Statistical Analysis Plan
Pfizer Protocol TTI-621-01/C4961001

A Phase 1a/1b Dose Escalation and Expansion Trial of TTI-621, a Novel Biologic Targeting CD47, in Subjects with Relapsed or Refractory Hematologic Malignancies and Selected Solid Tumors

Sponsor:	**Pfizer Inc.**
Study Drug:	**TTI-621/PF-07901800**
SCDI Protocol Number:	**HEMREF 43**
Sponsor Protocol Number:	**TTI-621-01/C4961001**
Prepared By:	**Sarah Cannon Development Innovations**

Statistical Analysis Plan

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
1.0	26JUL2016	Original document
2.0	02NOV2022	Updates made to align with changes made to the protocol, notes-to-file, and Pfizer's recommendations

PPD

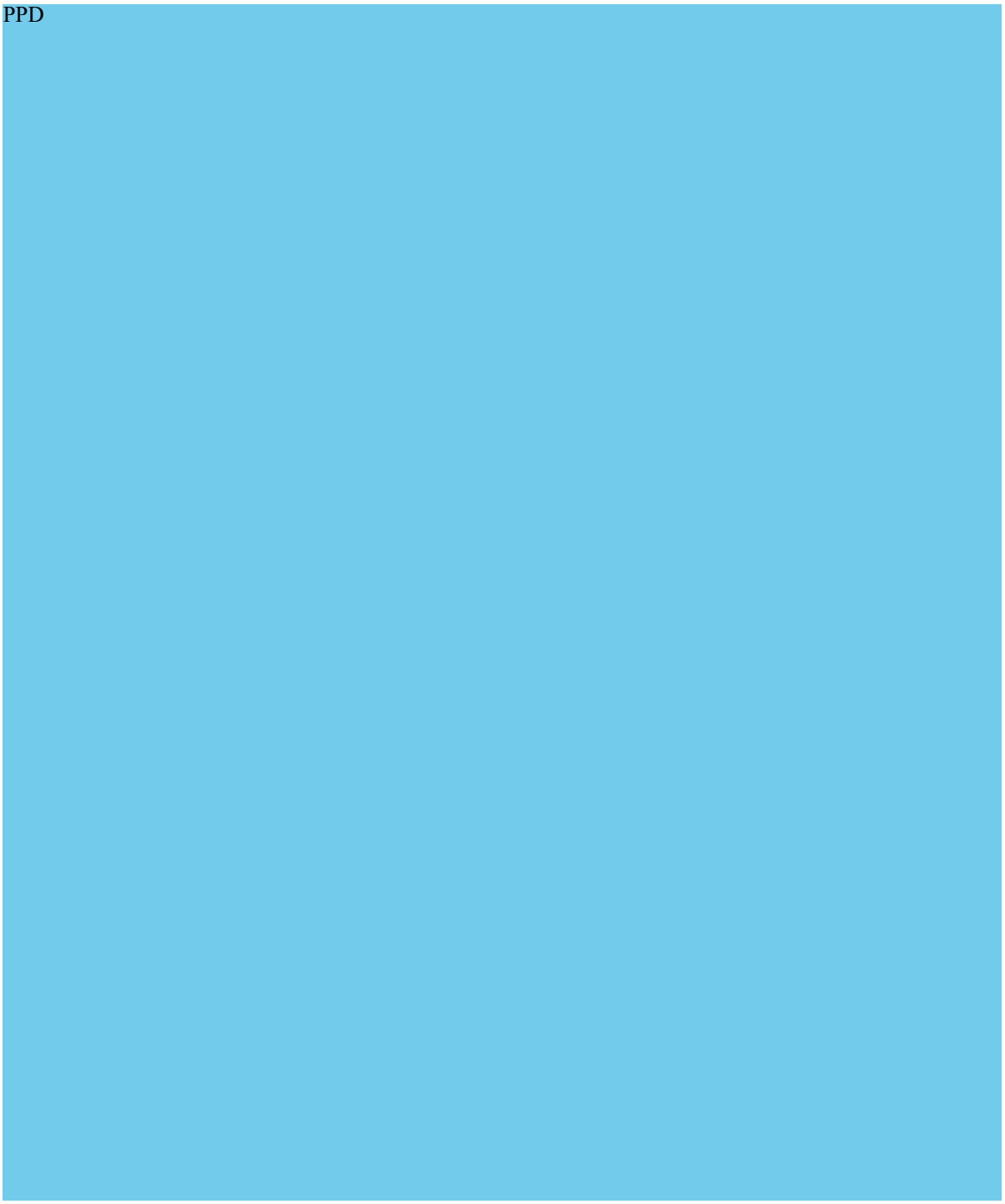

Table of Contents

List of Abbreviations

ADA	antidrug antibodies
ADaM	Analysis Dataset Model
AE	adverse event
AML	acute myeloid leukemia
BMI	body mass index
CD47	transmembrane protein and the target of TTI-621
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CR	complete response
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HL	Hodgkin lymphoma
IMWG	International Myeloma Working Group
IV	intravenous(ly)
JAMA	Journal of the American Medical Association
LCL	lower confidence limit
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI	National Cancer Institute
NA	not applicable
NE	not evaluable
ORR	overall response rate
PD	progressive disease
PDx	pharmacodynamics
PET	probability of early termination
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	preferred term
PTCL	peripheral T-cell lymphoma

RAEB	refractory anemia with excess blasts
RD	recommended dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	stringent complete response
SRC	safety review committee
SD	stable disease
SDTM	Study Data Tabulation Model
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TTI-621	investigational product
VGPR	very good partial response
WHODRUG	World Health Organization Drug Dictionary

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe in detail the statistical summaries to be performed by Sarah Cannon Development Innovations for Pfizer study *TTI-621-01, A Phase 1a/1b Dose Escalation and Expansion Trial of TTI-621, a Novel Biologic Targeting CD47, in Subjects with Relapsed or Refractory Hematologic Malignancies and Selected Solid Tumors*. The scope of this document includes statistical analyses to be prepared for the abbreviated Clinical Study Report (aCSR).

This SAP is based on version 9.0 of Clinical Protocol TTI-621-01 (dated 20 Feb 2019) and version 14.0 of Case Report Form (CRF) TTI-621-01 (dated 17 Apr 2020). If amendments are made to either of these documents, this SAP will be updated as appropriate.

Statistical analyses to be performed by Pfizer Inc. or by vendors other than Sarah Cannon Development Innovations are outside of the current scope of this document. In particular, it is currently planned that analyses of pharmacokinetic/pharmacodynamic (PK/PDx) data will take place outside of Sarah Cannon Development Innovations; the text of the SAP describing these analyses has been provided as-is to Sarah Cannon Development Innovations for inclusion in the SAP.

1.1 Study Objectives and Endpoints

Study TTI-621-01/C4961001 has four parts.

1.1.1 Phase 1a Dose Escalation (Part 1)

The primary objective of the escalation phase of the study is to characterize the safety profile and dose limiting toxicities (DLT) of TTI-621 in order to identify the MTD and/or the optimal dose in adult subjects with advanced relapsed or refractory lymphomas.

Primary endpoints are:

- Dose Limiting Toxicities (DLTs) at escalated doses of TTI-621
- Incidence and severity of AEs

DLT is defined for Phase 1a Dose Escalation (Part 1) as any of the following treatment-emergent events occurring during the DLT treatment/ observation period (including the predose tests on Day 22):

- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with bleeding (with the exception of brief, easily-controlled epistaxis, mild gum bleeding or normal menses) or with any requirement for platelet transfusions
- Grade 4 anemia, unexplained by underlying disease
- Grade 4 neutropenia lasting more than 5 days
- Febrile neutropenia of any duration (ANC < 1.0 x 10^9/L, fever > 38.5°C)
- Grade 3 or higher non-hematologic toxicity except for alopecia and nausea controlled by medical management
- Grade 3 or 4 hemorrhage

- Grade 3 or 4 cytokine release syndrome

Secondary objectives include characterization of the pharmacokinetics (PK) of TTI-621, development of antidrug antibodies, and pharmacodynamics through various biomarker studies. (Analyses of PK/PDx data will take place outside Sarah Cannon Development Innovations.)

Secondary endpoints are:

- PK profile, PD, ADA

1.1.2 Phase 1b Dose Expansion (Parts 2 and 3)

The primary objective of the expansion phase of the study is to further characterize the safety of TTI-621 in an expanded number of primary hematologic malignancies and selected solid tumors, and to evaluate the safety of individual subject TTI-621 dose intensification.

Primary endpoints are:

- Incidence and severity of AEs

Secondary objectives include additional characterization of PK, pharmacodynamics, and development of ADA; and to gain preliminary evidence of the antitumor activity of TTI-621 in subjects with a variety of hematologic malignancies and selected solid tumors. In addition, the safety of TTI-621 will be evaluated in combination with other anti-cancer agents.

Secondary endpoints are:

- PK profile, PD, ADA
- Overall response rate, duration of response, and progression-free survival
- Part 3: CTCL and PTCL: organ system overall response rate

1.1.3 Phase 1b Dose Optimization (Part 4)

The primary objective of the dose optimization phase is to further evaluate the safety and tolerability of TTI-621 at dose levels higher than the initially recommended Phase 1b dose of 0.2 mg/kg (as determined during Phase 1a dose escalation) and the MTD will be re-assessed per revised DLT criteria following a 3+3 dose escalation schema. The DLT criteria are revised based on the totality of safety data collected thus far from the Phase 1a and 1b dose expansion phase of the study. The starting dose for this further dose evaluation will be the highest dose of TTI-621 evaluated (0.5 mg/kg) during Phase 1b dose expansion following dose intensification regimens permissible per protocol (Part 2 and Part 3).

Primary endpoints are:

- Dose Limiting Toxicities (DLTs) at escalated doses of TTI-621
- Incidence and severity of AEs

A DLT is defined in Phase 1b Dose Optimization (Part 4) as any of the following TEAEs that occur during the DLT period and that are considered at least possibly related to study treatment by the investigator. Note that any AEs for which the relationship to study treatment cannot be ruled out should be considered possibly related:

- Grade 4 thrombocytopenia (<25 × 10^9/L) lasting >72 hours or a platelet count ≤10 × 10^9/L at any time
- ≥ Grade 3 thrombocytopenia with bleeding (except epistaxis or gingival bleeding that is less than 24 hours in duration and does not require medical intervention, or normal menses) or requiring platelet transfusions
- Grade 4 anemia, unexplained by underlying disease
- Grade 4 neutropenia lasting >72 hours
- Grade 3 febrile neutropenia lasting >72 hours
- Grade 4 febrile neutropenia
- Grade 3 or higher non-hematologic toxicity with the following exceptions:
  - Grade 3 nausea and/or vomiting lasting <72 hours with standard supportive care
  - Transient Grade 3 fatigue lasting ≤72 hours
  - Transient asymptomatic Grade 3 laboratory abnormalities considered not clinically significant following agreement between investigators and the sponsor's medical monitor and that last <72 hours with standard supportive care
- Other ≥ Grade 2 TTI-621-related non-hematologic toxicities that, in the opinion of the investigator, require a dose reduction or discontinuation of TTI-621

Secondary objectives include characterization of the PK, PD, immunogenicity, and preliminary evidence of antitumor activity of TTI-621 in subjects with relapsed and/or refractory CTCL at higher dose levels of TTI-621.

Secondary endpoints are:

- PK profile, PD, ADA
- Overall response rate and duration of response
- CTCL: organ system overall response rate

1.2 Investigational Plan

1.2.1 Overall Study Design

The escalation and expansion phases will be conducted as a multicenter, open-label trial of single-agent TTI-621 and TTI-621 in combination with other therapies in subjects with relapsed or refractory hematologic malignancies and selected solid tumors; the study will be conducted in 4 parts. Neither randomization nor blinding will be utilized.

1.2.2 Phase 1a Escalation – Part 1

Subjects in the escalation phase will be enrolled in sequential dose cohorts utilizing the 3 + 3 design shown below starting at Cohort 1. (Cohort 0 represents a contingency de-escalation dose level in the event that tolerance issues are encountered in Cohort 1.)

Cohort	N	Once-weekly Dose
0	3 (+3)	0.01 mg/kg
1	3 (+3)	0.05 mg/kg
2	3 (+3)	0.1 mg/kg
3	3 (+3)	0.3 mg/kg
4	3 (+3)	1 mg/kg

5	3 (+3)	3 mg/kg
6	3 (+3)	10 mg/kg

Each cohort will initially enroll 3 subjects to receive TTI-621 once weekly for 3 weeks. If none of the 3 subjects experience DLT after 3 weeks of dosing and observation, then enrollment in the next cohort may proceed. If 2 or 3 of the 3 subjects experience DLT, then dosing in that cohort will stop and 3 additional subjects will be enrolled at a lower dose (de-escalation). If exactly 1 of the 3 subjects experiences DLT, then an additional 3 subjects will be enrolled in the cohort. If none of the 3 additional subjects experience DLT after 3 weeks of dosing and observation, then enrollment in the next cohort may proceed. If 1 or more of the additional 3 subjects experience DLT, then dosing in that cohort will stop and 3 additional subjects will be enrolled at a lower dose (de-escalation).

Subjects who discontinue the study during the first 3 weeks for reasons other than toxicity or who experience a delay in dosing of more than 3 days for reasons other than DLT will be replaced.

The escalation and de-escalation rules for the escalation phase are summarized in the table below.

Subject Number						
1	2	3	4	5	6	Decision
No subjects have DLT						Escalate
One subject has DLT			No subjects have DLT			Escalate
			One or more subjects have DLT			De-escalate
Two subjects have DLT						De-escalate

The highest dose level at which 6 subjects are treated and observed for 3 weeks, with at most 1 subject experiencing DLT, will be declared the MTD.

Subjects may continue to receive TTI-621 after the 3 week DLT observation period until disease progression, unacceptable toxicity, or other reason for treatment discontinuation occurs.

Sample Size

The planned sample size is not based on a specific statistical hypothesis but on experience in the conduct of similar trials in subjects with cancer.

For the planned 3+3 dose-escalation design, the probabilities of escalating to the next dose level for a given true rate of DLT are as follows.

True Incidence of DLT	Probability of Escalation
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17

60%	0.08
70%	0.03
80%	0.01

Thus, if the true underlying proportion of DLT is low (e.g., ≤10% at the current dose level, there is a high probability (>=0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (e.g., ≥60%) at the current dose level, there is a low probability (≤0.08) of escalation to the next dose level.

1.2.3 Phase 1b Expansion – Part 2

In the expansion phase, Part 2, subjects with a broader variety of hematologic malignancies and selected solid tumors will be treated at a TTI-621 dose based on the putative optimal dose in order to further define safety, characterize the efficacy, and evaluate the safety of individual subject TTI-621 dose intensification. A cohort of subjects with CD20-positive malignancies will also be enrolled and treated with TTI-621 plus rituximab to characterize the safety and efficacy of the combination. Similarly, a cohort of subjects with classic HL (cHL) will be treated with TTI-621 plus nivolumab to characterize the safety and efficacy of the combination.

The disease cohorts and schedule of treatments administered in the expansion phase Part 2 are summarized in the table below.

	Expansion Cohort	**TTI-621 Starting Dose (mg/kg/wk)**	**Combination Partner Dose**
Monotherapy	IBCL (closed)	0.2	NA
	ABCL (closed)	0.2	NA
	TCL (closed)	0.2	NA
	HL (closed)	0.2	NA
	CLL (closed)	0.2	NA
	ALL (closed)	0.2	NA
	MM (closed)	0.2	NA
	AML (closed)	0.2	NA
	MDS (closed)	0.2	NA
	MPN (closed)	0.2	NA
	SCLC (closed)	0.2	NA
Combination Therapy	Rituximab combination: CD20-positive malignancy	0.1	375 mg/m^2 /wk for up to 8 cycles[a]
	Nivolumab combination: cHL	0.1	per FDA approved package insert for cHL[b]

NA: not applicable
[a] Subjects may continue on TTI-621 monotherapy upon completion of combination partner regimen/unacceptable toxicity to the combination regimen
[b] Subjects who have unacceptable toxicity to the combination regimen may continue to receive TTI-621 monotherapy

Sample Size

The planned sample size for each cohort is not based on a specific statistical hypothesis but is based largely on clinical and feasibility considerations in light of the number of distinct cohorts to be evaluated.

In particular, since the primary objective of the expansion phase is to "further characterize the safety of TTI-621 in an expanded number of primary hematologic malignancies and to confirm the optimal dose of TTI-621 that was identified in Phase 1a", then the sample size chosen for each expansion phase cohort is not based on efficacy considerations.

Although the sample sizes for the expansion cohorts are not based on efficacy considerations, it is possible to evaluate the probabilities of observing a specified number of responses (out of 12 subjects) for various hypothesized response rates. These are provided in the table below.

True Response Rate	Probability of Observing Specified Number of Responses (out of 12 subjects)						
	0	≥1	≥2	≥3	≥4	≥5	≥6
10%	0.282	0.72	0.34	0.11	0.03	0.00	0.00
20%	0.069	0.93	0.73	0.44	0.21	0.07	0.02
30%	0.014	0.99	0.91	0.75	0.51	0.28	0.12
40%	0.002	1.00	0.98	0.92	0.77	0.56	0.33
50%	0.000	1.00	1.00	0.98	0.93	0.81	0.61
60%	0.000	1.00	1.00	1.00	0.98	0.94	0.84
70%	0.000	1.00	1.00	1.00	1.00	0.99	0.96
80%	0.000	1.00	1.00	1.00	1.00	1.00	1.00
90%	0.000	1.00	1.00	1.00	1.00	1.00	1.00

For example, the probability of observing no responses is low (0.002=0.2%) when the true response rate is 40%. Similarly, the probability of observing 3 or more responses is high (0.92=92%) when the true response rate is 40%. When the true response rate is only 10%, the probability of observing 3 or more responses is 11%.

The ability to draw statistical conclusions about response rates in a cohort of size 12 is limited. This is illustrated by the following table of 95% confidence intervals (CIs) for various numbers of responding subjects.

Number of Responders	Observed Response Rate	95% CI[1]
0	0%	(0%, 26%)
1	8%	(0%, 38%)
2	17%	(2%, 48%)
3	25%	(5%, 57%)
4	33%	(10%, 65%)
5	42%	(15%, 72%)
6	50%	(21%, 79%)
7	58%	(28%, 85%)

8	67%	(35%, 90%)
9	75%	(43%, 95%)
10	83%	(52%, 98%)
11	92%	(62%, 100%)
12	100%	(74%, 100%)

[1] Confidence intervals have been calculated using the Clopper-Pearson method.

For the Phase 1b portion (Part 2) of the study, the cohort size for selected cohorts has been increased to 40 subjects. This is to improve the precision of the overall response rate (ORR) estimate. For example, for an ORR of 30%, in 10 subjects, the lower confidence limit (LCL) of a 95% one-sided confidence interval is 8.7%, or a distance of 21.3% (30-8.7) from the ORR. When the sample size is increased to 40 for the same ORR, the LCL is 18.3%, or a distance of 11.7% (30-18.3) from the ORR. This anticipated improvement in the precision of the point estimate will be particularly important given the relative heterogeneity of the enrolled population.

1.2.4 Phase 1b Dose Expansion – Part 3

In the expansion phase, Part 3, based upon preliminary observations of response, 2 cohorts (subjects with CTCL and PTCL), will be evaluated separately, using the Simon 2-stage design, for the potential to be further studied. Dose intensification was required for all newly enrolled subjects starting at Week 3, in 0.1 mg/kg weekly increments, to a maximum of 0.5 mg/kg/week (see Protocol Section 6.5.4 for details).

The disease cohorts and schedule of treatments administered in the expansion phase Part 3 are summarized in the table below.

	Expansion Cohort	TTI-621 Starting Dose (mg/kg/wk)	Combination Partner Dose
Monotherapy	CTCL	0.2	NA
	PTCL	0.2	NA

NA: not applicable

Sample Size

For the Phase 1b (Part 3) expansion cohorts for CTCL and PTCL, the cohort size has been selected based upon a Simon optimal 2-stage design, with the low and high boundaries of the response rate being 10% (not effective) and 30% (warrants further study) respectively, and a power of 90% and an alpha of 0.05. The calculations were performed using PASS 14 (NCSS, 2015) and the Optimum design chosen. The total sample size is 35 subjects per cohort under the scenario described below. For the first stage, a total of 18 subjects will be enrolled in each cohort. At the end of Stage 1, if 2 or fewer responders are observed per cohort, enrollment in this cohort will be terminated, otherwise, enrollment will proceed to the second stage and an additional 17 subjects will be enrolled per cohort for a total of 35 subjects per cohort. At the end of the second stage, if 6 or fewer responders are observed per

cohort, the drug will be rejected for further testing in this indication. The probability of early termination (PET) = 0.734 at the end of the first stage if the true response rate is less than 10%.

N1	R1	PET	N	R	Average N	Alpha	Beta
18	2	0.734	35	6	22.53	0.047	0.098

1.2.5 Phase 1b Dose Optimization – Part 4

In the dose optimization phase, Part 4, the safety and tolerability of TTI-621 at higher dose levels beyond the initially recommended Phase 1b dose of 0.2 mg/kg (as determined during Phase 1a dose escalation) and the highest dose of TTI-621 evaluated (0.5 mg/kg) during Phase 1b dose expansion following dose intensification permissible per protocol, will be evaluated. This Phase 1b dose optimization phase will aim at re-defining MTD following 3+3 dose escalation schema and a revised DLT criteria based on the totality of safety data collected thus far from Phase 1a and 1b dose expansion phase of the study. In Phase 1b dose optimization of the study (Part 4), further dose escalation of TTI-621 will be pursued in subjects with relapsed and/or refractory CTCL following a 3+3 escalation design and using a revised DLT criteria. Dose optimization will proceed following review of the data obtained from the Phase 1b Part 3, stage 1 cohorts of CTCL and PTCL subjects. Alternative dosing schedules, intermediate doses, and other optimization options may be considered by the SRC following review of available data.

Part 4 Q2W is an expansion to Part 4 Cohort 5 (P4-5). Dosing is done at the 2.0 mg/kg dose level and explores a TTI-621 biweekly (every other week) dosing schedule.

Sample Size

Up to 6 DLT evaluable subjects may be enrolled at each dose level evaluated during the escalation phase. The number of subjects enrolled at each dose level and the dose-step increments between adjacent dose levels will be based on a 3 + 3 dose escalation scheme (protocol Section 3.2.2). Once the MTD or a recommended dose is estimated (with the required six DLT-evaluable subjects at that dose level), an additional six subjects will be treated at that dose level (for a total of twelve subjects). These additional subjects will allow further examination of the safety and tolerability of the dose and a preliminary examination of the efficacy of the dose. With twelve subjects, if the observed response rate is 33%, the lower bound of a two-sided 90% confidence interval would be 0.12. The maximum width of the 90% CI would be 0.51.

We expect to accrue approximately 25 subjects in Part 4. The actual number required will depend upon the observed safety profile, which will determine the number of subjects per dose level, as well as the number of dose escalations required to achieve the MTD or the recommended dose

1.2.6 Timing of Analysis Reporting

Separate sets of tables, figures, and listings (TFLs) will be produced for Phase 1a and for each of the Phase 1b parts. Regular interim reviews of safety data will be held during the escalation phase, but no interim analyses for efficacy are planned for

either Phase 1a or Phase 1b parts. A single Clinical Study Report will be written after enrollment and follow-up is complete for the study.

1.2.7 Responsibilities

Activities related to the development, approval, and maintenance of the SAP (sans specified portions provided by Pfizer Inc.), along with applicable study analysis and reporting will be the responsibility of assigned Sarah Cannon Development Innovations study team members. After completion of the final CSR, all applicable datasets, outputs, programs, and specification documents, including interim safety reviews, will be transferred to the Sponsor for archiving.

2 Analysis Populations

The analysis of data will focus on the following analysis sets.

Safety Analysis Set

The Safety Analysis Set is the primary population for analyses of safety data and consists of all subjects who receive at least 1 dose of study treatment.

DLT-evaluable set (for Part 1 and non-Q2W Part 4 only)

The DLT-evaluable set consists of 1) subjects who have received all 3 doses within the DLT evaluation period, OR 2) subjects who experienced an adverse event (AE) meeting DLT criteria during that time. Those who drop out of the study during the DLT evaluation period for reasons other than toxicity or who experience a delay in dosing of more than 3 days for reasons other than DLT are considered unevaluable for DLT.

The DLT evaluation period consists of the first 21 days on study for subjects initially assigned to Part 1 and non-Q2W Part 4. For subjects who experienced a treatment delay, the DLT observation period will extend 7 days beyond the third dose of TTI-621.

Full Analysis Set

The Full Analysis Set is the primary population for all analyses of efficacy-related data. The Full Analysis Set is identical to the safety analysis set, which includes all subjects who received at least 1 dose of study treatment.

Response-Evaluable Set (for Part 3 only)

The Response-Evaluable Set will serve as a secondary population for the analysis of overall response for Part 3. The Response-Evaluable Set is a subset of the Full Analysis Set, with subjects excluded if they withdraw from the study without post-baseline assessment of overall response for a reason other than early progression or safety.

PK-evaluable Set

The Pharmacokinetic (PK)-evaluable Set consists of treated subjects with adequate blood sampling to estimate at least 1 pharmacokinetic PK parameter.

Immunogenicity-evaluable Set

The immunogenicity analysis population includes all treated subjects with at least 1 ADA sample (pre-dose or post-treatment) analyzed. If a subject only has pre-dose baseline data and no post-treatment immunogenicity data, this subject is not evaluable for subject-level ADA and NAb status and should not be included in subject-level data analysis (eg. overall ADA/NAb incidence, duration of ADA/NAb response).

3 Analyses and Summaries

The statistical analyses performed for this study will be summarized by the following unless indicated otherwise:

- Initial assigned dose levels or initial assigned dosing schedules (in the case of Part 4 biweekly) for Part 1 and Part 4 (Dose Escalation cohorts)
- Monotherapy or combination therapy for Part 2 and Part 3
- Indication within monotherapy and by combination therapy for Part 2 and Part 3

The statistical analyses will be performed using SAS® version 9.2 or later (SAS Institute Inc., Cary NC). Programming specifications will be prepared which describe the datasets and variables created for this study. The datasets will be prepared using the most recent version of the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and Analysis Dataset Model (ADaM). The source SDTM and ADaM datasets from which a statistical analysis is performed (including interim safety reviews) will be archived with the Sponsor.

The following data conventions will be employed in the study.

- Summary tables for continuous variables will contain the following statistics: N (number in population); n (number with data); mean; standard deviation; median; minimum; and maximum. Selected tables also may include 2-sided 95% confidence intervals (CIs) on the mean, calculated using a t-distribution approximation.
- Summary tables for categorical variables will include: N (number in denominator); n (number in numerator); and percent. Selected tables also may include 2-sided 95% CIs for the percent, calculated using the Clopper-Pearson method.
- Data from all study centers will be pooled for all analyses.
- The baseline value for a given parameter is the last value prior to the time of the first dose. A value is considered to be post-baseline if it is obtained after the time of the first dose.
- Study Day is defined as Calendar Date – Date of First Treatment + 1 if the calendar date is on or after the date of the first treatment, and Calendar Date – Date of First Treatment if the calendar date is before the date of the first treatment.
- Partial dates will be displayed as partial dates in listings and missing dates will be displayed as missing. The corresponding Study Day for partial or missing dates will be displayed as missing in listings.
- Unless specifically noted later in this SAP, missing data will not be imputed.

3.1 Subject Disposition

The number of subjects in each of the following subsets will be presented by cohort and overall.

- Safety Analysis Set
- DLT Evaluable Analysis Set (for Part 1 and non-Q2W Part 4 only)
- Full Analysis Set
- Response-Evaluable Set (for Part 3 only)
- PK-Evaluable Set
- Immunogenicity-evaluable Set

The number and percentage of subjects will be calculated based on the full analysis set as applicable:

- Discontinued study treatment (overall and by reason, for each drug)
- Discontinued study (overall and by reason)
- Follow-up status

The duration of study participation (defined as Date of study discontinuation – date of first dose + 1) will be summarized for subjects in the Safety Analysis Set.

All disposition data will be presented in a listing, with a flag for treatment discontinuation and a flag for study discontinuation related to COVID-19.

3.2 Demographics and Baseline Characteristics

The following variables will be summarized for the Full Analysis Set.

- Demographics (age, sex, race, and ethnicity) and Physical Characteristics (weight in kg, height in cm, and body mass index (BMI) in kg/m^2)
  - Age will be calculated as the difference between the informed consent date and the birth date, rounded to the nearest year. (The corresponding SAS function is 'yrdif' with the 'AGE' option, rounded to the nearest year.)
  - Subjects in more than one race category will be categorized as 'Multiple'.
  - Weight measurements in pounds will be converted to kilograms using: 1 pound = 0.453592 kg
  - Height measurements in inches will be converted to centimeters using: 1 inch = 2.54 cm
- Number and percent of subjects by primary cancer diagnosis
- Number and percent of subjects having history of systemic therapy, radiation, surgery, transplant, and/or transfusion
- Number and percent of subjects by baseline Eastern Cooperative Oncology Group (ECOG) performance status
- Number and percent of subjects having Medical Dictionary for Regulatory Activities (MedDRA) coded medical history conditions by System Organ Class (SOC) and Preferred Term (PT).

3.3 Protocol Deviation

Major protocol deviations will be summarized for the full analysis set. In addition, a listing of Major protocol deviations and a listing of protocol deviations related to COVID-19 will be provided.

3.4 Extent of Exposure

The analysis population for exposure is the Safety Analysis Set by:

- Initial assigned dose levels or initial assigned dosing schedules (in the case of Part 4 biweekly) for Part 1 and Part 4 (Dose Escalation cohorts)
- Monotherapy or combination therapy for Part 2 and Part 3

For each study drug administered (TTI-621, nivolumab, and rituximab), the following measures of exposure will be summarized.

- Total number of doses received
- Cumulative dose (in mg/kg for TTI-621, mg for nivolumab, and mg/m^2 for rituximab)
- Average dose (in mg/kg for TTI-621, mg for nivolumab, and mg/m^2 for rituximab) = Cumulative dose / total number of doses received
- Duration of treatment (days) = Date of last dose date – date of first dose + *n*
    - where *n* is as follows, for the respective study drug:
        - For TTI-621 for subjects not assigned to Part 4 Q2W, n=7
        - For TTI-621 for subjects assigned to Part 4 Q2W, n=14
        - For Rituximab, n=7
        - For Nivolumab, n=14

The following categorical summaries of exposure also will be provided for each study drug administered (TTI-621, nivolumab, and rituximab).

- Number and percent of subjects having a dose interruption
- Number and percent of subjects by reason for dose interruption
- Number and percent of subjects having a dose reduction
- Number and percent of subjects by reason for dose reduction

For the purposes of these analyses, dose interruption generally indicates all instances in which a subject experiences a delay in the scheduled administration of study drug and the corresponding fields are populated on the respective treatment CRF form.

For the purposes of these analyses, dose reduction generally indicates all instances in which the subject is treated at a lower dose level different to their extant assigned dose level and when the corresponding fields are populated on the respective treatment CRF form.

In subjects who received intrapatient dose escalation (IDE), the range of weeks at each dose level of TTI-621 will be presented. Details are as follows:

- Subjects will be considered as having dose escalated if their C1D1 actual dose level is as assigned and they experience at least one instance of dose increase such that their actual dose level is greater than their assigned dose level.
- Summarization will be presented by maximum TTI-621 dose level administered.
- The range of weeks at each dose counts the number of weeks the subject was actually treated with TTI-621 at the given dose level.

Descriptive statistics for the compliance rate will be provided.

The compliance rate for each subject will be calculated as follows.

$$Compliance\ rate = 100 * \frac{Cumulative\ \ dose\ of\ study\ drug\ received}{Cumulative\ \ dose\ of\ study\ drug\ planned}.$$

where $Cumulative\ \ dose\ of\ study\ drug\ received$ is the total sum of the Dose per Administration field per subject and $Cumulative\ dose\ of\ study\ drug\ planned$ is the total sum of the Planned Dose per Administration field per subject captured on or derived

from the corresponding study drug treatment CRF. The unit of cumulative dose is mg/kg for TTI-621, mg for nivolumab, and mg/m^2 for rituximab, respectively.

3.5 Safety Analyses

The analysis population for safety is the Safety Analysis Set by:

- Initial assigned dose levels or initial assigned dosing schedules (in the case of Part 4 biweekly) for Part 1 and Part 4 (Dose Escalation cohorts)
- Monotherapy or combination therapy for Part 2 and Part 3

3.5.1 Adverse Events

Adverse events (AEs) are recorded by the sites in the CRFs according to CTCAE v4.03. The CRFs also identify the following characteristics of each AE:

- The start date and end dates of the AE
- The outcome of the AE
- The severity grade of the AE
- The relationship of the AE to study treatment TTI-621 (related or unrelated)
- The relationship of the AE to rituximab or nivolumab in the combination therapy, if applicable (related or unrelated)
- Whether the AE was a Dose Limiting Toxicity (DLT) for dose escalation portion (Part 1 and non-Q2W Part 4)
- Whether the AE was a Serious Adverse Event (SAE)
- Study treatment actions (for any administered anti-cancer therapy) taken in response to the AE
- Other actions taken in response to the AE

Verbatim AE terms will be coded into preferred term (PT) and system organ class (SOC) by Pfizer using the most recent version of MedDRA available at time of analysis.

Treatment-emergent adverse events (TEAEs) are defined as AEs having a start date on or after the date of the first dose of study drug and on or before the date of the last dose of study drug plus 30 days. AEs starting more than 30 days after the final study drug administration will be included in listings, but not in summary tables. AEs outside the on-treatment period will be flagged in the listings.

Adverse events of special interest include the following:

- Thrombocytopenia: Haematopoietic thrombocytopenia – SMQ Broad
- Other Cytopenias:
  - Haematopoietic cytopenias affecting more than on type of blood cell – SMQ- Broad
  - Haematopoietic leukopenia – SMQ - broad and narrow
- Anemia: Haematopoietic erythropenia – SMQ – broad
- Hemorrhage: Haemorrhage terms (excl laboratory terms) – SMQ narrow
- Infusion related reactions
- ALT/AST elevations

An overview summary will be provided of the number and percentage of subjects in each of the following categories as applicable:

- at least one TEAE
- at least one TEAE of Grade ≥ 3

- at least one related TEAE
- at least one related TEAE of Grade ≥ 3
- at least one serious TEAE
- at least one related serious TEAE
- at least one TEAE leading to drug withdrawal of TTI-621
- at least one TEAE leading to drug withdrawal of rituximab
- at least one TEAE leading to drug withdrawal of nivolumab
- at least one related TEAE leading to drug withdrawal of TTI-621
- at least one related TEAE leading to drug withdrawal of rituximab
- at least one related TEAE leading to drug withdrawal of nivolumab
- at least one TEAE leading to drug interruption of TTI-621
- at least one TEAE leading to drug interruption of rituximab
- at least one TEAE leading to drug interruption of nivolumab
- at least one TEAE leading to drug reduction of TTI-621
- at least one TEAE leading to drug reduction of rituximab
- at least one TEAE leading to drug reduction of nivolumab
- at least one TEAE leading to death
- at least one related TEAE leading to death
- at least one TEAE of special interest Thrombocytopenia SMQ (broad)
- at least one TEAE of special interest Other Cytopenias SMQ (broad)
- at least one TEAE of special interest Anemia SMQ (broad)
- at least one TEAE of special interest Hemorrhage SMQ (narrow)
- at least one TEAE of special interest Infusion related reactions
- at least one TEAE of special interest ALT/AST elevations

For summaries of the number and percent of subjects by SOC and/or PT, subjects reporting multiple TEAEs within the same SOC/PT will be counted only once for that SOC/PT. SOCs and PTs in summaries will be displayed in order of decreasing total frequency of TEAEs.

Summaries of TEAEs and serious TEAEs by SOC, PT, and severity grade will be presented. For this summary, subjects reporting multiple TEAEs within the same SOC or PT will be counted only once for that SOC or PT using the highest severity grade.

Summaries of TEAEs and serious TEAEs by SOC, PT, and relationship to study drug will be presented. For this summary, subjects reporting multiple TEAEs within the same SOC or PT will be counted only once for that SOC or PT using the strongest causal relationship.

Separate summaries by SOC and PT will be presented for the following types of AEs:

- TEAEs by maximum severity grade
- TEAEs of any grade and Grade ≥ 3 severity
- Related TEAEs by maximum severity grade
- Related TEAEs of any grade and Grade ≥ 3 severity
- All serious TEAEs
- Related serious TEAEs
- DLTs (for Part 1 and non-Q2W Part 4 dose escalation cohorts only)
- TEAEs leading to drug withdrawal of TTI-621
- TEAEs leading to drug withdrawal of rituximab
- TEAEs leading to drug withdrawal of nivolumab
- Related TEAE leading to drug withdrawal of TTI-621

- Related TEAE leading to drug withdrawal of rituximab
- Related TEAE leading to drug withdrawal of nivolumab
- TEAEs leading to drug interruption of TTI-621
- TEAEs leading to drug interruption of rituximab
- TEAEs leading to drug interruption of nivolumab
- TEAEs leading to drug reduction of TTI-621
- TEAEs leading to drug reduction of rituximab
- TEAEs leading to drug reduction of nivolumab
- TEAEs leading to death
- Related TEAEs leading to death

The following TEAEs of special interest will be summarized by SMQ and PT as applicable:

- Thrombocytopenia (broad)
- Other Cytopenias (broad)
- Anemia (broad)
- Hemorrhage (narrow)

The following TEAEs of special interest will be summarized by PT:

- Infusion related reactions
- ALT/AST elevations

The following listings will be presented:

- All AEs (including whether or not the AE is defined as a TEAE, as well as other identifying characteristics from the AE CRF)
- All DLTs
- AEs leading to death
- COVID-19 related AEs

3.5.2 Deaths

Death information for subjects in the Safety Analysis Set will be summarized by frequency (number and percentage) for the following:

- All deaths
- Deaths with a date of occurrence on or after the date of the first dose of study drug to on or before the date of the last dose of study drug plus 30 days
- Reason for Death

A subject-level listing will also be provided that includes the following information:

- Treatment group/cohort
- Last dose of study treatment (drug name and dose)
- Date of first dose of study treatment
- Date of last dose of study treatment
- Date of death
- Primary cause of death
- Preferred terms (PT) of any AEs with Fatal outcome
- PT of any Grade 5 AEs
- Whether or not the death occurred within 30 days after last dose of study treatment

- Flag for death due to COVID-19

3.5.3 Laboratory Data

Laboratory data will be converted as needed to a standard set of units. Only lab values considered abnormal relative to baseline will be considered for the following.

Quantitative laboratory results reported as "< X", "<= X", "> X", or ">= X", will be converted to X for the purpose of severity grading, but will be presented as recorded in data listings.

Severity grades will be programmatically calculated using Journal of the American Medical Association (JAMA) ranges (Iverson 2007) and Common Terminology Criteria for Adverse Events (CTCAE) criteria (National Cancer Institute 2010) when available. Laboratory values considered to be normal by CTCAE criteria will be assigned a severity grade of 0. Laboratory values obtained more than 30 days after the last study drug administration will be included in listings but not in summary tables.

CTCAE severity grades will be summarized by shift tables for each hematology and chemistry parameter. The shift tables will display the number and percent of subjects by baseline severity grade and maximum post-baseline severity grade.

JAMA normal range categories (low, normal, or high) will be summarized by shift tables for each hematology and chemistry parameter. The shift tables will display the number and percent of subjects by baseline and post-baseline categories. Subjects will be counted in the post-baseline category of normal only if all post-baseline values are within the JAMA normal range. Subjects will be counted in the post-baseline category of high if at least one post-baseline value is above the JAMA normal range, and will be counted in the post-baseline category of low if at least one post-baseline value is below the JAMA normal range. Subjects having both low and high post-baseline values will be counted twice in the shift table.

All laboratory data will be displayed in listings. Values meeting CTCAE severity criteria, outside of JAMA normal ranges, or assessed as abnormal will be flagged in the listings.

3.5.4 Prior and Subsequent Systemic Therapies

Systemic therapy regimens are collected on two CRFs:
- Prior Systemic Therapy
- Subsequent Systemic Therapy

Medications collected on both CRFs will be coded by Pfizer to preferred terms by means of the World Health Organization Drug Dictionary (WHODRUG).

Subjects reporting multiple medications within the same PT will be counted only once for that PT on medication summaries. PTs in summaries will be displayed in order of decreasing total frequency of occurrence.

Prior Systemic Therapies will be summarized by PT and by:
- Initial assigned dose levels or initial assigned dosing schedules (in the case of Part 4 biweekly) for Part 1 and Part 4 (Dose Escalation cohorts)

- Monotherapy or combination therapy for Part 2 and Part 3
- Indication within monotherapy and by combination therapy for Part 2 and Part 3

In addition, a listing will be provided that contains the verbatim medication term, PT, therapy start and end dates, study drug start date, duration of therapy, route of administration, best overall response, and the reason the therapy ended.

Subsequent Systemic Therapies will be summarized by PT. In addition, a listing will be provided. This listing will contain the verbatim medication term, PT, therapy start date, and the study day on which the therapy started.

3.5.5 Blood Transfusions

Blood transfusions performed during the study will be summarized by the number and percent of subjects having each transfusion element (platelets, packed red blood cells, etc.). For each subject and transfusion element, the total number of transfusions and cumulative element units will be calculated. These calculated values will be summarized by descriptive statistics.

A listing will be provided containing each subject's blood transfusion data and transfusion-related medical history.

3.5.6 Antidrug Antibodies

The analysis of antidrug antibodies will be performed by Sarah Cannon Development Innovations.

Final individual subject results from the ADA and NAb assay (as appropriate) will be presented in the listings and the incidence summarized by descriptive statistics in tabular form by cohort.

Summary tables that show the number and percentage of subjects that fall into the following categories will also be produced by cohort:

Treatment-induced ADA	Baseline ADA titer is missing or negative and subject has ≥ 1 post-treatment positive ADA titer.
Treatment-boosted ADA	Baseline ADA titer is positive and subject has a ≥ 4-fold dilution increase in ADA titer from baseline in ≥ 1 post-treatment sample. If ADA titer is log10 transformed, a 4-fold dilution increase is equivalent to 0.602 unit increase in titer (log10) from baseline. If ADA titer is log2 transformed, a 4-fold dilution increase is equivalent to 2 unit increase in titer (log2) from baseline.
ADA-positive subject	A subject with ≥ 1 treatment-induced or treatment-boosted ADA response.
ADA-negative subject	An ADA evaluable subject without treatment-induced or treatment-boosted ADA response. Subject either has (1) all ADA-negative results

	throughout the study or (2) is ADA positive at baseline but did not become treatment-boosted post-dose.
ADA incidence	The percent of ADA-positive subjects in a treatment group/cohort or study.
Treatment-induced NAb	Baseline NAb titer is missing or negative or ADA-negative and subject has ≥ 1 post-treatment positive NAb titer.
Treatment-boosted NAb	Baseline NAb titer is positive and subject has a ≥ 4-fold dilution increase in NAb titer from baseline in ≥ 1 post-treatment sample. If NAb titer is log10 transformed, a 4-fold dilution increase is equivalent to 0.602 unit increase in titer (log10) from baseline. If NAb titer is log2 transformed, a 4-fold dilution increase is equivalent to 2 unit increase in titer (log2) from baseline.
NAb-positive subject	An ADA-positive subject with ≥ 1 treatment-induced or treatment-boosted NAb response. For ADA-positive (treatment-boosted) subjects, subject is NAb positive only if the subject has ≥1 treatment-induced or treatment-boosted NAb response at the visit where the subject has a treatment-boosted ADA response. For visits where the subject did not show a boosted ADA response, the subject is classified as NAb-negative for the visit even if the subject has post-treatment positive NAb titer for that visit.
NAb-negative subject	NAb evaluable participant who is either (1) an ADA-negative subject or (2) an ADA-positive subject without treatment-induced or treatment-boosted NAb response (i.e. subject has all NAb-negative results throughout the study or subject is NAb positive at baseline but did not become treatment-boosted post-dose). Note: in the event a subject is ADA-positive at baseline but did not show a boosted response post-treatment, subject is classified as ADA-negative and NAb-negative at the subject level even if the subject has post-treatment positive NAb titer. As such all ADA-negative subjects are NAb-negative regardless of NAb titer data."
NAb incidence	The percent of NAb-positive subjects in a treatment group/cohort or study.
Transient ADA	An ADA-positive subject with (1) a treatment-induced or treatment-boosted ADA sample detected only at 1 sampling time (excluding the last time point) post-treatment, or (2) treatment-induced or treatment-boosted ADA samples detected at ≥ 2 time points where the first and last positive samples (irrespective of any negative samples in between) are separated by < 16 weeks, and the subject's last sample is ADA negative.
Persistent ADA	An ADA-positive subject with first and last positive ADA samples (treatment-induced or treatment-boosted) detected over a period of ≥ 16 weeks post-treatment, irrespective of any negative samples in between

Indeterminate ADA	An ADA-positive subject who is not persistent or transient
Transient NAb	A NAb-positive subject with (1) a treatment-induced or treatment-boosted NAb sample detected only at 1 sampling time (excluding the last time point) post-treatment, or (2) treatment-induced or treatment-boosted NAb samples detected at ≥ 2 time points where the first and last positive samples (irrespective of any negative samples in between) are separated by < 16 weeks, and the subject's last sample is NAb negative or ADA negative
Persistent NAb	A NAb-positive subject with first and last positive NAb samples (treatment-induced or treatment-boosted) detected over a period of ≥ 16 weeks post-treatment, irrespective of any negative samples in between.
Indeterminate NAb	A NAb-positive subject who is not persistent or transient.

Titers will be reported if applicable.

3.6 Pharmacokinetic Analysis

The PK analysis will be performed by Pfizer and reported separately. Sarah Cannon Development Innovations will provide the PK listing to be included in the CSR.

3.6.1 Serum Concentrations

Pharmacokinetic blood samples for determination of TTI-621 serum concentrations will be collected in accordance with the regimen specified in the schedule of events. The concentrations as reported by the bioanalytical lab will be used without rounding for all analyses.

For serum concentration data, all values below the limit of quantification (BLQ) will be set to 0 for summary statistics and graphs. Individual serum concentrations of TTI-621 will be summarized at each time point using descriptive statistics. Individual concentration plots and median data by dose cohorts graphs will be produced. All graphs will be presented using both linear and semi-logarithmic scales. The above descriptive summary will be performed for the PK-evaluable Set.

All TTI-621 serum concentrations will be presented in a by-subject listing. Additionally, time elapsed since dosing and deviation from scheduled time point will be presented.

3.6.2 Pharmacokinetic Parameters

Pharmacokinetic parameter estimation will be performed using non-compartmental analysis on individual serum concentration-time data. The actual sampling times will

be used for all calculations, except as noted above. For the PK parameter calculation, BLQ serum concentrations occurring before Tmax will be set to 0, except for a BLQ value occurring between two measurable concentrations, in which case it will be set to missing. BLQ concentrations occurring in pre-dose (trough) samples during the multiple dosing phase will be set to zero. Pharmacokinetic parameter estimates and summaries will be completed for subjects in the PK Population having sufficient measurable concentrations to define the PK profile. For any subject whose extrapolated AUC from the last time point where the concentration is above the limit of quantification to infinity exceeds 20% of the total AUC, the $AUC_{0-\infty}$ from the subject will be excluded from the calculation of the descriptive statistics.

Pharmacokinetic parameter estimates after the single dose will include Cmax, Tmax, AUC0-t, AUC0-168 where appropriate and as data permit. For the multiple dosing phase, Cmax, Tmax, Cmin, Cavg, AUC0-t, AUC0-tau, CL will be calculated if data permit. Additional PK parameters may be reported if appropriate.

The non-compartmental parameters will not be reported to any greater precision than that of the concentration data. All parameters will be reported to 3 significant figures. Parameter values will be rounded to the same precision used in data listings prior to any statistical analysis or descriptive summaries.

The below precision will be used for descriptive and statistical summary of PK parameters:

1. Geometric Means, Medians and their %CV and Confidence Intervals (CIs) – 1 more significant figure than the data
2. Standard Deviation – 1 more significant figure than means
3. CV% – whole numbers
4. Minimum, Maximum – same significant figures as the data
5. Ratios, CIs (log transformed data) – 2 decimal places

For parameters which are direct time observations, Median and Range will have the same significant figures as the data.

The definitions and the associated rules for the PK parameter calculation are summarized in the table below.

Cmax	Maximum observed concentration, occurring at time Tmax. If all observations are below the limit of quantification (BLQ), Cmax will be reported as zero.
Tmax	Time of maximum observed concentration. If the maximum observed concentration is not unique, then the first maximum is used. If all observations are BLQ, Tmax will be reported as not determined (ND).
AUC0-t	Area under the curve from the time of dosing to the time of the last measurable concentration calculated using the trapezoidal rule. If all concentrations are BLQ, AUClast will be reported as zero
Cmin	Minimum observed concentration occurring at time Tmin.
AUC0-tau	The partial area from dosing time to Tau, (i.e. 0-168 h).

Rac (Multiple dosing)	Observed accumulation ratio will be calcluated as: Rac = $AUC_{T,ss}$ / $AUC_{T,(first\ dose)}$.
CL	An estimate of total body clearance computed from the steady state data, calculated as Dose/AUC0-tau.
Cavg	Average concentration during a dosing interval, calculated as AUC0-tau divided by tau.

The calculated PK parameters will be summarized using descriptive statistics, including arithmetic and geometric means, SD, arithmetic and geometric %CV, median, minimum, and maximum. For Tmax only the median and the range will be reported. All data will be summarized by subject, dose, cohort and the study part.

Dose proportionality will also be assessed based on the data acquired during the dose escalation phase using descriptive statistics.

TTI-621 serum concentrations from this study may be pooled with data from other studies and analyzed using population PK approaches. In addition, a model-based approach may be used to explore the potential relationship between TTI-621 exposure metrics and efficacy, safety, and/or biomarker endpoints. These analyses, if conducted, will be reported in separate report(s).

3.7 Efficacy

Efficacy analyses will be conducted using the Full Analysis Set. Overall response will additionally be presented for the Response-Evaluable Set in Part 3.

The efficacy analyses for this study will be summarized by:

- Initial assigned dose levels or initial assigned dosing schedules (in the case of Part 4 biweekly) for Part 1 and Part 4 (Dose Escalation cohorts)
- Indication within monotherapy and by combination therapy for Part 2 and Part 3

3.7.1 Overall Response Rate

For each subject, a disease-specific overall assessment will be made by the investigator. The table below indicates the responder and non-responder CRF categories for each type of malignancy.

Type of Hematologic Malignancy	**CRF**	**CRF variable label**	**CRF Assessment Categories (* indicates responder category, ** indicates progressive disease category)**
Lymphoma (Hodgkin or Non-Hodgkin)	Response Assessment – Cheson Lugano Classification 2014	"Overall Visit Response at This Assessment"	CR*, PR*, SD, PD**, NE

Multiple Myeloma	Response Assessment – IMWG	"Overall Objective Response at this assessment"	CR*, sCR*, VGPR*, PR*, SD, PD**, Clinical Relapse**, NE, NA
Acute Myeloid Leukemia	AML Response Assessment – Cheson 2003	"Overall Objective Response at This Assessment"	Morphologic leukemia-free state*, Morphologic complete remission*, Cytogenetic complete remission*, Molecular complete remission*, Partial Remission*, Treatment Failure, Unknown
Chronic Lymphocytic Leukemia	Response Assessment – Hallek 2008	"Overall Visit Response at This Assessment"	Complete Response or Complete Remission*, Complete Response or Complete Remission with Incomplete Marrow Recovery*, Partial Response*, Relapse or Progressive Disease**, Stable Disease, Unknown
Myelodysplastic Syndrome (RAEB-1 or RAEB-2)	Response Assessment – MDS	"Overall Objective Response at this assessment"	CR: Marrow*, CR*, PR*, SD, PD**, NE, NA

A subject will be considered to be a responder if the subject had at least two consecutive assessments at which the subject is identified as a responder according to the table above. A subject will be considered to have progressive disease if the subject had at least one assessment at which the subject is identified as having progressive disease according to the table above. The earliest of the consecutive dates at which a responder assessment is made will be the Date of Response. The earliest date at which a progressive disease assessment is made will be the Date of Progression.

In the full analysis set and the response evaluable set, the Overall Response Rate (ORR) is defined as follows.

$$ORR = 100 * \frac{Number\ of\ responders}{Total\ number\ of\ subjects}.$$

(Note that subjects having a response of NE, NA, Unknown, or missing are included in the denominator in this calculation and summarized as non-responders.)

3.7.2 Duration of Response and Progression Free Survival Time

The time-to-event endpoints measured in this study are defined in terms of the following dates.

- Date of first dose = Date of first dose as recorded on Treatment CRF
- Date of response = Earliest of the consecutive dates at which subject is assessed in a responder category
- Date of last non-PD assessment = Date of last non-missing assessment other than NE, NA, or Unknown
- Date of progression = Date at which subject is first assessed as having progressive disease
- Date of initiation of anticancer treatment = Earliest concomitant medication start date for concomitant medications identified by sponsor as being anticancer treatments

- Date of death = Date of death from any cause as recorded on Death Page CRF

The following time-to-event endpoints will be calculated for each subject.

- DOR for subjects who achieved an objective response = Duration of response (in weeks) = [min(Date of progression) – Date of response + 1]/7
- PFS = Progression free survival time (in weeks) = [min(Date of progression, Date of death) - Date of first dose + 1]/7

In the case of missing dates (ie, subjects without an event), the following censoring rules will be applied.

Endpoint	Censor if:	Censoring date = Minimum of indicated dates		
		Date of last non-PD assessment	Date of initiation of anticancer treatment	Date of death
DOR	Death prior to progression			X
DOR or PFS	Subsequent anticancer therapy is initiated in the absence of documented progression		X	
	Death or progression after >=2 assessments of NE, NA, Unknown, or Missing	X		
	Alive & progression free	X	X	

DOR and PFS will displayed in listings.

The number of subjects with event for DOR and PFS will be summarized. Median time to event, the 25th and 75th percentiles of time to event, along with 95% CI for DOR and PFS will be estimated according to the Kaplan-Meier estimate using the Brookmeyer-Crowley method.

Additionally, the PFS rate at selected landmarks (e.g., 6 months) and corresponding 95% CIs will be estimated using the Kaplan-Meier method. Greenwood's formula will be used to calculate the standard errors of the Kaplan-Meier estimate and upper and lower limits of the 95% CI.

3.7.3 Organ system-specific overall response rate

In subjects with CTCL and PTCL (in Parts 3 and 4), the organ system-specific response rates will be presented by: in skin, lymph nodes, blood, and visceral organs. (Olsen, 2011)

4 References

Iverson C, Christiansen S, Flanagin A, et al. AMA Manual of Style: A Guide for Authors and Editors. 10th ed. New York, NY: Oxford University Press; 2007. © American Medical Association.

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. June 14, 2010.

Olsen EA, Whittaker S, Kim YH, et al. (2011). Clinical End Points and Response Criteria in Mycosis Fungoides and Sézary Syndrome: A Consensus Statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 29, 2598-2607.

SAS Institute Inc. (2011): The SAS System, Version 9.3. Cary, NC. SAS Institute Inc.

5 Tables, figures, and listings

A separate document will be maintained that identifies all tables, figures, and listings (TLFs) to be provided for the CSR. This document will be updated as appropriate during TFL development.