16 APPENDICES

16.1 STUDY INFORMATION

16.1.9 DOCUMENTATION OF STATISTICAL METHODS

STATISTICAL ANALYSIS PLAN APPROVAL

AUTHOR:

[redacted]

APPROVED BY:

[redacted]

[redacted]

[redacted]

STATISTICAL ANALYSIS PLAN

Study Title:	A Combined Phase 1/2 Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of TP-0903 in Patients with Previously Treated Chronic Lymphocytic Leukemia (CLL)
Sponsor	Tolero Pharmaceuticals, Inc. 3900 N Traverse Mountain Blvd, Suite 100 Lehi, UT 84043
Protocol Number	TP-0903-102
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Analysis Plan Date	April 13, 2020

STATISTICAL ANALYSIS PLAN APPROVAL

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ABBREVIATIONS AND DEFINITIONS

ADaM	analysis data model
AE	adverse event
ATC	anatomical therapeutic chemical
BMI	body mass index
BOR	best objective response
bpm	beats per minute
BP	blood pressure
CI	confidence interval
CR	complete response
CRF	case report form
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DBP	diastolic blood pressure
DLT	dose limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	end-of-study
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HR	heart rate
ICH	International Committee for Harmonization
IP	Investigational Product
ITT	intent to treat
IU	international units
IWCLL	International Workshop on CLL
K-M	Kaplan-Meier
mmHg	millimeters of mercury
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
MTD	maximum tolerated dose
NCS	not clinically significant
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival

PK	pharmacokinetic
PR	partial response
PT	preferred term
PPT	partial prothrombin time
QTcF	corrected QT interval (using Fridericia's correction formula)
RP2D	recommended Phase 2 dose
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System (software)
SBP	systolic blood pressure
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UNK	unknown
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

The Statistical Analysis Plan (SAP) describes the data analysis specifications for Tolero Pharmaceuticals. protocol TP-0903-102 titled: "*A Combined Phase 1/2 Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of TP-0903 in Patients with Previously Treated Chronic Lymphocytic Leukemia (CLL)*". It details the inferential statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol.

This version of the SAP was prepared in accordance with the protocol TP-0903-102 Amendment 2 dated November 13, 2018. Other related documents are the annotated patient case report forms (version 1.0, 16AUG2018) and the corresponding Medrio electronic data capture (EDC) data dictionary.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations, and all alternatives or additional statistical analyses that may be performed will be described in a SAP Addendum and in the clinical study report. This SAP supersedes the statistical considerations identified in the protocol.

NOTE: On January 14, 2020 the investigative sites were notified of the decision by Tolero Pharmacetucial to close this study due to lack of accrual. This SAP will reflect the latest protocol (Amendment 2) language along with the current status where appropriate.

Enrollment status as of January 14, 2020:

- **Phase 1: 3 patients enrolled.**
  - **Group 1: one patient enrolled at the TP-0903 25 mg flat dose.**
  - **Group 2: two patients enrolled. Both were at the TP-0903 20 mg flat dose group in combination with ibrutinib at the same dose that they were receiving immediately prior to study enrollment.**
- **Phase 2: no patients enrolled**

This study terminated enrollment before MTD and RP2D was identified.

Effiacy endpoints will not be analyzed via statistical methods due to low enrollment in Phase 1 and no enrollment in Phase 2. Patient listings, patient profiles, and swimmers plot will be used to display the efficacy data.

Safety data will be displayed using patient listings and patient profiles.

2. OVERVIEW OF STUDY DESIGN

Experimental Design:

This is a combined Phase 1/2 study of oral TP-0903 in patients with previously treated CLL/SLL. In both Phase 1 and Phase 2, study participants will be assigned to one of two defined patient groups:

- Group 1 (TP-0903 monotherapy): Patients with CLL/SLL who are intolerant to, or have progressed on, B-cell receptor antagonists and/or BCL-2 antagonists
- Group 2 (TP-0903 and ibrutinib combination therapy): Patients with CLL/SLL who have progressed on ibrutinib, yet the treating provider considers continuation of ibrutinib therapy to be in the best interest of the patient.

Both groups of patients will be treated identically with TP-0903 and will undergo the same study assessments.

Phase 1

Current Status: As of January 14, 2020, 3 patients were enrolled the Phase 1 portion of this study.

Planned: Patients will be enrolled in Group 1 and Group 2 in cohorts of 3 to 6 patients simultaneously. Group 2 will start at one dose level below the Group 1 starting dose. In each group, escalation of the TP-0903 dose will follow a standard 3+3 design with sequential cohorts of three patients treated with incrementally higher doses of TP-0903 until a dose-limiting toxicity (DLT) is observed and the maximum tolerated dose (MTD) is established. Once the first patient at a dose level is enrolled, the second and third patients may be enrolled after 3 weeks if the initial patient has not experienced a DLT or any unacceptable toxicity.

If 1 of 3 patients in a cohort experiences a DLT, up to 3 additional patients will be treated at that dose level. If no additional DLTs are observed in the expanded 3- to 6-patient cohort within 28 days after the last patient was first dosed, the dose will be escalated in a new cohort of 3 patients. If 2 or more of 3 to 6 patients at a given dose level experience a DLT during the first cycle, then the MTD will have been exceeded and up to a total of 6 patients will be

treated at the previous lower dose level. If 0 or 1 of 6 patients experiences a DLT at this previous lower dose level, this dose will be declared the MTD.

The MTD is defined as the dose at which ≤1 of 6 patients experience a DLT during Cycle 1 with the next higher dose having at least 2 of 3 to 6 patients experiencing a DLT during Cycle 1. Once the MTD or preliminary RP2D is identified, an expansion cohort of up to 6 patients will be enrolled in each patient group to confirm safety/suitability of the preliminary RP2D, to collect additional biomarker data, and to further explore efficacy.

Additional dose levels, schedules, or disease indications of TP-0903 may be explored, as appropriate, based on the modulation of key biomarkers and the safety profile and clinical signals of activity.

Phase 2

Current Status: As of January 14, 2020, no patients were enrolled the Phase 2 portion of this study.

Planned: In Phase 2, patients will be enrolled in Group 1 (TP-0903 monotherapy) and Group 2 (TP-0903 combination therapy with ibrutinib) based on the Simon 2-stage design. In Stage 1, up to 13 patients will be enrolled into each patient group (total of 26 patients). If there are no responses among these 13 patients in each group, the study will be stopped. Otherwise, Stage 2 will open to enroll 14 additional patients in each group for a total of 27 patients per group. If 4 or more responses are observed among 27 patients, the conclusion will be that the study treatment is worthy of further investigation. When the true response rate of 20% (alternative hypothesis) is tested against the null hypothesis response rate of 5%, this design yields a Type I error rate of 0.05 and power of 80%.

If both patient groups enroll through Stage 2, it is anticipated that the total enrollment for Phase 2 will be 54 patients.

Any patient who withdraws from the study for treatment-related toxicity prior to being evaluated for response in Phase 2 will be considered a nonresponder. Patients who drop out of the study for other reasons prior to being assessed for response will be considered unevaluable and may be replaced. Enrollment in either patient group may be stopped at any point once ≥4 patients have had a response to treatment, but the maximum enrollment in each patient group in Phase 2 will be 27 evaluable patients.

Study treatment:

Phase 1:

Group 1: TP 0903 (monotherapy). The starting dose for TP 0903 (monotherapy) will be a 25-mg flat dose. The study drug will be administered orally once daily for 28 days (each cycle is 28 days; no drug-free period).

NOTE: As of January 14, 2020, one patient was enrolled in Group 1 at the TP-0903 25 mg flat dose.

Group 2: TP-0903 and ibrutinib combination therapy. The starting dose of TP-0903 will be a 20-mg flat dose. TP-0903 will be administered orally once daily for 28 days (each cycle is 28 days; no drug-free period). Patients will also receive ibrutinib at the same dose that they were receiving immediately prior to study enrollment.

NOTE: As of January 14, 2020, two patients were enrolled in Group 2. Both were at the TP-0903 20 mg flat dose group in combination with ibrutinib at the same dose that they were receiving immediately prior to study enrollment.

Phase 2:

Group 1: TP 0903 (monotherapy) will be ther recommended Phase 2 dose (RP2D) determined during Phase 1.

Group 2: TP-0903 and ibrutinib combination therapy will be ther recommended Phase 2 dose (RP2D) determined during Phase 1.

NOTE: The Phase 2 portion of this study did not enroll any patients.

Number of patients planned:

Up to 108 patients (up to 27 patients in each group (Group 1 and Group 2) in both Phase 1 (n=54) and Phase 2 (n=54).

NOTE: As of January 14, 2020, Phase 1 Group 1 enrolled one patient and Phase 1 Group 2 enrolled two patients. Phase 2 did not enroll any patients.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Phase 1 Primary Objectives

- To characterize the safety and toxicity profile of TP-0903 when administered orally once daily for 28 days (each cycle is 28 days; no drug-free period) in the following patient groups:

- Group 1 (TP-0903 monotherapy): those with CLL/SLL who are intolerant to, or have had progressive disease on B-cell receptor antagonists, BCL-2 antagonists or other investigational treatments for CLL/SLL
- Group 2 (TP-0903 and ibrutinib combination therapy): those with CLL/SLL who have progressed on ibrutinib, yet the treating provider considers continuation of ibrutinib therapy to be in the best interest of the patient.

- To determine the Recommended Phase 2 Dose (RP2D) of TP-0903 when administered orally on this schedule to the defined patient groups.

3.1.2 Phase 1 Secondary Objectives

- To observe patients for any evidence of antileukemic activity of oral TP 0903 by determining the Objective Response Rate ([ORR], ie, rate of complete response [CR] plus rate of partial response [PR] in the defined patient groups according to guidelines set forth by the 2018 International Workshop on CLL (IWCLL)
- To evaluate the pharmacokinetics (PK) of oral TP-0903 in the defined patient groups.

3.1.3 Phase 1 Exploratory Objectives

- To study potential biomarkers relevant to disease and pharmacodynamics (PD) of oral TP-0903 in the defined patient groups through assessment of analytes including, but not limited to, soluble AXL, AXL expression and phosphorylation, growth arrest specific 6 (GAS6), and mesenchymal transcription factors in peripheral blood samples and bone marrow.

3.1.4 Phase 2 Primary Objectives

- To determine the ORR in the two defined patient groups according to guidelines set forth by the 2018 IWCLL.

3.1.5 Phase 2 Secondary Objectives

- To determine the Duration of Response (DoR, ie, the time from tumor response to disease progression)
- To determine the Progression-free Survival (PFS, ie, the time from first dose to objective tumor progression or death)
- To determine the rate of Overall Survival (OS, ie, the time from first dose to death from any cause).

3.1.6 Phase 2 Exploratory Objectives

- To study potential biomarkers relevant to disease and pharmacodynamics (PD) of oral TP-0903 in the defined patient groups through assessment of analytes including, but not limited to, soluble AXL, AXL expression and phosphorylation, growth arrest specific 6 (GAS6), and mesenchymal transcription factors in peripheral blood samples and bone marrow.

3.2 Study Endpoints

3.2.1 Safety Endpoints

Safety will be monitored from the time of the first dose until 30 days after the last dose of TP-0903. During Phase 1, the safety endpoints will be evaluated after Cycle 1. The dose escalation committee will have access to complete safety profiles of all patients receiving TP 0903 to enable decision making.

The primary safety endpoint is to assess the tolerance and toxicity of continuous orally administered TP-0903 through evaluation of physical examinations, vital signs, laboratory parameters, solicited and unsolicited adverse events (AEs) including DLTs, and all causes of mortality up to 30 days from the last dose in both phases of the study.

Overall safety profile will be characterized by type, frequency, severity, seriousness, timing, duration, and relationship of study drug to AEs and laboratory abnormalities.

Treatment-emergent adverse events (TEAEs), namely, those with initial onset or that worsen in severity after the first dose of TP-0903 will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All DLTs will be reported and the MTD and RP2D identified.

NOTE: This study terminated enrollment before MTD and RP2D was identified.

3.2.2 Efficacy Endpoints

The primary efficacy endpoint of the Phase 2 study is to determine the ORR (rate of CRs plus PRs) in the defined patient groups according to guidelines set forth by the 2018 IWCLL.

Secondary efficacy endpoints include DoR, PFS, and OS

Efficacy assessments will be performed on Day 28 of Cycle 2 and then every even cycle thereafter (ie, Cycle 4/Day 28, Cycle 6/Day 28, etc). Response rates will be calculated in Stage 1 and Stage 2 as per the Simon 2 stage design.

NOTE: Effiacy endpoints will not be analyzed via statistical methods due to low enrollment in Phase 1 and no enrollment in Phase 2.

3.2.3 Pharmacokinetic (PK) Endpoints

Plasma PK analysis of oral TP-0903 will be performed at protocol-specified time points during Cycle 1 in all patients enrolled in the Phase 1 study (Section 7.3 of the protocol). Known metabolites of TP-0903, if any, may also be evaluated. No PK assessments will be conducted during Phase 2.

Standard plasma PK parameters will be calculated, including: maximum observed plasma concentration (Cmax), time to Cmax (peak time) (Tmax), area under the plasma concentration curve (AUC) from time 0 to 24 hours (AUC0-24), AUC from time 0 to infinity (AUC0 inf), AUC from time 0 to time t (AUCt), half-life (t1/2), and clearance using noncompartmental methods (CL). If data permit, dose proportionality and accumulation ratio will be estimated in Phase 1 Cycle 1.

3.2.4 Pharmacodynamic (PD) Endpoints

Potential biomarker assessments will be evaluated during Phase 1 and Phase 2 (Section 7.4 of the protocol). Blood for potential biomarker assessments including, but not limited to, soluble AXL, AXL expression and phosphorylation, GAS6 and mesenchymal transcription factors.

4. SAMPLE SIZE JUSTIFICATION

Phase 1

Current Status: As of January 14, 2020, 3 patients have been enrolled the Phase 1 portion of this study.

Planned: Patients will be enrolled for each patient group (TP-0903 monotherapy and combination therapy with ibrutinib) in cohorts of 3 to 6 patients. Escalation of the TP-0903 dose will follow a standard 3+3 design with sequential cohorts of 3 patients treated with incrementally higher doses of TP-0903 until a DLT is observed and the MTD is established.Based on the standard oncology 3+3 dose escalation design, the total number of patients to be enrolled cannot be precisely determined as the sample size is dependent upon the observed safety profile, which will determine the number

of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD. It is anticipated that 12 to 21 patients will be required to achieve MTD dose level. Once the MTD or preliminary RP2D is identified, an expansion cohort of approximately six patients will be enrolled in each patient group to confirm safety/confirm the suitability of the preliminary RP2D, to collect additional biomarker data, and to further explore efficacy. It is expected that up to 27 patients will be enrolled in each patient group (Group 1: TP-0903 monotherapy and Group 2: TP-0903 combination therapy with ibrutinib).

Phase 2

Current Status: As of January 14, 2020, no patients have been enrolled the Phase 2 portion of this study.

Planned: The statistical power calculations for each patient group (monotherapy and combination therapy) are based on the Simon 2 stage minimax design.

- Stage 1, up to 13 evaluable patients will be enrolled and treated at the RP2D identified in the Phase 1 part of this study. Stage 2 may be initiated at any point after confirming a response (CR or PR) in at least one Stage 1 patient. If there are no responders among 13 evaluable Stage 1 patients, the study will be stopped after Stage 1.
- Stage 2, 14 patients will be enrolled to bring the total enrollment in Phase 2 (including Stage 1 patients) to 27 evaluable patients. Stage 2 patients will also receive the RP2D dose identified in the Phase 1 study. If 4 or more responses are observed in 27 patients, the conclusion will be that the combination regimen is worthy of further investigation. When the true response rate of 20% (alternative hypothesis) is tested against the null hypothesis response rate of 5%; this design yields a Type I error rate of 0.05 and power of 80%.

If both patient groups (TP 0903 monotherapy and combination therapy with ibrutinib) enroll through Stage 2, it is anticipated that the total enrollment for Phase 2 will be 54 patients (Group 1: TP-0903 monotherapy [n=27] and Group 2: combination therapy [n=27]).

Planned Sample Size Description per Amendment #2

Patient Group	Phase 1		Phase 2	
	Dose Escalation	Dose Expansion	Simon Stage 1	Simon Stage 2
Monotherapy	12 - 21	6	13	+14 = 27
Combination Therapy	12 - 21	6	13	+14 = 27
Total	**24 - 42**	**12**	**26**	**+28 = 54**

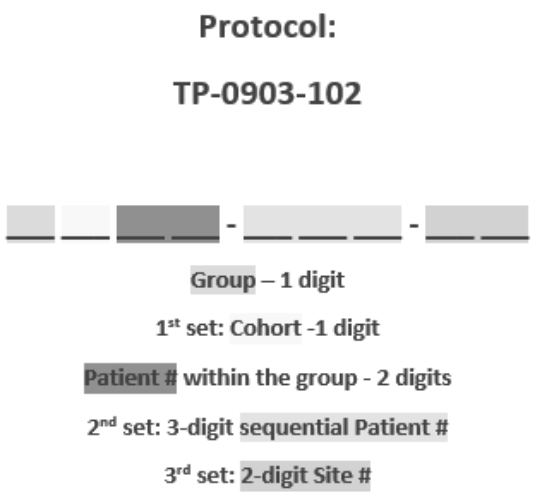
Any patient who withdraws from Stage 1 or 2 for treatment-related toxicity or disease progression or dies prior to being evaluated for response, will be considered a nonresponder. Patients who drop out for other reasons prior to being assessed for response will be considered unevaluable and may be replaced.

Enrollment into Phase 2 can open in a specific group (monotherapy or combination therapy) once MTD has been reached in that group. Enrollment into Phase 2 may be stopped at any point once ≥4 patients have had a response to treatment, but the maximum enrollment in Phase 2 will be 27 evaluable patients per patient group.

5. RANDOMIZATION, BLINDING, AND REPLACEMENT OF PATIENTS

All enrolled patients will be assigned to either Group A (TP-0903 monotherapy) or Group B (TP-0903 and ibrutinib combination therapy) based on sequential timing of enrollment. There will be no central, compute generated randomization schedule/system in place for individual patient assignment into Group A or Group B. Within Group, patients will be assigned to a dose level cohort in sequential order of enrollment in the Phase 1 part of the study, and subsequently in Phase 2 at the RP2D dose identified from Phase 1.

Patients will be assigned a patient number according to the figure below:



Since this is an open-label study, blinding is not performed as part of this study design.

The study will be managed by the Sponsor and/or its designee and all sites must receive authorization from the Medical Monitor for enrollment of any eligible patient. Patients will be enrolled from all participating centers.

Patients who are lost to follow-up or withdraw consent for study participation prior to administration of study drug may be replaced, at sponsor's discretion.

6. DEFINITIONS OF PATIENT POPULATIONS TO BE ANALYZED

This study will have three analysis populations:

- Intent-to-Treat (ITT) analysis set includes all patients who were enrolled into the study.
- Safety analysis set consists of all patients who received any amount of study treatment (TP-0903).

7. PLANNED ANALYSES

7.1 Interim Analysis

For Phase 1, the safety data will be monitored continuously per standard Phase 1 oncology practices.

For Phase 2, since the Simon 2-stage design will be employed, response rate data will be assessed after Stage 1 to determine if the study will go forward to Stage 2.

NOTE: No patients enrolled in Phase 2, so no interim analysis will take place.

7.2 Final Analysis

The final listings and patient profiles will be conducted once the clinical database has been locked. **For this study, the database will be locked with three patients enrolled.**

8. DATA PRESENTATION AND HANDLING

8.1 General Summary Table and Individual Patient Data Listing Considerations

Due to only 3 patients enrolled and treate, only patient listings and patient profiles will be prepared for purposes of an abbreviated clinical study report.

Listings will also be sorted by group, dose cohort, and patient number. Listings will also include visit number, visit date/time and days relative to the initiation of study treatment.

8.2 General Summary Table and Patient Data Listing Format Considerations

The tables, figures and listings will be numbered using a decimal system to reflect main levels of unique listings and sub-levels of replicate tables and listings with two digits per level (e.g., Table XX.YY.ZZ. …).

1. The first level number will be consistent with the corresponding Clinical Study Report (CSR) appendix in which the listings will appear. For example, the individual patient data listings will appear in Appendix 16 (and will be numbered 16.XX.YY).
2. Each listing title will be complete, accurate and concise. The last line of the title will provide the analysis group being summarized (e.g., Safety Population).

8.3 Data Management

All data will be recorded by the site in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be patient to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

Database build, AE coding, medication coding, data cleaning will be conducted according to the Vantage Data Designs Data Management Plan for this specific study.

Derived datasets will be created using SAS® software. Patient listings and patient profiles will be generated using the currently supported version at the time of data analysis (currently version 9.4).

8.4 Data Presentation Conventions

Date variables: formatted as DDMMMYYYY for presentation. Time will be formatted in military time as HH:MM for presentation.

Extra measurements (such as unscheduled or repeat assessments) will be included in patient listings.

All listings will be produced in landscape orientation using Times New Roman 9-point font. Output files will be created in rich text file (RTF) format.

Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 9.5).

8.5 Treatment Comparisons

The following labels for dose level will be used on all listings, in the following order:

Group 1 (Monotherapy) Cohort 1	Dose Level 25 mg
Group 2 (Combination) Cohort 1	20 mg

8.6 Definitions, Computations, Derived Data

- Screening: Screening is defined as ≤ 14 days prior to Cycle 1 Day 1 prior to the first study drug administration.
- Baseline: Measurements taken at Screening or prior to receiving the first dose of study drug; whichever is latest.
- Study Day and Cycle Day follows the CDISC standard and is defined as:
    - On-study Assessment Days (Assessment date – First date of study drug dosing of the first cycle) + 1, where the assessment date is on or after the first date of dosing of the first cycle;
    - Screening Days (Assessment date – First date of study drug dosing of the first cycle), where the assessment date is before the first date of dosing of the first cycle. For this protocol, screening days are from -14 to -1.
    - There will be no Study Day 0.

  - "Study Day x" (where x>0) refers to the number of days from first dosing date in Cycle 1. For example, Study Day 1 is Cycle 1 Day 1.

- Visit Nomenclature: Nominal visits nomenclature on the CRFs and the scheduled visit will be used for summary tables.
  - Scheduled visits for the Treatment Period are: "Screening", "Cycle x Day 1" (where x = 1, 2, 3, … 9), Days 1, 5, 8, 15,21,28 (same as day 1 of next cycle) or "End of Study".
  - 30-day follow-up visits is 30 days after the last dose of study drug.

- Response Criteria: Appendix F of the protocol presents a summary of the IWCLL guidelines 2018 that can be utilized as a quick reference for this study. If there are items not outlined below, further detail and clarification can be obtained from the referenced Blood journal article authored by Hallek et al [25].
- The best objective response rate (OOR): The best ORR recorded from the start of the treatment until disease progression/recurrence. For data programming purposes, this will be taken directly from eCRF dataset OR, variable name ORRESP.
- Dose Limiting Toxicity (DLT) is defined as any one of the following events observed within Cycle 1, regardless of attribution unless clearly and incontrovertibly related to the underlying disease or extraneous causes (such as progressive disease):
  - Any Grade ≥3 nonhematologic toxicity
  - Any Grade 3 AE that does not resolve to ≤Grade 1 within 72 hours with use of supportive care
  - Any AST and ALT elevation ≥5 × ULN accompanied by serum bilirubin levels >2 × ULN
  - Any Grade ≥3 electrolyte disturbances (eg, hyperkalemia, hypophosphatemia, hyperuricemia) that do not resolve within <72 hours
  - Any Grade ≥3 elevations in creatinine
  - Any Grade 5 toxicity
  - Any instance of febrile neutropenia
- Maximum Tolerated Dose (MTD): If 1 of 3 patients in a cohort experiences a DLT, up to 3 additional patients will be treated at that dose level. If no additional DLTs are observed in the expanded 3- to 6 patient cohort within 28 days after the last patient was first dosed, the dose will be escalated in a new cohort of 3 patients. If 2 or more of 3 to 6 patients at a given dose level experience a DLT during the first cycle, then the MTD will have been exceeded and up to a total of 6 patients will be treated at the

previous lower dose level. If 0 or 1 of 6 patients experiences a DLT at this previous lower dose level, this dose will be declared the MTD.

The MTD is defined as the dose at which ≤1 of 6 patients experience a DLT during Cycle 1 with the next higher dose having at least 2 of 3 to 6 patients experiencing a DLT during Cycle 1.

- Dose Expansion: Once the MTD or preliminary RP2D is identified, an expansion cohort of up to 6 patients will be enrolled in each patient group to confirm safety/suitability of the preliminary RP2D, to collect additional biomarker data, and to further explore efficacy.
- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes;
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes;
- 1 pound = 0.454 kg and 1 kg = 2.2 pounds;
- 1 inch = 2.54 cm and 1 cm = 0.3937 inches;
- Body mass index (BMI) calculated as [weight (lbs) / height $(in)^2$] x 703;
- Age will be calculated in years relative to the date of study consent based on the following SAS statement: Age = ([Consent Date - Date of Birth] / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes;

9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The listings for the disposition and safety, and efficacy data will be the responsibility of the study Biostatistician at Vantage Data Designs. All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by group, dose cohort, patient number and assessment date/time.

The currently supported version of SAS software (9.4 or later) will be used to perform all data analyses. The actual SAS version used will be presented in the Clinical Study Report.

9.1 Multicenter Studies

Data from all participating sites will be pooled in the listings.

9.2 Other Strata and Covariates

Not applicable for this study.

9.3 Examination of Subgroups

Not applicable for this study.

9.4 Multiple Comparisons and Multiplicity

Not applicable for this study.

9.5 Missing Data and Dropouts

Not Applicable.

9.5.1 Adverse Events

Not Applicable.

9.5.2 Concomitant Medications

Not Applicable.

9.5.3 Other Situations

The original data will be presented in the listings.

10. STUDY POPULATION

All disposition, baseline and demographic listings will be conducted on the Safety population.

10.1 Patient Enrollment and Disposition

Enrollment and disposition will be listed for all enrolled patients (defined as those patients who signed informed consent form). The patient listing of enrollment will be presented by investigator site. The patient disposition listing will include:

- Patients who were enrolled
- Patients in Group 1 and Group 2
- Patients who complete the protocol.
- Reasons for withdrawal from study
- Reasons for patients with treatment failure.

All patients enrolled in the study will be accounted for in the listing.

A patient listing of whether or not all inclusion and exclusion criteria were met and if not, which criteria were not met, by patient, will also be presented.

10.2 Protocol Violations or Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or Good Clinical Practice (GCP). The noncompliance may be either on the part of the patient, the investigator, or the study site staff. Since capturing every specific protocol deviation is not part of the eCRF database, but they will be identified and documented by Tolero Pharmaceuticals study monitors/project manager prior to database lock.

All protocol deviations will be detailed in patient listings and discussed in the clinical study report.

10.3 Demographics

Demographic characteristics will include age, gender, race, and ethnicity.

All demographic data will be listed by patient.

10.4 Baseline Characteristics

Baseline characteristics of initial diagnosis / current disesase status will include (but not limited to) baseline weight, height, body mass index (BMI), ECOG performance status, time from initial diagnosis to baseline (months), CLL/SLL type, CLL RAI stage, SLL Lugano stage, disease bulk, group, at high risk for Tumor Lysis Syndrome.

Baseline characteristics of symptoms suggestive of active disease will include (but not limited to: unintentional weight loss ≥10% within the previous 6 months, unintentional weight loss ≥10% since last SSAD assessment, marked fatigue, fevers ≥100.5°F (or 38.0°C) for ≥2 weeks without evidence of infection, night sweats for ≥1 month without evidence of infection

All baseline characteristics data will be listed by patient. Medical history and pregnancy tests will also be listed.

10.5 Past Medical Therapies / Surgeries for Cancer Related Indications

All past medical therapies and surgeries for cancer will also be listed by patient.

10.6 Concomitant Medications

Concomitant and prior medications will be presented in patient listings.

10.7 Study Drug Administration and Exposure

Study drug administration will be presented in patient listings. From the patient listings, the following information can be summarized in the clinical study report:

- Doses per treatment cycle per week: Doses for each cycle/week the patient is on the study will be categorized by: 7 doses, 6 doses, 5 doses, 4 doses, 3 doses 2 doses, 1 dose, 0 doses.
- Doses per cycle.
- Cycle 1 only: were more than 4 doses missed and were doses missed on consecutive days.
- Total number of treatment cycles completed.
- Total number of doses taken across the entire study.
- Reasons for stopping at each treatment cycle.

11. EFFICACY ANALYSIS

Effiacy endpoints will not be analyzed via statistical methods due to low enrollment in Phase 1 and no enrollment in Phase 2. Patient listings, patient profiles, and swimmers plot will be used to display the efficacy data.

Efficacy results will be presented for only Phase 1 of this study. The efficacy assessments will be performed on Day 28 of Cycle 2 and then every even cycle thereafter (ie, Cycle 4/Day 28, Cycle 6/Day 28, etc).

The Safety Population will be used for all efficacy displays.

11.1 Primary Endpoint

Objective response to treatment with TP-0903 will be noted using the definitions of response found in Appendix E of the protocol. A summary of the 2018 IWCLL guidelines is provided in Appendix F of the protocol and is further summarized here:

GROUP	PARAMETER	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline) [a]	Increase ≥50% from baseline or from response	Change of –49% to +49%
	Liver and/or spleen size [b]	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of –49% to+49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of –49% to+49%

B	Platelet count	≥100,000/µl	≥100,000/µl or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of –49 to +49%
	Hemoglobin	≥11.0 g/dl (untransfused and without erythropoietin)	≥11.0 g/dl or increase ≥50% over baseline	Decrease of ≥2 g/dl from baseline secondary to CLL	Increase <11.0 g/dl or <50% over baseline, or decrease <2 g/dl
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

If there are items not outlined above, further detail and clarification can be obtained from the referenced Blood journal article authored by Hallek et al.

The best objective response rate (CR, PR, SD, PD, NE) by the investigator-based assessment is defined as the percent of patients with a "best overall response" of CR or PR according to 2018 IWCLL criterion over the time point assessments.

The Overall Response EDC Form (dataset OR, variable name ORRESP) stores the objective response assessed by the investiagator based on 2018 IWCLL criteria for each patient at each study visit. These data be presented in the individual patient listings and swimmers plot.

11.2 Secondary Endpoints

Secondary endpoints will not be analyzed via statistical methods due to low enrollment in Phase 1 and no enrollment in Phase 2.

Duration of Response (DOR) will only include patients with CR or PR and is defined as the number of days from the initial documentation of an objective response to the most current evaluation of that response or to documentation of progression or death. Patients who had an initial response and did not progress will be censored at their date of last assessment.

Patient listings and swimmmers plot will be used to display DoR.

Progresson Free Survival (PFS) is defined as the time from first dose until objective tumor progression or death. Patient listings and swimmmers plot will be used to display the progression times.

Overall Survival (OS) is defined as the duration between the date of treatment initiation (Study Day 1) to the date of death, regardless of the cause of death. Patient listings will be used to display survival times.

12. SAFETY ANALYSIS

Safety will be evaluated from adverse events (including serious AEs and/or deaths), laboratory results, vital signs, physical examination, study drug exposure, and concomitant medications.

The Safety Population is defined as all enrolled patients who received any amount of study treatment will be utilized for all safety displays.

The safety data will be presented in the individual patient listings and patient profiles only.

12.1 Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as all AEs that begin on or after the date of the first administration of study drug. Related AEs are those reported as possibly related, probably related, or related to TP-0903. The verbatim terms of the Treatment Emergent Adverse Events (TEAE) will be coded to preferred terms (PT) and system organ classes (SOC) per MedDRA® (Medical Dictionary for Regulatory Activities) Version 21.0 (or later).

All reported AEs (including non-TEAEs) will be listed, documenting all information collected on the eCRF including verbatim term, MedDRA preferred term, MedDRA system organ class, start date, stop date, severity and relationship to TP-0903, action taken, and outcome.

The TEAEs will be graded by the Investigator in terms of:

- Severity graded 1-5 according to CTCAE v5.0:
    - 1=Mild, 2=Moderate, 3=Severe, 4= Life Threatening, 5=Fatal.
- Relation to TP-0903:
    - 'Related' includes events where the causality was reported as 'Possibly Related', or 'Probably Related', or 'Definitely Related', or where the relationship was not reported on the eCRF.
    - 'Not Related' includes events where the study drug causality was reported as 'Unrelated 'or 'Unlikely Related' on the eCRF.

Patient listings will be provided to display all TEAEs reported by the three patients enrolled in this study.

12.2 Serious Adverse Events

A listing of patients who reported a serious adverse event will be presented in a patient listing. The data will be obtained from the AE dataset where any of the Seriousness Criteria of 1-6 is checked (note: AESAE criteria 7 = NOT serious).

12.3 Adverse Events Leading to Discontinuation from Study

A listing of patients and the adverse events which led to study discontinuation from the study will be included. The specific AE will be identified from the AE dataset under Action Taken (AEACT)=8: Discontinued from Study due to this AE.

12.4 Deaths Due to Adverse Event

A listing of patients who died on study will be included. The specific AE leading to death will be identified from the AE dataset where Outcome (AEOUT)= 5: Death related due to this AE or Severity (AESEV)=5: Fatal/Grade 5.

12.5 Dose Limiting Toxicity (DLT) and Maximum Tolerate Dose (MTD)

All DLTs will be listed by dose cohort and patient. The MTD will be identified. The specific DLT will be identified from the AE dataset: AEDLT=Yes.

12.6 Clinical Laboratory Tests

Safety laboratory assessments will be conducted on as specified in Schedule of Assessments (Section 18).

All laboratory tests (hematology, clinical chemistry, urinalysis, coagulation, immunoglobulin, TS labs) values, units, normal ranges, flags collected in the clinical database (i.e., results that are outside the normal ranges will be flagged with “L” (below normal range) or “H” (above normal range)) will be included in by-patient listings for further medical review.

12.6.1 Hematology

Hematology laboratory tests are planned to include: WBC, RBC, Hemoglobin, Hematocrit, MCV, Platelet Count, % Neutrophils, % Lymphocyte, % Monocytes, % Eosinophils, % Basophils, Absolute Neutrophils, Absolute Lymphocytes, Absolute Monocytes, Absolute Eosinophils, Absolute Basophils.

All Hematology test results will be presented in the patient listings.

12.6.2 Chemistry

Chemistry laboratory tests are planned to include: Sodium, Potassium, Chloride, Bicarbonate (CO2), Calcium, Glucose, Blood Urea Nitrogen (BUN), Creatinine, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, AST / SGOT, ALT / SGPT, Lactate Dehydrogenase (LDH), Magnesium, Uric Acid, Phosphorus.

All Chemistry test results will be presented in the patient listings.

12.6.3 Coagulation

Coagulation laboratory test are planned to include: PT and aPTT.

All Coagulation test results will be presented in the patient listings.

12.6.4 Urinalysis

All Urinalysis test results will be presented in the patient listings.

12.6.5 Immunoglobulin

Immunoglobulin laboratory tests are planned to include: Direct Antiglobulin, Serum β2-microglobulin, Serum IgA, Serum IgG, Serum IgM, Serum IgE, and Serum IgD.

All Immunoglobulin test results will be presented in the patient listings.

12.6.6 TS Labs (only if subject is indicated as at high-risk for TLS)

TS labs are planned to include: Uric Acid, Phosphate, Potassium, Calcium, Creatinine.

All TS Lab test results will be presented in the patient listings.

12.7 Vital Signs and Weight

Vital signs will be conducted on as specified in Schedule of Assessments (Section 18):

Vital sign parameters to be assessed include:

- Blood pressure (systolic and diastolic [mmHg]);
- Heart rate (beats per minute [bpm]);
- Respiratory rate (bpm)
- Temperature (°F)
- Weight (lbs).

All vital sign tests will be included in patient listings for further medical review.

12.8 12-Lead Electrocardiogram (ECG)

The ECG parameters (PR interval, QRS duration, QT, QTc, and QTcF) will be summarized descriptively (n, mean, SD, median, range) by group and dose cohort at each time point for both the observed values and the change from baseline values.

12-lead ECG will be performed on Day 1 of each cycle prior to dosing.

All ECG test results will be included in patient listings for further medical review.

12.9 ECOG Performance Status

ECOG performance status will be assessed at Screening, and Day 1 of Cycle 1, 2, 3+, etc., and end of study (EOS). The ECOG performance status categories (6-point scale):

0 - Fully active, able to carry on 3 all pre-disease performance without restriction.

1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.

2 - Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4 - Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5 – Dead.

All ECOG scores will be included in patient listings for further medical review.

12.10 Physical Examination and Pregnancy Test

Complete physical examination will be conducted on as specified in the Schedule of Assessments (Section 18). The complete physical examination will include dermatological, HEENT, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, psychiatric, other. A determination of normal, abnormal, not done will be made for each body system examination. All Physical Examination findings will be presented in individual patient listings for further medical review.

Significant findings made after the start of study medication which meet the definition of an AE will be recorded on the AE eCRF.

Women of childbearing potential will have a urine or serum pregnancy test as specified in the Schedule of Assessments (Section 18). Individual patient data listings of will be displayed for pregnancy test results.

13. PHARMACOKINETIC (PK) ANALYSIS

Plasma PK analysis of oral TP-0903 will be performed in Cycle 1 on Days 1 and 28 in all patients enrolled in the Phase 1 portion of this study. Known metabolites of TP-0903, if any, may also be evaluated. No PK assessments will be conducted during the Phase 2 portion of this study. Standard plasma PK parameters will be calculated, including: Cmax, Tmax, AUC from time 0 to 24 hours (AUC0-24), AUC0-inf, AUC from time 0 to time t (AUCt), half-life (t1/2), and clearance using noncompartmental methods (CL). If data permit, dose proportionality and accumulation ratio will be estimated in Phase 1 Cycle 1.

Cycle	Day	Time Points
1	1	Predose, 1 hr, 2 hrs, 6 hrs
	2	Predose / 24 hr post Day 1 dose
	28	Predose, 1 hr, 2 hrs, 6 hrs
2	1	Predose / 24 hr post Day 28 dose
3+	1	Predose

PK samples should be drawn on the protocol-specified day.

PK data analysis will be performed by Tolero R&D group or sponsor PK consultant.

14. PHARMACODYNAMIC (PD) ANALYSIS

The PD endpoints, including biomarker assessments, will be evaluated during the study for potential biomarkers including, but not limited to, soluble AXL, AXL expression and phosphorylation, GAS6, and mesenchymal transcription factors

The above samples will be collected at timepoints described in the following table:

Cycle	Day	Time Points
1	1	Predose, 2 hrs, 6 hrs
	2	Predose / 24 hr post Day 1 dose
	8	Predose
2+	1	Predose

PD data analysis will be performed by Tolero R&D group and/or sponsor PD consultant.

15. COMMITMENT TO GOOD STATISTICAL PRACTICE

15.1 Definition of Good Statistical Practice

International Conference on Harmonisation (ICH) Guidance on Statistical Principles for Clinical Trials (ICH E9) implicitly defines good statistical practice. Good statistical practice includes both appropriate statistical designs to minimize bias and to maximize precision of analysis plus operational excellence to assure credibility of results. The scientific design associated with any clinical trial is found in the protocol and in a more detailed pre-specified statistical analysis plan such as this one.

NOTE: For this study, since only three pateints enrolled at the time of study enrollment termination, patient listings and patient profiles will be utilized to present the data.

15.2 Data Management and Use of CDISC Standards

Data standards for clinical development of drugs have been defined and are maturing under various initiatives through the Clinical Data Interchange Standards Consortium (CDISC).

Tolero Pharmaceuticals will use third party vendors for clinical data collection and data analysis. Clinical data will be managed by Vantage Data Designs (US based CRO). and will be captured in electronic case report form (eCRF) by the Medrio EDC platform. The “raw” data contained in the eCRF clinical database will then be converted into Study Data Tabulation Model (SDTM) datasets per CDISC standards. The SDTM datasets will be utilized in creating the patient lisitngs and patient profiles. These CDISC data conversions will be conducted by Vantage Data Designs.

Other applicable standards include regulatory guidance’s from the Food and Drug Administration (FDA), ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3), and ICH Guidance for Good Clinical Practice (ICH E6).

15.3 Testing/Validation Plan and Software System

Statistical Analysis Software (SAS) version 9.4 or later will be used to create thepatient data listings and patient profiles. All SAS computer programs will be validated using industry standard validation procedures including independent quality control programming.

16. STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

The analyses described are based on the final clinical study protocol TP-0903-102 Amendment 2 dated November 13, 2018. This SAP supersedes the statistical

considerations identified in the protocol. A summarization of this study and the effects on this SAP is described below:

On January 14, 2020 the investigative sites were notified of the decision by Tolero Pharmacetucial to close this study due to lack of accrual. This SAP will reflect the latest protocol (Amendment 2) language along with the current status where appropriate.

Enrollment status as of January 14, 2020:

- **Phase 1: Three patients enrolled.**
  - **Group 1: one patient enrolled at the TP-0903 25 mg flat dose.**
  - **Group 2: two patients enrolled. Both were at the TP-0903 20 mg flat dose group in combination with ibrutinib at the same dose that they were receiving immediately prior to study enrollment.**
- **Phase 2: no patients enrolled**

This study terminated enrollment before MTD and RP2D was identified.

Effiacy endpoints will not be analyzed via statistical methods due to low enrollment in Phase 1 and no enrollment in Phase 2. Patient listings, patient profiles, and swimmers plot will be used to display the efficacy data.

Safety data will be displayed using only the patient listings and patient profiles.

17. REFERENCES

1. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H, et al. Guidelines for Diagnosis, Indications for Treatment, Response Assessment and Supportive Management of Chronic Lymphocytic Leukemia (An Update of the NCI-sponsored guidelines from the International Workshop on Chronic Lymphocytic Leukemia). Prepublished online March 14, 2018; doi:10.1182/blood-2017-09-806398. Available from: http://www.bloodjournal.org/content/early/2018/03/14/blood-2017-09-806398.
2. FDA Draft Guidance for Industry: Clinical Trial Imaging Endpoint Process Standards. March 2015.
3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Good Clinical Practice: Consolidated Guidance (E6), April 1996.
5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
6. International Federation of Pharmaceutical Manufacturers and Associations. Medical Dictionary for Regulatory Activities (MedDRA). Version 21.0. Reston, Virginia, USA; 2008.
7. Protocol TP-0903-102: A Combined Phase 1/2 Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of TP-0903 in Patients with Previously Treated Chronic Lymphocytic Leukemia (CLL). Amendment 2, November 13, 2018.
8. SAS Institute Inc. SAS Version 9.4. Cary, NC, USA; 2002-2003.
9. Simon R. Optimal Two-Stage Designs for Phase II Clinical Trials; Controlled Clinical Trials 1989;10(1):1–10.
10. WHO Collaborating Center for International Drug Monitoring. WHO Drug Dictionary. June 2018 B2 Enhanced edition. Uppsala, Sweden; 2008.

18. SCHEDULE OF ASSESSMENTS

		Cycle 1						Cycle 2			Cycle ≥3						
Cycle Day	Screening (Day -14 to Day 1)	–72 hr to Day 1	1	8 (±3)	15 (±3)	22 (±3)	28 (±3)	1 (±2)	15 (±3)	28 (-4)	1 (±2)	15 (±3)	28 (-4)	End-of-Study Visit[a]	30-day *(+14)* Follow-Up[b]	LTFU[w] Year 1 (± 7 days) (Monthly)	LTFU[w] Year 2 (±14 days) (Every other Month)
Procedure/Assessment																	
Signed informed consent	X																
Medical history[c]	X																
Full physical examination	X [m,n]	X	X					X			X		X[m,n]	X			
Abbreviated physical examination[d]				X	X	X			X			X					
Height (cm)	X																
Weight (kg)	X	X						X			X			X			
Baseline signs/symptoms			X														
Vital signs[e]	X	X	X	X	X	X		X	X		X	X		X			
ECOG performance status	X		X					X			X			X			
Serum chemistry[f]	X	X	X	X	X	X		X	X		X	X		X			
CBC with differential and platelet counts	X	X	X	X	X	X		X	X		X	X		X			
Coagulation parameters (PT and aPTT)	X																
TLS labs[y]			X														
Urinalysis[g]	X																
Pregnancy test[h]	***X***	X						X			X			X			
Confirm eligibility[i]		X															
12-lead ECG including assessment of QTcF[j]	X		X					X			X			X			
Concomitant medications[k]	X	X	X	X	X	X		X	X		X	X		X	X		
Assess AEs[l]			X	X	X	X		X	X		X	X		X	X		
Disease assessment[m]	X									X			X[n]	X[o]			
Bone marrow	X									X[v]			X[v]	X[v]			
CT scan[p]	X									X			X[n]	X[o]			
PET scan	X[x]																
Blood for disease assessment	X									X[q]			X[q]	X[q]			
Blood for biomarkers[r]			X	X				X			X			X[o]			
PK blood samples[s]			X				X				X						

Study drug administration[t]			Daily	Daily	Daily				
Dosing diary[u]			Daily	Daily	Daily				
Telephone contact								X	X

AE: adverse event; aPTT: activated partial thromboplastin time; β-hCG: beta human chorionic gonadotropin; CBC: complete blood count; CLL: chronic lymphocytic leukemia; CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; IWCLL: International Workshop on Chronic Lymphocytic Leukemia; MRD: minimal residual disease; PK: pharmacokinetic; PT: prothrombin time; QTcF: corrected QT interval (using Fridericia's correction formula); ***SLL: small lymphocytic lymphoma;*** TLS: tumor lysis syndrome

Notes:

a If, at any time, a patient discontinues study treatment, a visit should be scheduled as soon as possible and within 14 days of the last dose of study drug or within 14 days of the decision to discontinue study treatment. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the End-of-Study Visit rather than having the patient return for an additional visit.

b Patients must ***undergo*** a safety evaluation ***in which the condition of the patient during*** 30 days after the last dose of study drug ***can be assessed***. ***There is a visit window of up to 14 days after completion of the 30 days from the last dose (ie, within 45 days after last dose of study drug).***

c Complete medical history including histologically confirmed diagnosis of CLL***/SLL***

d Abbreviated physical examination (AE- or symptom-directed).

e Vital signs to include: body temperature, respirations, heart rate, blood pressure.

f Full serum chemistry panel to include: blood urea nitrogen, phosphorus, magnesium, lactate dehydrogenase, creatinine, uric acid, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase. Collection of blood for analysis of serum electrolytes, immunoglobulin, and direct antiglobulin will be conducted at screening only (*Appendix E*).

g Urinalysis to include: color, specific gravity, pH, bilirubin, ketones, glucose, occult blood (hemoglobin), leukocyte esterase, protein, urobilinogen, nitrites, white blood cells, red blood cells, casts, crystals, bacteria (*Appendix E*).

h Urine or serum sample for beta-human chorionic gonadotropin pregnancy test from females of childbearing potential.

i Review all inclusion and exclusion criteria to determine if patient has met all eligibility criteria for enrollment into the study. Obtain Medical Monitor (or designee) approval to enroll patient.

j 12-lead ECG will be performed on Day 1 of each cycle prior to dosing (predose).

k Including all prescription drugs, nonprescription drugs, and nutritional supplements.

l AEs will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (*Appendix D*). When the NCI CTCAE grade is not available, the Investigator will use the following severity grading: mild, moderate, severe, life-threatening, or fatal.

m Disease assessment per 2018 IWCLL guidelines 2018 (*Appendix F*), including review of constitutional symptoms to include unintentional weight loss, fatigue, fevers, and night sweats will be completed at Screening, Cycle 2/Day 28, and then every other cycle on Day 28 (Cycle 4, Cycle 6, etc).

n Day 28 of every EVEN cycle (ie, Cycle 4, Cycle 6, etc).

o If ≥8 weeks since last response assessment, disease status will be assessed as per IWCLL guidelines 2018 (*Appendix F*). If patient has unequivocal evidence of disease progression, then this reassessment may be eliminated.

p CT scan of neck, chest, abdomen, and pelvis evaluation of lymphadenopathy, hepatomegaly, and splenomegaly.

q Collect blood only at CR for determination of MRD (central lab assessment)

r Collect blood for PD PBMCs, plasma and serum at C1D1 pre-dose, 2 hr, 6 hr and 24 hr postdose (predose C1D2), C1D8 predose and Day 1 of every cycle and EOS

s PK samples will be collected only in the Phase 1 portion of the study, on Days 1 and 28 of Cycle 1 just before dosing and at 1, 2, 6, and 24 hours postdose (prior to the next daily dose of TP-0903) and on Day 1 of each subsequent cycle. ***PK samples should be collected on protocol-specified days, regardless of visit windows.***

t Study drug should be taken in the morning after an overnight fast with up to 200 mL or 7 ***fluid*** ounces of water at least 1 hour before ingesting any food or other medications. For patients in Group 2, ibrutinib should be taken as directed and per the approved label instructions.

u Patients will be given a Patient Dosing Diary *(Appendix I*) in which to record the date, time, number of capsules taken, whether a dose was missed, or if patient vomited for both TP-0903 and ibrutinib. Patients will be instructed to bring their diary and all study drug bottles to each follow-up clinic visit so that the diary can be reviewed by study personnel and a capsule count performed to ensure dosing compliance.

v Collect bone marrow at CR for determination of MRD (central lab assessment)

w Long-term follow up for survival 2 years: Year 1- monthly contacts (±7 days) starting 1 month after completion of EOS; Year 2- contacts every other month for the following: date of death, date of relapse, or continued remission

x PET scan to rule out Richter's Transformation to be completed within 14 days of first dose

y TLS labs to be assessed at baseline (predose) and at 6 hours and 24 hours post dose (real-time [STAT] review) in patients at high risk for TLS (ie, patients with any LN ≥10 cm, or ALC ≥25 × 10^9/L and any LN ≥5 cm)