DLTs will be defined as AEs at least possibly related to SM-88 used with MPS and are detailed in Table 15 below.

For Part 2:

For subjects who experience one of the following DLTs, the dosing of SM-88 must be stopped until the toxicity has resolved to ≤ Grade 1 or returns to baseline level within 28 days from the DLT event.

- If after the allowed dose reduction, or the temporary elimination of the related component(s) of MPS, the drug-related DLT is not resolved to ≤ Grade 1 within 28 days, the subject must permanently discontinue SM-88 and must be removed from study, and follow early termination procedures with follow-up performed as shown in the study schedule.
- Reinitiation of SM-88 can only occur after consultation with the Medical Monitor.
- Subjects are to receive all components of MPS when given at the reduced dose of SM-88, as described in Section 8.1.
- If a subject has a second episode of a related or possibly drug- related DLT, SM-88 may be discontinued for 28 days while mitigating measures are attempted.
- If after restarting therapy, the DLT continues, the subject will be removed from the study.
- Supportive care should be implemented for all AE toxicities.

Based on the preclinical profile (there was no NOAEL) and ongoing and previous experience, with no DLT or MTD yet detected, the protocol specifies a dose interruption for any DLTs. Further, there is precedent for no dose reduction and only a dose delay or termination for DLTs (for example, liposomal doxorubicin palmar plantar erythema is often treated with dose delay and not dose reduction). In Part 2, as detailed elsewhere, dose reductions of SM-88 are allowed.

Persistent toxicity associated with SM-88 is unexpected based on the above. Utilizing a treatment holiday and then restarting at the same dose may allow clearer evaluation of whether observed AEs are drug-related or disease-related. The protocol also utilizes a Data Safety Monitoring Board (DSMB) that will be regularly monitoring the overall safety of the trial and evaluating any potentially serious safety signals. If the DSMB identifies any serious safety signals, the trial protocol will be amended to address concerns or pause enrollment until subject safety can be fully evaluated.

Table 15: Dose-Limiting Toxicities Criteria for SM-88 used with MPS

Hematologic	CTCAE Grade ≥3 Neutropenia or febrile neutropenia
	CTCAE Grade ≥3 Thrombocytopenia
	CTCAE Grade ≥3 Anemia (irrespective of its association with bleeding)
Gastrointestinal	CTCAE Grade ≥3 Nausea (of ≥72 hours duration with maximal supportive care)
	CTCAE Grade ≥3 Vomiting (of ≥72 hours duration with maximal supportive care)
	CTCAE Grade ≥3 Diarrhea (of ≥72 hours duration with maximal supportive care)
Metabolism	CTCAE Grade ≥3 Hypoalbuminemia (> 24-hour duration with repletion)
	CTCAE Grade ≥3 Hypocalcemia (> 24-hour duration with repletion)
	CTCAE Grade ≥3 Hypokalemia (> 24-hour duration with repletion)
	CTCAE Grade ≥3 Hypomagnesemia (> 24-hour duration with repletion)
	CTCAE Grade ≥3 Hyponatremia (> 24-hour duration with repletion)
	CTCAE Grade 3 Hypophosphatemia (> 24-hour duration with repletion)
Cardiac disorders	CTCAE Grade ≥3 Heart failure
Hepatobiliary disorders	CTCAE Grade ≥3 Hepatobiliary disorders
	CTCAE Grade ≥3 Hepatic failure
Renal and urinary disorders	CTCAE Grade ≥3 Acute kidney injury
	CTCAE Grade ≥3 Chronic kidney disease

8.4.3. Risk Mitigation/Discontinuation of MPS components of SM-88 used with MPS

For toxicity attributable to the MPS agents, a dose reduction adjustment of the individual components is not allowed in Part 1. In Part 2, if any of the methoxsalen, phenytoin, or sirolimus (MPS) components are considered to be associated with a DLT, the individual component(s) may be discontinued for up to 28 days while mitigating measures are attempted (e.g., changing the timing of phenytoin to address phenytoin-related fatigue).

This may be applied to any or all of the MPS components. If after 28 days the DLT continues, the subject will be removed from the study.

8.5. Dose Interruption / Discontinuation of Control Arm (Physician's Choice) Therapy

In the case of adverse events or DLT in the control arm, refer to the prescribing information for dose interruption, risk mitigation or discontinuation.

8.6. Description and Handling of Product

8.6.1. SM-88 used with MPS

For Part 1 and for subjects randomized to SM-88 in Part 2:

Tyme, Inc. designee ALMAC will provide:

- SM-88 (D,L-alpha-metyrosine), in 230 mg capsules.
- Methoxsalen, in 10 mg capsules.
- Phenytoin, in 50 mg tablets.
- Sirolimus, in 0.5 mg tablets.

Investigational product will be dispensed to the subject at the study site. Adequate supply of investigational product will be dispensed to fulfill dosing requirements per cycle.

Investigational product will be labeled according to applicable regulatory requirements. All investigational products will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

All components of SM-88 used with MPS should be kept in a secure area and stored as follows:

- SM-88 should be stored at room temperature 15 to 25 degrees C (59° to 77°F) and protected from light and moisture (USP Controlled Room Temperature).
- Methoxsalen capsules should be stored at 25 degrees C (77°F) (excursions permitted); temperatures between 15 to 30 degrees C (59° to 86° F) are acceptable, and protected from light and moisture (USP Controlled Room Temperature). Preserve in a tight, light-resistant container as defined in the USP.
- Phenytoin should be stored at room temperature 20 to 25 degrees C (68° to 77°F) and protected from light and moisture (USP Controlled Room Temperature), dispensed in tight (USP), child-resistant containers.
- Sirolimus should be stored at room temperature 20 to 25 degrees C (68° to 77° F) and protected from light and moisture (USP Controlled Room Temperature). Dispense in a tight, light-resistant container as defined in the USP.

8.6.1.1. Drug returns from subjects

Subjects will be asked to return all bottles, whether empty or not, to the site. Unused SM-88, and MPS components, must be returned to pharmacy for counting and recording in the subject's Drug Accountability Log.

8.6.1.2. Drug destruction

Returned, unused or expired drugs should be destroyed only once permission has been granted by the Sponsor, as per the following table:

Table 16: Drug Dispensing Guidelines

Expired drug	Once authorized to do so by Sponsor, expired drug can be destroyed per local SOP or sent back to ALMAC if no such SOP exists
Drug left unused/not dispensed	Once authorized to do so by Sponsor, drug can be sent back to ALMAC
Subject returns	Upon receipt, number of capsules returned to be recorded on subject's Drug Accountability Log. At the end of the study, once authorized to do so by the Sponsor, any unused drug should be destroyed by the site. Accountability for the IP returned is logged in to the visit in which the IP was dispensed.

8.6.2. Part 2: Control Arm (Physician's Choice)

All Physician's Choice medication is to be sourced and funded locally. Drugs will be prescribed, tracked, and dispensed according to the local policy/SOPs for standard of care treatment.

8.6.2.1. Drug returns from subjects

Subjects randomized to capecitabine will be asked to return all bottles, whether empty or not, to the pharmacy for counting and recording in the subject's Drug Accountability Log.

8.6.2.2. Drug destruction

Returned, unused or expired drugs should be destroyed only once permission has been granted by the Sponsor as per "Subject returns" in Table 15 above.

8.7. Randomization and Blinding

This is a prospective, open-label, randomized Phase 2/3 trial design in pancreatic cancer subjects. The first part was a dose-selection study, examining at least 36 evaluable subjects who had failed at least one line of prior chemotherapy. Subjects were randomized between two doses of SM-88.

The subjects in Part 2 will be randomized 1:1 between SM-88 used with MPS, or Physician's Choice (from the treatment options noted in this protocol). The randomization will be balanced by investigative site, PS (ECOG 0-1 vs 2), and Physician's Choice of control group treatment as identified before Randomization. That is, prior to Randomization, each physician will choose from among the treatment options for the control group, and this choice will then be implemented as a balancing factor for Randomization and a stratification factor in the analysis of the results.

8.8. Concomitant Medications

Subjects will be instructed to consult the Investigator or other appropriate study personnel before taking any new medications or supplements during the study.

Concomitant medications taken within 30 days prior to baseline will be recorded. At each study visit, all concomitant medications taken since the previous visit, including prescription and non-prescription medications, vitamin and mineral supplements, herbal and naturopathic remedies, and supportive therapies, will be recorded.

- Treatment with any other anticancer agents is not allowed.
- Use of locally determined illegal drugs within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication and for the duration of the trial, including follow-up, will not be allowed.
- Use of the following medications is discouraged: Medications that are clinically known to induce or inhibit metabolic enzymes or transporters, including CYP3A4, CYP2C9, CYP2C19, and p-glycoprotein (Pgp) must be used with caution or avoided. Known strong inhibitors or inducers of CYP3A4, CYP2C9 or CYP2C19, such as those listed below, are not allowed:
    - CYP2C9:
        - Strong inhibitors: fluconazole
        - Strong inducers: none known
    - CYP2C19:
        - Strong inhibitors: fluconazole, fluvoxamine, ticlopidine
        - Strong inducers: none known
    - CYP3A4:
        - Strong inhibitors: atazanavir, boceprevir, ciclosporin, clarithromycin, conivaptan, danazol, erythromycin, gemfibrozil, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir,

posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole,
- Strong inducers: avasimibe, carbamazepine, phenobarbital, rifabutin, rifampin, St. John's Wort
- Delavirdine
- Cyclosporine
- Calcineurin inhibitors

- Medications that are clinically known to induce or inhibit metabolic enzymes or transporters, including CYP3A4, CYP2C9, CYP2C19 and Pgp must be used with caution or avoided.
- Use of medications that are known to significantly prolong the QT interval is discouraged.
- Cannabis or its products may not be used as a cancer therapy. Cannabis derivatives, including hemp, may be used by as supportive therapy, e.g., continued for nausea.
- Initiation of any new medication intended as an anti-neoplastic is not permitted.

8.9. Treatment Compliance

Treatment compliance will be assessed at each study visit after Day 1 and up to the end of the treatment period. Treatment compliance will be measured by counting capsules/tablets/bottles of SM-88 used with MPS or Physician's Choice components. Deviation from the prescribed dosage schedule will be recorded in the case report form (CRF).

SM-88 used with MPS subjects should be encouraged to be on a low-carb diet. Inability to maintain a low-carb diet does not exclude subjects from participation in the trial.

9. ASSESSMENT OF EFFICACY

Efficacy evaluations and endpoints will be performed at the times indicated in the Time and Events Schedule.

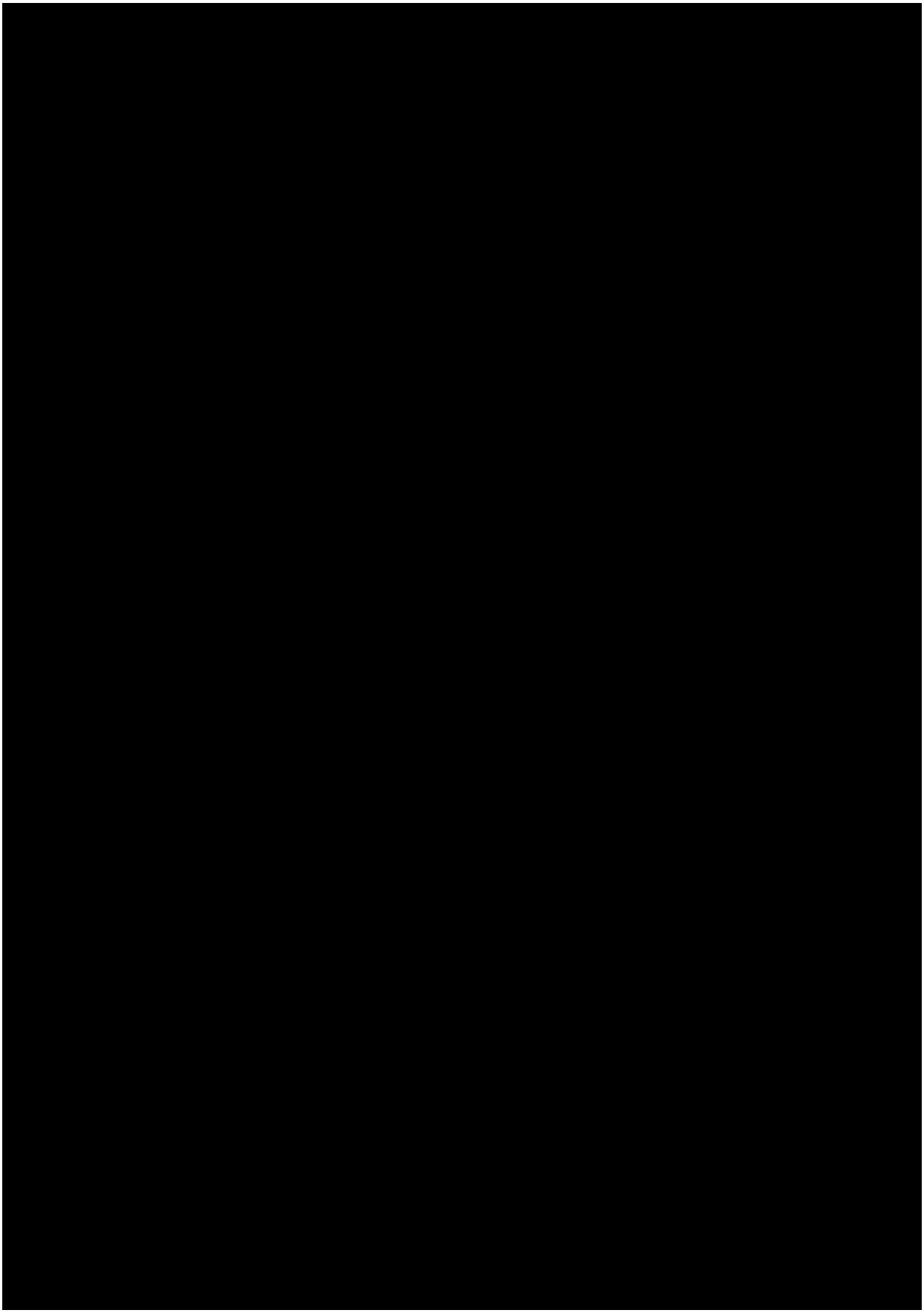
For Part 2 of this study, a total of approximately 250 subjects will be enrolled to obtain 125 subjects who have received one dose of SM-88 and 125 subjects in the control arm (Physician's Choice) and are thus evaluable for the primary endpoint of OS. In addition, a per-protocol population will be assessed for efficacy using efficacy evaluations after 4 full cycles of therapy (e.g., after confirmation of response per RECIST 1.1 in Part 1, and 2 full cycles in Part 2).

9.1. Overall Survival (OS)

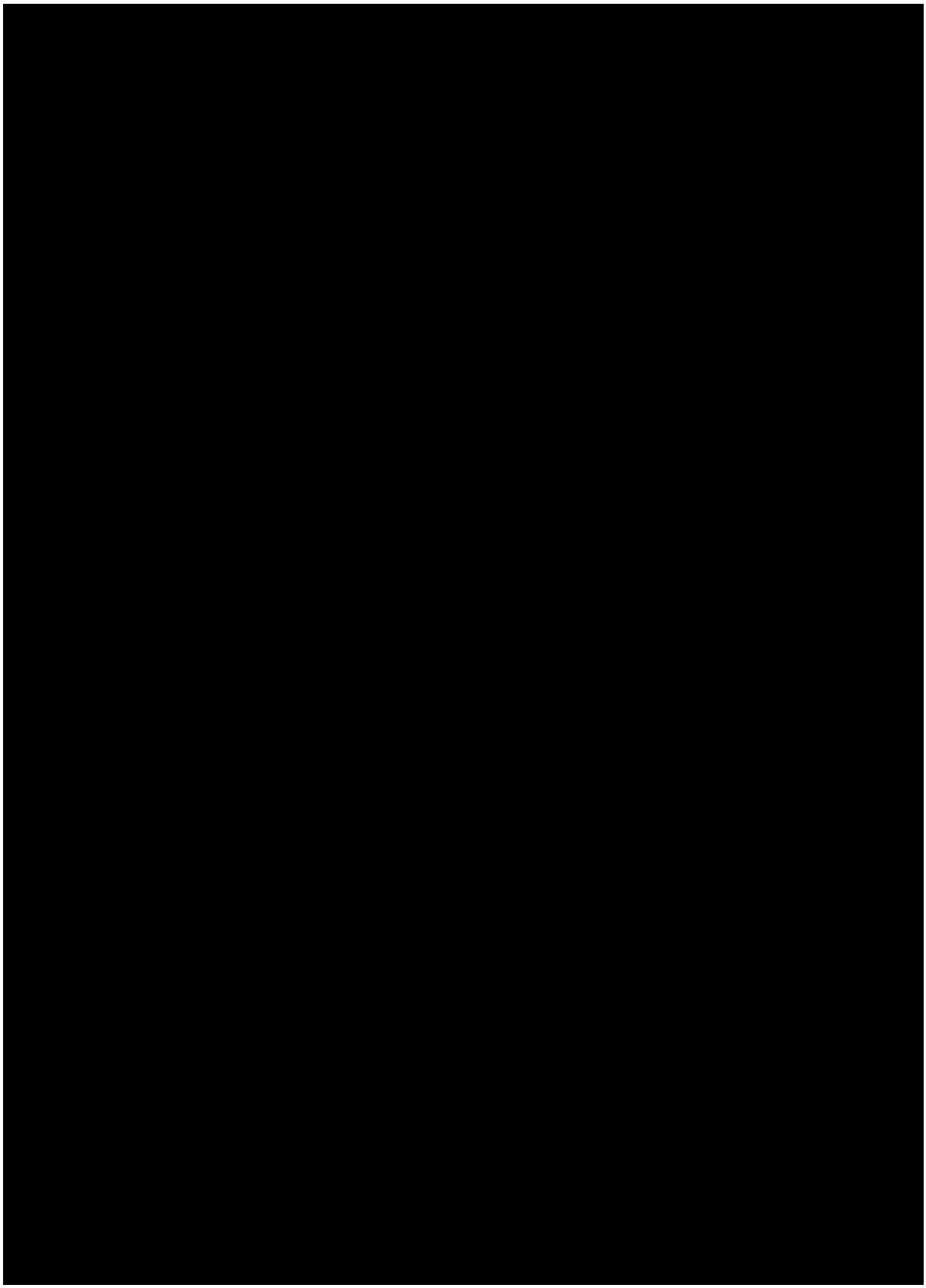
The primary endpoint of OS is defined as the time from Randomization until death from any cause. OS will be censored at the date of the last follow-up visit or last survival assessment contact (whichever is later) for subjects who were still alive, or whose survival status is unknown at the time of the analysis.

9.2. Progression-Free Survival (PFS)

PFS is defined as the time from the subject's date of Randomization to the date of first documentation of Progressive Disease (PD) or death due to any cause. PD can be defined clinically or radiographically, per Investigator assessment.



10. PHARMACOKINETIC ASSESSMENT



11. ASSESSMENT OF SAFETY

11.1. Safety Parameters

Safety evaluations will be performed at the times indicated in Table 5, Table 6, Table 7, Table 8, and Table 9 in all enrolled subjects.

11.1.1. Demographics and History

A complete medical history, including cancer history, will be obtained by the Investigator or qualified designee during screening. Cancer history will include data from the subject's pathology reports, including tumor grade, histology, BRCA 1 and 2, MSI, PD-L1, CDKN2A, SMAD4, KRAS, ATM, ATC, PALB2, HER-2, ERCC1, IGF-1, IDO, MEK, PTEN, and ARID1A, if available.

Subject demographics will also be recorded at screening.

11.1.2. Vital Signs

Vital signs will include blood pressure, respiratory rate, pulse, oxygen saturation, weight and temperature. All scheduled vital signs will be measured before any blood draws scheduled for the same time point. Measurements should be taken per institutional guidelines. The time of the previous study drug administration will be recorded.

11.1.3. Physical Examination

The Investigator or qualified designee will perform complete physical examinations at screening and at the end of treatment visits. At all other study visits, an abbreviated physical examination will be performed to monitor for changes. Body weight should be measured at each physical examination. Height should be measured at screening.

11.1.4. Electrocardiogram

12-lead ECG reporting ventricular rate, PR, QRS, QT, and QTc intervals should be obtained at the visits indicated in the Time and Events Schedules. All scheduled ECGs will be collected in triplicate (for time-matched PK sampling) or single reports, and will be performed before any blood draws scheduled for the same time point. Subjects should be resting quietly and free of distraction for 10 minutes prior to ECG collection. The Investigator or a qualified designee will review all ECGs. The time of the previous study drug administration will be recorded. ECGs will be performed at Screening (single), Day 1 of Cycles 1 and 2 (time-matched to PK sample collection for subjects in SM-88 arm only), and at subjects' Day 28 follow-up visit (single).

11.1.5. Safety Laboratory Assessments

Laboratory samples for the appropriate analyses should be taken at the times indicated in the Time and Events Schedule tables. Local laboratories at each site will be responsible

for analysis of all safety laboratory samples. The date and time that each sample is collected should be recorded. All clinical laboratory results will be reviewed by the Investigator, or a qualified designee, for clinical significance.

The laboratory analytes listed in Table 17 will be tested. White blood cell (WBC) differentials will be reported as absolute counts. Other safety and efficacy laboratory measures, as listed in Section 9.5, include CEA, LDH, total alkaline phosphatase, bone-specific alkaline phosphatase, cortisol, hemoglobin, WBC, ANC, leptin, cholesterol, triglycerides, NLR and levels of SM-88, methoxsalen, phenytoin, and sirolimus.

11.1.6. Ophthalmologic Exam (only required for those subjects enrolled in Part 1)

Studies may require that Investigators arrange to obtain information critical to the study that cannot be obtained at the Investigator's site. Since this study protocol requires testing with special equipment or expertise that may not be available at the Investigator's site, the Investigator may make arrangements for an outside facility to perform the test. In this case, the results are usually provided directly to the Investigator, who then submits the information to the Sponsor. If the Investigator retains the services of a facility to perform study assessments, the Investigator should take steps to ensure that the facility is adequate (e.g., has the required certification or licenses).

The Sponsor will allow providers licensed in the local regulatory consistent with the following guidance:

- The exam can be performed by an individual whom the PI considers suitably trained.
- This exam can be performed as part of the Standard of Care (SOC).
- Further, although it is expected that an ophthalmologic exam, as part of the SOC, would have been performed recently within the protocol-specified window, if that is not the case, the Sponsor will reimburse the site for conducting an ophthalmologic exam as per local SOC, provided that it meets the minimum requested fields of the EDC.
- Screening exam window is within 1 year of Randomization into the study.

Data collected during the SOC visit will be entered in the EDC system. Data fields provided by Tyme, and to be collected for the Ophthalmology exam, will include the following:

- Record OU at baseline (+30 days) for all subjects and q 12 mo (+30 days) for those subjects subsequently randomized to SM-88 used with MPS arm of treatment
- Acuity best corrected
- Acuity Uncorrected
- Correction factor/RX
- Cataracts present? – If subject has cataracts, they should be graded per clinician SOC, who must use the same methodology of grading for follow-up evaluations.

a) Retina evaluation - normal, or not [if not, describe per clinician SOC; must use same for follow-up evaluation]

The PI will evaluate the subject at each visit for clinically significant changes in visual signs and symptoms.

Table 17: Safety Laboratory Analytes

Serum Chemistry	Hematology	Urinalysis
Sodium	Erythrocyte count	Color
Potassium	Hematocrit	Specific gravity (Part 2)
Chloride	Absolute reticulocyte count	pH (Part 2)
Glucose	Mean cell volume	Protein
Blood urea nitrogen	Mean cell hemoglobin	Glucose
Creatinine	Mean cell hemoglobin concentration	Ketones
	Leukocytes	Blood
Alanine aminotransferase	Neutrophils	Bilirubin
Aspartate aminotransferase	Lymphocytes	Urine N-telopeptide
Total bilirubin	Monocytes	Leukocyte esterase
Total protein	Basophils	Nitrites
Albumin	Eosinophils	
Calcium	Platelets	
Magnesium		
Phosphate		
Total Cholesterol		
HDL		
LDL		
Triglycerides		

Other Laboratory Tests
SM-88
Phenytoin
Methoxsalen
Sirolimus
Other Laboratory Tests for Screening Only
Serum cortisol International normalized ratio (INR) Human immunodeficiency virus (HIV) Hepatitis B surface antigen Hepatitis C virus Pregnancy test (urine or serum)

11.2. Adverse Events (AE)

11.2.1. Definition of Adverse Events

11.2.1.1. Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, whether or not considered drug-related. An AE can therefore be any favorable, unfavorable and/or unintended sign (including an abnormal clinical laboratory, ECG, or vital sign finding), symptom, or disease temporally associated with the use of a medicinal product. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

11.2.1.2. Serious Adverse Event (SAE)

An AE is considered serious if, in the view of either Investigator or Sponsor, it results in any of the following outcomes:

- Death, unless attributable to the cancer progression
- A life-threatening AE

An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include

an AE that, had it occurred in a more severe form, might have caused death. The determination of whether an AE is life-threatening can be based on the opinion of either the Investigator or Sponsor. Thus, if either believes that it meets the definition of life-threatening (possible examples listed below), it must be considered life-threatening for reporting purposes:

- In subject hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject or subject may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in subject hospitalization, or the development of drug dependency or drug abuse.

This definition of a serious adverse event (SAE) permits either the Sponsor or the Investigator to decide if an event is serious. Because SAEs are critically important for the identification of significant safety problems, the FDA believes taking into account both the Investigator's and the Sponsor's assessment is important. For example, the Investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event. If either the Sponsor or Investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for possible expedited reporting.

11.2.2. Relationship to Investigational Product or Study Procedures

The Investigator or qualified Sub-Investigator is responsible for assessing the relationship to the investigational product using clinical judgment and the following considerations:

- No (Not Related): Evidence exists that the AE has an etiology other than the investigational product. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- Yes (Related): There is reasonable possibility that the event may have been caused by the study drug.

The relationship to study procedures (e.g., invasive procedures, such as venipuncture) should be assessed using the following considerations:

- No (Not Related): Evidence exists that the AE has an etiology other than the investigational product.
- Yes (Related): The AE occurred as a result of the protocol procedures (e.g., venipuncture).

11.2.3. Assessment of Severity

The severity of AEs will be graded using CTCAE, version 4.03 (National Cancer Institute CTCAE web site). For each episode, the highest severity grade should be reported.

If a CTCAE criterion does not exist, the Investigator should use the appropriate grade as shown in Table 18.

Table 18: Grading of Adverse Event Severity

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

The distinction between the seriousness and the severity of an AE should be noted. Severity is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for SAEs listed in Section 11.2.1.2.

11.2.4. Reporting Adverse Events

The occurrence and nature of each subject's preexisting conditions will be recorded at screening, including clinically significant signs and symptoms of the disease under treatment. After the informed consent form is signed, any change in the conditions and the occurrence and nature of any AEs will be recorded, as described in the sections above. AEs occurring after a subject has taken the last dose of investigational product should be collected until 28 days after the last dose. All AEs should be followed up until resolution or until the AE is stable.

Cases of pregnancy that occur in the partner of a subject enrolled in this study, including fetal outcome, should be reported.

Site personnel must inform the Tyme Medical Monitor or the Clinical Research Organization (CRO) Medical Monitor of any SAE within 24 hours of the Investigator's awareness of the event. If the Medical Monitor is contacted by telephone, the site personnel must immediately follow-up with official notification on study-specific SAE forms.

12. STATISTICS

A preliminary summary of the statistical analyses planned for this study is provided in the sections below. Additional analyses may be conducted as deemed appropriate and will be detailed in a Statistical Analysis Plan (SAP).

Descriptive statistics will be employed to summarize the data. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum); categorical variables will be presented as frequency counts and percentages.

Time-to-event analyses will be reported by Kaplan-Meier quartiles and curves. Data listings will be created to support each table and to present all data.

12.1. Hypotheses

[redacted]

Part 1 Sample Size (Original Trial Design)

The first 36 subjects enrolled in the study will be randomized to two different dose levels of SM-88 for PK assessments and dose-selection for continued testing (see treatment plan above). Randomization will be conducted by interactive web randomization system (IWRS). The sample size will provide PK results to ensure acceptably precise estimates of traditional parameters (e.g., Cmax, T_{max}, t½ and AUC). To adequately estimate the t½, 36 subjects are needed ($n=ZP^2POP^2P/\varepsilon P^2$ P where Z=1.96; O is the standard deviation from Tyme's previously reported PK, which is approximately 3 hours and the acceptable ε is 1 hour). Similarly, to accurately estimate the OS at 6 months, assuming an OS of 90% would be significant, with Z=1.96, β=0.9 and α=0.1, then the initial cohort at 36 subjects for the PK portion of the trial will provide a 90% CI of OS ± 10%.

The selected SM-88 dose will then be used for the expansion cohort for the additional subjects to reach 99 evaluable subjects who have completed at least two full cycles of therapy at a single dose level (i.e., 81 subjects in the expansion cohort) for an overall approximate 80% power to detect at least a 16% ORR by BICR using modified RECIST 1.1 with a one sided $\alpha = 0.05$.

Part 2 Sample Size

Part 2 of the trial was amended to become a Phase 2/3, two-arm study with SM-88 versus a Physician's Choice control. The trial will accrue 250 subjects, with 125 in each arm.

The primary objective for Part 2 of this trial is to determine the OS of SM-88 used with MPS vs. the control arm. The primary endpoint of Part 2 will be the time from Randomization to death from any cause.

The primary endpoint is OS, and it was estimated that the control group would have a median survival time of approximately 3 months, based on reports in the literature, while the SM-88 group would have a median survival time of approximately 4.5 months (i.e., hazard ratio of 0.667). In order to have 80% power, using a two-sided log-rank test with a significance level of 0.025, a total of 234 events will be required. It is estimated that n=250 subjects (125 subjects in each arm) will need to be enrolled to achieve 234 events.

To account for dropouts of subjects who withdraw for reasons other than any of the outcomes (death, PD, or toxicity), additional subjects may be enrolled to ensure adequate number of subjects who have received at least one dose of the study treatments (the primary study per protocol cohort). The total number of subjects consented will depend on the number of subjects receiving study treatment.

Randomization will be 1:1, balanced by investigative site, ECOG PS (0-1 vs. 2), and Physician's Choice of control group treatment as identified before Randomization.

12.2. Analysis Considerations

12.2.1. Analysis Populations

The following analysis populations will be used for the data reporting of the response and toxicity data. All results will be first described using simple descriptive statistics.

Safety Population: All subjects enrolled in the study who receive at least one dose of study drug will be included in the safety population. This will be the population for the safety analyses and for summarization of baseline/demographic characteristics.

Quarterly safety assessments of the entire cohort will be conducted depending on the number of subjects available for analysis. These quarterly assessments by the DSMB and Sponsor will begin no later than after the first 36 subjects have completed at least one cycle.

Intent-to-Treat (ITT) Population: All subjects enrolled in the study and randomized to treatment will be included in the intent-to-treat population. This will be the population for the primary efficacy analyses.

Modified Intent-to-Treat (mITT) Population: All subjects in the ITT population who receive at least one dose of study drug will be included in the modified intent-to-treat population.

Evaluable Population: All subjects in the ITT population enrolled in the study who receive at least 1 cycle (28 days) of study drug will be included in the evaluable population. This same population will be used by the DSMB, PIs and Sponsor to determine the RP2D.

Evaluable 4-Cycle Population: All subjects in the ITT population who received at least 4 cycles (28 day cycles) of study drug and 2 imaging assessments past baseline will be included in the Evaluable 4-Cycle Population. This population will exclude those subjects who received treatment of less than 4 cycles or those who received less than 50% of the anticipated treatment during the first 16 weeks of the trial for reasons other than a DLT.

Pharmacokinetic Population: The PK Population will include all subjects who undergo plasma/blood PK sampling and have at least one evaluable assay result.

Per-Protocol (PP) Population: The per-protocol (PP) population will include subjects in the Evaluable population who did not have major protocol deviations. A protocol deviation will be considered major it potentially has an impact on the assessment of efficacy for that patient. The determination of major deviations will occur prior to database lock, and any such deviations will be presented in listings.

12.2.2. Exploratory Combined Population

[redacted]

12.2.3. Initial Analysis

For Part 1, a cohort of 36 subjects will be randomized one-to-one to the SM-88 component at either 230 mg b.i.d or 460 mg b.i.d. Once the 36-subject cohort has completed 16 weeks (4 cycles, 2 scheduled imaging assessments) of treatment, an analysis of safety and efficacy will be conducted.

[redacted]

Note that the statistical tests in the above table will be used to inform the decision-making process, but that clinical judgment (especially as related to the overall safety profile of the two dose groups) will be used to make the final dose selection decision based on the consensus of the clinical judgment of PIs, DSMB, and Sponsor.

Acknowledging that the power will be very low for virtually any conditions, we will only use the formal statistical testing to help inform a decision. The selected dose will then be used for the expansion cohort.

12.3. Final Analysis

12.3.1. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, ophthalmologic examinations (Part 1 only), vital signs measurements, ECG readings and drug levels at various time points during the study, and by the documentation of AEs.

Dose-limiting toxicities will also be listed and summarized by dose cohort in the randomized portion of the Phase 2.

AE verbatim text will be coded and classified by body system and preferred (coded) term using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs, both serious and non-serious, will be listed. AE summaries by study part and treatment group, of the number and percent of subjects reporting each event at least once will be generated.

Clinical chemistry and hematology data will be summarized at each scheduled assessment. Results will be flagged using toxicity grades, if available, or as normal or abnormal (high or low) with reference to standard reference ranges.

ECOG Performance Status assessments will be listed and summarized by the originally assigned dose level for a given combination regimen. Vital signs will be recorded for each subject at all measured time points. A descriptive summary, including change from baseline pre-dose time points will also be presented.

Other safety data will be summarized descriptively by treatment and assessment time. Details will be provided in the SAP.

12.3.2. Efficacy Analyses

Part 1

Primary Objectives

[redacted]

[redacted]

Secondary Objectives

PFS is defined as the time from the subject's date of Randomization to the date of first documentation of PD, or clinical (radiographic or symptomatic per Investigator assessment) or death due to any cause, or RECIST by blinded independent radiology review. PFS will be summarized by using a Kaplan-Meier plot, quartile estimates, along with 2-sided 95% CIs. PFS will be censored at the date of the last follow-up visit for the subjects who were still alive and had no documented disease progression.

OS is defined as the time from Randomization until death from any cause. Kaplan-Meier estimates and associated two-sided 90% CIs of OS at 6, 12 and 18 months will be presented along with median OS time. OS Kaplan-Meier curves will also be presented. OS will be censored at the date of the last follow-up visit for subjects who were still alive, or whose survival status is unknown at the time of the analysis.

[redacted]

Part 2

Primary Objectives

The primary objective of this part of the study is to determine the OS time to event characteristics of the SM-88 used with MPS vs. the control arm.

The primary endpoint of OS is defined as the time from Randomization until death from any cause. OS will be censored at the date of the last follow-up visit or last survival assessment contact (whichever is later) for subjects who were still alive, or whose survival status is unknown at the time of the analysis. The efficacy of SM-88 used with MPS will be compared to Physician's Choice for OS, using a log-rank test, stratified by the randomization stratification factors of investigative site, Physician's Choice, and ECOG PS. The analysis will not be stratified by individual investigative site since there are a large number of sites and it is expected that many will have only a few subjects. However, aggregate site factors, such as distance traveled to the site or high vs. low accruing sites, will be included for analysis. An exploratory analysis by site may be conducted (e.g., early vs. late enrollment, high vs. low recruitment). A Kaplan-Meier plot, and quartile estimates with 2-sided 95% CIs will also be presented, along with Kaplan-Meier estimates and 95% confidence intervals for OS at 6, 12 and 18 months.

Key Secondary Objective

PFS is defined as the time from the subject's date of Randomization to the date of first documentation of Progressive Disease (PD) or death due to any cause. PD can be defined clinically or radiographically, per Investigator assessment. PFS will be summarized by using Kaplan-Meier plot, quartile estimates, along with 2-sided 95% CIs. PFS will be censored at the date of the last follow-up visit for the subjects who were still alive and had no documented disease progression. The analysis of treatment differences in PFS will be conducted using the same methods as for the primary analysis of OS, described above.

Additional Secondary Objectives

[redacted]

Exploratory Objectives

[redacted]

12.3.3. Interim Analysis

The statistical plan as described in the protocol was designed to conduct the final OS analysis when 234 total events have occurred, which is expected to happen approximately one (1) year after the last subject is enrolled. Given the poor prognosis of the control arm subjects, as reported in the literature, a planned interim efficacy analysis will be performed, allowing for the possibility of early stopping for efficacy. The planned interim efficacy analysis, with the chance for early stopping, will be conducted when 75% of the approximately 234 assumed total events have been reached. It is estimated that the planned interim efficacy analysis will occur at around 15-18 months into the trial.

The primary endpoint is OS, and it was estimated that the control group would have a median survival time of approximately 3 months, based on reports in the literature, while the SM-88 group would have a median survival time of approximately 4.5 months (i.e., hazard ratio of 0.667). In order to have 80% power, using a two-sided log-rank test with a significance level of 0.025, a total of 234 events will be required. It is estimated that n=250 subjects (125 subjects in each arm) will need to be enrolled to achieve 234 events.

It is estimated that 75% of the approximately 234 assumed total events would occur at around 15-18 months into the trial. The decision rule boundary for early stopping due to efficacy will be based on the O'Brien-Fleming method (O'Brien and Fleming 1979; Lan and DeMets 1983), using the actual information fraction at the time of the interim via the alpha spending approach of Lan and DeMets (1983). For illustration, if the interim occurred at precisely 75% information, it would then only stop for efficacy at that point (and declare the drug to be a success) if the p-value was less than 0.0079. This yields a probability of early stopping at the interim of 51%, based on a total sample size of n = 250, i.e., the maximum sample size required in this design.

12.3.4. Pharmacokinetic Analyses

12.3.4.1. Non-compartmental Pharmacokinetic Analyses

Plasma/blood concentrations of SM-88 (both isomers), methoxsalen, phenytoin, and sirolimus (MPS) will be determined by validated assays. In Part 1, PK analysis of SM-88 (both isomers), methoxsalen, phenytoin, and sirolimus concentration-time data will be conducted by non-compartmental methods. The following PK parameters will be determined if data permit:

- C_{max}
- T_{max}
- $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and/or AUC_{tau}
- λz
- $t_{½}$
- CL/F
- Vz/F

In Part 2, population PK analysis modeling will be employed.

13. RESPONSIBILITIES

13.1. Investigator Responsibilities

13.1.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (2013), International Conference on Harmonization (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.

The Investigator will ensure that the basic principles of Good Clinical Practice, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC, which shall be adhered to.

Since this is a clinical trial conducted under IND oversight, the Investigator will ensure that 21 CFR, Part 54, 1998, is adhered to. A clinical trial conducted under IND oversight is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Investigators and all Sub-Investigators must provide documentation of their financial interest or arrangements with Tyme, Inc. or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any Sub-Investigator. The Investigator and Sub-Investigator agree to notify Tyme, Inc. of any change reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

13.1.2. Institutional Review Board Approval

This protocol 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) will be submitted by the Investigator to an IRB. Approval from the IRB must be obtained before starting the study and should be documented in a letter to the Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol or other documents described in the above paragraph after receipt of IRB approval must also be submitted to the IRB for approval before implementation.

13.1.3. 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 utilize an IRB-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

13.1.4. Treatment Withdrawal

During the course of the trial, a subject may withdraw early from treatment. This may happen for a number of reasons, including:

- Unacceptable toxicity, including but not limited to:
    - Life-threatening Grade 4 toxicity.
    - Repetition of non-life-threatening Grade 4 toxicity despite per protocol dose reduction.
    - Delay of a treatment cycle for more than 28 consecutive days beyond the due date
- Objective evidence of PD as determined by CT scan and/or X-ray and/or ultrasound and/or clinical examination
- Clinical decision by the Investigator that continued participation in the trial is contrary to the subject's best interests
- Patient decision to discontinue treatment (as opposed to continued participation in all other aspects of the study, e.g., following for OS). When a subject stops treatment early, an 'End of Treatment' Form should be completed, and any other relevant form (for example, a SAE Form). The reason for withdrawing from treatment early should be clearly documented in the medical records. An off-study visit assessment should be performed and the results of the evaluations and observations reported in the CRF.

13.1.5. Withdrawal of Consent

Withdrawal of consent represents that rare subject who has expressed a wish to withdraw from the study altogether. Under these circumstances, the site needs to document all relevant discussions in the subject notes and notify the Sponsor CRO. Under these conditions, ongoing SAEs require follow up until resolution. Some local IRBs may allow continued determination of OS based on publicly available data (e.g., social media).

13.1.6. Confidentiality

The Investigator must assure that subjects' personal health information will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB, or laboratory. 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.

The Investigator agrees that all information received from Tyme, Inc., including but not limited to the Investigator Brochure, this protocol, CRFs, the investigational product, and any other study information, remain the sole and exclusive property of Tyme, Inc. 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 Tyme, Inc. 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.

13.1.7. 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: the Investigator's study file, and the subject clinical source documents.

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

The Investigator will keep records of laboratory tests, clinical notes, subject medical records, and any other appropriate documents in the subject files as original source documents for the study.

All clinical study documents must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated 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 required by applicable regulatory requirements, by local regulations, or by an agreement with Tyme, Inc. The Investigator must notify Tyme, Inc. before destroying any clinical study records.

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

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and Tyme, Inc. to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 2 years for purposes of this study.

13.1.8. Case Report Forms

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each subject within a reasonable time period after data collection. The completed original CRFs are the sole property of Tyme, Inc. and should not be made available in any form to third parties, except for authorized representatives of Tyme, Inc. or appropriate regulatory authorities, without written permission from Tyme, Inc.

The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all data entered on the CRFs and any other data collection forms. The CRFs must be signed by the Investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

13.1.9. Drug Accountability

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused investigational product. This includes acknowledgment of receipt of each shipment of investigational product (quantity and condition), subject dispensing records, and returned or destroyed investigational product. Dispensing records will document quantities received from Tyme, Inc. and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, and the initials of the person dispensing the investigational product.

The Investigator or his/her designee will be responsible for maintaining accurate records of investigational product dispensing and collection and for returning all unused investigational product to Tyme, Inc. or its designee at the end of the study. Detailed instructions for return of investigational product will be provided upon request and when required.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

13.1.10. Audits and Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from Tyme, Inc. or its representatives, to IRBs, or to regulatory authority or health authority inspectors.

13.1.11. Protocol Compliance

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

13.2. Sponsor Responsibilities

13.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Tyme Inc. All protocol modifications must be submitted to the IRB in accordance with local requirements. Approval must be obtained before changes can be implemented.

13.2.2. Study Report, Presentations and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). Tyme, Inc. 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.

After conclusion of the study, Investigators in this study may not share, communicate, orally present, or publish in any manner, including scientific journals or other scholarly media, without the explicit written approval of Tyme, Inc. No such communication, presentation, or publication will include Tyme, Inc. confidential information (see Section 13.1.6).

The Investigator will submit any proposed abstract, publication or presentation along with details of the respective scientific journal or presentation forum, at least 30 days before the publisher or meeting deadline for submission of the publication or presentation, respectively. The Investigator will comply with Tyme, Inc. 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.

13.2.3. Data and Safety Monitoring

There is a DSMB that will be in place to monitor the safety and progress of the trial, and to make the decision regarding early stopping for efficacy at the interim analysis in Part 2.

13.3. Joint Investigator/Sponsor Responsibilities

13.3.1. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the CRFs for consistency.

The monitor is responsible for routine review of the CRFs 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 CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

13.3.2. Access to Information for Auditing or Inspection

Representatives of regulatory authorities or of Tyme, Inc. 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 Tyme, Inc. Medical Monitor immediately. The Investigator agrees to provide to representatives of a regulatory agency or Tyme, Inc. access to records, facilities, and personnel for the effective conduct of any inspection or audit.

13.3.3. Study Discontinuation

The Sponsor reserves 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) and IRBs. In terminating the study, Tyme, Inc. and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

14. APPENDIX A: SM-88 MOA

The components of SM-88 used with MPS are thought to be effective in altering cancer cell metabolism and as antineoplastics (Liu et al., 2004; Enriquez-Navas et al., 2016; Joka et al., 2014).

SM-88 used with MPS related agents have been previously described to possess characteristics now proposed by several groups as anticancer agents (Ruggiero et al., 2012; Engel and Evens, 2006; Lordan et al., 2008; Vejux and Lizard, 2009; Leonarduzzi et al., 2007; Kasichavanula et al., 2014; Gibbons 2002; Imaoka et al., 2004; Hu et al., 2005; Steffen et al., 2006; Trachootham et al., 2009) and have been used clinically in the treatment of other neoplastic conditions (Perry et al., 1990). Similarly, CYP3A4 inducers, including phenytoin, have been "repurposed" for other novel off-label uses (Fillekes et al., 2013). In some cases, repurposed, off-label uses of untraditional anti-neoplastic non-cytotoxic drugs have been associated with an OS significantly longer than the standard of care (Watkins et al., 2015). When considering repurposing drugs approved for uses outside of cancer treatments for use in cancer therapies, the history of prior clinical use often provides support for safe use in cancer subjects, especially when approved uses require higher doses than proposed for use in cancer treatment (Perry et al., 1990; Bremner et al., 2003).

Here we discuss possible mechanisms of action for the four components of SM-88 used with MPS.

SM-88:

Tyrosine isomers are employed in SM-88 to interfere with the cancer cell's ability to create peptides, especially high turnover ones (Ruggiero et al., 2012; Hosios et al., 2016). Biopsies and other results suggest that there is increased inflammation associated with SM-88 activity (Personal communication, QRI JS, proprietary unpublished data) consistent with an attenuation of a barrier between tumors and the host immune system. It is interesting to note that in today's research environment that mucin is a one such high turnover glycoprotein, important as a barrier against the host immune system, which is exploited by current immune-oncology therapies. Equally interesting is that specific changes in dietary amino acid supplementation is also recognized as affecting mucin production (Faure et al., 2006). It is encouraging that in 2016 and 2017, the FDA approved amino acids for imaging of cancers, and as therapy for a hematologic disorder, respectively:
(https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503920.htm ; https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm566097.htm?platform=hootsuite).

Cancer's altered glucose utilization, and preferred amino acid/lipid use as energy sources, may be considered similar to a ketotic state (Epstein et al., 2014). Therefore, a preferential utilization of the tyrosine isomers and reactive lipid species may be further enhanced after a short fast just before administering SM-88 used with MPS, as specified

in the treatment protocol. Current imaging makes use of a related mechanism and recommends fasting to enhance tyrosine-based and other PET imaging, e.g., ^{18}F-fluoro-α-methyl tyrosine (Wang et al., 2011; Suzuki et al., 2014). FDG-PET, also demonstrates that mammalian target of rapamycin (mTOR) inhibitors are able to further reduce glucose uptake by cancer cells and would therefore also support the hypothesis that SM-88 components increase alternative energy substrate utilization such as the substituted tyrosine and induced reactive oxygen lipid species (Chen et al., 2013; Boers-Sonderen et al., 2014).

The sirolimus and SM-88 components of the regimen may also be acting through additional pathways. For instance, induction of L-type amino acid transporter (LAT1) is important in the prognosis and potential treatment of numerous cancer types. LAT1 also facilitates the intracellular delivery of amino acids including tyrosine (Stretton et al., 2015; Yazawa et al., 2015; Ruggiero et al., 2012). SM-88 used with MPS provides a mixture of non-nutritive tyrosine isomers that are unable to be used in cellular metabolism (Ruggiero et al., 2012).

Phenytoin:

Cytochrome P4503A4-inducing agents (e.g., phenytoin), stimulate the synthesis of reactive oxygen lipid species such as cholesterol, oxysterols, and related lipoproteins. These in turn are a source of high oxidizing potential molecules (Wang and Yi, 2008; Engel and Evens, 2006; Lordan et al., 2008; Lordan et al., 2009a; Lordan et al., 2009b; Vejux and Lizard, 2009; Leonarduzzi et al., 2007; Kasichayanula et al., 2014; Gibbons, 2002; Imaoka et al., 2004; Pedruzzi et al., 2004; Hu et al., 2005; Steffen et al., 2006; Trachootham et al., 2009). Elevated levels of cholesterol, and oxidized cholesterol (oxysterols) can have direct effects on the membrane to disaggregate portions and make them “leaky”, or to affect cholesterol rafts, thus disrupting cell signaling (Simons and Toomre, 2000; Janes et al., 1999; Gniadecki et al., 2002). ROS, such as these lipids, also stimulate apoptosis (Gniadecki et al., 2001; Kim et al., 2006).

Deprived of glucose and needing amino acids, cancer cells actively takes up lipids as fuel. This increase uptake of lipids and shift to lipid metabolism, is routed to the mitochondria for oxidation (Gniadecki et al., 2001; Kim et al., 2006). There, high levels of cholesterol and oxysterols in the presence of melanin, overwhelm the protective mechanisms that prevent free radical damage, inducing mitochondrial oxidation, depolarization, and apoptosis (Mostert et al., 2012; Gray-Schopfer et al., 2007). The propensity for lipids to be spontaneously peroxidized and to stimulate oxidative stress provides another SM-88 mechanism for targeted cancer cell damage and death (Akladios et al., 2015).

Methoxsalen:

Melanin contributes to the lethal interaction of cells with deleterious reactive oxygen species. Melanin functions as an intracellular catalyst similar to platinum, but with less toxicity (McGinness, 1972; McGinness, 1974; Menter et al., 1990). Melanin-inducing agents are utilized in clinical oncology to treat resistant cancers when combined with oxidizing agents (Edelson et al., 1987; Wozniak et al., 2009). They are not cytotoxic unless used with an energy source (e.g., reactive lipid oxidative species).

Sirolimus:

Sirolimus, like other mTOR inhibitors, is an essential regulator of cellular lipids, protein synthesis, and proliferation (Shigemitsu et al., 1999; Hara et al., 1998; Lin et al., 1995; Hay and Sonenberg, 2004). This is at least partly mediated by effects on insulin, serine/threonine protein kinase B (AKT) and insulin-like growth factor (IGF) (Patti et al., 1998; Xiao et al., 2011; Cheng et al., 2010). Even at low doses, these mechanisms may reduce the availability of typical extracellular nutrients, e.g. glucose, thus increasing the tumor cells' already exaggerated metabolic demand to use alternative energy sources i.e., lipids and amino acids (again part of the Warburg effect) provided by the other components of SM-88 (Proud 2007; Vendelbo et al., 2014; Motzer et al., 2014; Joka et al., 2014; Gillies et al., 2015).

15. APPENDIX B: DETAILED DESCRIPTIONS OF ADVERSE EVENTS

Related to Phenytoin

Withdrawal Precipitated Seizure, Status Epilepticus

Abrupt withdrawal of phenytoin in epileptic subjects may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative anticonvulsant medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, more rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an anticonvulsant not belonging to the hydantoin chemical class.

Suicidal Behavior and Ideation

Phenytoin can increase the risk of suicidal thoughts or behavior in subjects. Subjects should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. The increased risk of suicidal thoughts or behavior can occur as early as one week after starting treatment and persist for the duration of treatment. Should suicidal thoughts and behavior emerge during treatment, Investigators need to consider whether the emergence of these symptoms in any given subject may be related to the disease being treated. Subjects, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence of or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported with phenytoin treatment. The onset of symptoms is usually within 28 days but can occur later. Phenytoin should be discontinued at the first sign of a rash, unless the rash is clearly deemed not drug-related. If signs or symptoms suggest SJS/TEN, phenytoin should be discontinued and not re-administered. If a rash occurs, the subject should be evaluated for signs and symptoms of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see next paragraph).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multiorgan hypersensitivity

DRESS, also known as Multiorgan hypersensitivity, has been reported in subjects taking phenytoin. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute

viral infection. Eosinophilia is often present. Because this disorder varies in its expression, other organ systems not noted here may be involved, and it is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the subject should be evaluated immediately. Phenytoin should be discontinued and not re-administered if an alternative etiology for the signs or symptoms cannot be established.

Hypersensitivity

Subjects with a history of hypersensitivity to phenytoin, its inactive ingredients, or other hydantoins; or a history of prior acute hepatotoxicity attributable to phenytoin, are excluded from this trial (see Exclusion Criteria). If there is a history of hypersensitivity reactions to structurally similar drugs, such as carboxamides (e.g., carbamazepine), barbiturates, succinimides, and oxazolidinediones (e.g., trimethadione) in the subject or immediate family members, care must be taken to avoid potential subjects' hypersensitivity to phenytoin. Discontinue and do not re-administer phenytoin if subjects exhibit hypersensitivity to phenytoin during the study.

Hepatic Injury

Cases of acute hepatotoxicity, including infrequent cases of acute hepatic failure, have been reported with phenytoin. These events may be part of the spectrum of DRESS or may occur in isolation. Other common manifestations include jaundice, hepatomegaly, elevated serum transaminase levels, leukocytosis, and eosinophilia. The clinical course of acute phenytoin hepatotoxicity ranges from prompt recovery to fatal outcomes. In these subjects with acute hepatotoxicity, Phenytoin should be immediately discontinued and not re-administered.

Hematopoietic Complications

Hematopoietic complications, some fatal, have occasionally been reported in association with Phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs of DRESS. In all cases of lymphadenopathy, follow-up observation for an extended period is indicated.

Effects on Vitamin D and Bone

The chronic use of phenytoin in subjects with epilepsy has been associated with decreased bone mineral density (osteopenia, osteoporosis, and osteomalacia) and bone fractures. Phenytoin induces hepatic metabolizing enzymes. This may enhance the metabolism of vitamin D and decrease vitamin D levels, which may lead to vitamin D

deficiency, hypocalcemia, and hypophosphatemia. Consideration should be given to screening with bone-related laboratory and radiological tests as appropriate and initiating treatment plans according to established guidelines.

Renal or Hepatic Impairment or Hypoalbuminemia

Because the fraction of unbound phenytoin is increased in subjects with renal or hepatic disease, or in those with hypoalbuminemia, the monitoring of phenytoin serum levels should be based on the unbound fraction in those subjects.

Exacerbation of Porphyria

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in subjects with porphyria.

Teratogenicity and Other Harm to the Newborn

In this study, female subjects must either be of non-reproductive potential, not breast-feeding or must have a negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on Day 1 (see Inclusion Criteria). Subjects who are found pregnant during the study must discontinue treatment immediately.

Phenytoin may cause fetal harm when administered to a pregnant woman. Prenatal exposure to phenytoin may increase the risks for congenital malformations and other adverse development outcomes.

Increased frequencies of major malformations (such as orofacial clefts and cardiac defects), and abnormalities characteristic of fetal hydantoin syndrome, including dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits, have been reported among children born to epileptic women who took phenytoin alone or in combination with other antiepileptic drugs during pregnancy. There have been several reported cases of malignancies, including neuroblastoma.

The overall incidence of malformations for children of epileptic women treated with antiepileptic drugs, including phenytoin, during pregnancy is about 10%, or two-to three-fold that in the general population.

A potentially life-threatening bleeding disorder related to decreased levels of vitamin K-dependent clotting factors may occur in newborns exposed to phenytoin in utero. This drug-induced condition can be prevented with vitamin K administration to the mother before delivery and to the neonate after birth.

Slow Metabolizers of Phenytoin

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be caused by limited

enzyme availability and lack of induction, and it appears to be genetically determined. If early signs of dose-related CNS toxicity develop, serum levels should be checked immediately.

Hyperglycemia

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic subjects.

Serum Phenytoin Levels above Therapeutic Range

Serum levels of phenytoin sustained above the therapeutic range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction and/or cerebellar atrophy. Accordingly, at the first sign of acute toxicity, serum levels should be immediately checked. Since dose reduction of phenytoin is not applicable in this study due to the dose of phenytoin being one 50 mg tablet, dosing with phenytoin should be terminated.

Overdosage

The lethal dose in pediatric subjects is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, blurred vision, nausea, and vomiting. The subject may become comatose and hypotensive. Death is caused by respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin serum levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL; dysarthria and lethargy appear when the serum concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery. Irreversible cerebellar dysfunction and atrophy have been reported.

Treatment is nonspecific since there is no known antidote. The adequacy of the respiratory and circulatory systems should be carefully observed, and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in pediatric subjects. In acute overdosage, the possibility of other CNS depressants, including alcohol, should be borne in mind.

Information for Subjects

Advise subjects to read the FDA-approved subject labeling for phenytoin. The counseling information included in the FDA-approved prescribing information is described below.

Administration Information

Advise subjects taking phenytoin of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, e.g., surgery, etc.

Withdrawal of Phenytoin

Advise subjects not to discontinue use of phenytoin without consulting with their healthcare provider. Phenytoin should normally be gradually withdrawn to reduce the potential for increased seizure frequency and status epilepticus.

Suicidal Ideation and Behavior

Counsel subjects, their caregivers, and families that antiepileptic drugs, including phenytoin, may increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Potential Signs of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Other Systemic Reactions

Advise subjects of the early toxic signs and symptoms of potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy, facial swelling, and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. Advise the subject that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, advise the subject that these signs and symptoms should be reported even if mild or when occurring after extended use.

Effects of Alcohol Use and Other Drugs and Over-the-Counter Drug Interactions

Caution subjects against the use of other drugs or alcoholic beverages without first seeking their physician's advice.

Inform subjects that certain over-the-counter medications (e.g., antacids, cimetidine, and omeprazole), vitamins (e.g., folic acid), and herbal supplements (e.g., St. John's wort) can alter their phenytoin levels.

Hyperglycemia

Advise subjects that phenytoin may cause an increase in blood glucose levels

Gingival Hyperplasia

Advise subjects of the importance of good dental hygiene in order to minimize the development of gingival hyperplasia and its complications.

Neurologic Effects

Counsel subjects that phenytoin may cause dizziness, gait disturbance, decreased coordination and somnolence. Advise subjects taking DILANTIN not to drive, operate complex machinery, or engage in other hazardous activities until they have become accustomed to any such effects associated with phenytoin.

Use in Pregnancy

In this study, female subjects must either be of non-reproductive potential, not breast-feeding or must have a negative urine or serum pregnancy test within 28 days of study treatment, confirmed prior to treatment on Day 1 (see Inclusion Criteria). Inform pregnant women and women of childbearing potential that use of phenytoin during pregnancy can cause fetal harm, including an increased risk for cleft lip and/or cleft palate (oral clefts), cardiac defects, dysmorphic skull and facial features, nail and digit hypoplasia, growth abnormalities (including microcephaly), and cognitive deficits.

Advise women of childbearing potential to use effective contraception during the study while using phenytoin, keeping in mind that there is a potential for decreased hormonal contraceptive efficacy.

Instruct subjects to notify their physician if they become pregnant or intend to become pregnant during the study, and to notify their physician if they are breastfeeding or intend to breast feed during the study. Encourage subjects to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy.

Related to Methoxsalen

Protection from Ultraviolet A (UVA) on the Eye (Part 1 only)

UVA-absorbing wrap-around sunglasses should be worn during daylight for 24 hours after methoxsalen ingestion. The protective eyewear must be designed to prevent entry of stray radiation to the eyes, including that which may enter from the sides of the eyewear. The protective eyewear is used to prevent the irreversible binding of methoxsalen to the proteins and DNA components of the lens. Cataracts form when enough of the binding occurs. Visual discrimination should be considered in choosing the eyewear, along with subject's well-being and comfort.

Protection from UVA on the Skin

Subjects must avoid sun exposure, even through window glass or cloud cover, for at least 8 hours after methoxsalen ingestion. If sun exposure cannot be avoided, the subject should wear protective devices such as a hat and gloves, and/or apply sunscreens which contain ingredients that filter out UVA radiation (e.g., sunscreens containing benzophenone and/or p-aminobenzoic (PABA) esters which exhibit a sun protective factor equal to or greater than 15). These chemical sunscreens should be applied to all areas that might be exposed to the sun (including lips). Exposure to sunlight and/or ultraviolet radiation may result in "premature aging" of the skin.

Laboratory Tests

Subjects should have an ophthalmologic examination prior to start of therapy, and thence yearly (Part 1 only). Subjects should have routine laboratory tests prior to the start of therapy and at regular periods thereafter if subjects are on extended treatments.

Overdosage

In the event of methoxsalen overdosage, induce emesis and keep the subject in a darkened room for at least 24 hours. Emesis is most beneficial within the first 2 to 3 hours after ingestion of methoxsalen, since maximum blood levels are reached by this time.

Related to Sirolimus

Increased Susceptibility to Infection and Possible Development of Lymphoma

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression. Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections such as tuberculosis, fatal infections, and sepsis. Subjects receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the subject.

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis and hypersensitivity vasculitis, have been associated with the administration of sirolimus. Discontinue and do not re-administer sirolimus if subjects exhibit hypersensitivity during the study.

Angioedema

Sirolimus has been associated with the development of angioedema. The concomitant use of sirolimus with other drugs known to cause angioedema, such as angiotensin-converting enzyme (ACE) inhibitors, may increase the risk of developing angioedema. Elevated sirolimus levels (with/without concomitant ACE inhibitors) may also potentiate angioedema. In some cases, the angioedema has resolved upon discontinuation or dose reduction of sirolimus. Since dose reduction of sirolimus is not applicable in this study due to the dose of sirolimus being one 0.5 mg tablet, dosing with sirolimus should be terminated when angioedema occurs.

Fluid Accumulation and Impairment of Wound Healing

There have been reports of impaired or delayed wound healing in subjects receiving sirolimus, including lymphocele and wound dehiscence. mTOR inhibitors such as sirolimus have been shown in vitro to inhibit production of certain growth factors that may affect angiogenesis, fibroblast proliferation, and vascular permeability. Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in subjects treated with sirolimus. Appropriate measures should be considered to minimize such complications. Subjects with a body mass index greater than 30 kg/P^{m2}P may be at increased risk of abnormal wound healing based on data from the medical literature.

There have also been reports of fluid accumulation, including peripheral edema, lymphedema, pleural effusion, ascites, and pericardial effusions (including hemodynamically significant effusions and tamponade requiring intervention in children and adults), in subjects receiving sirolimus. Discontinue and do not re-administer sirolimus if subjects exhibit fluid accumulation.

Hyperlipidemia

Increased serum cholesterol and triglycerides requiring treatment occurred more frequently in subjects treated with sirolimus compared with azathioprine or placebo controls in clinical studies. There were increased incidences of hypercholesterolemia (43-46%) and/or hypertriglyceridemia (45-57%) in subjects receiving sirolimus compared with placebo controls (each 23%). The risk/benefit should be carefully considered in subjects with established hyperlipidemia before initiating an immunosuppressive regimen including sirolimus.

Any subject who is administered sirolimus should be monitored for hyperlipidemia. If detected, interventions such as diet, exercise, and lipid-lowering agents should be initiated as outlined by the National Cholesterol Education Program guidelines.

In clinical trials of subjects receiving sirolimus plus cyclosporine or Sirolimus after cyclosporine withdrawal, up to 90% of subjects required treatment for hyperlipidemia and hypercholesterolemia with anti-lipid therapy (e.g., statins, fibrates). Despite anti-lipid management, up to 50% of subjects had fasting serum cholesterol levels >240 mg/dL and

triglycerides above recommended target levels. The concomitant administration of sirolimus and HMG-CoA reductase inhibitors resulted in adverse reactions such as CPK elevations (3%), myalgia (6.7%) and rhabdomyolysis (<1%). In these trials, the number of subjects was too small and duration of follow-up too short to evaluate the long-term impact of sirolimus on cardiovascular mortality.

During sirolimus therapy with or without cyclosporine, subjects should be monitored for elevated lipids, and subjects administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

Decline in Renal Function

In this study, subjects treated, or anticipated to be treated, with cyclosporine are excluded (see Exclusion Criteria) because long-term administration of the combination of cyclosporine and sirolimus is associated with deterioration of renal function. Subjects treated with cyclosporine and sirolimus were noted to have higher serum creatinine levels and lower glomerular filtration rates compared with subjects treated with cyclosporine and placebo or azathioprine controls. The rate of decline in renal function in these studies was greater in subjects receiving sirolimus and cyclosporine compared with control therapies.

Appropriate adjustment of the immunosuppressive regimen, including discontinuation of sirolimus and/or cyclosporine, should be considered in subjects with elevated or increasing serum creatinine levels. In subjects at low- to moderate-immunologic risk, continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only subjects. Caution should be exercised when using agents (e.g., aminoglycosides and amphotericin B) that are known to have a deleterious effect on renal function. In subjects with delayed graft function, sirolimus may delay recovery of renal function.

Proteinuria

Periodic quantitative monitoring of urinary protein excretion is recommended. In a study evaluating conversion from calcineurin inhibitors (CNI) to sirolimus in maintenance renal transplant subjects 6-120 months post-transplant, increased urinary protein excretion was commonly observed from 6 through 24 months after conversion to sirolimus compared with CNI continuation. Subjects with the greatest amount of urinary protein excretion prior to sirolimus conversion were those whose protein excretion increased the most after conversion. New onset nephrosis (nephrotic syndrome) was also reported as a treatment-emergent adverse reaction in 2.2% of the sirolimus conversion group subjects in comparison to 0.4% in the CNI continuation group of subjects. Nephrotic range proteinuria (defined as urinary protein to creatinine ratio >3.5) was also reported in 9.2% in the sirolimus conversion group of subjects in comparison to 3.7% in the CNI continuation group of subjects. In some subjects, reduction in the degree of urinary

protein excretion was observed for individual subjects following discontinuation of sirolimus.

The safety and efficacy of conversion from CNI to sirolimus in maintenance renal transplant subjects have not been established.

Latent Viral Infections

Immunosuppressed subjects are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus-associated nephropathy, which has been observed in renal transplant subjects receiving immunosuppressants, including sirolimus. This infection may be associated with serious outcomes, including deteriorating renal function and renal graft loss. Subject monitoring may help detect subjects at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for subjects who develop evidence of BK virus-associated nephropathy.

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal have been reported in subjects treated with immunosuppressants, including sirolimus. PML commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed subjects, physicians should consider PML in the differential diagnosis in subjects reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in subjects who develop PML. In transplant subjects, physicians should also consider the risk that reduced immunosuppression represents to the graft.

Interstitial Lung Disease/Non-Infectious Pneumonitis

Cases of ILD (including pneumonitis, BOOP, and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in subjects receiving immunosuppressive regimens including sirolimus. In some cases, the ILD was reported with pulmonary hypertension (including pulmonary arterial hypertension) as a secondary event. In some cases, the ILD has resolved upon discontinuation or dose reduction of sirolimus. The risk may be increased as the trough sirolimus concentration increases.

Increased Risk of Calcineurin Inhibitor-Induced Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathy

In this study, subjects treated, or anticipated to be treated, with a calcineurin inhibitor are excluded (see Exclusion Criteria). The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA).

Different Sirolimus Trough Concentration Reported between Chromatographic and Immunoassay Methodologies

Currently in clinical practice, sirolimus whole blood concentrations are being measured by various chromatographic and immunoassay methodologies. Subject sample concentration values from different assays may not be interchangeable.

Skin Cancer Events

Subjects on immunosuppressive therapy are at increased risk for skin cancer. Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Overdosage

Reports of overdose with sirolimus have been received; however, experience has been limited. In general, the adverse effects of overdose are consistent with the adverse reactions section.

General supportive measures should be followed in all cases of overdose. Based on the low aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent. In mice and rats, the acute oral LD50 was greater than 800 mg/kg.

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