STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE 1B TRIAL OF HU5F9-G4 IN COMBINATION WITH AVELUMAB IN SOLID TUMOR PATIENTS AND CHECKPOINT INHIBITOR NAÏVE OVARIAN CANCER PATIENTS WHO PROGRESS WITHIN 6 MONTHS OF PRIOR PLATINUM CHEMOTHERAPY**

PROTOCOL NUMBER:	5F9006
STUDY DRUG:	Magrolimab (Hu5F9-G4)
VERSION NUMBER:	1.0
SPONSOR:	Forty Seven Inc
PLAN PREPARED BY:	PPD
DATE:	22 July, 2020

Confidentiality Statement

Forty Seven

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APPROVAL

Upon review of this document, including table, listing, and figure shells, the undersigned approves the Statistical Analysis Plan. The analysis methods and data presentation are acceptable.

Signature	Date
PPD	7/22/20
PPD Forty Seven Inc.	
PPD	7/23/20
PPD Forty Seven Inc.	

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ATC	anatomical\therapeutic\chemical
CTCAE	Common Terminology Criteria for Adverse Events
CTSC	Clinical Trial Steering Committee
DLT	dose-limiting toxicity
DOR	duration of response
eCRF	electronic case report form
GCIG	Gynecologic Cancer InterGroup
irRECIST	Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-related Response Criteria
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetics
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SOC	system organ class
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse event
TTP	time to progression
WHO	World Health Organization

1 INTRODUCTION

This document outlines the statistical methods and variable definitions to be implemented during the analyses of data in evaluation of efficacy, safety, pharmacokinetics (PK) and immunogenicity of the clinical trial described in the Forty Seven Inc. protocol for Study 5F9006 entitled "A Phase 1b Trial of Hu5F9 G4 in Combination with Avelumab in Solid Tumor Patients and Checkpoint Inhibitor Naïve Ovarian Cancer Patients Who Progress within 6 Months of Prior Platinum Chemotherapy" Amendment 3, dated 22 December 2018. Analyses of biomarker data are out of scope of this SAP and will be described in a separate document.

Analysis methods specified in this document take precedence over those described in the protocol should there be any difference.

1.1 Study Design

This is an open label, multicenter, Phase 1b trial investigating the combination of magrolimab and avelumab in patients with solid tumors and checkpoint inhibitor-naïve ovarian cancer who progressed within 1-6 months of receiving platinum containing chemotherapy. Checkpoint-inhibitor-naïve patients are defined as those who have not been previously treated with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab, tremelimumab, or any other antibody or drug specifically targeting T-cell co-regulatory proteins).

The study will be conducted in 2 parts:

- Part 1: safety run-in cohort
- Part 2: expansion cohort

1.1.1 Part 1 Safety Run-In Cohort

In Part 1 of the study, patients with solid tumors will be treated with magrolimab + avelumab to examine the safety and PK of this study treatment. A safety run-in cohort will treat 6 patients evaluable for dose limiting toxicity (DLT).

The dose levels and schedules for both study drugs are described in protocol synopsis Table 2. Specifically, in the first dose level cohort, patients will be treated with a priming dose of magrolimab at 1 mg/kg on Day 1, followed by 4 weekly doses at 30 mg/kg on Days 8, 15, 22, and 29 in a 35-day long Cycle 1. In the second dose level cohort, patients will be treated with a priming dose of magrolimab at 1 mg/kg on Day 1, followed by 5 doses at 45 mg/kg on Days 8, 11, 15, 22, and 29 in a 35-day long Cycle 1.

In both dose level cohorts, on Days 8 and 22, 800 mg avelumab will be administered. On any day when both drugs are administered, magrolimab infusion will begin at least 1 hour after completion

of the avelumab infusion. Starting in Cycle 2, the cycle length will be 28 days, and magrolimab will be administered at 30 mg/kg in the first dose level cohort or 45 mg/kg in the second dose level cohort, in combination of 800 mg avelumab, every 2 weeks on Days 1 and 15 in each cycle.

DLT will be monitored from administration of the priming dose on Day 1 to the end of Cycle 1 (Day 35). The first patient in each dose level cohort will be treated for 14 days prior to enrolling additional patients. If no more than one DLT event occurs after the 6 patients evaluable for DLT assessment have safely completed the DLT assessment period in a safety run-in cohort, the dose level will be deemed to be safe by the Clinical Trial Steering Committee (CTSC). The recommended dose and schedule must have a DLT rate less than 33%. The decision will be made by the CTSC after all available clinical, CCI and PK data are reviewed. CCI

1.1.2 Part 2 Expansion Cohort

In Part 2 of the study, patients with checkpoint-inhibitor-naïve ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma who have previously progressed within 1 – 6 months of receiving platinum chemotherapy will be treated with the recommended dose and schedule determined by CTSC in the expansion cohort, in order to confirm safety, PK, CCI and to document preliminary efficacy in this population. Study treatment may be continued until an unacceptable drug related toxicity occurs or until disease progression according to irRECIST. Pre-treatment and on-treatment biopsy sample collection is mandatory, unless medically not feasible determined by the Investigator and Sponsor (refer to protocol section 7.3.11).

1.2 Study Objectives and Endpoints

PRIMARY	
OBJECTIVES	**ENDPOINTS**
• To investigate the safety and tolerability of magrolimab + avelumab in the safety run-in cohorts of patients with advanced solid tumor • To confirm the safety and tolerability and to evaluate the anti-tumor activity of magrolimab + avelumab, based on RECIST v1.1 (Eisenhauer 2009), in patients with checkpoint-inhibitor-naïve ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma who have previously progressed	• DLT events and adverse events (AEs) graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 4.03 or customized AE severity grading for hemagglutination and microangiopathy, as defined in protocol Section 6.5.1.3. • Objective response rate (ORR) as defined by the investigator according to RECIST v1.1.

within 1 – 6 months of receiving platinum chemotherapy	
SECONDARY	
OBJECTIVES	**ENDPOINTS**
• To determine a recommended dose of magrolimab + avelumab in patients with advanced solid tumor • To examine the PK profile of magrolimab in combination with avelumab • To examine the immunogenicity of magrolimab in combination with avelumab • To evaluate the anti-tumor activity of magrolimab + avelumab based on irRECIST (Bohnsack 2014) and, where applicable, the Gynecologic Cancer Intergroup (GCIG) response criteria (Rustin 2011), in patients with checkpoint-inhibitor-naïve ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma who have previously progressed within 1 – 6 months of receiving platinum chemotherapy • To assess additional efficacy endpoints including duration of response (DOR), time to tumor progression (TTP), progression-free survival (PFS), and overall survival (OS) in patients with checkpoint-inhibitor-naïve ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma who have previously progressed within 1 – 6 months of receiving platinum chemotherapy • To evaluate the impact of magrolimab in combination with avelumab on the myeloid cell populations in the tumor microenvironment, as assessed in sequential tumor biopsies, in patients with platinum resistant ovarian cancer	• Recommended dose and schedule of magrolimab + avelumab • Serum concentrations of magrolimab collected at selected time points • Anti-drug antibodies to magrolimab • ORR as defined by the investigator according to irRECIST and GCIG response criteria. • DOR, TTP, PFS, and OS • Immunohistochemical staining of myeloid cells in formalin-fixed, paraffin-embedded tissues

1.3 Sample Size Determination

This trial will include a total of up to 40 patients. This sample size includes both Parts 1 and 2 of the study, allowing for patient replacement if not evaluable for DLT assessment in Part 1. In Part 1, it is assumed that no more than 2 DLT events in each cohort of 6 DLT evaluable patients would occur. In Part 2, it is planned to enroll a single expansion cohort of 20 patients with checkpoint-inhibitor-naïve ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma who have previously progressed within 1 – 6 months of receiving platinum chemotherapy. No formal hypothesis testing will be done. This sample size will provide about 45% power to have the lower bound of the 80% confidence interval of ORR to exclude 10% if the ORR is 30% or higher.

2 ANALYSIS SETS

- **DLT Evaluable Analysis Set**: includes patients in Part 1 who either experienced any DLT event any time after initiation of the first infusion of magrolimab or any infusion of avelumab and during the 5-week DLT assessment period, or who received at least 4 (or 5 if assigned to the second dose level 45 mg/kg) complete infusions of magrolimab at the maintenance level and 2 complete infusions of avelumab. Patients who are not evaluable for dose review decisions will be replaced in the cohort.
- **All Treated Patients**: includes all patients who received at least 1 dose of any study drugs. Summary tables of disposition, demographics and other baseline characteristics, and safety data will be performed on the All Treated Patients.
- **Efficacy Analysis Set**: includes checkpoint inhibitor-naïve patients with ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma, who have previously progressed within 6 months of receiving platinum chemotherapy and received at least one dose of magrolimab during this study. Primary efficacy analysis will be performed on the Efficacy Analysis Set.
- **PK Analysis Set**: includes patients who received any amount of magrolimab with at least one detectable post-treatment serum concentration of magrolimab are evaluable for PK analysis.
- **Immunogenicity Analysis Set:** includes patients with at least one reported ADA result will be included in the immunogenicity analysis set.

3 PATIENT INFORMATION

Disposition, demographics and other baseline characteristics, medical history, disease history, prior anticancer treatment, prior and concomitant medications, premedication, and extent of exposure to the study treatment will be presented for All Treated Patients.

3.1 Patient Disposition

The disposition table will include the following summaries: the number of patients treated, the number of patients who discontinued from the study treatment and of those from the study, reasons for discontinuation, duration of treatment (months), and duration of follow up (months). The summaries will be provided for each dosing cohort (Part 1) or the expansion cohort (Part 2), or at each maintenance dosing level.

3.2 Protocol Deviations

Patients with important protocol deviations will be identified and documented by the clinical team.

3.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics including age, sex, ethnicity, race, weight as well as disease characteristics will be summarized.

3.4 Medical History

A listing will be provided for medical history.

3.5 Prior Cancer Treatments

The number and percentage of patients with each type of prior anticancer treatment (prior radiotherapy, prior cancer-related surgery, and prior cancer-related systemic therapy) will be summarized. The number of prior lines of cancer-related systemic therapies will also be summarized.

3.6 Prior and Concomitant Medications

Concomitant medication verbatim terms on electronic case report forms (eCRFs) will be coded to Anatomical/Therapeutic/Chemical (ATC) class and Preferred Names using the World Health Organization (WHO) Drug Dictionary Enhanced (version March 1, 2014).

Concomitant medications will be summarized by WHO ATC class and preferred name. The summarization includes all the concomitant medications taken any time while on study treatment (ie, from the date of first dose through the date of last dose of the study treatment), with exception of the premedication described in Section 6.1.2 of the protocol, which will be summarized separately (see the next subsection). Each patient will be counted once for each preferred name, and each ATC class.

Prior medication is defined as any medication with a start date prior to the date of first dose, regardless of when the stop date is. A listing of prior medication together with concomitant medications will be provided.

Premedication is required before administration of the first 2 infusions of magrolimab (inclusive of the priming dose) and before the first 4 infusions of avelumab. The number and percentage of patients who received the following premedication will be summarized:

- Oral acetaminophen 650 to 1000 mg and oral or intravenous diphenhydramine 25 mg, or comparable regimen on the date of but prior to the first 2 infusions of magrolimab (inclusive of the priming dose)
- An antihistamine and acetaminophen (for example, 25 to 50 mg intravenous or oral diphenhydramine and 500 to 650 mg oral acetaminophen) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab

3.7 Extent of Exposure

Exposure to study treatment will be summarized in each cohort. Descriptive statistics will be provided for the following data for each study drugs (magrolimab, avelumab): treatment duration; total number of study drug infusions; cumulative dose administered; the number of missed/delayed doses, including those due to AE; the number of dose reductions; the number of dose interruptions, including those due to AE; and median time to first missed, delayed, or interrupted dose due to AE or dose reduction.

4 EFFICACY ANALYSIS

Confirmed best response based on RECIST v1.1 and best response based on GCIG criteria will be summarized. The primary analysis will be based on the Efficacy Analysis Set, in which the ovarian cancer patients had documented progression within 6 months of receiving platinum chemotherapy and did not have any data that showed prior anticancer therapy of checkpoint inhibitor. A sensitivity analysis will be based on all ovarian cancer patients. ORR, defined as the proportion of patients who achieve a complete or partial response, will be calculated based on patients with measurable disease at baseline, with 95% confidence interval provided.

DOR will be calculated for patients with confirmed response as time from the initial response until disease progression.

PFS is defined as the duration of time from dose initiation to the first date of objectively documented disease progression per RECIST v1.1 or death, whichever occurred at first. Patients who do not have documented disease progression and did not die will be censored at their last tumor assessment date. OS is defined as the duration of time from dose initiation to the date of death due to any cause. Patients who did not die will be censored at their last known alive date. Both PFS and OS will be summarized using Kaplan-Meier methods and summary statistics will include their 95% confidence intervals.

Efficacy data for patients who had solid tumors other than ovarian cancer will be reported in listings.

5 PHARMACOKINETIC ANALYSES

5.1 Pharmacokinetic Analysis

The PK Analysis Set will be used in the analysis of PK data. Descriptive statistics of magrolimab concentration data will be provided. Individual and mean serum concentration-time profiles of magrolimab per cohort for each study part will be generated. Non-compartmental PK data analysis may be performed when data allows and PK parameters such as Cmax and AUC will be reported when appropriate. Additional parameters may be calculated as deemed appropriate.

5.2 Immunogenicity Analysis

The prevalence, incidence and titer of anti-magrolimab antibodies (antidrug antibodies or ADA) will be evaluated for individual patients and will be listed and summarized for each dose cohort for each study part and for the pooled patient population. ADA incidence, prevalence, and transience versus persistence will be summarized. CCI [redacted]

6 SAFETY ANALYSIS

All safety analyses will be performed by the actual magrolimab maintenance dose level based on the Safety Analysis Set.

6.1 Adverse Events

Treatment-emergent adverse events (TEAE) will be summarized in each cohort. TEAEs are defined as those AEs that worsened or occurred during or after a patient's first dose of any study drug and those existing AEs that worsened during the study and within 30 days after the last administration of any study drug or initiation of new anticancer therapy, whichever occurred first. If it cannot be determined whether the AE is treatment-emergent due to a partial onset date then the AE will be included in the TEAE summary. Verbatim terms on eCRFs will be coded to system organ class (SOCs) and preferred terms (PTs) using the Medical Dictionary for Regulatory Activities Version 19.0. NCI-CTCAE Version 4.03 will be used to summarize type and severity of the events, except for hemagglutination and microangiopathy events, which will be assessed per the protocol specified (Section 6.5.1.3) severity scoring.

The following summaries will be performed:

- Overview of AEs.
- Patient incidence of TEAEs by PT.
- Patient incidence of treatment-related adverse events (TRAEs) by PT.
- Patient incidence of TEAEs by SOC and PT, showing each grade and overall.
- Patient incidence of serious TEAEs by SOC and PT, showing each grade and overall.
- Patient incidence of TRAEs by SOC and PT.
- Patient incidence of Grade 3 or higher TEAEs by SOC and PT.
- Patient incidence of Grade 3 or higher TRAEs by SOC and PT.
- Patient incidence of TEAEs as part of an infusion reaction identified by the investigator by SOC and PT, showing each grade and overall.
- Patient incidence of TEAEs leading to study drug discontinuation by SOC, PT, and worst grade.
- Patient incidence of TEAEs leading to dose interruption by SOC and PT.
- Patient incidence of TEAEs leading to dose delay/reduction by SOC and PT.

A further summary of the number of patients experiencing DLT events and the average number of infusions in these patients will be tabulated.

Listings of all AEs including TEAEs, TEAEs related to either magrolimab or avelumab, Grade 3 or higher TEAEs, TEAEs that the investigator identified as part of an infusion reaction, serious TEAEs, TEAEs leading to study discontinuation, TEAEs leading to interruption or dose delay/reduction, DLT events, and deaths will be provided.

6.2 Deaths

All deaths and causes of death on study will be summarized and listed.

6.3 Clinical Laboratory Evaluation

Selected laboratory parameters (serum chemistry, hematology, prothrombin time / international normalized ratio, and activated partial thromboplastin time) will be summarized.

Laboratory parameters will be graded according to CTCAE Version 4.03. The worst postbaseline CTCAE grade will be summarized using a shift table to assess changes from baseline for the key variables. Summaries of treatment-emergent laboratory toxicities of serum chemistry and hematology will be tabulated by counts and percentages.

Laboratory data listings will include CTCAE grades and flags for those values outside the reference ranges. Urinalysis examination will only be presented in a data listing.

6.4 Vital Signs

Vital sign measurement results will only be provided in a data listing.

6.5 Physical Examination

Physical examination results will only be provided in a data listing.

6.6 Electrocardiogram

Electrocardiogram results will only be provided in a data listing.

6.7 Peripheral Blood Smear

Peripheral blood smear parameters will be summarized using frequency counts with percentages at each time point.

7 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The following modifications have been made to the analyses specified in Protocol Amendment 3:

- The definition of treatment-emergent period is updated to specify an end date for each patient's reporting period to be within 30 days after the last administration of study drug or initiation of new anticancer therapy, whichever occurred first.
- The Dose Evaluation Set is renamed as the DLT Evaluable Analysis Set for the same purpose of DLT assessment. Patients who experienced any DLT event are evaluable for DLT as long as the patient received any infusion of magrolimab, regardless of dose level, or any infusion of avelumab. Patients who didn't experience any DLT event are evaluable only if they completed the scheduled study treatment that was assigned, based on the protocol synopsis Table 2. During the 5-week DLT assessment period, in addition to 2 infusions of avelumab, patients assigned to dose cohort 1 receive 4 magrolimab infusions at 30 mg/kg and patients assigned to dose cohort 2 receive 5 magrolimab infusions at 45 mg/kg.
- The definition of Efficacy Analysis Set is modified to support the summary of efficacy data. First, included in the summary are checkpoint inhibitor-naïve patients with ovarian cancer, fallopian tube cancer and primary peritoneal carcinoma who have previously progressed within 6 months of receiving platinum chemotherapy, according to the target patient population for the expansion cohort in the Part 2 for efficacy evaluation. Second, patients who received at least one dose of magrolimab are included to support the primary analysis of PFS and OS, as well as BOR.
- Endpoint TTP will not be summarized.
- The tumor assessment based on irRECIST will not be reported.

8 REFERENCES

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Rustin GJ, Vergote I, Eisenhauer E, et al. Gynecological Cancer Intergroup. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011 Feb;21(2):419-23.