NCT #: NCT03512756

Statistical Analysis Plan

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

Prepared for:

Tyme, Inc.

Protocol Number: Tyme-88-Panc

Version 1 MAR 2022

Prepared by:

EMB Statistical Solutions, LLC

Revision History

Version	Date	Revision Author	Comments
1.0	29 MAR 2022	[redacted]	Original

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

SIGNATURE PAGE

[redacted]

18-Apr-2022

Date

EMB Statistical Solutions, LLC

[redacted]

4/18/2022 | 10:28:47 EDT

Date

Tyme, Inc.

Table of Contents

1 Study Information

1.1 Background

This statistical analysis plan (SAP) is based on Protocol TYME-88-PANC Version 8 dated 12 May 2020, and describes the analysis variables and statistical procedures that will be used to analyze and report the results of the trial using the latest available operational protocol.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports".

This trial was originally designed to be in two parts. Part 1, whose goal was to evaluate the Overall Response Rate (ORR) via RECIST 1.1 and determine the Recommended Phase 2 Dose (RP2D) was completed in 2019.

As this study was terminated early, this SAP represents an abbreviated analysis of what was originally planned for the study.

1.1.1 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:** An 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 Part 2 will be randomized 1:1 (open-label) either to the SM-88 arm or Physician's Choice of therapy for the Control Arm, with a planned efficacy analysis to be performed when 75% of total events (assuming 234 total events) are reached. This could result in early stopping for efficacy.

For all subjects, treatment will continue until apparent PD (as defined in the protocol), unacceptable toxicity, death, or any of the treatment discontinuation criteria are met. 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.

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.

The Physician's Choice therapy must include exactly one of the following:

- **Capecitabine** (1000 mg/m2 orally twice a day, Days 1-14 on a 21-day cycle)
- **Gemcitabine** (1000 mg/m2 IV on Days 1, 8, and 15 on a 28-day cycle)
- **5-FU** (2400mg/m2 continuous IV infusion over 46 hours on Day 1 and 15 on a 28-day cycle)

1.1.2 Number of Subjects

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.

1.2 Study Objectives

The original objectives as stated in the protocol are as follows. Some objectives have been modified for this SAP, and are documented here with an SAP note.

1.2.1 Part 1

1.2.1.1 Primary Objective

[redacted]

1.2.1.2 Secondary Objectives

[redacted]

1.2.1.3 Safety Objectives

[redacted]

[redacted]

1.2.2 Part 2

1.2.2.1 Primary Efficacy Objective

The primary efficacy objective of this study is to determine the OS of subjects treated with SM-88 used with methoxsalen, phenytoin, and sirolimus (MPS) vs the Control Arm (Physician's Choice).

1.2.2.2 Key Secondary Efficacy Objective

- Evaluate investigator-determined PFS.

1.2.2.3 Additional Secondary Efficacy Objectives

[redacted]

1.2.2.4 Exploratory Objectives

[redacted]

1.2.2.5 PK/Safety Objectives

[redacted]

1.3 Efficacy Endpoints

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.

[redacted]

1.3.1.1 Time-to-Event Efficacy Endpoints

Unless stated otherwise, the time-scale will be in weeks.

1.3.1.2 Overall Survival (OS)

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

1.3.1.3 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. For Part 1, PD can only be determined radiographically (BICR). For Part 2, PD will be determined as per investigator assessment.

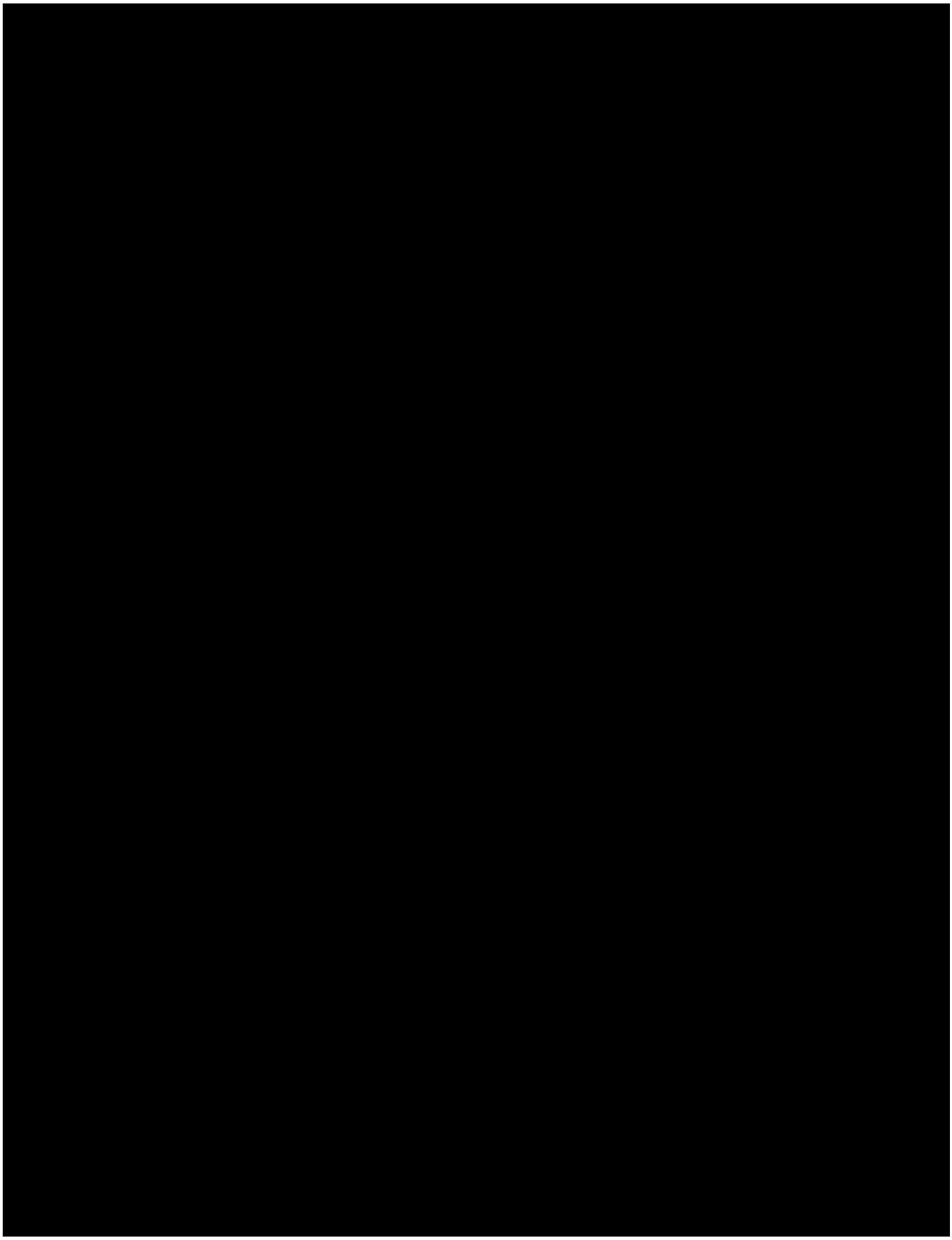
For subjects who do not have a definitive date of death or disease progression, PFS will be censored at the date of the last follow-up visit which included a progression assessment for which they were still alive and without disease progression. This includes subjects who are either:

- Still alive without documented PD at the time of analysis.
- PFS status unknown at the time of the analysis.

1.3.1.4 Time to subsequent therapy

There will be no analyses on the time to subsequent therapy.

[redacted]



[redacted]

1.4 Pharmacokinetic Endpoints

PK assessments are outside the scope of this SAP.

1.5 Safety Endpoints

[redacted]

1.5.5 Ophthalmologic Exam (Part 1 only)

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.
    - 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.

1.5.6 Adverse Events

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.

1.5.6.1 Treatment-Emergent AEs

An AE is said to be treatment-emergent (TE) if it occurs or worsen after the baseline visit.

1.5.6.2 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 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.

1.5.6.3 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).

1.5.6.4 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 below:

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.

2 Statistical Methods

2.1 General Methods

Any changes to the finalized SAP made prior to database lock will require a SAP amendment. Any changes to the planned analyses after database lock will be documented in the CSR.

Some of the analyses detailed here may be more explicit or in some aspects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

2.1.1 Definition of Baseline

The baseline visit is defined in the protocol as the day of initial dosing (Cycle 1 Day 1). Superseding this definition, in this SAP, the baseline visit will be defined as the last assessment made on or after the randomization date that is also before the first date of administration of any study drug (including Physician's Choice, SM-88, methoxsalen, phenytoin, or sirolimus). If no such visit exists, the baseline visit will be the randomization date or screening date, whichever is later. Change from baseline will be calculated as the value at a given time point minus the baseline value.

2.1.2 Programming Conventions

EMB Statistical Solutions will have responsibility for performing analyses. All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

The eCRF data for all subjects will be provided in Standard Data Tabulation Model (SDTM) datasets. Analysis Data Model (ADaM) datasets will be developed from the SDTM datasets for use in table and figure production.

2.1.3 Reporting Conventions

The formats for the tables, listings, and figures described in this SAP will be provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the CSR.

All study data from the eCRFs as well as derived variables will be provided in subject data listings. An indication of specific listings for each data type will not be indicated in the text of subsequent SAP sections. Data listings supplied as part of the CSR will be sorted by study center number concatenated with subject number, assessment dates, and/or time point.

The following conventions will be applied to all data presentations and analyses:

- Continuous variables will generally be summarized by the number of subjects, mean, standard deviation, median, minimum, and maximum. Unless otherwise specified, the

minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data

- Categorical variables will be summarized by the number and percentage of subjects within each category. Unless otherwise specified, the percentage will be presented in parentheses to one decimal place. Frequency and percentage values of 0 will be presented as '0' rather than '0 (0)'.
- All summary tables will include the analysis population sample size (i.e. number of subjects) in each treatment group.
- Date variables will be formatted as DDMMMYYYY for presentation.

Unless stated otherwise, summaries for each part will be provided by randomization arm as appropriate.

2.1.4 Handling of Missing Data

The number of non-missing efficacy values will be reported. For response rates such as ORR, subjects who withdraw from the trial prior to a response (or whose response is unknown) will be included in the analysis as non-responders.

If adverse event start dates are missing or incomplete, the following rules will apply for determining if an event is to be considered treatment emergent: if start date is completely missing, start date will be set as same day as start of treatment. If start date is incomplete, the date closest to start of treatment will be assumed, without compromising the incomplete data available for the start date.

No additional imputation is planned for this study.

2.2 Analysis Populations

The statistical analyses will be performed based on the following subject populations.

2.2.1 Safety Population

All subjects enrolled in the study who receive at least one dose of study drug will be included in the safety population, and assigned to the treatment they actually received. This will be the population for the safety analyses and for summarization of baseline/demographic characteristics.

2.2.2 Intent-to-Treat (ITT) Population

All subjects consented in the study and randomized to treatment will be included in the intent-to-treat population, and assigned to the treatment they were randomized to. This will be the population for the primary efficacy analyses.

2.2.3 Evaluable Population

All subjects in the ITT population who receive at least 1 cycle of study drug (21 days), as identified in the eCRF, will be included in the evaluable population. Note, if the ITT Population is equivalent to the Evaluable Population, the Evaluable Population will be used in place of the ITT Population for all tables, figures, and listings.

2.2.4 Pharmacokinetic (PK) Population

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

2.3 Study Subjects

For each Part, the following will be summarized:

2.3.1 Subject Disposition

The number of subjects who fail screening along with reasons for failure will be shown in total, using the number of screen failures as the denominator. The number of randomized subjects in each arm will be shown.

Using the ITT population as the denominator , the number and percentage of subjects in the following categories will be summarized:

- Analysis population (Safety, ITT, etc.)
- Consented to survival follow-up
- Discontinued study before day 21 (overall and by prior lines of therapy: 2 lines vs. 3+ lines, including primary reason for withdrawal for overall group)
- Discontinued study (including primary reason for withdrawal).
- Discontinued study drug (including primary reason)

Subject disposition, including end-of-study status, will be included as a listing. Additionally, a separate listing of (1) subjects who withdrew between randomization and 1st dose and (2) subjects excluded from the Evaluable Population, will be provided, and will include any provided reason(s) for withdrawal (if applicable).

2.3.2 Protocol Deviations

The number of subjects with protocol deviations (and number of deviations) will be summarized (any deviation and major deviations only). Details of all protocol deviations will be included as a listing.

2.3.3 Baseline and Demographic Characteristics

Subject baseline and demographic data will be summarized for the Safety population. At the screening visit, demographic information including age, sex, race and ethnicity will be collected and recorded in the eCRF for each subject.

2.3.4 Cancer History

A complete medical history, including cancer history etc., will be obtained by the investigator or qualified designee during screening . A summary of pancreatic cancer history will be provided, and will include TNM staging, stage at initial diagnosis, years since diagnosis, disease type (recurrent or progressive), metastatic status, and family history. The number of anti-pancreatic cancer therapies will also be summarized.

For Part 1 only, a listing containing each subject's prior chemotherapies will be provided.

2.3.5 Non-Cancer Medical History

A complete medical history will be collected as part of the screening assessment and include all clinically relevant past or coexisting medical conditions or surgeries. The medical history will be updated prior to treatment on Baseline/Day 1 should new findings be present since the screening visit. Findings will be recorded in the eCRF.

Medical and surgical histories will be omitted from analyses.

2.3.6 Medications, and Procedures

Prior and concomitant medications will not be summarized. Concomitant medications will be provided as a listing only, along with new systemic therapies

2.4 Efficacy Analyses

2.4.1 Datasets Analyzed

All efficacy variables will be analyzed based on either the ITT or Evaluable Populations. Some analyses utilizing the ITT Population may be repeated on the Evaluable Population as sensitivity analyses. Response rates such as ORR, DCR, and SBR will impute subjects with missing responses as non-responders. Other summary statistics will be computed for each efficacy endpoint using the Observed Cases (OC) with no imputation for missing data.

2.4.2 Part 1 Efficacy Analyses

2.4.2.1 Primary Efficacy Analysis (ITT Population)

[redacted]

2.4.2.2 Secondary Efficacy Analyses

[redacted]

2.4.3 Part 2 Efficacy Analyses

Unless stated otherwise, analyses will be performed for both the ITT and Evaluable Populations.

2.4.3.1 Primary Efficacy Analysis

OS for SM-88 used with MPS will be compared to Physician's Choice for OS, using the Log-Rank test, stratified by the randomization stratification factors (1) Physician's Choice made pre-randomization and (2) baseline ECOG performance status (0-1 vs. 2). The p-value from the Log-Rank test will be reported.

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. The plot will be produced for both ITT and Evaluable Populations.

2.4.3.2 Key Secondary Efficacy Analysis

The analysis of treatment differences in PFS will be conducted using the same methods as for the Part 2 primary analysis of OS, described above. The plot will be produced for the Evaluable Population only.

2.4.3.3 Other Secondary Efficacy Analyses

[redacted]

2.4.4 Sensitivity Efficacy Analyses

For select outcomes, additional sensitivity analysis summary tables will be provided. These analyses are as follows:

[redacted]

Part II	OS		X
	PFS		X

2.5 Safety Analysis

All safety data will be summarized descriptively by treatment group based on the safety population using the Observed Cases (OC). There are no planned inferential statistical analyses of safety endpoints.

2.5.1 Adverse Events

AE verbatim text will be coded and classified by body system and preferred (coded) term using the Medical Dictionary for Regulatory Activities (MedDRA) v20.1. All SAEs will be listed. AE summaries by treatment group, of the number and percent of subjects reporting each event at least once will be generated. Dose-limiting toxicities will also be listed and summarized by dose cohort.

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 17 of the protocol.

An overall summary of AEs will be provided, and will include the number of AEs, and number (%) of subjects, for the following categories:

- Any AE
- Any TEAE
    - Any Treatment-Related TEAE
    - Any Dose Limiting Toxicity
    - Any Severe (Grade >=3) TEAE
    - Any TEAE resulting in treatment discontinuation
    - Any TEAE resulting in study discontinuation
    -
- Any Serious AE
    - Any SAE resulting in death
    - Any SAE resulting in hospitalization
    - Any life-threatening SAE
    - Any SAE resulting in disability/incapacity
    - Any SAE resulting in congenital abnormality
    - Any Treatment-Related SAE

The following summaries of AEs will be provided as individual summary tables.

- TEAEs by System Organ Class and PT – related to study drug
- TEAEs by System Organ Class and PT – by maximum severity where grade >=3
- SAEs by System Organ Class and PT – related vs unrelated and grade >=3 vs <3

- AEs by PT – resulting in death
- AEs by PT – resulting in treatment discontinuation
- AEs by PT – resulting in study discontinuation
- DLTs by PT

Listings of AEs will be provided for SAEs, AEs resulting in change in dose and/or study discontinuation, and AEs resulting in death.

2.5.2 Extent of Exposure

The exposure to study drug will be summarized for all subjects in the Safety Population. This will include the time in study, duration of exposure, number of cycles started, and amount of each study drug (SM-88, Sirolimus, Methoxsalen, Phenytoin) taken.

For Part 2 only, this summary will include Physician's Choice arms of Capecitabine, Gemcitabine, and 5-FU.

2.5.3 Other Safety Analyses

Laboratory measurements will summarize abnormal values (e.g. above ULN or below LLN) only. These values will be summarized as (1) change from baseline to lowest value below LLN and (2) change from baseline to highest value above ULN across subjects with abnormal values for each laboratory parameter. The number of subjects in each category will be included.

All remaining safety parameters will be summarized by each scheduled assessment and their change from baseline using descriptive statistics . This includes:

- Laboratory measurements
- Abnormal ECGs
    - ECGs are collected in triplicate, and the average at each visit will be used for descriptive summaries.

Listings will be provided for the following safety endpoints:

- Dose limiting toxicities
- Abnormal ECGs
- Abnormal Ophthalmologic Exam (Part 1 Only)

For ECGs, the worst result of the triplicate findings will be used for flagging normal/abnormal.

2.6 Determination of Sample Size

Part 1:

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, Tmax, t½ and AUC). To adequately estimate the t½, 36 subjects are needed ($n = ZP^2POP^2P/\epsilon P^2P$ where $Z = 196$; 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:

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 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.

2.7 Interim Analysis

The statistical plan was designed to conduct the final OS analysis at 1 year after the last patient was enrolled. Given the poor prognosis of the Control Arm patients, as reported in the literature, a planned efficacy analysis will be performed when 75% of events are reached. This could result in early stopping for efficacy.

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 a significance level of α=0.025 at the interim and 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 were 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.

Using an overall significance level of α=0.05, if the trial continues after the interim the drug will be declared successful at the final analysis if the p-value is less than 0.0489.

2.8 Pharmacokinetic Analyses

Population PK analysis modeling will be employed, the specifics of which are outside the scope of this SAP.

2.9 Changes in the Analysis Planned in the Protocol

No investigative or aggregate site factors, such as distance travelled to the study site, or accrual rate of site, will be included as covariate adjustments for any analyses.

OS confidence intervals will be at the 95% level, rather than 90% level.

The following analysis populations have been removed: Modified ITT population, Evaluable 4-Cycle population, Per-Protocol population.

Only investigator-determined response was available for Part 2; only BICR RECIST will be used for PFS in Part 1.

The following secondary efficacy objectives were not performed:

As mentioned in ”Definition of Baseline”, the baseline visit is defined in the protocol as the day of initial dosing (Cycle 1 Day 1). Superseding this definition, in this SAP, the baseline visit will be defined as the last assessment made on or after the randomization date that is also before the first date of administration of anu study drug (including Physician’s Choice, SM-88, methoxsalen, phenytoin, or sirolimus). If no such visit exists, the baseline visit will be the randomization date or screening date, whichever is later.

3 Reference List

There are no other references beyond those that are included in the protocol

4 Schedule of Events

Please refer to Tables 5 through 8 in the protocol for treatment specific schedules of events.