TOLERO PHARMACEUTICALS
Sumitomo Dainippon Pharma Global Oncology

AMENDED CLINICAL STUDY PROTOCOL

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)
Protocol Number:	TP-0903-102 ***Amendment 2***
IND Number:	139577
Study Drug/Agents:	TP-0903
Phase of Development:	Phase 1/2
Medical Monitor:	[redacted]
Safety Reporting: [redacted]	[redacted]
Sponsor:	Tolero Pharmaceuticals, Inc 3900 N Traverse Mountain Blvd Suite 100 Lehi, UT USA 84043
Date of Version Final:	24 May 2018
Date of Amendment 1:	26 June 2018
Date of Amendment 2:	***13 November 2018***

PROTOCOL SIGNATURE PAGE

SPONSOR SIGNATURE

I have carefully read the protocol, TP-0903-102 Amendment ***2***, 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)" and confirm that this is the approved current version.

[redacted]

INVESTIGATOR'S SIGNATURE

I have carefully read this protocol, TP-0903-102 Amendment ***2***, and commit to conduct the study as outlined herein, in accordance with the International Council for Harmonisation (ICH), Good Clinical Practices (GCPs), and the Declaration of Helsinki, and comply with the obligations and requirements of the clinical Investigator and other requirements as listed in Title 21 of the United States Code of Federal Regulations (CFR) and other applicable regulations.

Investigator's Signature	Date (DD/MMM/YYYY)
Printed Name	Name of Institution/Research Facility
Phone Number	Email Address

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ABBREVIATIONS

AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration curve
AUC_{0-12}	Area under the plasma concentration curve from time 0 to 12 hrs
AUC_{0-24}	Area under the plasma concentration curve from time 0 to 24 hrs
AUC_{0-inf}	Area under the plasma concentration curve from time 0 to infinity
AUC_t	Area under the plasma concentration curve from time 0 to time t
$AUC_{0-Tlast}$	Area under the plasma concentration curve from time 0 to the time of the last concentration
BP	Blood pressure
BMI	Body mass index
BMSC	Bone marrow stromal cells
BTK	Bruton's tyrosine kinase
CBC	Complete blood count
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CL	clearance using noncompartmental methods
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CR	Complete response (remission)
CRA	Clinical research associate
CRC	Colorectal cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DoR	Duration of Response
DSMB	Data Safety Monitoring Board
EC_{50}	Effective concentration in 50% of test subjects
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme linked immunosorbent assay
EMT	Epithelial-to-mesenchymal transition
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
FISH	Fluorescence in-situ hybridization
GAS6	Growth arrest specific 6
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hERG	Human ether-a-go-go

HIV	Human immunodeficiency virus
HR	Heart rate
IC_{50}	Inhibitory concentration in 50% of test subjects
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGHV	Immunoglobin heavy-chain variable (region)
IND	Investigational New Drug (application)
IO	Immune-oncology (therapy)
IRB	Institutional Review Board
ITP	Idiopathic thrombocytopenic purpura
ITT	Intent-to-treat
IWCLL	International Workshop on CLL
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LN	Lymph node
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRT	Mean residence time
MTD	Maximum tolerated dose
NADPH	Nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall survival
PD	Pharmacodynamic
PD	Progressive disease
PDAC	Pancreatic ductal adenocarcinoma
PET	Positron emission tomography (scan)
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response (remission)
PT	Prothrombin time
QTcF	Corrected QT interval (using Fridericia's correction formula)
RBC	Red blood cell
RP2D	Recommended Phase 2 dose
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System (software)
SD	Stable disease
SGF	Simulated gastric fluid
SLL	Small Lymphocytic Lymphoma
SOP	Standard operating procedure(s)
$t_{1/2}$	Half-life
$t_{1/2(e)}$	Elimination half-life
TLS	Tumor lysis syndrome
T_{max}	Time to maximum observed plasma concentration (peak time)
TNBC	Triple negative breast cancer
TEAE	Treatment-emergent adverse event

ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

PROTOCOL SYNOPSIS

Title of Study:	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)
Clinical Phase:	1/2
Study Indication:	Previously Treated CLL/SLL (Small Lymphocytic Lymphoma)
Patient Population:	Adult patients 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 1-TP-0903 monotherapy); *or* have progression of disease on ibrutinib, yet the treating provider considers continuation of ibrutinib therapy to be in the best interest of the patient (Group 2-TP-0903 and ibrutinib combination therapy)
Planned Enrollment and Study Duration:	The study is expected to take up to 36 months to enroll 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).
Objectives:	***Phase 1*** *Primary:* • 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: o 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 o 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 *Secondary:* • 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

	Exploratory: • 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 ***Phase 2*** *Primary:* • To determine the ORR in the two defined patient groups according to guidelines set forth by the 2018 IWCLL *Secondary:* • 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) *Exploratory*: • 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
Study 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*** 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. It is expected that up to 27 patients will be enrolled in each patient group for a total of up to 54 patients (TP-0903 monotherapy and combination therapy with ibrutinib). 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*** 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. ***Supportive Care Measures*** Supportive care will ***include***: • Careful monitoring of patients at high risk for tumor lysis syndrome (TLS) (ie, patients with any lymph node [LN] ≥10 cm, or absolute lymphocyte count [ALC] ≥25 $\times 10^9$/L and any LN ≥5 cm) by collection of blood and real-time (STAT) review of TLS laboratory parameters (ie, uric acid, potassium, phosphate, calcium, and creatinine) on Day 1 of Cycle 1 at baseline (predose) and at 6 hours and 24 hours post dose. • Infection Prevention (ie, prophylactic antibiotic, antiviral, and/or antifungal therapy) to be initiated according to each institution's standardized protocols
Inclusion Criteria:	To be eligible for participation, patients must meet all of the following inclusion criteria: 1. Are ≥18 years old 2. Have an established, pathologically confirmed diagnoses of CLL/small lymphocytic lymphoma (SLL) requiring therapy according to the 2018 IWCLL guidelines 3. Have received at least one prior therapy for CLL/SLL and can be classified in one of two patient groups: • Group 1 (TP-0903 monotherapy): Patients 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): 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. 4. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 5. Have adequate hematologic function: • Absolute neutrophil count (ANC) ≥500/μL • Platelet count ≥30,000/μL • Hemoglobin ≥8 g/dL in the absence of transfusions within the previous 2 weeks

	6. Have adequate organ function: • Creatinine clearance ≥30 mL/min • Alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) level ≤2.5 × upper limit of normal (ULN) • Have a total bilirubin level ≤1.5 × ULN (unless secondary to Gilbert syndrome, hemolysis, or leukemia) 7. Have acceptable coagulation status: • Activated partial thromboplastin (aPTT) and prothrombin time (PT) ≤1.5 × ULN 8. Have a negative pregnancy test (in females of childbearing potential) 9. Be nonfertile or agree to use an adequate method of contraception. Sexually active patients and their partners must use an effective method of contraception (hormonal or barrier method of birth control, or abstinence) prior to study entry and for the duration of study participation and for at least 30 days after the last study drug dose. Should a woman become pregnant or suspect that she is pregnant while participating in this study, she should inform her treating physician immediately 10. Have read and signed the Institutional Review Board (IRB)-approved informed consent form (ICF) prior to any study-related procedure. (In the event that the patient is rescreened for study participation or a protocol amendment alters the care of an ongoing patient, a new ICF must be signed.) 11. Are able to comply with the requirements of the entire study
Exclusion Criteria:	Patients meeting any one of these exclusion criteria will be prohibited from participating in the study. 1. Have undergone prior autologous or allogeneic stem cell transplant within ≤3 months, have not recovered from transplant associated toxicities, or requires graft versus host immunosuppressive therapy 2. Have known central nervous system (CNS) involvement 3. Have Richter's transformation of CLL 4. Have received any monoclonal antibody therapy directed at treatment of the patient's malignancy within 2 weeks prior to anticipated first dose 5. Have received any anticancer therapy including chemotherapy, radiotherapy, or an investigational anticancer drug within less than 5 half-lives of the last dose of that treatment

	• This exclusion criterion is not applicable to patients requiring continuation on ibrutinib. (Note: Certain patients with a rapidly rising white blood cell count while on ibrutinib may need to remain on this drug for medical reasons. These patients will need to be approved by the Medical Monitor and treated in accordance with the protocol.) 6. Have received >20 mg/day of prednisone and 0.1 mg/day of mineralocorticoids within 7 days prior to anticipated first dose 7. Have a corrected QT interval of >450 msec (males) and >470 msec (females) using Fridericia's correction formula 8. Have a significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, or cardiovascular disease or any other medical condition that, in the opinion of the Investigator, would adversely affect his/her participation in the study 9. Are pregnant and/or nursing, or refuse to use appropriate contraceptives during the course of the study and for at least 30 days after the last dose of study drug 10. History of another malignancy in the last 5 years except for the following adequately treated: • Local basal cell or squamous cell carcinoma of the skin • Carcinoma in situ of the cervix or breast • Papillary, noninvasive bladder cancer • Early stage prostate cancer for which observation is clinically indicated • Other Stage 1 or 2 cancers currently in complete remission • Any other cancer that has been in complete remission for 2 years or surgically cured. The Medical Monitor may be contacted for additional determination of acceptable prior cancer history. 11. Have known gastrointestinal disorders (eg, malabsorption syndrome), complications (eg, dysphagia), or surgery that could make consumption or absorption of oral medications problematic 12. Have an uncontrolled systemic infection (viral, bacterial, or fungal) or fever and neutropenia within 7 days prior to anticipated first dose 13. Have active and uncontrolled autoimmune cytopenias for 2 or more weeks including autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) 14. Have received prior therapy with an AXL inhibitor

	15. Have exhibited allergic reactions to a similar structural compound, biological agent, or formulation 16. Are unwilling or unable to comply with procedures required in this protocol 17. Have a history of severe adverse reaction (eg, hypersensitivity reaction, anaphylaxis) to sulfonamides
Study Treatment:	***Phase 1*** • The starting dose for TP-0903 in Group 1 (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). Patients may continue to receive TP-0903 in 28-day cycles at the same dose given during Cycle 1 until they experience unacceptable toxicity or unequivocal disease progression. No intrapatient escalation of the TP-0903 dose is permitted. • 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. Patients should continue with the combination of ibrutinib and TP-0903 for at least 3 months after study start. After that time, patients can either continue with combination therapy or discontinue ibrutinib and continue with TP-0903 monotherapy at the discretion of the Investigator in consultation with the Medical Monitor. Patients may continue to receive TP-0903 in 28-day cycles at the same dose given during Cycle 1 until they experience unacceptable toxicity or unequivocal disease progression. Ibrutinib may be stopped and reinitiated at the discretion of the Investigator and in consultation with the Medical Monitor; however, the total time patients may receive treatment with ibrutinib is 2 years. ***Phase 2*** • Group 1 (TP-0903 monotherapy): The starting dose of TP-0903 will be the RP2D determined during Phase 1. TP-0903 will be administered orally at a fixed dose once daily for 28 days (each cycle is 28 days; no drug-free period) with repeated cycles permitted until a patient experiences unacceptable toxicity or unequivocal disease progression. • Group 2 (TP-0903 and ibrutinib combination therapy): The starting dose of TP-0903 will be the RP2D determined during Phase 1. Patients will also receive ibrutinib at the same dose that they were receiving immediately prior to study enrollment. Both TP-0903 and ibrutinib will be administered orally at fixed

	doses once daily for 28 days (each cycle is 28 days; no drug-free period). Patients should continue with the combination of ibrutinib and TP-0903 for at least 3 months after study start. After that time, patients can either continue with combination therapy or discontinue ibrutinib and continue with TP-0903 monotherapy at the discretion of the Investigator in consultation with the Medical Monitor. Patients may continue to receive TP-0903 in 28-day cycles at the same dose given during Cycle 1 until they experience unacceptable toxicity or unequivocal disease progression. Ibrutinib may be stopped and reinitiated at the discretion of the Investigator in consultation with the Medical Monitor; however, the total time patients may receive treatment with ibrutinib is 2 years.

Study Assessments:	These assessments will be conducted during both the Phase 1 and Phase 2 studies.
	
	Predose
	
	<u>Screening/Baseline Period (Within 14 Days Prior to First Dose)</u>:
	
	• Complete medical history including histologically confirmed diagnosis of CLL/SLL
	• Conduct full physical examination, including height (cm), weight (kg), and review the following constitutional symptoms suggestive of active disease:
	  o Unintentional weight loss ≥10% within previous 6 months
	  o Marked fatigue
	  o Fevers ≥100.5°F or (38.0°C) for ≥2 weeks without evidence of infection
	  o Night sweats for ≥1 month without evidence of infection
	• Record vital signs (body temperature, respirations, heart rate, and blood pressure)
	• Assess ECOG Performance Status (*Appendix B*)
	• Assess baseline disease status according to 2018 IWCLL guidelines (*Appendix H*) within 28 days of Cycle 1 Day 1:
	  o Perform a computed tomography (CT) scan of neck, chest, abdomen, and pelvis for evaluation of lymphadenopathy, hepatomegaly, and splenomegaly; (within 28 days of Cycle 1 Day 1)
	  o Collect bone marrow and aspirate with matched peripheral blood sample
	  o The following should be obtained (within 28 days of Cycle 1 Day 1):
	  – Molecular cytogenetics FISH (Fluorescence in Situ Hybridization) for del(13q), del(11q), del(17p), add(12) [peripheral blood]
	  – Karyotyping with CpG ***(or institutional standard)*** stimulation [bone marrow]

	– TP53 mutation analysis [peripheral blood] – IGHV (Immunoglobulin Heavy-chain Variable region) mutational analysis [peripheral blood] • PET (Positron Emission Tomography) scan to assess for possible Richter's transformation (within 14 days of first dose) • Evaluate laboratory parameters (*Appendix E*): o Hematology (complete blood count [CBC] with differential and platelet count) o Full serum chemistry panel o Coagulation parameters (PT and aPTT) o Urinalysis o Serum immunoglobulins o Direct antiglobulin o Serum ß2-microglobulin • Perform 12-lead electrocardiogram (ECG) including assessment of QTcF • ***Serum or urine pregnancy test in females of childbearing potential*** • Record concomitant medications (including all prescription drugs, nonprescription drugs, and nutritional supplements within the past 14 days <u>Within 72 hours of C1D1:</u> *(not required to be repeated at Cycle 1 Day 1 if within 3 days prior to first dose)* • Conduct full physical examination, including weight (kg) • Record vital signs (body temperature, respirations, heart rate, and blood pressure) • Evaluate laboratory parameters (hematology and full serum chemistry panel) • Record concomitant medications • Serum or urine pregnancy test in females of childbearing potential • Review all inclusion/exclusion criteria to determine patient eligibility ***Treatment Period*** • Day 1 of each cycle o Full physical examination, including weight (kg) o Record vital signs prior to first dose o Assess ECOG Performance Status o Assess TLS labs (Cycle 1/Day 1 only) o Serum or urine pregnancy test in females of childbearing potential

- Perform 12-lead ECG including assessment of QTcF

- Weekly (Days 1, 8, 15, 22) unless otherwise noted
  - Abbreviated physical examination (adverse event [AE]- or symptom directed) (exclude Day 1)
  - Vital signs (body temperature, respirations, heart rate, blood pressure)
  - Evaluate laboratory parameters (hematology and full serum chemistry panel)
  - Record concomitant medications
  - Assess for AEs
- Day 28 of Cycle 2 and every EVEN cycle thereafter (ie, Cycle 4, Cycle 6, etc)
  - Response assessments per 2018 IWCLL guidelines (*Appendix F*)
  - CT scan of neck, chest, abdomen, and pelvis for evaluation of lymphadenopathy, hepatomegaly, and splenomegaly
  - Review of the following constitutional symptoms suggestive of active disease:
    - Unintentional weight loss ≥10% within previous 6 months
    - Marked fatigue (ie, ECOG PS 2 or worse)
    - Fevers ≥100.5°F or (38.0°C) for ≥2 weeks without evidence of infection
    - Night sweats for ≥1 month without evidence of infection
- If clinical and laboratory results indicate possible CR:
  - Collect bone marrow and aspirate with matched peripheral blood sample for CBC and determination of MRD (central lab assessment)

Long-term Follow-up for Patient Survival (Phase 2 only)

All patients enrolled and treated in the Phase 2 study will be contacted by telephone to assess for date of death, date of relapse, or continued remission beginning the month after the patient completes the end-of-study assessments up to a maximum of 2 years regardless of how many treatment cycles a patient receives.

Year	Phone Calls
1 (Date of 30-Day FU + 12 mths)	Every month
2 (14 - 24 mths after Date of 30-Day FU)	Every other month

Pharmacokinetic Assessments:	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*). 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 (C_{max}), time to C_{max} (peak time) (T_{max}), area under the plasma concentration curve (AUC) from time 0 to 24 hours (AUC_{0-24}), AUC from time 0 to infinity (AUC_{0-inf}), AUC from time 0 to time t (AUC_t), half-life ($t_{1/2}$), and clearance using noncompartmental methods (CL). If data permit, dose proportionality and accumulation ratio will be estimated in Phase 1 Cycle 1.
Pharmacodynamic Assessments:	Potential biomarker assessments will be evaluated during Phase 1 and Phase 2 (*Section 7.4*) as follows: • Blood for potential biomarker assessments including, but not limited to, soluble AXL, AXL expression and phosphorylation, GAS6 and mesenchymal transcription factors
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 20.0 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. A Data Safety Monitoring Board (DSMB) will monitor key outcomes from the study during the Phase 2 study.

<table>
<tr><td>DLT Definitions:</td><td>Phase 1
A DLT is defined as any one of the following events <u>observed within Cycle 1</u>, regardless of attribution unless clearly and incontrovertibly related to the underlying disease or extraneous causes (such as progressive disease; other decreases in the white blood cell count, or in circulating granulocytes, are not to be considered, since a decrease in the white blood cell count is a desired therapeutic endpoint):
• 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</td></tr>
<tr><td>Efficacy Endpoints:</td><td>Phase 2
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
• 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.</td></tr>
<tr><td>Pharmacokinetic Endpoints:</td><td>Blood samples will be collected from all patients enrolled in the Phase 1 study for plasma PK analysis of oral TP-0903 (Section 7.3) at the following time points:
<table>
<tr><th>Cycle</th><th>Day</th><th>Time Points</th></tr>
<tr><td rowspan="3">1</td><td>1</td><td>Predose, 1 hr, 2 hrs, 6 hrs</td></tr>
<tr><td>2</td><td>Predose / 24 hr post Day 1 dose</td></tr>
<tr><td>28</td><td>Predose, 1 hr, 2 hrs, 6 hrs</td></tr>
<tr><td>2</td><td>1</td><td>Predose / 24 hr post Day 28 dose</td></tr>
<tr><td>3+</td><td>1</td><td>Predose</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Pharmacodynamic Endpoints:</td><td>Blood samples will be collected from all patients during each cycle in the Phase 1 and Phase 2 studies for analysis of potential biomarkers. (Section 7.4) at the following time points:
<table>
<tr><th>Cycle</th><th>Day</th><th>Time Points</th></tr>
<tr><td rowspan="3">1</td><td>1</td><td>Predose, 2 hrs, 6 hrs</td></tr>
<tr><td>2</td><td>Predose / 24 hr post Day 1 dose</td></tr>
<tr><td>8</td><td>Predose</td></tr>
<tr><td>2+</td><td>1</td><td>Predose</td></tr>
<tr><td>End of Study</td><td>--</td><td>--</td></tr>
</table></td></tr>
<tr><td>Statistical Analysis:</td><td>Sample Size
<u>Phase 1</u>
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).
<u>Phase 2</u>
The statistical power calculations for each patient group (monotherapy and combination therapy) are based on the Simon 2-stage minimax design. In 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. In 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]).</td></tr>
</table>

	Safety Analysis All patients who receive any dose of TP-0903 will be included in the summaries and listings of safety data. In all summaries, emphasis will be placed on TEAEs. AEs will be summarized by the frequency of patients experiencing TEAEs corresponding to body systems and MedDRA preferred term and by worst NCI CTCAE v5.0 grade. Summaries will also be provided of TEAEs judged by the investigator to be related or possibly related to TP-0903 and/or combination therapy. AEs resulting in discontinuation of TP-0903 treatment or withdrawal from the study, Grade 3 or higher, serious adverse events (SAEs), and deaths on-study will be tabulated. All DLTs will be reported and the MTD and RP2D identified. Other safety assessments (eg, clinical laboratory parameters, vital signs, and ECG) will be summarized for each TP-0903 dose level by observed values at each assessment and changes from baseline using descriptive statistics. **Efficacy Analysis** ORR will be summarized by number and percentage of patients meeting the definition of ORR along with the corresponding exact 95% confidence intervals. Time-to event endpoints (DoR, PFS, and OS) will be summarized by Kaplan-Meier methods (median, 95% confidence interval (CI), number of events, number censored, and Kaplan-Meier figures). Additional analyses may be performed to assist the Sponsor in planning future studies. **Pharmacokinetic Analysis** PK parameters will be estimated using standard noncompartmental analysis and according to FDA guidance. Actual sample collection times will be used rather than scheduled collection times. Plasma concentrations of oral TP-0903 will be summarized by descriptive statistics, including mean, n, standard deviation, coefficient of variation, minimum, maximum, and median. A validated bioanalytical method for the detection of TP-0903 in human plasma has been developed prior to this study to establish assay sensitivity, specificity, linearity, and reproducibility. Plasma concentrations below the limit of quantification will be treated as “0”. Imbedded missing plasma concentrations (ie, missing values between 2 observed values) will be estimated using linear extrapolation. This is consistent with using the trapezoidal rule to calculate AUC. Other missing plasma concentrations will be excluded from calculations to estimate PK parameters. If data permit, dose proportionality and accumulation ratio will be estimated in Phase 1 Cycle 1.

	Pharmacodynamic Analysis The PD relationships of TP-0903 exposure with exploratory biomarkers will be quantified using the Spearman rank correlation statistic to examine the relationships between response and treatment (ordered categorical dependent variables) and changes from baseline values of PD endpoints (continuous independent variables). **Interim Analysis** In Phase 1, safety data will be monitored continuously per standard Phase 1 oncology study practices. In Phase 2, since the Simon 2-stage design will be employed, response rate data will be assessed after Stage 1 and Stage 2.

1. INTRODUCTION

1.1 Background

TP-0903 is an inhibitor of AXL kinase, which is known to be a central regulator of oncogenesis and a driver of resistant cancer phenotypes [1]. AXL is a receptor tyrosine kinase (RTK) that is upregulated in many hematological malignancies and solid tumors [2]. It is involved in multiple cancer-promoting biological processes including cell proliferation, differentiation, motility, and survival. Along with its other family members, MER and TYRO3, AXL is an important regulator of the mesenchymal phenotype which allows cancer cells to grow in an anchorage-independent manner, metastasize, and most importantly, drive resistance to targeted cancer therapeutics, traditional chemotherapies, and immuno-oncology agents [3, 4, 5].

TP-0903 has shown potent inhibition of AXL kinase and other TAM family members in a biochemical kinase assay. TP-0903 demonstrates corresponding activity in cancer cell lines and mouse xenograft efficacy models. TP-0903 is shown to block cancer cell epithelial-to-mesenchymal transitions, as evidenced by decreased cancer cell migration induced by the AXL receptor ligand, growth arrest specific 6 (GAS6), and decreased expression of mesenchymal cell markers, such as Slug and Snail. TP-0903 is shown to inhibit the phosphorylation of AKT as a result of GAS6 treatment in multiple cancer cell lines. TP-0903 is shown to be antiproliferative towards cancer cell lines in culture with effective concentration (EC_{50}) values in the submicromolar range. Treatment with TP-0903 is shown to cause tumor regressions (>100% tumor growth inhibition) in mouse xenograft efficacy models of acute myeloid leukemia (AML), non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), colorectal carcinoma (CRC), ovarian cancer, and other tumor models using well-tolerated dosing regimens. Additionally, TP-0903 has potent activity at modulating the immune system and demonstrates activity in an immune-competent syngenic model of triple negative breast cancer (TNBC) both as a single agent and in combination with immune-oncology (IO) therapies.

Several hematological malignancies are dependent on aberrant AXL signaling for sustained survival through pro-survival and cross-talk to other RTK pathways, such as fibroblast growth factor receptor (FGFR) [6, 7]. Therefore, targeting hematological malignancies with TP-0903 as a single agent to down-regulate AXL-dependent signaling pathways is a strategy of high interest. AXL was identified as a potential therapeutic target in chronic lymphocytic leukemia (CLL) by studying the interaction between CLL B-cells and bone marrow stromal cells (BMSC). It was found that CLL utilizes microvesicles to constitutively activate AXL signaling in both the diseased B-cells and the associated BMSCs [8]. TP-0903 was shown to induce apoptosis in CLL B-cells taken directly from patients at concentrations as low as 100 nM [6]. Importantly, this was observed when the CLL B-cells were cocultured in the protected niche of BMSCs. TP-0903 was equally potent against CLL cells regardless of risk factor. Indeed, CLL patients with 17p/TP53-deletions have an upregulated AXL dependency [9]. Current treatment is different for 17p/P53-deletion patients given the aggressive nature of this disease and the lack of curable therapy for this subtype. In addition, those patients with CLL who have been previously treated with ibrutinib become resistant to ibrutinib and, therefore, would benefit from this treatment as it appears that AXL inhibition works in circumstances where Bruton's tyrosine kinase (BTK) inhibitors have lost their efficacy [6]. Note, ibrutinib as a single agent has not

been demonstrated to be curative in relapsed/refractory CLL. Biomarkers to help define which CLL patients derive the maximal benefit seem to be very unclear at this time. Some previously published studies have suggested that 20% expression of AXL in CLL patients would be a good target patient population for drugs such as TP-0903. However, no absolute threshold of AXL expression seems to correlate to TP-0903 response [6]. Clearly, there is an unmet medical need for patients with CLL who have 17p/TP53-deletions and those patients who have progressed following treatment with a BTK inhibitor.

In preclinical studies, it is shown that TP-0903 is not a significant inhibitor of in vitro human ether-à-go-go-related gene (hERG) channel activity at submicromolar concentrations [10, 11]. Good Laboratory Practice (GLP) toxicology studies in rats and dogs have shown that TP-0903 is generally well tolerated at the doses that were evaluated [12, 13]. Potential target organs of toxicity include the bone marrow, gastrointestinal tract and the thymus. A cardiopulmonary safety study was conducted in female beagle dogs. Based on all of the data collected in this study, there was no evidence of cardiopulmonary pharmacological adverse effects of TP-0903 following a single, oral dose up to 2.0 mg/kg [14].

1.2 Rationale

TP-0903 is a novel oral inhibitor that targets AXL kinase and reverses the mesenchymal phenotype associated with advanced cancers. TP-0903 has demonstrated profound single agent activity in CLL B-cells taken directly from patients even if the patient has high risk factors (ie, 17p/P53 deletions) or progressed on other agents (ie, ibrutinib). TP-0903 is currently being evaluated in patients with refractory solid tumors (TP-0903-101). This proposed study is designed to identify the maximum tolerated dose (MTD), safety profile and recommended Phase 2 dose (RP2D) of TP-0903 when administered orally once daily for 28 days on a 28-day cycle to patients with previously treated CLL. Treatment cycles may be repeated if the patient continues to show benefit and if TP-0903 is reasonably well tolerated.

2. DRUG INFORMATION – TP-0903

A comprehensive review of TP-0903 is contained in the Investigator's Brochure provided by the Sponsor. This document should be reviewed prior to initiating the study.

2.1 Background

TP-0903 is a potent biochemical inhibitor of AXL kinase, part of the TAM family of RTKs. AXL was originally cloned from patients with chronic myeloid leukemia. When overexpressed, it exhibits transforming potential. AXL overexpression has been reported in a variety of cancers including pancreatic cancer, colon cancer, thyroid carcinoma, breast cancer and hematological malignancies [3]. AXL is constitutively active in CLL and TP-0903 demonstrated strong activity at targeting these cells compared to normal cells.

2.2 Chemistry

To date, the drug substance utilized in the preparation of the drug product was a mono-tartrate salt (Form B). In a second drug product manufacturing campaign, the same drug substance was used, but the 4-mg and 16-mg strengths were packaged into color-coded capsules. Results from additional development work on the TP-0903 drug substance including testing multiple tartrate salt polymorph forms for solubility, stability, reproducibility upon preparation and other physical attributes, as well as toxicology and pharmacokinetics, identified a more suitable, di-tartrate form of the drug substance, Form A, which has been selected for future clinical use. The polymorph forms tested all exhibited similar solubility, toxicity, and pharmacokinetics characteristics compared to the drug substance used in the current clinical form of TP-0903 (Form B). The di-tartrate salt form of TP-0903 that was selected was based on reproducibility compared to the current clinical form.

A summary of important chemical characteristics of both drug substance forms is presented in Table 1.

Table 1. Nomenclature and Notable Chemical Characteristics of Both Clinical Drug Substance Forms (B and A)

2.3 Drug Description

Study drug is supplied as 1-, 4-, 16-***, 25-, and 100-mg*** doses in hard, gelatin capsules (size #3 ***for the 1-, 4-, 16-, and 25-mg doses; size #0 for the 100-mg dose***) ***that are manufactured under current clinical Good Manufacturing Practices (cGMP) for investigational use***.

2.4 Mechanism of Action

The observed mechanism of action of TP-0903 in cells and in preclinical animal models is consistent with AXL kinase being the dominant pharmacological target. AXL belongs to the family of RTKs called the TAM receptors. This family includes AXL, TYRO3, and MER. The TAM receptors are defined by a combination of 2 immunoglobulin-like domains and dual fibronectin type III repeats in the extracellular region of the protein [15]. Two ligands, GAS6 and protein S have been identified for the TAM receptors [3]. These ligands are vitamin K-dependent proteins that exhibit 43% amino-acid sequence identity and share domain structures.

Inhibition of AXL signaling by a dominant-negative receptor mutant (AXL-DN) suppresses experimental gliomagenesis, migration, and invasion, and leads to long-term survival of mice after intracerebral glioma implantation compared with AXL wild-type transfected tumor cells [16]. Additionally, AXL is detected at higher levels in metastases or malignant tumors compared to normal tissues or primary tumors, and a higher level is associated with a poor clinical outcome [4, 5]. AXL can also exist as a soluble molecule (sAXL), which is generated by ADAM10-mediated proteolysis and is associated with GAS6 in the blood. The biological function of sAXL has not been well characterized; however, GAS6 in circulation can bind to sAXL rendering it incapable of stimulating the AXL receptor [17].

More recently, the role of AXL in tumorigenesis has focused on its regulation of a process called epithelial-to-mesenchymal transition (EMT). In EMT, epithelial cells lose their adhesion-dependence and become more migratory, invasive, and generally more resistant to treatment, all of which are properties of mesenchymal stem cells. Epithelial-to-mesenchymal transition is a natural process required for embryonic development and wound healing; however, the same process is utilized by cancer cells to initiate metastasis and enable drug resistance. Targeting the EMT process has been hypothesized as a potential strategy to suppress the spread of cancer to both neighboring and distant tissues and to sensitize cancer cells to standard-of-care treatments. Due to the central role of AXL in regulating EMT, it has emerged as an important therapeutic target, especially for tumor types that rely heavily on EMT for drug resistance.

AXL was identified as a potential therapeutic target in CLL by studying the interaction between CLL B-cells and bone marrow stromal cells (BMSC). It was found that CLL utilizes microvesicles to constitutively activate AXL signaling in both the diseased B-cells and the associated BMSCs [8].

2.5 Preclinical Studies

2.5.1 In Vitro Pharmacology

TP-0903 was designed to be a potent and selective inhibitor of AXL kinase. In a biochemical kinase assay, TP-0903 inhibited the activity of AXL kinase with an inhibitory concentration in 50% of test subjects (IC_{50}) of 12 nM. A number of additional biochemical assays have been performed to determine the in vitro potency of TP-0903 against other protein kinases. In addition to AXL kinase, TP-0903 shows potent inhibition of several other protein kinases in the low nanomolar range in these biochemical assays, including MER and TYRO3.

2.5.1.1 TP-0903 effects on Gas6-induced epithelial-to-mesenchymal transition (EMT)

The mesenchymal phenotype in many cancer cells is central to the pathogenesis of tumors. Increased AXL expression in tumor cells is strongly associated with enhanced chemoresistance, proliferation, and migration, each of which are features of the mesenchymal phenotype. In order to investigate the on-target effects of TP-0903, the compound was tested in cell migration assays stimulated by the cognate ligand of AXL, GAS6. TP-0903 completely inhibited migration of AsPC-1 cells in this EMT dependent migration assay. TP-0903 also decreased the expression of mesenchymal

cell markers, such as Slug and Snail, in cells from hematological cancers and solid tumors.

2.5.1.2 Effect of TP-0903 on GAS6/AXL-dependent Phospho-signaling Pathways

To determine the on-target effects of TP-0903 on downstream signaling from AXL kinase, an enzyme-linked immunosorbent assay (ELISA) using the Meso Scale Discovery platform was used to detect the phosphorylation of AKT, following AXL stimulation with GAS6. Indicated cell lines were serum-starved for 4 hours, treated with TP-0903 for 2 hours, and stimulated with GAS6 for 10 minutes. TP-0903 inhibited GAS6-mediated induction of phospho-AKT in a concentration-dependent manner in 3 different cell lines, confirming that TP-0903 inhibits AXL kinase in cultured cancer cells (*Figure 1*).

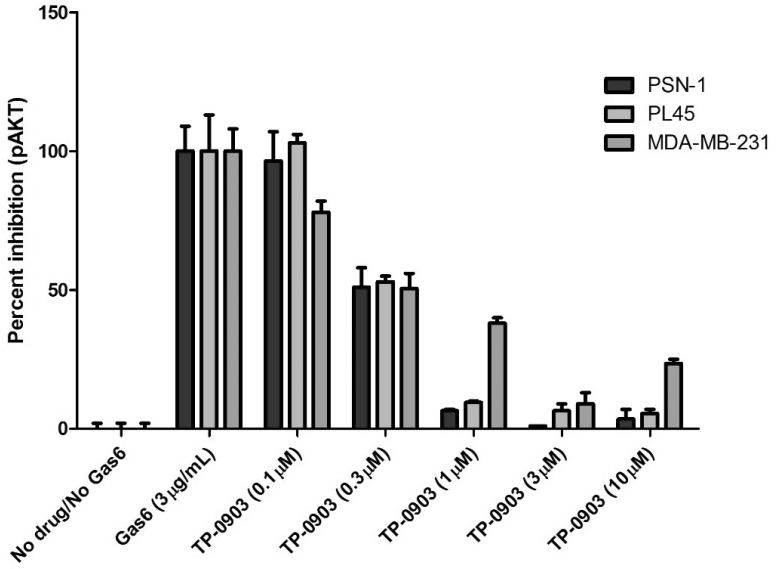


Figure 1 TP-0903 Inhibits GAS6/AXL-mediated Phospho-AKT Activity

2.5.1.3 Antiproliferative Activity in Cancer Cells

TP-0903 was evaluated for its in vitro anticancer efficacy against a panel of cultured cancer cell lines. The IC_{50} values observed ranged from 0.0145 µM to 0.205 µM. The greatest sensitivity was observed in the A549 lung carcinoma cell line (*Table 2*).

Table 2 Activity of TP-0903 in Human Cancer Cell Lines

Cell Line	Cell Type	TP-0903, IC_{50} (μM)
A549	Lung carcinoma	0.0145
H1650	Lung carcinoma	0.0699
Panc-1	Pancreatic carcinoma	0.078
HL-60	Acute promyelocytic leukemia	0.205
MV4-11	Acute myeloid leukemia	0.0586

2.5.1.4 Effect of TP-0903 on CLL B-cells

AXL was found to be overexpressed and constitutively active in CLL B-cells taken directly from patients (*Figure 2*) [18]. The CLL B-cells from 2 different patients showed overexpression of AXL compared to T-cells from the same patients. Additionally, normal B-cells from a healthy volunteer did not have elevated AXL expression. Furthermore, 10 CLL patients (including P1 and P2) were evaluated for AXL activation/phosphorylation (P-AXL) and total AXL expression by western blot analysis. Seven of the 10 patients showed high AXL activation.

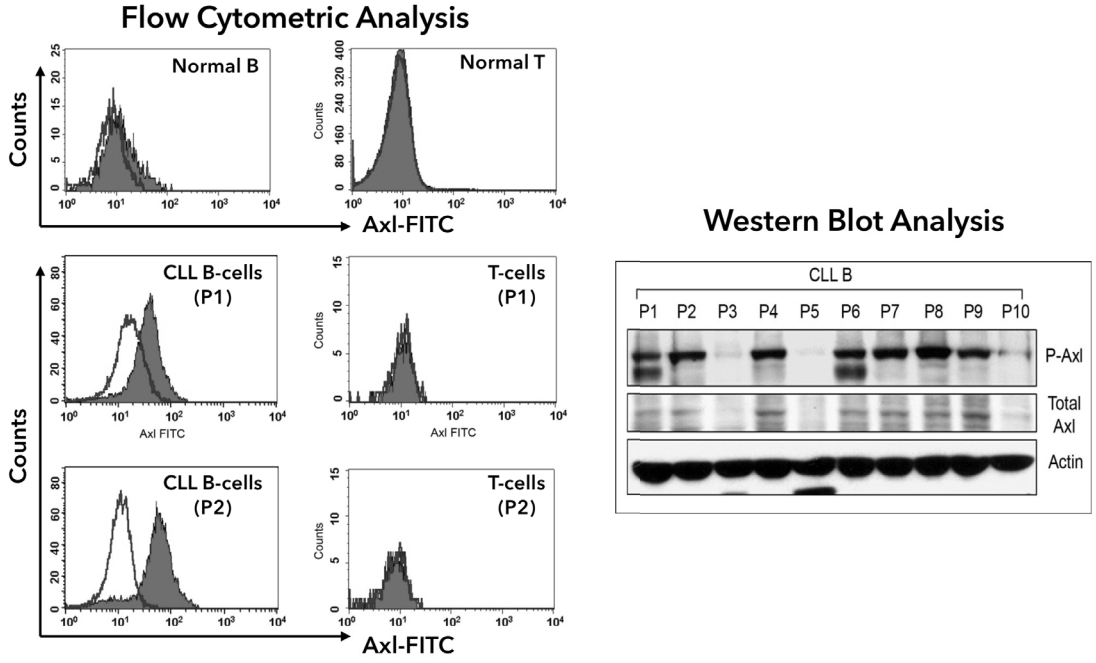


Figure 2 AXL Overexpression and Activation in CLL B-cells Taken Directly from Patients

TP-0903 has been extensively evaluated against CLL B-cells taken directly from CLL patients. In 20 CLL samples from low-risk patients, TP-0903 had an average EC_{50} of inducing apoptosis between 125 to 175 nM. Similarly, in 18 CLL samples from high-risk patients, the average EC_{50} was around 150 nM (*Figure 3*) [6].

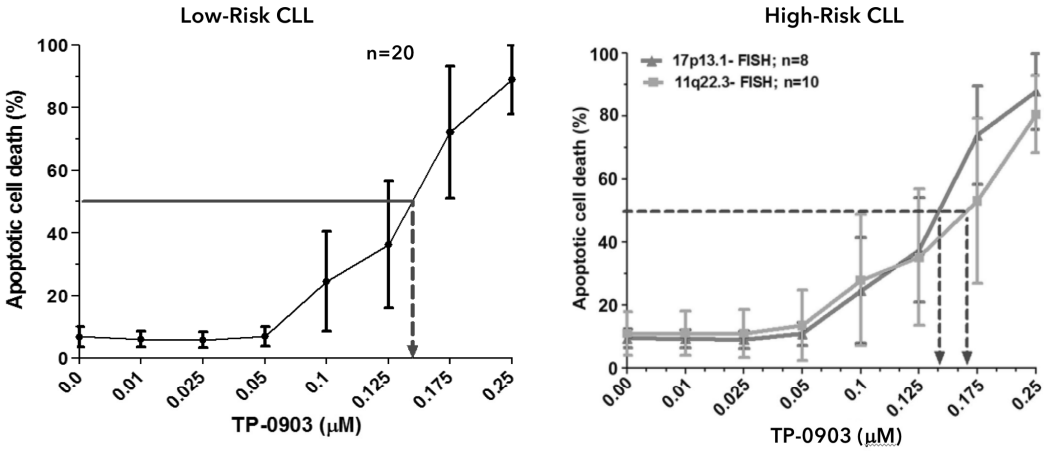


Figure 3 TP-0903 Potently Induces Apoptosis in CLL Cells Regardless of Risk Factors

Similar activity was observed in CLL B-cells co-cultured with BMSCs with no effect on the viability of the BMSCs (*Figure 4*) [6]. Typically, BMSCs provide a protective niche that shelters CLL B-cells from the therapeutic effect of drugs. TP-0903 appears to overcome this protective niche and demonstrates potent activity in this co-culture environment.

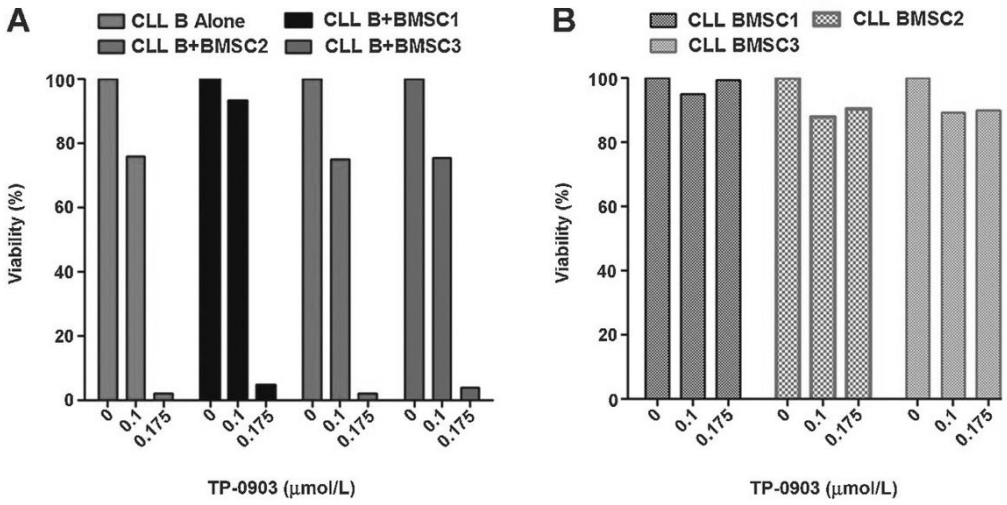


Figure 4 TP-0903 Potently Targets CLL B-cell Viability Even in the Presence of BMSCs

To determine if the induction of apoptosis from TP-0903 treatment correlated with the inhibition of AXL, CLL B-cells were treated with TP-0903 and AXL activation was determined by western blot (*Figure 5*) [6]. TP-0903 down-regulates the phosphorylation and activation of AXL in CLL cells, which is consistent with the observed strong apoptotic response, regardless of CLL risk category.

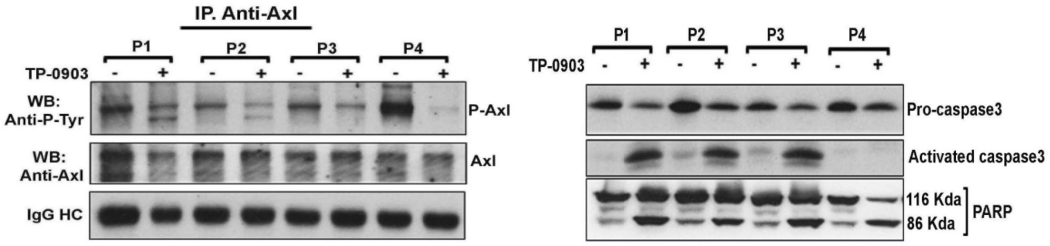


Figure 5 TP-0903 Potently Targets AXL Signaling in CLL B-cell, which Correlates with the Induction of Apoptosis (Cleaved Caspase3)

An additional, independent study separate from the studies listed above demonstrated TP-0903 is very active (IC_{50} <500 nM) in CLL cells acquired from patients exposed to or progressed on ibrutinib (*Figure 6*) [19] and other targeted agents.

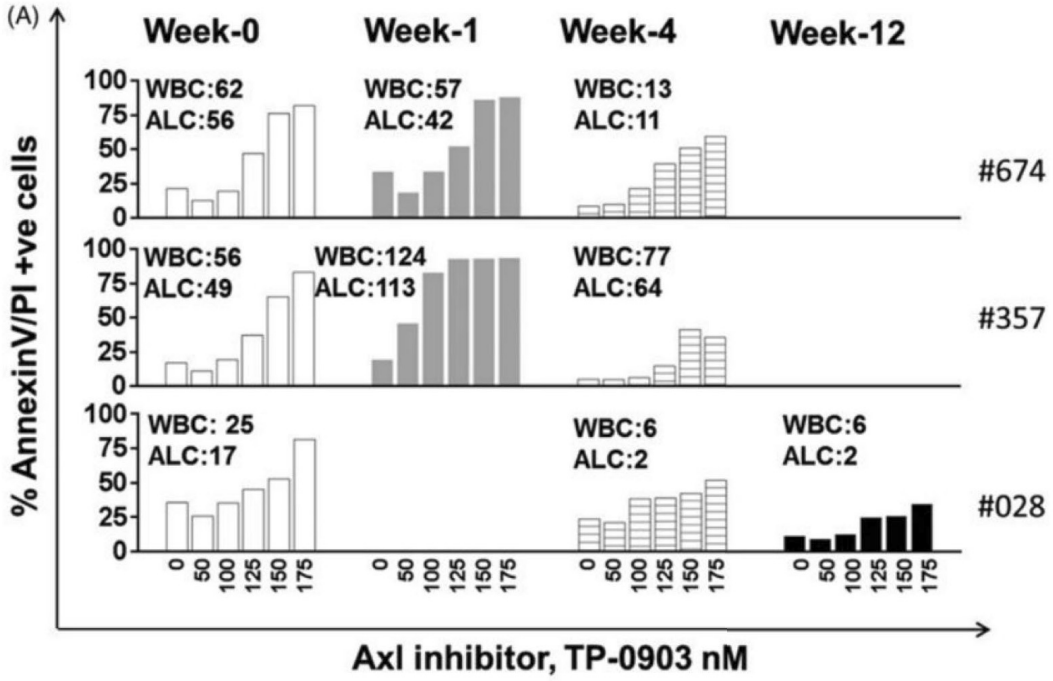


Figure 6 Induction of Apoptosis by TP-0903 in Lymphocytes from CLL Patients Before (Week 0) and After (Weeks 1, 4 and 12) Ibrutinib Therapy (3 Samples from Single Patient)

2.5.2 In Vivo Pharmacology

2.5.2.1 Single Agent Activity in Tumor-bearing Animal Models

The in vivo efficacy of TP-0903 was evaluated using 2 xenograft tumor models, the MV4-11 AML model and the A549 lung carcinoma model. All tumor models were implanted subcutaneously in the hind flank of the athymic nude mice. Tumor volumes were allowed to grow to a medium size (approximately 100 mm^3) before stratification and initiation of dosing. General health, tumor volumes, and body weights were followed over the course of the study. In both xenograft models, TP-0903 caused regression in starting tumor sizes without any adverse effects on body weights (*Figure 7*).

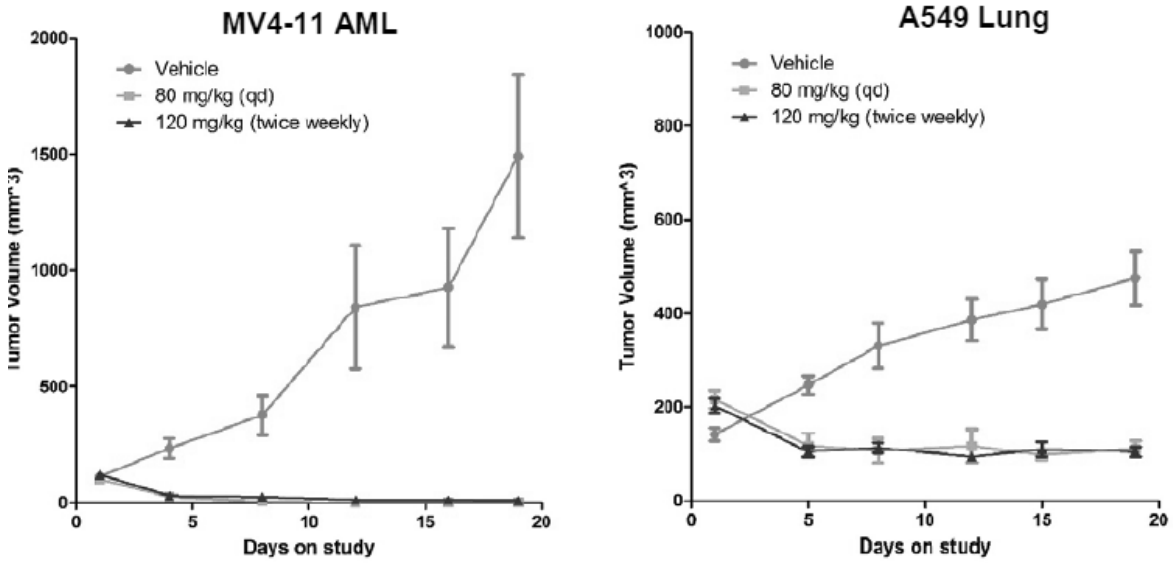


Figure 7 Tumor Growth Reduction in Leukemia and Lung Carcinoma Mouse Xenograft Models

2.5.3 Safety Pharmacology

A number of assays were performed to evaluate the potential effects of TP-0903 on hERG activity.

2.5.3.1 Effects on hERG Channel Function

Biochemical binding to the hERG channel was evaluated using the Predictor™ hERG Fluorescence Polarization Assay (Invitrogen). Results showed that TP-0903 is a weak biochemical inhibitor of hERG activity, exhibiting an IC_{50} greater than 1 µM. In addition, 3 separate hERG patch-clamp experiments were also conducted, 2 using HEK-293 cells [20, 21] and 1 using CHO cells [11]. The data from cell-based Study No. 191081 suggests that TP-0903 inhibits hERG activity by greater than 50% at 1 µM in transfected HEK-293 cells. However, data from the 2 other patch-clamp assays conducted in both HEK-293 and CHO cells are more consistent with the data from the

cell-free biochemical screen, concluding that hERG inhibition is not significant (>50%) below 1 µM of TP-0903.

2.5.3.2 Receptor Panel Screening

TP-0903 was screened through the "Safety 44 panel" of safety-associated receptors and enzymes offered by Cerep [11]. TP-0903 inhibited only 15 of these assays when screened at the highest dose tested at 10 µM. Based on animal pharmacokinetic data, animal efficacy models and toxicology data, 10 µM concentrations have not been reached in animals and are not expected to be achieved in future human studies. Therefore, off-target receptor inhibition is not expected to lead to significant toxicity concerns in future testing of TP-0903.

2.5.3.3 Cardiovascular Safety Assessment in Dogs

Tolero sponsored a study to examine the potential toxicity and toxicokinetics of TP-0903 when administered orally to dogs for 28 consecutive days as well as the progression or regression of any effects following a 14-day treatment-free recovery period (Nucro-Technics Study No. 302456) [12].

Electrocardiograms (ECGs) (6 limb leads) were obtained for all animals once during the pretreatment period and on Day 27 of dosing at approximately 1.5 hours postdose; close to the time to C_{max} (peak time) (T_{max}) (2 hr ±30 minutes). Tracings were assessed for gross changes indicative of cardiac electrical abnormalities. Heart rate (HR) (lead II), rhythm or conduction abnormalities were also evaluated. Each ECG was evaluated for HR, rhythm, P wave duration, QRS duration, PR interval, and QT duration. The morphology of the QRS complexes was evaluated in the frontal plane leads for gross abnormalities. ECGs were evaluated by a Board-certified Veterinary Cardiologist.

Blood pressure (BP) using a noninvasive technique was recorded at approximately the same time as ECGs, and included HR, and systolic/diastolic BP.

The HR, PR interval, P wave duration, and QRS duration were within normal limits for all groups and there was no significant difference noted between groups at the different time points. The QT interval was within normal limits for all groups and all time points. Prestudy HR was significantly lower in the high dose group compared to all other groups and was considered an incidental finding. No arrhythmias were noted in the different groups at the different time points.

2.5.4 Nonclinical Absorption, Distribution, Metabolism and Excretion Studies

2.5.4.1 Drug Transporter Effects

TP-0903 was tested in a bidirectional cell permeability assay using confluent monolayer of Caco-2 cells in a 96-well based format. Fenoterol, Propranalol, and Digoxin were used as controls. The efflux ratio (mean apparent permeability [Papp] A to B / mean Papp B to A) for TP-0903 was determined to be 1.49. Although mass recovery was low, this data suggests that TP-0903 is not a substrate for P-glycoprotein and is a compound of moderate permeability.

2.5.4.2 CYP450 Effects

TP-0903 was evaluated for the inhibition of human cytochrome P450 (CYP) isozymes using human liver microsomes in the presence of NADPH. At 10 µM, TP-0903 inhibited the activity of only isoform 2C19 by more than 50% out of the isozymes selected for testing. The IC_{50} values were determined against all the CYP isozymes used in the panel and, consistent with the percent inhibition data, only 2C19 was inhibited at a concentration lower than 10 µM (IC_{50} 4.4 µM).

2.5.4.3 Liver Microsome Stability Studies

The stability of TP-0903 in the presence of isolated microsomes from 3 species (human, rat and dog) were determined. The concentration of TP-0903 was measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) with reference to a standard curve. The $t_{1/2}$ of TP-0903 ranged from 4.3 minutes in humans to 4.9 minutes in dogs.

2.5.4.4 Metabolite Profile and Identification

To identify potential first-pass metabolites, TP-0903 was incubated in the presence of human hepatocytes for 2 hours and the composition of the resulting mixture of compounds was determined by LC-MS/MS. Following the 2-hour incubation, 55% of the parent compound remained and 7 metabolites were observed. The 3 major metabolites result from demethylation of the dimethyl sulfonamide (M3) or N-Methyl piperazine (M4) and oxidation (M7). The proposed metabolites are shown in *Figure 8*.

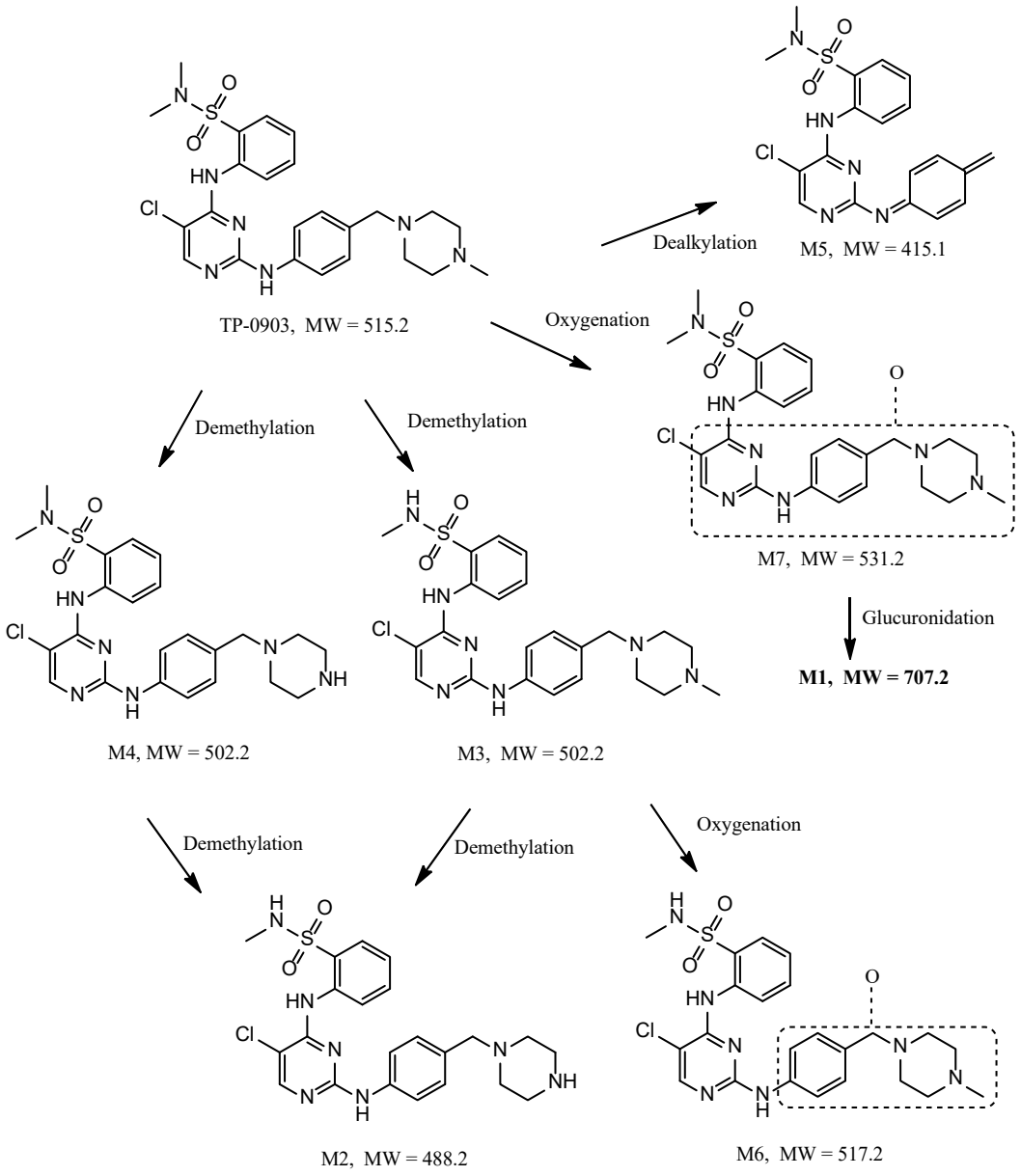


Figure 8 Identified Metabolites of TP-0903 Exposed to Human Hepatocytes

2.5.4.5 Serum Albumin Binding

The serum albumin binding levels for TP-0903 were determined using human plasma in a dialysis plate-based assay. The free fraction of TP-0903 was measured by LC-MS/MS, by reference to a standard curve, and warfarin was used as a control. Data showed that TP-0903 has moderate human serum albumin binding (7% unbound). Recovery of protein bound drug (80.3 %) indicated the binding was reversible.

2.5.4.6 pKa of TP-0903

The pKa values for TP-0903 were determined by titration using ultraviolet metric detection. The pKa was determined in aqueous buffer and separately in the presence of 2 cosolvents (80% methanol and 60% DMSO). The final pKa values were calculated as an average of the 3 values obtained under different solvent conditions with the exception of pKa 3, for which the pKa value determined in DMSO was excluded. The final pKa values for pKa1, pKa2, and pKa3 were 3.02, 3.96, and 7.81, respectively.

2.5.4.7 pH-dependent Solubility of TP-0903

The equilibrium solubility of TP-0903 tartrate was determined in the following media: pH 3.5, 4.5, 5.5, 6.5 USP buffers, 0.1N HCl, SGF, fasted state simulated intestinal fluid, and fed state simulated intestinal fluid. As expected, based on the pKa determination, TP-0903 showed greatest solubility in acidic media.

2.5.5 Animal Toxicology and Pharmacokinetics

2.5.5.1 Rat Studies

2.5.5.1.1 7-day Repeated Oral Dose Range-finding Study of TP-0903 with Single and Repeated Dose PK in Rats (Study No. 293892)

A 7-day repeated oral dose range-finding study of TP-0903 with single and repeated dose pharmacokinetics (PK) was performed in rats [22]. Groups of 4 male and 4 female rats received 2, 4, or 8 mg/kg of TP-0903 dissolved in 1% Tween 80 / 5% D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) / water (v/v/v) by oral gavage once daily for 7 consecutive days followed by a 7-day observation period.

Analysis of all generated data, clinical observations, body weight, body weight changes, food consumption, clinical pathology evaluations, gross necropsy, and organ weights revealed that dose levels of TP-0903 at 2 and 4 mg/kg/day administered orally once a day for 7 days were well tolerated in both males and female rats. The plasma levels and exposure (based on area under the plasma concentration curve [AUC] from time 0 to 12 hours (AUC_{0-12}) displayed a linear increase with dose following a single, 3 and 7 days of dosing at 2 and 4 mg/kg/day with higher exposures in females compared to males and plasma levels that did not change during treatment.

At a dose of 8 mg/kg, male rats tolerated the 7 day repeated doses of TP-0903 well and plasma concentrations of TP-0903 did not change during treatment. In contrast, female rats treated orally with TP-0903 at 8 mg/kg/day showed treatment-related toxicity including decreased food consumption, weight loss, pallor, diarrhea, and melena. The most prominent hematological finding at the end of treatment was a reduction of white blood cells associated with severe neutropenia. The main findings in gross necropsy for the female rats that were moribund sacrificed on Day 8 were spleen enlargement, renal pallor, and bone marrow as well as reduction of abdominal fat and muscle mass (cachexia). Plasma concentrations of TP-0903 in female rats at a dose of 8 mg/kg were higher compared to male rats and much higher on Day 7 compared to Day 3 indicative of a dose accumulation effect.

Pharmacokinetic studies of TP-0903 revealed a rapid absorption with T_{max} values similar, between male and female rats, across all doses and days of dosing, ranging from 0.5–2.0 hrs. The magnitude of the plasma AUC from time 0 to the time of the last concentration ($AUC_{0\text{-}Tlast}$) displayed a gender bias, being approximately 1.5-2-fold higher in females compared to males, with the only exception being high dose females following 7 days of dosing where the $AUC_{0\text{-}Tlast}$ was 5.8-fold higher. Maximum observed plasma concentration (C_{max}) and $AUC_{0\text{-}Tlast}$ dropped slightly with increasing days of dosing, with the exception of high dose females where $AUC_{0\text{-}Tlast}$ did not change from Day 1 to Day 3 and increased from Day 3 to Day 7 by approximately 2-fold. Following a single dose and 3 days of dosing the $AUC_{0\text{-}12}$ increased in a linear fashion between doses for both male and female rats. On the seventh day of dosing, the relationship between increasing dose and $AUC_{0\text{-}12}$ deviated from linearity in female rats, due to a larger than expected increase of the high dose $AUC_{0\text{-}12}$ suggesting that there was dose accumulation of TP-0903.

2.5.5.1.2 28-day Repeated Oral Dose Toxicity and Toxicokinetic Study of TP-0903 in Rats (Study No. 302457)

The potential toxicity and toxicokinetics of TP-0903 when administered orally to rats daily for 28 days was evaluated [13]. Groups of 10 male and 10 female rats received 0.5, 2, or 4 mg/kg/day of TP-0903 dissolved in 1% Tween 80 / 5% TPGS / water (v/v/v) by oral gavage once daily for 28 consecutive days. A control group (10 males/10 females) was dosed with the vehicle only. The progression or regression of any effects were evaluated during an additional 14-day treatment-free period in the control group and in rats dosed at 2 and 4 mg/kg/day.

There were no treatment-related observations recorded during the 28 days of dosing or 14-day treatment-free period in the control group. Mean body weights and mean body weight gains of the male rats in the high dose group were significantly lower at the end of treatment; however, this was not observed in the females of this group.

The main finding of toxicological relevance in the hematology evaluations was a slight reduction of reticulocyte counts in the high dose group which may reflect reduced erythropoiesis. This finding appeared to be transient since reticulocyte counts in the high dose recovery group were comparable to the control group. Coagulation, serum chemistry, and urinalysis evaluations did not reveal any test item treatment-related findings.

TP-0903 was rapidly absorbed following oral administration, with the majority of the T_{max} values between 1–2 hrs in both males and females. There was no evidence of dose accumulation observed on Days 1, 15, and 28 of dosing. Females had higher C_{max} values than males at all doses and on all days of dosing but there were no differences in the T_{max} values and the higher C_{max} values in females were not associated with differences in clinical, clinical pathology and anatomo-histopathological findings. The elimination half-life ($t_{1/2(e)}$), determined from the available data of dose groups of 2 and 4 mg/kg ranged from 2.3-8.9 hours and was similar in both genders. TP-0903 exhibited a high volume of distribution suggesting for a large tissue distribution.

There were no gross findings of toxicological relevance observed in gross necropsy examinations performed at the end of treatment and recovery periods. The only finding of possible toxicological relevance in the organ weight evaluation was a lower weight of thyroid with parathyroids in male rats dosed with the test item; however, there were no abnormal findings in the histopathology of thyroid and parathyroids.

The abnormalities found in histopathology of the high dose rats included small acute hemorrhages in mesenteric lymph nodes in 5 animals and focal inflammatory infiltrates and/or focal lobular atrophy in pancreas of 3 control and 7 high dose animals. These findings were equivocal and it could not be determined whether they were related to test item treatment. While exposure to the test item had a dose-related effect on the body weight of male rats in the high dose group and was associated with a transient mild reduction in erythropoiesis in males and females, no underlying mechanism of action was apparent from the histopathology evaluations. Hematopoiesis evaluated in the spleen and bone marrow tissues were similar in the high dose and control groups.

Based on all data generated, including clinical observations, body weights, food consumption, ophthalmoscopy, clinical pathology, toxicokinetics, gross pathology and histopathology, the No Observed Adverse Effect Level (NOAEL) of TP-0903 following 28 days of repeated oral dosing in rats was determined to be 2 mg/kg/day.

2.5.5.2 Dog Studies

2.5.5.2.1 Single Oral Dose and 7-Day Repeated Oral Dose Toxicity and Pharmacokinetic Study of TP-0903 in Dogs (Study No. 294865)

This study established a dose level by a single oral dose (Part A) and determined the toxicity and PK of TP-0903 (Part B) dissolved in 1% Tween 80 and 5% vitamin-E TPGS in water following 7 days of repeated oral dosing in Beagle dogs [23]. Doses were administered via a stomach tube at a dose volume of 2 mL/kg after overnight fasting. Food was offered approximately 1 hour after dosing.

Three groups of dogs, each consisting of 1 male and 1 female, received a single TP-0903 dose of 0.25, 0.5, or 1 mg/kg and observed for 14 days (Part A). Salivation was observed in the high dose (1 mg/kg) male dog approximately 30 minutes postdose. Emesis was observed in the high dose female dog approximately 60 minutes postdose. All dogs completed the treatment period and survived the scheduled observation period. There were no other observations of toxicological relevance seen in hematology and serum chemistry evaluations.

In Part B of the study, 3 groups of dogs, each consisting of 2 males and 2 females, received TP-0903 for 7 consecutive days at doses of 0.25, 0.75, or 1.25 mg/kg/day followed by 7-day observation period. A control group comprised of 1 male and 1 female received vehicle only.

All dogs completed the treatment and observation periods and survived to scheduled necropsy. Analysis of all generated data, including clinical observations, body weights, food consumption, clinical pathology, gross necropsy, and organ weights revealed no test article treatment-related significant toxicity in dogs that were treated orally with

TP-0903 up to 1.25 mg/kg/day for 7 days. Clinically, TP-0903 caused emesis at the initial dose level of 0.25 mg/kg/day and up to 1.25 mg/kg/day.

Pharmacokinetic studies of TP-0903 revealed a rapid absorption with T_{max} values similar between male and female dogs, across all doses and days of dosing, ranging from 0.5–6.0 hours. The magnitude of the plasma $AUC_{0\text{-}Tlast}$ did not display a gender bias. Oral $t_{(1/2)e}$ and mean residence time (MRT) values were slightly longer following 7 days of dosing. The $AUC_{0\text{-}Tlast}$ increased linearly with dose across genders and following a single and 7 days of dosing. At the doses employed, there was little evidence of dose accumulation for TP-0903 in Beagle dogs following 7 days of repeated dosing.

2.5.5.2.2 Seven-day, Three Times Per Day, Repeated Oral Dose Toxicity and Pharmacokinetic Study of TP-0903 in Dogs (Study No. 298717)

This study evaluated the toxicity and pharmacokinetics of TP-0903 following 7 days of 3 times a day, repeated oral dosing in dogs [24]. This study was performed following the 7-day repeat dose, once a day repeat dose study (Study No. 294865) to support the determination of the MTD of TP-0903 in dogs.

To achieve sufficient systemic exposure at the high dose levels, 2 groups of 2 females were dosed with TP-0903 incorporated in gelatin capsules at dose levels of 3 or 6 mg/kg/day (1 or 2 mg/kg/dose).

In the 3 mg/kg/day dose group, both dogs had emesis on most of the dosing days with the vomiting time ranging from approximately 15 minutes to 2 or 6 hours postdose. Soft feces or diarrhea was observed from Days 3 or 7 to 14. One of the dogs had a 1.1 kg body weight loss over the 7-day treatment period and started to regain body weight, gaining 400 g, during the 7-day recovery period. The other dog gained 300 and 600 grams body weight over the 7 and 14-day periods, respectively.

Both dogs in the 6 mg/kg/day (2 mg/kg/dose × 3 days) dose group, showed various signs of toxicity early in the treatment phase. The severity of the clinical signs increased, and the health condition of the dogs deteriorated after each subsequent dose. The clinical signs mostly consisted of vomition, diarrhea, emaciation, anorexia, dehydration, apathy, and weight loss. Due to deteriorating health, the 2 dogs in this group were dosed only twice a day on Day 4 and dosing was skipped on Days 5 and 6, but the dogs were dosed for the PK evaluation on Day 7. After the end of treatment, the condition of animals continued to deteriorate, and their condition did not improve despite support with fluid therapy provided on Day 9. One dog was found dead the morning of Day 10 and the second dog was euthanized in moribund condition that same day.

Clinical pathology results in the dogs dosed at 6 mg/kg/day, on Day 8, showed slight increases in white blood cells (WBCs), red blood cells (RBCs) and neutrophils; increased hematocrit and hemoglobin values; and decreased reticulocyte counts in one of the dogs. In the other dog, there were increases in WBCs, RBCs, neutrophils, monocytes, and basophils; increased hematocrit and hemoglobin values; and decreased reticulocyte counts and platelets.

In the dogs dosed at 3 mg/kg/day, on Day 8, all hematology parameters were within the normal ranges for of the dogs. In the second dog there was a slight increase in RBC count; increased hematocrit and hemoglobin values; and reticulocyte count, although within the normal range, was decreased compared to the pretreatment count.

On Day 14, hematology results were within the normal reference ranges with exception of a slight increase in reticulocyte counts in 1 of the dogs of this group. The only serum chemistry parameters that were affected in the dogs dosed at 3 mg/kg/day were elevated ALT (almost twice the normal upper limit) in 1 of the dogs and elevated triglycerides in both dogs.

Pharmacokinetic analysis revealed that the plasma exposure to TP-0903 as measured by AUC from time 0 to infinity ($AUC_{0\text{-}inf}$) was not dose proportional and higher on Day 7 compared to Day 1 following the third dosing, and even more so for the 6 mg/kg/day dose compared to the 3 mg/kg/day dose. These observations were made despite the vomiting that occurred and a partial cessation of dosing at the 6 mg/kg/day dose, suggesting that there may be a tendency for dose-accumulation following consecutive days of dosing. C_{max} values were minimally impacted while T_{max} values were longer at the 6 mg/kg/day dose. Both the $t_{(1/2)e}$ and MRT values were slightly longer with increased days of dosing suggesting a change in the clearance mechanisms for TP-0903 with consecutive days of dosing.

Necropsy was performed on the dogs that were unscheduled sacrificed and found dead on Day 10. At necropsy, cachexia and dark yellowish and watery lower intestinal contents were observed in 1 dog. In the other dog, cachexia, hyperemia of the glandular portion of the stomach; hemorrhagic lower intestines and rectum; dark reddish black color of lower intestinal contents; and hyperemia in the cortex and medulla of the kidneys were observed.

The MTD of TP-0903 was reached following dosing of 1 mg/kg/dose 3 times per day (3 mg/kg/day) and the dogs recovered well within 1 week of cessation of treatment.

2.5.5.2.3 28-Day Repeated Oral Dose Toxicity Study of TP-0903 in Beagle Dogs followed by a 14-Day Recovery Period (Study No. 302456)

This study examined the potential toxicity and toxicokinetics of TP-0903 when administered orally to dogs for 28 consecutive days [12]. The progression or regression of any effects following a 14-day treatment-free recovery period was also assessed. Two groups of dogs (3 males/3 females) were dosed with TP-0903 incorporated in gelatin capsules at the following dose levels: 0.1, 0.5 mg/kg/day for 28 days and another group was dosed at 1 mg/kg/day for the first 14 days, followed by 2 mg/kg/day for the remaining 14 days of the treatment period. A control group of dogs was included in the study and was dosed with empty gelatin capsules.

All dogs completed the 28-day treatment period and survived until scheduled termination for necropsy. Clinical signs noted in the high-dose group during the treatment period included vomition, salivation, diarrhea, and/or soft feces. Vomition affected all dogs in the high-dose group and was observed in some dogs in the mid-dose group. Reduced food consumption was observed in 1 male and 1 female; whereas weight loss was observed in 1 out of 5 males and 2 out of 5 females in the

high-dose groups during Weeks 3 and/or 4 of treatment and following the dose increase from 1 mg/kg to 2 mg/kg. These signs were not observed at the end of the recovery period.

There were no ophthalmoscopy findings at the end of treatment in any of the animals.

Evaluation of clinical pathology data (hematology, coagulation, serum chemistry, and urinalysis) did not reveal any findings clearly attributable to the test item.

TP-0903 resulted in a dose-dependent increase in plasma concentrations. TP-0903 was quantified in some plasma samples following dosing at 0.1 mg/kg, however most plasma concentrations were below the lower limit of quantitation (0.2 ng/mL). The dose proportionality and linearity of plasma concentrations of TP-0903 following oral dosing could not be well characterized given the low plasma levels at the lowest dose. However, a comparison of the mid and high doses suggests that plasma concentrations in male and female dogs increased approximately in a dose proportional manner. At both the mid and high doses, all predose levels of TP-0903 were below the limit of quantification and for the high dose, the elimination half-lives were similar on all days of dosing, suggesting a lack of dose accumulation. The analysis of toxicokinetic data revealed a high clearance of TP-0903 in plasma that was caused from a large volume of distribution suggesting that TP-0903 was well distributed in tissues.

Gross pathology findings observed in a few animals in the high-dose group included hemorrhage in colon of 3 animals and cecum of 1 animal, as well as hyperemia in the pylorus in 1 dog and hyperemia in the rectum in another dog. The hemorrhages were likely agonal, but might indicate recent injury to the mucosa. No gross findings were observed in recovery animals in the high- and mid-dose groups.

There were no apparent differences in absolute and relative organ weights between the control group and test item groups (both genders) with the exception of a few incidental significant differences: higher mean weights of thyroids with parathyroids in the low-dose males and an increase in the mean weights for uterus sizes in Group 4 females, due to physiological luteal phase with endometrial hypertrophy.

Histopathological findings of possible toxicological significance included changes in the thymus and the lower gastrointestinal tract tissues.

- Thymic atrophy was found at the end of the treatment period in 3 out of 6 high-dose animals, 3 out of 6 mid-dose animals, 1 out of 6 low-dose animals, and 1 out of 6 control animals. This finding was also noted in 2 of 4 dogs in both the high- and mid-dose groups at the end of the recovery period. Thymic atrophy is a physiological response to stress and an expected finding in young dogs around the onset of sexual maturity, so these findings are considered to be nonspecific and indirectly related to the treatment-associated gastrointestinal effects.

- Minimal or mild degree of mucosal injury and inflammation in the small intestine were observed at the end of the treatment period in 1 mid-dose dog, 4 high-dose dogs, and 1 dog in the control group. At the end of the recovery period, 1 control dog, 1 mid-dose dog, and 2 high-dose dogs had similar mild

residual changes. The small intestinal mucosal injury associated with the high-dose regimen was considered to have returned to background level at the end of the 14-day recovery period.

- At the end of the treatment period, minimal or mild degree of mucosal injury and inflammation in the colonic mucosa was observed histologically in four animals in the high-dose group. These responses were characterized by increased amounts of cell debris in a few glands, associated with patchy neutrophil infiltrates, or focal areas of hemorrhage in the lamina propria. One control animal also had minimal injury to colonic glands without inflammation or hemorrhage. Similar findings were not observed in the large intestines in any of the animals of the mid-dose group. Minimal degeneration of the colon mucosal glands was observed at the end of the recovery period in one high-dose dog.

Evaluation of clinical observations, body weight assessment, food consumption, ophthalmology, ECGs, clinical pathology, gross necropsy, and organ weights did not reveal any findings of clinical or toxicological relevance in dogs dosed at 0.1 mg/kg/day. With the exception of vomiting, no other adverse findings of toxicological significance were found in dogs dosed with TP-0903 at 0.5 mg/kg/day. Emetogenic effect is a common finding observed in dogs dosed with kinase inhibitor drugs and could be attributed in part to a higher susceptibility of this species toward this class of drugs.

Administration of TP-0903 at a dose of 1 mg/kg/day for 14 days, followed by 2 mg/kg/day for 14 days was, for the most part, well tolerated by young male and female Beagle dogs used in this study. Emesis was the most obvious adverse effect occurring in this dose group and was more pronounced upon the dose increase to 2 mg/kg. Other clinical signs, including salivation, diarrhea or soft feces and reduction of body weight gains, were observed during the third and/or fourth weeks of treatment. Upon the ceasing of treatment, there were no clinical signs observed in the recovery animals. Histopathological findings indicated that the potential target organs of toxicity were the lower gastrointestinal tract and thymus. Upon completion of the treatment period, there were no clinical signs or histopathological findings observed in the recovery animals with the exception of thymic atrophy which was considered to be a stress-related nonspecific response and may have occurred during the treatment phase.

2.6 Clinical Studies

This is the second Phase 1 study of TP-0903 in humans, but the first in patients with a hematologic malignancy. Most of the toxicology findings observed with TP-0903 in preclinical drug safety studies were typical of antiproliferative compounds, including bone marrow (ie, neutropenia, thrombocytopenia, and anemia) and gastrointestinal effects (ie, vomiting, diarrhea, anorexia). Observations were largely reversible during the recovery period. They are not uncommon for anticancer agents and are expected to be manageable and/or reversible in the clinic.

2.7 Justification for Study Treatment Plan and Starting Dose

The starting dose was based on a thorough review of both the rat and dog GLP toxicology studies, as well as preliminary results from the ongoing Phase 1 study in patients with advanced metastatic or progressive solid tumors (Study No. TP-0903-101). TP-0903 was administered orally once each day for 28 days in the GLP toxicology studies. In the rat, all findings were reversible or felt not to be clinically significant and the NOAEL was determined as 2 mg/kg or 12 mg/m^2. Based on the animal toxicology and safety studies, the starting dose for TP-0903-101 was 1.5 mg/m^2/day. However, given the clinical experience now acquired in this solid tumor study and the lack of dose-limiting toxicities (DLTs) observed in any of the first 6 cohorts, the proposed starting dose for TP-0903 in Group 1 (monotherapy) will be a 25-mg flat dose. The starting dose will be approximately one dose level below the current Phase 1a solid tumor study. Group 2 patients (combination therapy) will start at one dose level below Group 1, or a 20-mg flat dose, to ensure safety particularly with the combination of ibrutinib and TP-0903. The use of a flat, rather than body size-based dose, particularly for orally administered drugs, is preferable as it facilitates the use of the drug by patients and physicians and reduces the number of dosage strengths needed, improving compliance.

Because TP-0903 has been well tolerated to date in the 101 solid tumor study, the proposed starting dose of 25 mg in the monotherapy arm is equivalent to 700 mg (25 mg × 28 days, or 80% of the current dose in the 101 solid tumor study). The proposed starting dose in the combination arm (ie, TP-0903 plus ibrutinib) will be 20 mg, which is a further 20% reduction from the 25 mg starting dose in the monotherapy arm. Tolero believes that the available safety information from the 101 solid tumor study, together with the lower starting doses suggested in this study, support the proposed continuous, 28-day dosing schedule.

2.8 Summary of Risk and Benefits

TP-0903 is a new inhibitor of AXL kinase that has shown promising preclinical activity against a variety of both hematological and solid tumor malignancies. Preclinical studies suggest that bone marrow, gastrointestinal tract, and the thymus may be potential target organs of toxicity. In the rat, reticulocyte counts were reduced; however, these findings were not observed in the dog. In the dog, minimal to mild injury to the mucosal lining as well as inflammation was noted in the small intestines and colonic mucosa. Thymic atrophy was also noted in the dog. With the exception of vomiting, no other adverse effects of significance were observed in the dog. The preclinical GLP toxicology studies suggest that the observed toxicities were reversible following a recovery period of 14 days with the exception of thymic atrophy.

As of 03 August 2018, 23 patients over 7 different dose cohorts have been treated with TP-0903 in the ongoing Phase 1 solid tumor study, TP-0903-101. No DLTs had been reported. ***National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and 4 events that occurred in one patient each included anemia, hypocalcemia, hypokalemia, hyponatremia, pleural effusion, urinary tract infection, ascites, hyperkalemia, hypertension, bacterial peritonitis, sciatica, and syncope. None of these events was considered study drug-related. The most common Grade 1 and 2 AEs (ie, those that occurred in ≥3 patients each [13%]) included nausea, vomiting, fatigue, anemia, diarrhea,***

hypoalbuminemia, decreased appetite, hypomagnesemia, tachycardia, and thrombocytopenia. Grade 1 and 2 AEs that occurred in ≥3 patients each (13%) and judged as at least 'Possibly' related to TP-0903 included diarrhea, nausea, vomiting, dysgeusia, and thrombocytopenia. There were no serious adverse events (SAEs) considered related to study drug or deaths on study to date.

3. STUDY OBJECTIVES

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 RP2D of TP-0903 when administered orally on this schedule to the defined patient groups

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

Exploratory Objective:

- 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

Phase 2

Primary Objective:

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

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)

Exploratory Objective:

- 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

4. INVESTIGATIONAL PLAN

4.1 Overall Study 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 1 of 2 groups:

- Group 1 (TP-0903 monotherapy): Patients who are intolerant to, or have had progressive disease on B-cell receptor antagonists and/or BCL-2 antagonists or other investigational treatments

- Group 2 (TP-0903 and ibrutinib combination therapy): Patients who have progression of disease on ibrutinib and 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. The study is expected to take up to 36 months to enroll 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). A schematic representation of the study design is provided in *Figure 9*.

Phase 1

Patients will be enrolled in Group 1 and Group 2 in cohorts of 3 to 6 patients simultaneously. Group 2 will start at 1 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 3 patients treated with incrementally higher doses of TP-0903 until a DLT is observed and the MTD is established. Once the first patient at a dose level is enrolled, the second and third patients will 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 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 for a total of up to 54 patients in Phase 1.

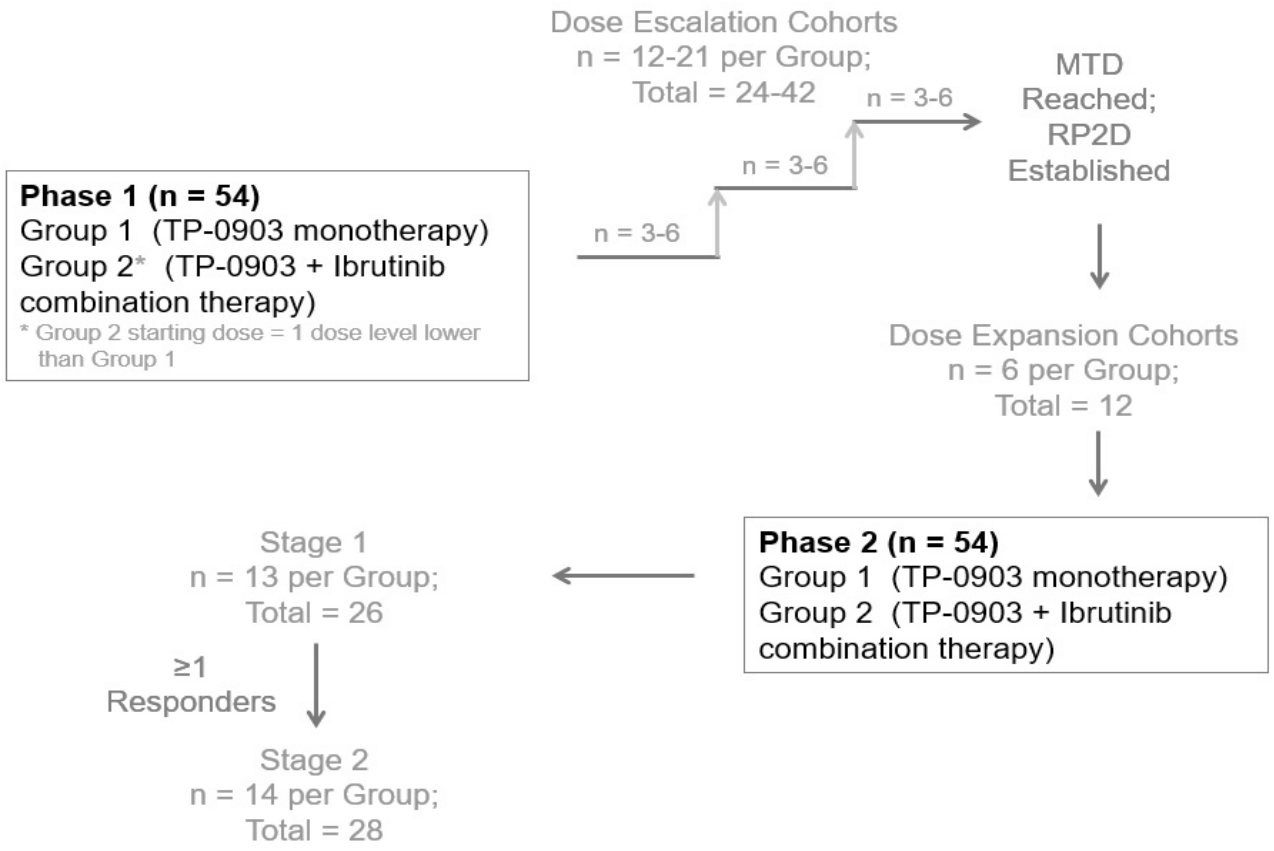
Additional dose levels, schedules or disease indications of TP-0903 may be explored, as appropriate, based on the modulation of key biomarkers, the safety profile and clinical signals of activity.

Phase 2

In Phase 2, patients will be enrolled in Group 1 and Group 2 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 zero 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.



MTD: maximum tolerated dose; RP2D: recommended Phase 2 dose

Figure 9 Study Design Schema

4.2 Assignment to Treatment

This is an open-label study; randomization and blinding will not be performed as per this study design. All patients will receive TP-0903 either alone or in combination according to the group into which they are enrolled in the Phase 1 part of the study, and subsequently in Phase 2 at the RP2D dose identified from Phase 1.

Patients will be enrolled from all participating centers. 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.

4.3 Patient Population

4.3.1 Number of Patients

A sufficient number of patients will be treated to establish the MTD of TP-0903 (up to 54 patients) in the Phase 1 part of the study and then up to 54 additional patients in Phase 2. Any patient who withdraws from the study before completing the Cycle 1 Day 28 assessments will be replaced unless that patient is withdrawn due to toxicity or has experienced a DLT.

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.

4.3.2 Inclusion Criteria

To be eligible for participation, patients must meet all of the following inclusion criteria:

1. Be ≥18 years old
2. Have an established, pathologically confirmed diagnoses of CLL/ Small Lymphocytic Lymphoma (SLL) requiring therapy according to the 2018 IWCLL guidelines
3. Have received at least one prior therapy for CLL***/SLL*** and can be classified in one of two 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 *or*
    - Group 2 (TP-0903 and ibrutinib combination therapy): Patients with CLL***/SLL*** who have progression of disease on ibrutinib and the treating provider considers continuation of ibrutinib therapy to be in the best interest of the patient
4. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2

5. Have adequate hematologic function:
    - Absolute neutrophil count (ANC) ≥500/μL
    - Platelet count ≥30,000/μL
    - Hemoglobin ≥8 g/dL in the absence of transfusions within the previous 2 weeks
6. Have adequate organ function:
    - Creatinine clearance ≥30 mL/min
    - Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) level ≤2.5 × upper limit of normal (ULN)
    - Have a total bilirubin level ≤1.5 × ULN (unless secondary to Gilbert syndrome, hemolysis, or leukemia)
7. Have acceptable coagulation status:
    - Activated partial thromboplastin (aPTT) and prothrombin time (PT) ≤1.5 × ULN
8. Have a negative pregnancy test (if female of childbearing potential)
9. Be nonfertile or agree to use an adequate method of contraception. Sexually active patients and their partners must use an effective method of contraception (hormonal or barrier method of birth control, or abstinence) prior to study entry and for the duration of study participation and for at least 30 days after the last study drug dose. Should a woman become pregnant or suspect that she is pregnant while participating in this study, she should inform her treating physician immediately.
10. Have read and signed the Institutional Review Board (IRB)-approved informed consent form (ICF) prior to any study related procedure. (In the event that the patient is rescreened for study participation or a protocol amendment alters the care of an ongoing patient, a new ICF must be signed.)
11. Be able to comply with the requirements of the entire study

4.3.3 Exclusion Criteria

Patients meeting any 1 of these exclusion criteria will be prohibited from participating in the study.

1. Have undergone prior autologous or allogeneic stem cell transplant within ≤3 months, have not recovered from transplant associated toxicities, or requires graft versus host immunosuppressive therapy
2. Have known central nervous system (CNS) involvement
3. Have Richter's transformation of CLL
4. Have received any monoclonal antibody therapy directed at treatment of the patient's malignancy within 2 weeks prior to anticipated first dose

5. Have received any anticancer therapy including chemotherapy, radiotherapy, or an investigational anticancer drug within less than 5 half-lives of the last dose of that treatment

    - This exclusion criterion is not applicable to patients requiring continuation on ibrutinib. (Note: Certain patients with a rapidly rising white blood cell count while on ibrutinib may need to remain on this drug for medical reasons. These patients will need to be approved by the Medical Monitor and treated in accordance with the protocol.)

6. Have received >20 mg/day of prednisone and 0.1 mg/day of mineralocorticoids within 7 days prior to anticipated first dose
7. Have a corrected QT interval of >450 msec (males) and >470 msec (females) using Fridericia's correction formula
8. Have a significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, or cardiovascular disease or any other medical condition that, in the opinion of the Investigator, would adversely affect his/her participation in the study
9. Are pregnant and/or nursing, or refuse to use appropriate contraceptives during the course of the study and for at least 30 days after the last dose of study drug
10. History of another malignancy in the last 5 years except for the following adequately treated:
    - Local basal cell or squamous cell carcinoma of the skin
    - Carcinoma in situ of the cervix or breast
    - Papillary, noninvasive bladder cancer
    - Early stage prostate cancer for which observation is clinically indicated
    - Other Stage 1 or 2 cancers currently in complete remission
    - Any other cancer that has been in complete remission for 2 years or surgically cured

    Medical Monitor may be contacted for additional determination of acceptable prior cancer history
11. Have known gastrointestinal disorders (eg, malabsorption syndrome), complications (eg, dysphagia), or surgery that could make consumption or absorption of oral medications problematic
12. Have an uncontrolled systemic infection (viral, bacterial, or fungal) or fever and neutropenia within 7 days prior to anticipated first dose
13. Have active and uncontrolled autoimmune cytopenias for 2 or more weeks including autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura (ITP)

14. Have received prior therapy with an AXL inhibitor

15. Have exhibited allergic reactions to a similar structural compound, biological agent, or formulation

16. Are unwilling or unable to comply with procedures required in this protocol

17. Have a history of severe adverse reaction (eg, hypersensitivity reaction, anaphylaxis) to sulfonamides

4.4 Study Treatment

This is a combined Phase 1/2 open-label study to investigate the safety, pharmacokinetics, pharmacodynamics, and clinical activity of TP-0903 in CLL patients. All patients enrolled in Group 1 will receive TP-0903 alone. All patients enrolled in Group 2 will receive TP-0903 and ibrutinib in combination.

Phase 1

Group 1 (TP-0903 monotherapy): The starting dose for TP-0903 in Group 1 (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).

Patients may continue to receive TP-0903 in 28-day cycles at the same dose given during Cycle 1 until they experience unacceptable toxicity or unequivocal disease progression. No intrapatient escalation of the TP-0903 dose is permitted.

Group 2 (TP-0903 in combination with ibrutinib): 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.

Patients should continue with the combination of ibrutinib and TP-0903 for at least 3 months after study start. After that time, patients can either continue with combination therapy or discontinue ibrutinib and continue with TP-0903 monotherapy at the discretion of the Investigator and in consultation with the Medical Monitor. Patients may continue to receive TP-0903 in 28-day cycles at the same dose given during Cycle 1 until they experience unacceptable toxicity or unequivocal disease progression.

Ibrutinib may be stopped and reinitiated at the discretion of the Investigator and in consultation with the Medical Monitor; however, the total time patients may receive treatment with ibrutinib is 2 years.

Phase 2

Group 1 (TP-0903 monotherapy): The starting dose will be the RP2D determined during Phase 1. TP-0903 will be administered orally once daily for 28 days (each cycle is 28 days; no drug-free period).

Dosing with TP-0903 may continue until a patient experiences unacceptable toxicity or unequivocal disease progression

Group 2 (TP-0903 in combination with ibrutinib): The starting dose will be the RP2D determined during Phase 1. 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.

Patients should continue with the combination of ibrutinib and TP-0903 for at least 3 months after study start. After that time, patients can either continue with combination therapy or discontinue ibrutinib and continue with TP-0903 monotherapy at the discretion of the Investigator and in consultation with the Medical Monitor. Patients may continue to receive TP 0903 in 28-day cycles at the same dose given during Cycle 1 until they experience unacceptable toxicity or unequivocal disease progression.

Ibrutinib may be stopped and reinitiated at the discretion of the Investigator and in consultation with the Medical Monitor; however, the total time patients may receive treatment with ibrutinib is 2 years.

4.4.1 TP-0903 Administration

TP-0903 is administered orally once daily for 28 days (each cycle is 28 days; no drug-free period). Dosing may be repeated every cycle in the absence of disease progression or unacceptable toxicity. 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.

4.4.2 Ibrutinib Administration

Administer ibrutinib orally once daily at approximately the same time each day. Swallow the capsules whole with water. Do not open, break, or chew the capsules.

4.4.3 Description of Phase 1 and Phase 2 Parts of Study

4.4.3.1 Phase 1

Evaluation of the safety and toxicity profile and determination of RP2D of TP-0903 will occur in Phase 1. The starting dose for TP-0903 in Group 1 (monotherapy) will be a 25-mg flat dose. Enrollment will be in cohorts of 3 to 6 patients using a standard 3+3 design for dose escalation until the MTD is established. The starting TP-0903 dose in Group 2 (TP-0903 combination therapy with ibrutinib) will be a 20-mg flat dose.

Once the first patient at a dose level is enrolled, the second and third patients will be enrolled after 3 weeks as long as the initial patient has not experienced any unacceptable toxicity. Once the last patient enrolled has completed Day 28 without observation of a DLT and the next higher TP-0903 dose level has not yet been studied, the dose will be increased following a modified Fibonacci dose escalation scheme in a new 3- to 6-patient cohort according to the dose levels provided in *Table 3*

Table 3 TP-0903 Proposed Dose Escalation

Dose Level	Proposed Daily Dose	Increment from Previous Dose[a]	No. of Patients Per Cohort
Group 1 (Monotherapy)			
1	25 mg	Starting Dose	3-6
2	33 mg	33%	3-6
3	45 mg	36%	3-6
4	58 mg	29%	3-6
5	75 mg	29%	3-6
6[b]	100 mg	33%	3-6
Group 2 (Combination)			
1	20 mg	Starting Dose	3-6
2	25 mg	25%	3-6
3	33 mg	33%	3-6
4	45 mg	36%	3-6
5	58 mg	29%	3-6
6	75 mg	29%	3-6
7[b]	100 mg	33%	3-6

a It is possible for additional and/or intermediate dose levels to be added during the course of the study.
b If clinically indicated, dose levels higher than 100 mg may be investigated.

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 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, and to further explore efficacy.

4.4.3.2 Phase 2

In Phase 2, patients will be enrolled in each group (TP-0903 monotherapy and combination therapy with ibrutinib) at the RP2D based on the Simon 2-stage design.

Stage 1

In Stage 1, for both patient groups (monotherapy and combination therapy), up to 13 patients with previously treated CLL will be enrolled and treated at the RP2D identified in the Phase 1 portion. If there are zero responses among these 13 patients, the study will be stopped. If there are ≥ 1 responders, additional patients will be enrolled in Stage 2.

Stage 2

In Stage 2, 14 additional patients will be enrolled for a total of 27 patients in each patient group (monotherapy and combination therapy). If 4 or more responses are observed among 27 patients, the conclusion will be that the study treatment is worthy of further investigation. If both patient groups enroll through Stage 2, it is anticipated that the total enrollment for Phase 2 will be 54 patients.

4.4.4 Missed Doses

It is important that patients keep track of their study drug administration, including any missed doses (whether due to oversight or illness [ie, vomiting]).

Regardless of cohort assignment, should a patient vomit after taking their TP-0903 dose, they should not attempt to retake the dose, but rather note the dose as being missed in their Patient Dosing Diary (*Appendix I*) and continue with regular dosing on the next day.

Patients cannot miss more than **4** doses of either TP-0903 or ibrutinib during Cycle 1 and the missed doses must not be on 4 consecutive days or the patient will be replaced.

If a dose of ibrutinib is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules of ibrutinib should not be taken to make up for the missed dose [27].

4.5 Management of Toxicities and Dosage Modification

4.5.1 Management of Toxicities

AEs may be treated with concomitant medications, as deemed clinically indicated by the Principal Investigator. All concomitant medications must be recorded in the source and on the appropriate electronic case report form (eCRF).

AEs that are moderate to severe in intensity (*see Appendix D)* for NCI-CTCAE toxicity grading) and considered *Possibly*, *Probably*, or *Definitely* related to study drug treatments may result in the termination of study treatment in the affected study patient. Such termination should be reviewed with the Sponsor's Medical Monitor at the earliest possible time (*Section 8.5*). Following review with the Sponsor's Medical Monitor, the study patient may be permanently withdrawn from the study depending upon the nature and severity of the event.

4.5.2 Dose-limiting Toxicities

A 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***; other decreases in the white blood cell count, or in circulating granulocytes, are not to be considered, since a decrease in the white blood cell count is a desired therapeutic endpoint***):

- 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

4.5.3 TP-0903 Dose Modifications

The dose of TP-0903 will not be reduced during Cycle 1. Doses of study drug may be adjusted for patients who receive multiple cycles of TP-0903. Dose reductions by one dose level will be permitted based on the observed toxicity that occurred during the preceding cycle. No dose re-escalations will be allowed for any patient who had a previous dose reduction due to toxicity or delayed recovery. All dose modifications will need to be discussed and approved with the Medical Monitor.

If a patient experiences toxicity, the patient may continue to receive TP-0903 as defined in *Table 4* ***and in conjunction with the guidelines set forth by the 2018 IWCLL Grading Scale for Hematologic Toxicity (Appendix C).***

Table 4 Guide to Dose Adjustments Based on Toxicities

Drug-Related AE	Action
Grade 1	Current dose level
Grade 2	Investigator's option to reduce dose by 1 dose level with agreement of the Medical Monitor
Grade 3[a]	Withhold, then reduce dose by 1 dose level upon recovery to ≤Grade 1 with agreement of the Medical Monitor.
Grade 4	Investigator and Medical Monitor review to determine if patient may continue on study with appropriate dose reduction upon recovery to ≤Grade 1.

a Excluding brief (based on the Investigator's judgment) Grade 3 vomiting or diarrhea with suboptimal management.

Dose reduction to the next lower dose level tested will be performed initially. If further toxicities occur during 1 or more cycles at the new reduced dose level, no further reductions will be permitted, and the patient should be discontinued from the study.

Patients who experience a DLT will be required to discontinue study participation, unless the Investigators and Medical Monitor determine that it is in the best interest of the patient to continue with the dose reduction and only upon recovery of the toxicity to Grade 2 or better.

Dose reduction will be required for patients who have a delay in treatment greater than 2 weeks due to a lack of recovery of any hematologic or nonhematologic toxicity, even if DLT criteria are not met. Subsequent retreatment of patients who are not able to be treated after a 2-week delay and who eventually recover will be discussed between Investigators and Medical Monitor taking into account the potential benefit/risk for the individual patient.

In addition, dose reductions will be permitted for patients who have toxicities that do not meet the criteria of a DLT and following discussion between the Investigator and the Medical Monitor. These toxicities will be discussed by the Investigators and Medical Monitor to determine if it would be in the best interest of the patient to continue to receive TP-0903 at the next previous dose level (*Appendix D*).

4.5.4 Ibrutinib Dose Modifications

The package insert for ibrutinib therapy should be followed by the treating physician. As per the ibrutinib label [27]: Interrupt ibrutinib therapy for any Grade 3 or greater non-hematological, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities. Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), ibrutinib therapy may be reinitiated at the starting dose. If the toxicity reoccurs, reduce dose by one capsule (140 mg per day). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue ibrutinib.

Recommended dose modifications are described below:

Toxicity Occurrence	CLL Dose Modification
First	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; May restart at 420 mg daily
Second	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; May restart at 280 mg daily
Third	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; May restart at 140 mg daily
Fourth	Discontinue ibrutinib

If ibrutinib is interrupted for a reason other than toxicity (eg, unrelated illness) the first instance of interruption must be restarted within 42 days. Subsequent study medication interruptions lasting more than 42 days, ibrutinib should be discontinued permanently.

4.6 Concomitant Medications and Therapies

4.6.1 Previous Therapies

During Screening, patients will be asked about all previous therapies and all medications used during the previous 14 days from anticipated first dose. This information will be recorded in the source documentation and appropriate eCRF along with the diagnosis or reason for use. If a branded product is being taken, the generic name should be reported, if known.

4.6.2 Concomitant Therapies

Concomitant therapies are any new or existing medications or therapy taken by the patient including:

- Drugs, including but not limited to, prescription, over-the-counter, birth control pills/patches/hormonal devices, and homeopathic preparations
- Nondrug therapies, including but not limited to, thermal/laser/radiation procedures, vitamins, herbal medicines/supplements.

Once the patient receives the first dose of study drug, recording of concomitant therapies will be limited to any new medication or modification of an existing medication taken for treatment of an AE. These therapies will be recorded in the source documents and appropriate eCRF along with the diagnosis or reason for use. Those therapies used for the treatment of an AE are to be linked to an AE and documentation of the AE must also be completed (*Section 8*).

If a branded product is being taken, the generic name should be reported, if known.

4.6.2.1 Permitted Therapies

Concomitant medications necessary for the health and well-being of the patient and that do not interfere with study assessments are permitted during the study at the Investigator's discretion. This includes the use of appropriate medications for the treatment of AEs and/or concurrent illnesses under the direction of the Principal Investigator. All such therapies must be recorded in the source and on the appropriate eCRF.

Treatment with hematopoietic colony stimulating growth factors such as granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor may not be initiated during Cycle 1 unless the patient has experienced a DLT. Initiation of treatment with erythroid-stimulating agents may not occur during the first cycle of therapy. If a patient has been on a steady dose of an erythroid-stimulating agent, they may continue to use the agent at the same dose during Cycle 1 and later cycles.

Supportive Care Measures

Supportive care will include:

- Careful monitoring of patients at high risk for tumor lysis syndrome (TLS) (ie, patients with any lymph node [LN] ≥10 cm, or absolute lymphocyte count [ALC] ≥25 × 10^9/L and any LN ≥5 cm) by collection of blood and real-time (STAT) review of TLS laboratory parameters (ie, uric acid, potassium, phosphate, calcium, and creatinine) on Day 1 of Cycle 1 at baseline (predose) and at 6 hours and 24 hours post dose.

- Infection Prevention (ie, prophylactic antibiotic, antiviral, and/or antifungal therapy) to be initiated according to each institution's standardized protocols

4.6.2.2 Prohibited Therapies

The following medications are excluded from concomitant use:

- Anticancer therapies (chemotherapy, radiation therapy, immunotherapy) within less than 5 half-lives of the last dose of that treatment.

    - *Note*: Patients enrolled in Group 2 (TP-0903 in combination with ibrutinib) will continue treatment with the combination for at least 3 months. Ibrutinib may be stopped and reinitiated at the discretion of the Investigator in consultation with the Medical Monitor; however, the total time patients may receive treatment with ibrutinib is 2 years.

- CYP2C19 Metabolizers: Patients who are known abnormal metabolizers of CYP2C19 (ie, extensive or poor) prior to study treatment should be monitored closely. If possible, the Investigator should cease patient's treatment with a CYP2C19 substrate prior to first dose, or at a minimum, switch to an alternative, but equivalent treatment that is not a CYP2C19 substrate (inhibitor or inducer). If a patient must remain on a CYP2C19 substrate, treatment with TP-0903 should proceed cautiously and the patient observed closely throughout the duration of the study.

- Group 2 patients (ie, TP-0903 in combination with ibrutinib) should avoid coadministration of strong or moderate CYP3A inhibitors (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort) as these substances may increase ibrutinib plasma concentrations.

- Group 2 patients should avoid coadministration of strong CYP3A inducers as these substances may decrease ibrutinib concentrations.

- Patients must not be taking H2-receptor antagonists such as cimetidine, ranitidine, and famotidine, or any proton pump inhibitors such as omeprazole, lansoprazole, esomeprazole and pantoprazole. Patients must stop these medications within 7 days prior to starting treatment.

4.6.3 Birth Control Requirements for Fertile Patients

Sexually active patients and their partners must use an effective method of contraception associated with a low failure rate prior to study entry and for the duration of study participation and for 30 days after the last dose of study drug. The following are considered effective contraceptives: (1) oral contraceptive pill; (2) condom plus spermicide; (3) diaphragm plus spermicide; (4) abstinence; (5) patient or partner surgically sterile; (6) patient or partner more than 2 years postmenopausal; or (7) injectable or implantable agent/device.

4.7 Protocol Deviations

It is expected that this study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety and well-being of the patient requires immediate intervention, based on the judgment of the Principal Investigator (or a responsible, appropriately trained and credentialed professional[s] designated by the Principal Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or error, the Principal Investigator or Designee must contact the Sponsor at the earliest possible time by telephone. This will allow an early joint decision to be made as to whether or not the patient should continue in the study. This decision will be documented in writing by both the Principal Investigator and the Sponsor.

5. ON-STUDY CLINICAL AND LABORATORY EVALUATIONS

The Schedule of Assessments is outlined in *Appendix A*. These assessments apply to both the Phase 1 and Phase 2 portions of the study unless specified.

5.1 Predose Assessments

5.1.1 Screening (Within 14 Days Prior to First Dose)

The following procedures and evaluations will be performed within 14 days prior to administration of the first dose of study drug, after the ICF is signed unless otherwise noted:

- Collect and document a complete medical history including histologically confirmed diagnosis of CLL***/SLL***
- Perform a full physical examination, including height (cm) and weight (kg) and review the following constitutional symptoms suggestive of active disease:
  - Unintentional weight loss ≥10% within previous 6 months
  - 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
- Record vital signs (body temperature, respirations, heart rate, blood pressure)
- Assess ECOG Performance Status (*Appendix B*)
- Evaluate laboratory parameters (*Appendix E)*
  - Full serum chemistry
  - Hematology (complete blood count [CBC] with differential and platelet count)
  - Coagulation parameters (PT and aPTT)
  - Urinalysis
  - Serum immunoglobulins
  - Direct antiglobulin
  - Serum ß2-microglobulin
- Perform a 12-lead ECG including assessment of corrected QT interval (using Fridericia's correction formula) (QTcF)
- ***Pregnancy test (urine or serum beta-human chorionic gonadotropin pregnancy test for females of childbearing potential)***
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements within the past 14 days

- Assess baseline disease status per 2018 IWCLL guidelines (*Appendix H*) (within 28 days of Cycle 1 Day1):
    - Perform a computed tomography (CT) scan of neck, chest, abdomen, and pelvis for evaluation of lymphadenopathy, hepatomegaly, and splenomegaly;
    - Bone marrow biopsy and aspirate with matched peripheral blood sample
    - The following should be obtained (within 28 days of Cycle 1 Day 1):
        - Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) [peripheral blood]
        - Karyotyping with CpG ***(or institutional standard)*** stimulation [bone marrow]
        - TP53 mutation analysis [peripheral blood]
        - Immunoglobulin heavy-chain variable (IGHV) mutational analysis [peripheral blood]
- ***Positron emission tomography (***PET***)*** scan to assess for possible Richter's transformation (within 14 days of first dose)

5.1.2 Within 3 Days Prior to First Dose

The following baseline procedures and evaluations will be performed any time within 3 days (72 hours) prior to administration of the first dose of study drug (not required to be repeated at Cycle 1 Day 1 if screening exams are within 3 days prior to first dose):

- Full physical examination, including weight (kg)
- Record vital signs (body temperature, respirations, heart rate, blood pressure)
- Evaluate laboratory parameters (*Appendix E*):
    - Full serum chemistry
    - Hematology (CBC with differential and platelet count)
    - Pregnancy test (urine or serum beta-human chorionic gonadotropin pregnancy test for females of childbearing potential)
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements
- Review all inclusion/exclusion criteria and determine if patient has met all eligibility criteria for inclusion in the study. Obtain Medical Monitor (or designee) approval to enroll patient. See Study Manual for detailed instructions on procedures on enrollment.

5.2 Treatment Assessments

5.2.1 CYCLE 1

5.2.1.1 Cycle 1: Day 1

- Full physical examination, including weight (kg)
- Record vital signs (temperature, respirations, heart rate, blood pressure) prior to first dose
- Obtain baseline signs and symptoms prior to first dose
- Assess ECOG Performance Status (*Appendix B*)
- Evaluate laboratory parameters (*Appendix E*):
    - Full serum chemistry
    - Hematology (CBC with differential and platelet count)
    - 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)
    - Pregnancy test (urine or serum beta-human chorionic gonadotropin pregnancy test for females of childbearing potential)
- Perform 12-lead ECG just prior to first dose, including assessment of QTcF
- Collect blood for analysis of PK parameters according to the schedule in *Section 7.3* in Phase 1 only
- Collect blood for exploratory biomarker assessments according to the schedule in *Section 7.4*
- Assess for AEs
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements

5.2.1.2 Cycle 1: Daily on Days 1 through 28

- Instruct patients to take TP-0903 and ibrutinib (for Group 2 patients) orally every day on Days 1 through 28 according to the guidelines detailed in *Section 4.4.1* ***and*** *Section 4.4.2*
- Instruct patients to record the date and time they took their dose(s) in their dosing diary (*Appendix I*)

5.2.1.3 Cycle 1: Weekly (Days 8, 15, and 22 [±3 Days])

Perform the following activities and evaluations weekly (or as otherwise indicated) during Cycle 1:

- Perform an abbreviated physical examination (AE- or symptom-directed)
- Record vital signs (temperature, respirations, heart rate, blood pressure)
- Evaluate laboratory parameters (*Appendix E*):
    - Full serum chemistry
    - Hematology (CBC with differential and platelet count)
- On Day 8, collect blood for exploratory biomarker assessments according to the schedule in *Section 7.4*
- Assess for AEs
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements

5.2.1.4 Cycle 1: Day 28

- On Day 28, collect blood for analysis of PK parameters according to the schedule in *Section 7.3* in Phase 1 only

5.2.2 CYCLE 2

5.2.2.1 Cycle 2: Day 1

- Full physical examination, including weight (kg)
- Record vital signs (temperature, respirations, heart rate, blood pressure)
- Evaluate laboratory parameters (*Appendix E*):
    - Full serum chemistry
    - Hematology (CBC with differential and platelet count)
    - Pregnancy test (urine or serum beta-human chorionic gonadotropin pregnancy test for females of childbearing potential)
- Assess ECOG Performance Status (*Appendix B*)
- Perform 12-lead ECG just prior to dosing including assessment of QTcF
- Collect blood for exploratory biomarker assessments according to the schedule in *Section 7.4*
- Assess for AEs
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements

5.2.2.2 Cycle 2: Daily on Days 1 through 28

- Instruct patients to take TP-0903 and ibrutinib (for Group 2 patients) orally every day on Days 1 through 28 according to the guidelines detailed in *Section 4.4.1* ***and*** *Section 4.4.2*
- Instruct patients to record the date and time they took their dose(s) in their dosing diary (*Appendix I*)

5.2.2.3 Cycle 2: Day 15 [±3 Days]

- Perform an abbreviated physical examination (AE- or symptom-directed)
- Record vital signs (temperature, respirations, heart rate, blood pressure)
- Evaluate laboratory parameters (*Appendix E*):
    - Full serum chemistry
    - Hematology (CBC with differential and platelet count)
- Assess for AEs
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements

5.2.2.4 Cycle 2: Day 28 (-4 Days)

- Disease assessment – Assess for response per 2018 IWCLL guidelines (*Appendix F*):
    - Review of the following constitutional symptoms suggestive of active disease:
        - Unintentional weight loss ≥10% within previous 6 months
        - 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
    - CT scan of neck, chest, abdomen, and pelvis evaluation of lymphadenopathy, hepatomegaly, and splenomegaly
- If clinical and laboratory results indicate possible CR:
    - Collect bone marrow and aspirate with matched peripheral blood for CBC and determination of MRD (central lab assessment)

5.2.3 CYCLES ≥3

Patients may continue to receive TP-0903 in 28-day cycles at the same dose given during Cycle 1 until they experience unacceptable toxicity or unequivocal disease progression.

5.2.3.1 Cycles ≥3: Day 1

Perform the following activities and evaluations on Day 1 of Cycle 3 and all subsequent cycles of treatment:

- Full physical examination, including weight (kg)
- Record vital signs (temperature, respirations, heart rate, blood pressure)
- Evaluate laboratory parameters (*Appendix E*):
    - Full serum chemistry
    - Hematology (CBC with differential and platelet count)
    - Pregnancy test (urine or serum beta-human chorionic gonadotropin pregnancy test for females of childbearing potential)
- Assess ECOG Performance Status (*Appendix B*)
- Perform 12-lead ECG just prior to dosing including assessment of QTcF
- Collect blood for analysis of PK parameters according to the schedule in *Section 7.3* in Phase 1 only
- Collect blood for exploratory biomarker assessments according to the schedule in *Section 7.4*
- Assess for AEs
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements

5.2.3.2 Cycles ≥3: Daily on Days 1 through 28

- Instruct patients to take TP-0903 and ibrutinib (for Group 3 patients) orally every day on Days 1 through 28 according to the guidelines detailed in *Section 4.4.1* ***and*** *Section 4.4.2*
- Instruct patients to record the date and time they took their dose(s) in their dosing diary (*Appendix I*)

5.2.3.3 Cycles ≥3: Day 15 (±3 Days)

Perform the following activities and evaluations during Cycle 3 and all subsequent cycles of treatment:

- Perform an abbreviated physical examination (AE- or symptom-directed)
- Record vital signs (temperature, respirations, heart rate, blood pressure)
- Evaluate laboratory parameters (*Appendix E*):
    - Full serum chemistry
    - Hematology (CBC with differential and platelet count)
- Assess for AEs
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements

5.2.3.4 Cycles ≥3: Day 28 (-4 Days)

Perform the following evaluations on Day 28 of every EVEN cycle (ie, Cycle 4, Cycle 6, etc):

- Disease assessment – Assess for response per 2018 IWCLL guidelines (*Appendix F*):
    - Review of the following constitutional symptoms suggestive of active disease:
        - Unintentional weight loss ≥10% within previous 6 months
        - 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
    - CT scan of neck, chest, abdomen, and pelvis evaluation of lymphadenopathy, hepatomegaly, and splenomegaly
- If clinical and laboratory results indicate possible CR:
    - Collect bone marrow and aspirate with matched peripheral blood for CBC and determination of MRD (central lab assessment)

5.3 End-of-Study Assessments

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.

- Perform a full physical examination including weight (kg)
- Record vital signs (temperature, respirations, heart rate, blood pressure)
- Evaluate laboratory parameters (*Appendix E*):
    - Full serum chemistry
    - Hematology (CBC with differential and platelet count)
    - Pregnancy test (urine or serum beta-human chorionic gonadotropin pregnancy test for females of childbearing potential)
- Assess ECOG Performance Status (*Appendix B*)
- Perform a 12-lead ECG including assessment of QTcF
- Disease assessment (if ≥8 weeks since last assessment) – Assess for response per IWCLL guidelines 2018 (*Appendix F*). If patient has unequivocal evidence of disease progression, then this reassessment may be eliminated:
    - Review of the following constitutional symptoms suggestive of active disease:
        – Unintentional weight loss ≥10% within previous 6 months
        – 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
    - CT scan of neck, chest, abdomen, and pelvis evaluation of lymphadenopathy, hepatomegaly, and splenomegaly
- If clinical and laboratory results indicate possible CR:
    - Collect bone marrow and aspirate with matched peripheral blood for CBC and determination of MRD (central lab assessment)
- Collect blood for exploratory biomarker assessments according to the schedule in *Section 7.4*
- Assess for AEs
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements

5.4 30-Day Safety Follow-Up Assessments

Patients must ***undergo*** a safety evaluation ***in which the condition of the patient during the*** 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 30 days from the last dose (ie, within 45 days after last dose of study drug).***The following assessments will be performed:

- Assess for AEs
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements as well as antineoplastic therapies since discontinuation of study drug

5.5 Long-term Follow-up for Patient Survival (Phase 2 only)

All patients enrolled and treated in the Phase 2 study will be contacted by telephone to assess for date of death, date of relapse, or continued remission beginning the month after the patient completes the end-of-study assessments up to a maximum of 2 years regardless of how many cycles study treatment a patient receives.

- Year 1: follow-up every month (± 7 days)
- Year 2: follow-up every other month (± 14 days)

6. OFF-STUDY CRITERIA

6.1 Withdrawal of Patients

All patients have the right to withdraw at any time during treatment without prejudice. Circumstances may occur under which a patient may be permanently removed from the study. The criteria used to justify withdrawal of a study patient are described below.

In the event of a premature withdrawal, the assessments for the End-of-Study visit, as detailed in the Schedule of Assessments (*Appendix A*), should be completed at the time of withdrawal, wherever possible, including dates of response and death. If the study patient is prematurely withdrawn due to an AE, attempts should also be made to clinically follow the study patient until the event is resolved, stable or permanent as determined by the Principal Investigator and Sponsor.

6.2 Reasons for Withdrawal

A patient may be permanently removed from the study for any of the following reasons:

- Disease progression;
- An excessive Grade 3-4 toxicity without a response to treatment or occurrence of any other AE, concurrent illness or laboratory abnormality which, in the opinion of the Principal Investigator, warrants the patient's permanent withdrawal;
- Patient noncompliance, defined as refusal or inability to adhere to the study schedule;
- At the request of the patient, Principal Investigator, the Sponsor, or regulatory authority;
- Patient is lost to follow-up;
- Patient becomes pregnant while on study;
- Patient begins another treatment for their disease; or
- Patient death.

6.3 Follow-Up for Patients Withdrawn from Study

Patients withdrawn from the study with an ongoing AE must be followed clinically until the event is resolved, deemed stable, deemed permanent, or a new treatment for CLL is initiated as determined by the Principal Investigator and Sponsor. A stable AE is defined as an AE that is not expected to change in nature, severity, or frequency. See *Section 8.4* through *Section 8.8* for reporting of AEs. Patients withdrawn from the study for pregnancy will be followed according to *Section 5.3* and *Section 5.4*. The pregnancy of any patient, or patient's partner, will be followed to term to record any birth defects/abnormalities at time of birth.

6.4 Termination or Suspension of Study

Should the Sponsor or their representatives, Investigators, or appropriate regulatory officials discover conditions during the study that indicate that the study or site involvement should be put 'On Hold' or 'Terminated', this action may be taken after appropriate consultation with the Sponsor, Investigators, and Study Monitors.

Conditions that may warrant termination of the study or involvement of a study site include, but are not limited to:

- If the Data Safety Monitoring Board (DSMB) recommends stopping the study due to safety concerns;
- The discovery of an unexpected, serious, unacceptable risk to patients enrolled in the study;
- Failure of the Investigator(s) to comply with pertinent clinical trial regulations; or
- Insufficient adherence to protocol requirements.

7. CRITERIA FOR EVALUATION

7.1 Safety Endpoints

Phase 1

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, comprised of Investigators, sponsor and CRO representatives, 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 AEs including DLTs, and all causes of mortality up to 30 days from the last dose in both phases of the study. In Phase 2, all causes of mortality will also be evaluated at 60 days from the last administered dose.

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 AEs (TEAEs), namely, AEs 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) v20.0 or higher and graded according to NCI CTCAE v5.0.

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

7.2 Efficacy Endpoints

Phase 2

The primary efficacy endpoint of the Phase 2 portion of the study is to determine the ORR (rate of CR or PR) in patients with previously treated CLL***/SLL*** according to IWCLL guidelines 2018 [25].

The secondary efficacy endpoints include:

- DoR, defined as the time from documentation of tumor response to disease progression.
- PFS, defined as the time from study enrollment until objective tumor progression or death.
- OS, defined as the time from study enrollment to death from any cause.

Efficacy assessments will be performed at Cycle 2/Day 28 and then every even cycle (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.

A DSMB will monitor key outcomes from the study during the Phase 2 portion of the study.

7.2.1 Response Criteria – 2018 IWCLL Guidelines

Disease response will be assessed at every 2 cycles per 2018 IWCLL guidelines (*Appendix F*).

7.3 Pharmacokinetic Endpoints

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: C_{max}, T_{max}, AUC from time 0 to 24 hours (AUC_{0-24}), AUC_{0-inf}, AUC from time 0 to time t (AUC_t), half-life ($t_{1/2}$), 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.

Plasma concentrations of oral TP-0903 will be summarized by descriptive statistics, including mean, n, standard deviation, coefficient of variation, minimum, maximum, and median. A validated bioanalytical method for the detection of TP-0903 in human plasma has been developed prior to this study to establish assay sensitivity, specificity, linearity, and reproducibility.

7.4 Pharmacodynamic Endpoints

The PD endpoints, including biomarker assessments, will be evaluated during the study as follows:

- Blood 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
End of Study	**--**	**--**

Analysis of the sample will be limited to evaluations that are relative to the activity of the study drug or biomarkers of underlying disease. Patients may withdraw consent and request through the study Investigator the destruction of their sample(s) at any time. The samples may be retained for no longer than 20 years after study completion or per local requirements.

8. ADVERSE EVENTS

8.1 Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not related to the drug product.

A suspected adverse reaction is any AE that had a reasonable possibility of being caused by the drug. For the purposes of Investigational New Drug (IND) safety reporting, reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An unexpected AE or unexpected suspected adverse reaction is an AE or suspected adverse reaction not listed in the current Investigator's Brochure, not listed at the specificity or severity that has been observed, or not consistent with the risk information described in the protocol.

Toxicities will be assessed according to the NCI CTCAE, v5.0 (*Appendix D*). When the NCI CTCAE grade is not available, the Investigator will use the following toxicity grading: mild, moderate, severe, life-threatening, or fatal.

GRADE 1 – Mild:	***Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated***
GRADE 2 – Moderate:	***Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]***
GRADE 3 – Severe:	***Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]***
GRADE 4 – Life Threatening:	***Life-threatening consequences; urgent intervention indicated***
GRADE 5 – Fatal	***Death related to AE***

a Instrumental activities of daily living (ADLs) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.2 Causality

Relationship of the AE to the study drug should be defined as follows:

Unrelated:	AE is clearly not related to the study drug (ie, there is no temporal association and no other possible cause [intercurrent illness, medication])
Unlikely:	AE is doubtfully related to the study drug
Possibly:	AE may be related to the study drug
Probably:	AE is likely related to the study drug
Definitely:	AE is clearly related to the study drug

8.3 Serious Adverse Events

An SAE is defined as any suspected adverse reaction at any dose that suggests a significant hazard, contraindication, side effect, or precaution, and results in the following outcomes:

- Death;
- A life-threatening event (ie, the patient is at immediate risk of death from the event as it occurred);
- An event that is persistently, significantly, severely, or permanently disabling, or requires intervention to prevent such disability;
- An event that requires inpatient hospitalization or prolongs hospitalization;
- A congenital abnormality/birth defect; or
- A medically significant event that may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed above.

In addition, any AE that results in termination of the patient from the study will be considered a potentially serious AE and must be reported to the Sponsor as described in *Section 8.5*.

8.4 Eliciting and Reporting Adverse Events

All AEs, regardless of severity, that occur during the study, will be documented in the study progress notes, and the AE eCRF will be completed. This includes both serious and nonserious AEs. ***Adverse events occurring from*** the time of the first dose will be captured.

All AEs noted by study staff or volunteered by study patients at any time will be recorded. Any unexpected AE ≥NCI CTCAE Grade 3 event that occurs during this study and up to 30 days after discontinuation of study drug or alternate cancer therapy, whichever occurs first, regardless of relationship, should be reported to the Medical Monitor at the next investigator or cohort

review call. The Principal Investigator or a qualified designated staff physician will conduct clinical assessments on all patients at each scheduled clinic visit. In addition, patients will be queried about any adverse symptoms they have experienced since the previous study visit. In order to avoid bias in eliciting events, suggestive questioning of the patients shall not occur.

A laboratory abnormality will be reported on the AE eCRF only if it is associated with clinical sequelae or requires a therapeutic intervention.

Adverse events will be reported and described in terms of intensity, seriousness, and causality, based on the Principal Investigator's judgment using protocol-defined definitions. ***For both laboratory and non-laboratory abnormalities, capture only the highest grade of an event using start/stop dates of the longest duration.*** Necessary counter measures will also be reported on the appropriate eCRF used to collect concomitant medications.

8.5 Serious Adverse Events and/or Adverse Events Requiring Discontinuation of Study Drug

Any SAE that occurs during this study and up to 30 days after discontinuation of study drug ***or initiation of alternate cancer therapy, whichever occurs first***, must be reported to the Medical Monitor within 24 hours of the Principal Investigator's awareness of the event, whether or not this reaction is considered to be associated with the use of the investigational drug. In addition, the occurrence of any AE leading to permanent discontinuation of study drug must also be reported to the Sponsor within 24 hours of the Principal Investigator's awareness of the event.

All SAEs must be scanned and emailed to the Sponsor/Medical Monitor.

Email: CRF@couranteoncology.com

It is expected that the Principal Investigator will provide or arrange appropriate supportive care for the study patient. A patient experiencing an SAE should be followed clinically until his/her health has returned to his/her baseline status, until all parameters have returned to normal or have otherwise been explained, or the patient begins an alternative treatment regimen. All telephone and scanned/emailed reports must be followed with a written SAE report form within 24 hours of the Principal Investigator's awareness of the SAE or nonserious event that required discontinuation of study drug. The SAE report form should be completed and signed by the Principal Investigator, scanned, and sent by email to the Sponsor as described above. The SAE report form is distinct and separate from the AE eCRF.

Grades for all SAEs and AEs, regardless of whether they trigger expedited reporting, must be captured in the eCRF.

8.6 Follow-Up of Adverse Events

Any AEs that are identified on the last scheduled visit must be recorded in the AE eCRF page and reported to the Sponsor according to the procedures outlined in *Section 8.4*.

Patients with unresolved previously reported AEs or new AEs identified on the last scheduled visit should be followed by the Principal Investigator until the AEs resolve, are deemed permanent or no longer clinically significant, or the patient begins an alternative treatment regimen. Resolution means that the patient has returned to his/her baseline state of health or the Principal Investigator does not expect any further improvement or worsening of the AE. The Principal Investigator should continue to report any significant follow-up information to the Sponsor up to the time that the AE has resolved. Any AEs reported by the patient to the Principal Investigator that occur after the last scheduled visit and are determined by the Principal Investigator to be reasonably associated with the use of study drug or meet the criteria of a reportable AE as described above, should be reported to the Sponsor.

Patients withdrawn from the study with an ongoing AE must be followed clinically until the event is resolved, deemed stable, deemed permanent, or the patient begins an alternative treatment regimen as determined by the Principal Investigator and Sponsor. A stable AE is defined as an AE that is not expected to change in nature, severity, or frequency. The Principal Investigator should continue to report any significant follow-up information to the Sponsor.

8.7 Patient Deaths

Every effort will be made in the case of patients who die to determine the cause of death. Information regarding a patient who dies more than 30 days after receiving study drug may be recorded on a Death Report Form (no SAE report is required). An SAE report is recorded only if the event leading up to the patient's death began within 30 days of the last dose of study drug.

The Death Report Form is distinct and separate from the AE eCRF.

8.8 Reporting Adverse Events to the Regulatory Authorities

The Sponsor will be responsible for reporting AEs to the Food and Drug Administration (FDA) as described in 21 CFR Section 312.32 (IND Safety Reports) and to other regulatory authorities according to local regulations.

In addition, the Principal Investigator is required by FDA regulations to notify the IRB promptly of all unexpected SAEs occurring at the Investigator's study site. The Principal Investigator is also required by FDA regulations to forward to the IRB all IND Safety Reports received from the Sponsor.

The Sponsor will also report SAEs in compliance with local regulatory requirements.

9. STUDY DRUG MANAGEMENT

9.1 TP-0903 Drug Product

The study drug, oral TP-0903, is supplied by Tolero Pharmaceuticals as a powder in hard gelatin capsules (size #3 ***for the 1-, 4-, 16-, and 25-mg doses; size #0 for the 100-mg dose***) and is manufactured under current Good Manufacturing Practices (cGMP) for investigational use.

TP-0903 capsules are formulated in 1-mg, 4-mg***, 16-mg, 25-mg, and 100-mg*** strengths and are packaged into ***round*** high-density polyethylene bottles with ***polyester*** coils ***as headspace fillers. Bottles are then heat-sealed, fitted with*** child-resistant caps***, and placed in low-density polyethylene bags as secondary packaging***.

Ibrutinib, an approved pharmaceutical product, will be provided by commercially available sources.

Ibrutinib capsules for oral administration are supplied as white opaque capsules that contain 140 mg ibrutinib as the active ingredient. Each white opaque capsule is marked with “ibr 140 mg” in black ink.

9.2 Study Drug Dispensing and Accountability

TP-0903 will be provided by the Sponsor to study centers as an investigational drug. The label and package for the drug product will be prepared in accordance with current regulatory requirements. The Investigator or designee will inventory and acknowledge receipt of all shipments of study drugs. The study drugs must be kept in a locked area with access restricted to designated study personnel.

An accurate and current accounting of the dispensing of the study drugs for each patient will be maintained on an ongoing basis by a member of the study site staff in a drug accountability log or equivalent document and will be verified by the Sponsor's study monitor. All drug supplies, including unused study drug, must be accounted for. A final inventory of the total amount of drug received at each study site against the amount used and returned must be recorded in the study drug accountability log or an equivalent document. Inventory and dispense records must be readily available for inspection by the study monitor and/or auditor, and open to government inspection at any time. Study drug destruction will be handled by the sites of open/used vials. Unopened study drug vials should be returned to the Sponsor or contract research organization (CRO) at the end of the study **after full drug accountability has been completed by the study monitor**.

9.3 Storage at Study Center

Study drug should be stored at room temperature ***(20°C – 25°C [68°F – 77°F] with excursions permitted to 15°C to 30°C [59°F to 86°F])***. Protection from light is not necessary.

Ibrutinib should be stored at room temperature between 68°F to 77°F (20°C to 25°C). Please follow approved label for all instructions on storage [27].

9.4 Compliance

Patients will receive both TP-0903 study drug and ibrutinib and will be followed as outpatients. The appropriate dose of TP-0903 to be dispensed will be determined by the patient's cohort assignment. The number of study drug capsules and dosage to be dispensed will be recorded in an inventory log to be periodically reviewed by a Sponsor's representative.

Please refer to the Pharmacy Manual for specifics regarding dispensing of TP-0903 capsules. Patients will also be given a Study Drug Administration Patient Dosing Diary (*Appendix I*) in which to record the date, time, and number of capsules taken and also if a dose was missed or if patient vomited for both TP0903 and ibrutinib. Patients will be instructed to bring their Administration 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.

Patients should be dispensed ibrutinib per institutional policy.

10. RECORD MANAGEMENT

10.1 Data Collection

The Principal Investigator must maintain required records for all study patients. Case report forms are used to record clinical study data and are an integral part of the study and subsequent reports. Data for this study will be recorded in the patient's source documents and into an eCRF system that must be kept current to reflect patient status during each part of the study. Patients are not to be identified by name on the eCRF. Appropriately coded identification (site number, patient identification number, and patient initials) should be used.

The eCRFs are not to be used as source documents. The Principal Investigator must keep accurate separate records of all patients' visits, being sure to include all pertinent study-related information. A statement should be made indicating that the patients have been enrolled in this clinical study and have provided written informed consent. Any AEs must be thoroughly documented. Results of any diagnostic tests conducted during the study should also be included in the source documents.

All data should be recorded completely and promptly in the eCRFs as soon after the visit as possible, but no later than 5 days. All queries are to be answered within 3 days of query date.

The Principal Investigator will allow the Sponsor, its representative, or an appropriate representative of the regulatory authorities to inspect study documents (eg, eCRFs, consent forms, study drug distribution forms, IRB/independent ethics committee [IEC] approval) and pertinent hospital or clinic records for confirmation of data throughout the study period.

10.2 Source Document Maintenance

Source documents, or source data, are defined as the records of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, hospital medical records, study progress notes, ICFs, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Principal Investigator and made available for inspection by representatives of the Sponsor or the regulatory authorities. The original signed ICF for each participating patient shall be filed with the records kept by the Principal Investigator, a copy filed in the patient’s medical records, and a copy given to the patient.

Source documents are necessary for the reconstruction and evaluation of a clinical study. The purpose of source documents is to provide proof of a participant’s existence, confirm that protocol-related procedures were completed and conducted per protocol, and to verify that data reported in the study eCRFs are accurate.

Source documents at a study site may be maintained in paper or electronic format and typically contain the types of information below. If electronic source documents are used, the Sponsor and study monitors will be given access to verify study data.

Source documents may include, but are not limited to:

- Notes from clinic physicians, nurses, and other study staff
- Reports of procedures and tests
- Flow sheets, checklists, and worksheets
- Patient diaries and study calendars
- Pharmacy records, accountability logs, and shipping receipts
- Study notes or memos to file
- Documentation of telephone calls, emails, and faxes
- Hospital admission forms and discharge summaries
- Sponsor- or site-generated study source document templates

Source documents must meet 5 fundamental principles of data quality ("ALCOA"). They must be:

- **A**ttributable – The data originator is identified. If data needs to be amended, the amender is identified.
- **L**egible – The source document must be readable. If handwritten, black or blue ink must be used, never pencil.
- **C**ontemporaneous – The document must be signed and dated when the information is first recorded, with any updates or corrections noted in real time as well.
- **O**riginal – The document must be the first place the information is recorded.
- **A**ccurate – The information must be error-free, and any conflicts with data recorded elsewhere must be reconciled.

10.3 Record Maintenance

The Principal Investigator must retain a comprehensive and centralized filing system of all clinical study-related documentation that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Principal Investigator must retain essential study documents (as specified in Section 8 of International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and as required by the applicable regulatory requirements) until at least 2 years after the last approval of a marketing application. Patient files and other source documents (including copies of protocols, eCRFs, original reports of test results, study drug dispensing logs, correspondence, ICFs, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution.

No study document will be destroyed without prior written agreement between the Sponsor and the Principal Investigator. Should the Principal Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

The Principal Investigator shall take responsibility for maintaining adequate and accurate hard-copy source documents of all observations and data generated during this study, including any data clarification forms received from the Sponsor. Such documentation is subject to inspection by the Sponsor and the FDA or other regulatory authorities.

10.4 Study Center File Management

It will be the responsibility of the Principal Investigator to assure that the study file at the study site is maintained. The study file for this protocol will contain, but will not be limited to, the information listed below:

- Investigator's Brochure, current version and all versions provided during the study period
- Final study protocol
- Protocol amendments (if applicable)
- Original ICF (blank)
- Revised ICFs and/or all addenda (if applicable)
- Copy of signed FDA Form(s) 1572
- Curricula vitae and medical licenses of Principal Investigator and Subinvestigators
- Financial disclosure form of Principal Investigator and Subinvestigators (if applicable)
- Department of Health and Human Services number for IRB, or other documentation of IRB compliance with FDA regulation (United States sites)
- Documentation of IRB/IEC approval of protocol, ICF, any protocol amendments, and any ICF revisions
- Annual IRB/IEC updates and approvals
- All correspondence between the Principal Investigator, IRB/IEC, and Sponsor or Sponsor's representative relating to study conduct
- Copies of all 7-day and 15-day Safety Reports submitted to the regulatory authorities (provided by Sponsor) and IRB/IEC correspondence documenting their submission
- Laboratory certifications
- Normal laboratory value ranges for tests required by the protocol for all laboratories that are utilized
- Clinical research associate (CRA) monitoring log
- List of signatures and delegation of authority for all study personnel
- Invoices for both receipt and return of study drug and drug inventory/accountability records

11. STATISTICAL ANALYSIS

This is a Phase 1/2, multi-center, single-agent, open-label study in which Phase 1 will employ the 3+3 dose escalation design and Phase 2 uses the Simon 2-stage design.

Results of statistical analyses, descriptive statistics, and supporting listings will be presented by study phase (Phase 1 and Phase 2) and patient group (TP-903 monotherapy and combination therapy with ibrutinib).

Statistical analysis for all safety and efficacy parameters will be primarily descriptive in nature. Categorical variables will be summarized by frequency distributions (number and percentages of patients), continuous variables will be summarized by mean, standard deviation, median, minimum, maximum, and time-to-event variables will be summarized using Kaplan-Meier methods and figures for the estimated median time. No formal statistical hypothesis testing is planned; however, if exploratory analyses are conducted and confidence intervals are provided for estimates, the 95% confidence intervals are consistent with a 2-sided 5% significance level. All analyses, summaries, and listings will be performed using Statistical Analysis System (SAS) software (version 9.4 or higher).

A detailed methodology for summary and statistical analysis of the data collected in this study will be documented in a Statistical Analysis Plan (SAP) that will be finalized prior to database lock. If any modifications to the analyses outlined in the protocol are made, these will be clearly documented in the SAP. Any major modifications of the study design or study endpoints and/or its analysis will also be reflected in a protocol amendment.

11.1 Sample Size

Phase 1

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 Phase 1 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 to confirm safety/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 (monotherapy and combination therapy).

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, the study will progress to Phase 2.

Phase 2

The statistical power calculations for each patient group (monotherapy and combination therapy) are based on the Simon 2-stage minimax design [27].

- 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 zero responders among 13 evaluable Stage 1 patients, the study will be stopped after Stage 1.

- Stage 2: Fourteen 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 (Group 1 and Group 2) enroll through Stage 2, it is anticipated that the total enrollment for Phase 2 will be 54 patients (n=27 for Group 1 [ie, TP-0903 monotherapy] and n=27 for Group 2 [ie, combination therapy]) ***(Table 5)***.

Table 5 Sample Size Description

	Phase 1		Phase 2	
Patient Group	**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.

11.2 Analysis Population Sets

This study will have 3 analysis populations:

- *Intent-to-Treat (ITT) Analysis Set* includes all patients who are enrolled in the study.
- *Safety Analysis Set* consists of all patients who receive study drug (TP-0903).
- *Response Evaluable Set* consists of patients who have at least one postbaseline efficacy assessment; patients without a postbaseline efficacy assessment will not be considered evaluable for the primary efficacy analysis. Patients who discontinue due to disease progression or die of treatment-related toxicity prior to having a disease assessment will be included in the Response Evaluable population.

11.3 Data Analyses

11.3.1 Patient Disposition

A detailed description of patient disposition will be provided and will include the following:

- The number of patients who are enrolled, included in the ITT, Safety, and Response Evaluable analysis sets.
- A summary of patient dose cohorts.
- A summary of patients who complete the protocol.
- A summary of reasons for withdrawal from study.
- A summary of reasons for patients with treatment failure.
- An account of all identified protocol violations.
- All patients enrolled in the study will be accounted for in the summation.

11.3.2 Demographic and Baseline Characteristics

Demographic characteristics including age, gender, race, and ethnicity will be presented in the form of tabulated summary statistics. Other patient baseline characteristics including but not limited to: weight, height, body mass index (BMI), initial stage of disease, prior therapies, and ECOG performance status will be presented similarly.

11.3.3 Concomitant Medications

The number and proportion of patients using different concomitant medications will be tabulated and summarized by World Health Organization (WHO) Drug anatomical therapeutic chemical (ATC) and preferred term.

11.3.4 Treatment Administration/Compliance

Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose intensity, and reasons for the deviations from planned therapy.

11.3.5 Efficacy Analysis

The primary efficacy endpoint is ORR, defined as the percent of patients with CR or PR according to IWCLL guidelines 2018, relative to the Response Evaluable population.

The secondary efficacy endpoints are as follows:

- DoR, defined as the time from documentation of tumor response to disease progression.
- PFS, defined as the time from first dose until objective tumor progression or death.
- OS, defined as the time from first dose to death from any cause.

ORR will be summarized by number and percentage of patients meeting the definition of ORR along with the corresponding exact 95% confidence intervals.

Time-to event endpoints (DoR, PFS, and OS) will be summarized by Kaplan-Meier methods (median, 95% CI, number of events, number censored, and Kaplan-Meier figures).

Additional analyses may be performed to assist the Sponsor in planning future studies.

11.3.6 Safety Analysis

Safety will be monitored during the period starting on the date of first dose and ending 30 days after the final administration 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 and will be able to take decisions accordingly.

All patients who receive any dose (any amount) of TP-0903 will be included in the summaries and listings of safety data. Overall safety profile will be characterized by type, frequency, seriousness, severity, timing, duration and relationship of study drug of AEs and laboratory abnormalities.

11.3.6.1 Adverse Events

AEs will be classified using the MedDRA classification system v20.0 or higher. The severity of the toxicities will be graded according to the NCI CTCAE v5.0.

In all summaries, emphasis will be placed on TEAEs, namely, those with initial onset or that worsen in severity after the first dose of TP-0903. AEs will be summarized by the frequency of patients experiencing TEAEs corresponding to body systems and

MedDRA preferred term and by worst NCI CTCAE v5.0 grade. Summaries will also be provided of treatment related TEAEs, namely, those judged by the investigator to be related or possibly related to TP-0903 and/or combination therapy.

AEs resulting in discontinuation of TP-0903 treatment or withdrawal from the study, Grade 3 or higher, SAEs, and deaths on-study will be tabulated. All DLTs will be reported and the MTD and RP2D identified.

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

11.3.6.2 Laboratory Parameters

Laboratory data will be summarized for the observed values at each scheduled assessment, together with the corresponding changes from baseline (the value obtained prior to dosing on Cycle 1/Day 1) using descriptive statistics.

For those analytes with CTCAE grades, abnormal laboratory values will be summarized by dose group and overall by shift tables displaying numerical values and percentages classified by Baseline grade (ie, grade prior to dosing on Cycle 1/Day 1) and maximum grade on treatment. All laboratory data will be presented in listings.

11.3.6.3 Electrocardiogram

The ECG parameters (PR interval, QRS duration, QT, QTc, and QTcF) will be summarized descriptively by dose cohort and overall for each time point for both the observed values and the change from Baseline to each postbaseline time point. The number and percentage of patients with QT or QTc (QTcF) outlier values (at any postbaseline time point), as defined in ICH E14, will be summarized.

11.3.6.4 Vital Signs and Physical Examination

Vital signs data will be summarized by the observed value at each scheduled assessment, together with the corresponding changes from Baseline using descriptive statistics.

Physical examination findings will be presented in data listings.

11.3.7 Pharmacokinetic Analysis

PK parameters will be estimated using standard noncompartmental methods and according to FDA guidance [26].

The PK parameters will include:

- C_{max} = maximum observed plasma concentration
- T_{max} = time to C_{max} (peak time)
- $AUC_{0\text{-}24}$ = area under the plasma concentration curve from time 0 to 24 hours
- $AUC_{0\text{-}inf}$ = AUC from time 0 to infinity
- AUC_t = area under the plasma concentration curve from time 0 to time t
- $t_{1/2}$ = half-life
- CL = clearance using noncompartmental methods

Actual sample collection times will be used rather than scheduled collection times. Plasma concentrations below the limit of quantification will be treated as “0”. Imbedded missing plasma concentrations (ie, missing values between 2 observed values) will be estimated using linear extrapolation. This is consistent with using the trapezoidal rule to calculate AUC. Other missing plasma concentrations will be excluded from calculations to estimate PK parameters.

11.3.8 Pharmacodynamic Analysis

The PD relationships of TP-0903 exposure with exploratory biomarkers will be quantified using the Spearman rank correlation statistic to examine the relationships between response to treatment (ordered categorical dependent variables) and changes from baseline values of PD endpoints (continuous independent variables).

11.4 Interim Analysis

Phase 1

Safety data will be monitored continuously per standard Phase 1 oncology study practices.

Phase 2

Since the Simon 2-stage design will be employed, response rate data will be assessed after Stage 1 and Stage 2.

12. PROTOCOL AMENDMENTS

Any permanent change to the protocol must be handled as a protocol amendment. Protocol amendments will be written by the Sponsor. All protocol amendments must be submitted in writing to the IRB/IEC, and the Principal Investigator must await IRB/IEC approval of the amendments before implementing the changes. However, a protocol change which is intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided that the IRB/IEC is notified within 5 days. The Sponsor should also be notified by telephone as soon as possible, ideally before the amendment is implemented and definitely within 5 days. The Sponsor will submit protocol amendments to the regulatory authorities.

When an amendment to the protocol substantially alters the study design and/or increases the potential risk to the patient, the currently approved written ICF will require similar modification and IRB/IEC approval. In such cases, repeat written informed consent will be obtained from patients currently enrolled in the study before expecting continued participation.

13. MONITORING

Before enrolling any participants, a study initiation visit, including protocol training, will be conducted for the study site. A Study Manual of Procedures will be provided to each study site. A record of study site personnel training will be maintained on the study site onsite training logs.

Clinical research associates and other applicable personnel will receive training before study initiation about the disease, applicable Standard Operating Procedures (SOPs), the protocol, and other study-specific items. Team organization, communication, and operational issues will also be discussed.

The conduct of the study will be closely monitored by representatives (CRAs) of the Sponsor or designee, to verify adherence to the protocol, ICH GCP guidelines, and applicable regulations. The CRA will verify eCRF entries by comparing them with Sponsor- or site-generated source documents and hospital, clinic, office, and/or study records which will be made available for this purpose. The CRAs will monitor the study as outlined in the Monitoring Plan prepared for the study.

During the study, CRAs will visit the study sites to assess and assure satisfactory enrollment rate, data recording, maintenance of required regulatory and drug accountability documentation, and compliance with the protocol. The CRAs will also be able to monitor the data remotely. The Principal Investigator will ensure that all requested materials, including patient medical records, eCRFs, source documents, laboratory records, and drug inventory records, will be available to the CRA. At the end of the study, a closeout visit will be performed.

The Principal Investigator will allow the Sponsor, its representatives, and/or any regulatory agency to have direct access to all study records, eCRFs, patient medical records, study drug dispensing records, the study drug storage area, and any other documents considered source documentation. The Principal Investigator also agrees to assist the representative, if required.

14. AUDITING

The study is conducted under the sponsorship of Tolero, in compliance with the applicable international and local regulatory requirements and applicable ICH guidelines, Declarations of Helsinki (1964, 1975, 1983, 1989, 1996, 2000, 2002, 2004, 2008, 2013) and in respect of the Sponsor or designee's SOPs for study conduct and monitoring.

Audits or inspections may be carried out by the Sponsor, its representatives, regulatory authorities, or IRBs/IECs before, during, or after the study. For audits performed by, or on behalf of, the Sponsor, audit findings will be provided by quality assurance, in writing.

15. ETHICS AND RESPONSIBILITY

15.1 Principal Investigator's Responsibilities

The Principal Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of GCP. The Principal Investigator shall administer the study drug only to patients under his/her personal supervision, or under the supervision of any Subinvestigator responsible to him/her, who are identified on the Form FDA 1572/Statement of Investigator. The Principal Investigator will provide copies of the study protocol, amendments, and Investigator's Brochure to all Subinvestigators, pharmacists, or other staff responsible for study conduct.

With the exception of eliminating an immediate hazard to a patient (refer to *Section 12*), the Investigator should not deviate from the protocol or implement any changes unless a protocol amendment has been written by the Sponsor and approved by the IRB/IEC.

Changes which involve only logistical or administrative matters are authorized. The Investigator should document and explain any deviation from the protocol.

The Investigator is responsible for adequate and safe medical care of patients during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study. Any additional data from these follow-up procedures must be documented and available to Sponsor who will determine whether or not the data need to be documented in the eCRFs.

15.2 Informed Consent

It is the ethical and legal responsibility of the Principal Investigator to ensure that each patient considered for inclusion in this study is given a full explanation of the protocol, in a language in which the patient is fluent, and in which the patient will clearly understand. This shall be documented on a written ICF, which shall be approved by the same IRB/IEC responsible for approval of this protocol. Each ICF shall include the elements required by local regulations. The Sponsor will draft this document in consultation with the Principal Investigator. The Principal Investigator agrees to obtain written approval of the ICF from the Sponsor before submission to the IRB/IEC.

Once the appropriate essential information has been provided to the patient and fully explained by the Principal Investigator (or his/her qualified designee) and it is felt that the patient understands the implications of participating in the study, the IRB/IEC-approved ICF shall be signed by the patient, a witness (when appropriate), and the Principal Investigator (or designee). Written informed consent will be obtained from each patient before any study-related procedures (including any pretreatment procedures) are performed. The patient shall be given a copy of the ICF once signed. The original shall be kept on file by the Principal Investigator and a second copy shall be placed in the patient's medical chart (or per electronic medical record SOP).

15.3 Institutional Review Board

This protocol and all amendments will be reviewed and approved by the IRB/IEC charged with this responsibility by the study site. Notification in writing of approval must come from the chairman or the secretary of the IRB/IEC and recorded in the meeting minutes where this protocol and associated ICF were discussed. The Principal Investigator shall not participate in the decision, and if he/she is an IRB/IEC member, the written approval must indicate such nonparticipation. The Principal Investigator shall submit status reports to the IRB/IEC no less frequently than annually (when applicable). The IRB/IEC must be notified by the Principal Investigator in writing of the interruption and/or completion of the study. The Principal Investigator must promptly report to the IRB/IEC all changes in the study (protocol amendments) and will not make such changes without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to patients. In these cases, the IRB/IEC must be notified within 5 days of the change. The Principal Investigator will promptly report to the IRB/IEC all unanticipated problems involving risk to patients or others. The Principal Investigator is required to maintain an accurate and complete record of all written correspondence to and from the IRB/IEC and must agree to share all such documents and reports with the Sponsor.

16. CONFIDENTIALITY

The details of this clinical study are confidential (with exception of listing on clinicaltrials.gov) and should not be discussed with persons outside of the study. The Investigator shall hold confidential, and not disclose directly or indirectly to any third party other than those persons involved in the study who have a need to know, the protocol, the data arising out of the study, or any other information related to the study or to Tolero's products or research programs that are provided by Tolero. All such persons must be instructed not to further disseminate this information to others. The Investigator shall not use the confidential information for any purpose other than study conduct. The foregoing obligations of confidence and nonuse assumed by the Investigator shall not apply to: (a) information that at the time of disclosure is in the public domain; (b) information that thereafter lawfully becomes part of the public domain other than through disclosure by or through you; (c) information that, as evidenced by the Investigator's written records, was known by the Investigator before Tolero's disclosure; (d) information that is lawfully disclosed to you by a third party not under any obligation of confidence to Tolero; or (e) information that is required to be disclosed by law or governmental regulatory agency, provided reasonable advance notice of such disclosure is given to Tolero.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study, without written permission from the Sponsor. However, the Sponsor, its representatives, regulatory authorities, and IRBs/IECs will be allowed full access to the records.

Patients will be identified only by initials and assigned patient number in eCRFs. Their full names may, however, be made known to a regulatory authority or other authorized official if necessary.

All data and discoveries arising out of the study, patentable or nonpatentable, shall be the sole property of Tolero.

In signing this protocol, the Principal Investigator agrees to the release of the data from this study and acknowledges the above confidentiality and publication policy. The provisions of this statement shall survive the completion of the study.

Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the Sponsor or regulatory authorities, or as required by law.

17. NONPROTOCOL RELATED RESEARCH

The Sponsor has a legal responsibility to report fully to regulatory authorities all the results of administration of investigational drugs. No investigative procedures other than those in this protocol shall be undertaken on the enrolled patients without the agreement of the IRB/IEC and the Sponsor's Medical Monitor.

18. PUBLICATIONS

The publication policy for the study will be described in the clinical study agreement. To avoid disclosures that could jeopardize proprietary rights, the Investigator agrees to give Tolero the right to review all manuscripts, abstracts, and presentations related to this study prior to their submission for publication or presentation. Tolero may use these data now and in the future for presentation or publication at Tolero's discretion or for submission to government regulatory agencies.

Authorship among Investigators generally will be based on the extent of significant contribution, including scientific and clinical, to the publication.

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APPENDIX A – 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)

APPENDIX B – ECOG PERFORMANCE STATUS SCALE

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* The ECOG Performance Status is in the public domain, therefore available for public use. To duplicate the scale, please cite the reference below and credit the Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.
Available at: http://www.ecog.org/general/perf_stat.html (accessed 29 January 2018).

APPENDIX C – 2018 IWCLL GUIDELINES GRADING SCALE FOR HEMATOLOGIC TOXICITY

Grade[a]	Decrease in Platelets[b] or Hb[c] (nadir) from Baseline Value (%)	Absolute Neutrophil Count/μL[d] (nadir)
0	No change to 10%	≥2,000
1	11%-24%	≥1,500 and <2,000
2	25%-49%	≥1,000 and <1,500
3	50%-74%	≥500 and <1,000
4	≥ 75%	<500

From the 2018 IWCLL Guidelines [25].

a Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from baseline will be recorded as grade 5.

b Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is <20,000/μL, this will be considered grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, 20,000/μL) was present baseline, in which case the patient is not evaluable for toxicity referable to platelet counts.

c Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.

d If the absolute neutrophil count (ANC) reaches <1,000/μL, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count, or in circulating granulocytes, are not to be considered, since a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was <1,000/μL prior to therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity but should be documented.

APPENDIX D – NCI COMMON *TERMINOLOGY* CRITERIA AND GRADING FOR ADVERSE EVENTS WHERE THE NCI *CTCAE* CRITERIA ARE NOT APPLICABLE

View the NCI CTCAE v5.0 criteria electronically at the following Web site:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

The study manual includes a copy of the NCI-CTCAE.

Grading for adverse events where the NCI Common Toxicity Criteria are not applicable:

GRADE 1 – Mild:	***Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated***
GRADE 2 – Moderate:	***Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]***
GRADE 3 – Severe:	***Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]***
GRADE 4 – Life Threatening:	***Life-threatening consequences; urgent intervention indicated***
GRADE 5 – Fatal:	***Death related to AE***

a Instrumental activities of daily living (ADLs) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b Self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

APPENDIX E – LABORATORY TESTS

Hematology	• Complete blood count with manual differential	• Platelet count
Full Serum Chemistry	• Blood urea nitrogen • Phosphorus • Magnesium • Lactate dehydrogenase • Creatinine • Uric acid • Total protein • Albumin • Calcium	• Glucose • Total bilirubin • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Electrolytes (sodium, potassium, chloride, and bicarbonate)
TLS Labs*	• Uric acid • Potassium • Phosphate	• Calcium • Creatinine
Immunoglobulin testing	• Serum immunoglobulin • Direct Antiglobulin	• Serum ß2-microglobulin
Coagulation	• Prothrombin time	• Activated partial thromboplastin time
Urinalysis	• Color • Specific gravity • pH • Bilirubin • Ketones • Glucose • Occult blood (hemoglobin)	• Leukocyte esterase • Protein • Urobilinogen • Nitrites • White blood cells • Red blood cells • Casts, crystals, bacteria
Cytogenetics and karyotyping	• Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes • Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation) • TP53 mutation status • IGHV mutational status	
Pharmacodynamic Tests	• Peripheral blood for chronic lymphocytic leukemia burden and minimum residual disease • Blood for exploratory pharmacodynamic and other biomarkers	
Other Tests	• Pregnancy test (urine or serum determination of beta-human chorionic gonadotropin in females of childbearing potential)	

*Real-time [STAT] review required for assessment of TLS labs.

APPENDIX F – RESPONSE CRITERIA

Below is 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].

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

a Sum of the products of 6 or less lymph nodes (as evaluated by CT scans and physical exam in clinical trials, or by physical exam in general practice).

b Spleen size is considered normal if < 13 cm. There is not firmly established, international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

CR = complete remission: all of the criteria have to be met

PR = partial remission: for a PR at least 1 of the parameters of group A and 1 parameter of group B need to improve if previously abnormal. If only one parameter of both groups A and B is abnormal prior to therapy, only 1 needs to improve

PD = progressive disease: at least one of the above criteria of group A or group B has to be met;

SD = stable disease: all of the above criteria have to be met. Constitutional symptoms alone do not define PD.

APPENDIX G – CYP2C19 SUBSTRATES, INDUCERS, AND INHIBITORS

Physicians should be aware of the possibility of drug interactions when TP-0903 is coadministered with drugs that are inhibitors or inducers of CYP2C19. Physicians should refer to the products label and to the drug interaction website provided below. The website listing cytochrome P450 inhibitors and inducers is updated on an ongoing basis and can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table. Below is a snapshot of the website as of 31 January 2016. **Attention should be focused on the 2C19 column**. Please note that the website also lists substrates of CYP2C19.

Cytochrome P450 Drug Interaction Table

SUBSTRATES

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
amitriptyline caffeine clomipramine clozapine cyclobenzaprine estradiol fluvoxamine haloperidol imipramine NDeMe mexilletine naproxen olanzapine ondansetron phenacetin⇨ acetaminophen⇨ NAPQI propranolol riluzole ropivacaine tacrine theophylline tizanidine verapamil (R)warfarin zileuton zolmitriptan	bupropion cyclophosphamide efavirenz ifosfamide methadone	paclitaxel torsemide amodiaquine cerivastatin repaglinide	NSAIDs: diclofenac ibuprofen lornoxicam meloxicam S-naproxen⇨Nor piroxicam suprofen Oral Hypoglycemic Agents: tolbutamide glipizide Angiotensin II Blockers: losartan irbesartan Sulfonylureas: glyburide glibenclamide glipizide glimepiride tolbutamide amitriptyline celecoxib fluoxetine fluvastatin glyburide nateglinide phenytoin--4-OH2 rosiglitazone tamoxifen	Proton Pump Inhibitors: lansoprazole omeprazole pantoprazole rabeprazole Antiepileptics: diazepam⇨Nor phenytoin(O) S-mephenytoin phenobarbitone amitriptyline carisoprodol citalopram chloramphenicol clomipramine cyclophosphamide hexobarbital imipramine N-DeME indomethacin R-mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil propranolol teniposide R-warfarin⇨8-OH	Beta Blockers: carvedilol S-metoprolol propafenone timolol Antidepressants: amitriptyline clomipramine desipramine imipramine paroxetine Antipsychotics: haloperidol perphenazine risperidone⇨9OH thioridazine zuclopenthixol alprenolol amphetamine aripiprazole atomoxetine bufuralol1 chlorpheniramine chlorpromazine codeine (⇨O-des-Me) debrisoquine dexfenfluramine dextromethorphan duloxetine	Anesthetics: enflurane halothane isoflurane methoxyflurane sevoflurane acetaminophen⇨ NAPQI aniline2 benzene chlorzoxazone ethanol N,N-dimethyl formamide theophylline⇨ 8OH	Macrolide antibiotics: clarithromycin erythromycin (not 3A5) NOT azithromycin telithromycin Antiarrhythmics: quinidine⇨3OH (not 3A5) Benzodiazepines: alprazolam diazepam⇨3OH midazolam triazolam Immune Modulators: cyclosporine tacrolimus (FK506) HIV Antivirals: indinavir nelfinavir ritonavir saquinavir Prokinetic: cisapride Antihistamines:

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
			torsemide S-warfarin		encainide flecainide fluoxetine fluvoxamine lidocaine metoclopramide methoxy-amphetamine mexilletine minaprine nebivolol nortriptyline ondansetron oxycodone perhexiline phenacetin phenformin promethazine propranolol sparteine tamoxifen tramadol venlafaxine		astemizole chlorpheniramine terfenadine Calcium Channel Blockers: amlodipine diltiazem felodipine lercanidipine nifedipine2 nisoldipine nitrendipine verapamil HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin NOT pravastatin simvastatin Steroid 6beta-OH: estradiol hydrocortisone progesterone testosterone Miscellaneous: alfentanyl aprepitant aripiprazole buspirone cafergot caffeine⇨TMU cilostazol cocaine codeine-N-demethylation dapsone dexamethasone dextromethorphan docetaxel domperidone eplerenone fentanyl

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
							finasteride gleevec haloperidol irinotecan LAAM lidocaine methadone nateglinide ondansetron pimozide propranolol quetiapine quinine risperidone NOT rosuvastatin salmeterol sildenafil sirolimus tamoxifen taxol terfenadine trazodone vincristine zaleplon ziprasidone zolpidem

INHIBITORS

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
fluvoxamine ciprofloxacin cimetidine amiodarone fluoroquinolones furafylline interferon methoxsalen mibefradil	thiotepa ticlopidine	gemfibrozil trimethoprim glitazones montelukast quercetin	fluconazole amiodarone fenofibrate fluvastatin fluvoxamine isoniazid lovastatin phenylbutazone probenicid sertraline sulfamethoxazole sulfaphenazole teniposide voriconazole zafirlukast	PPIs: lansoprazole omeprazole pantoprazole rabeprazole chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin ketoconazole modafinil oxcarbazepine probenecid ticlopidine topiramate	bupropion fluoxetine paroxetine quinidine duloxetine terbinafine amiodarone cimetidine sertraline celecoxib chlorpheniramine chlorpromazine citalopram clemastine clomipramine cocaine diphenhydramine doxepin doxorubicin escitalopram halofantrine histamine H1 receptor antagonists hydroxyzine levomepromazine methadone metoclopramide mibefradil midodrine moclobemide perphenazine ranitidine red—haloperidol ritonavir ticlopidine tripelennamine	diethyldithiocarbamate disulfiram	HIV Antivirals: indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone saquinavir telithromycin aprepitant erythromycin fluconazole grapefruit juice verapamil diltiazem cimetidine amiodarone NOT azithromycin chloramphenicol delaviridine diethyl- dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine star fruit voriconazole

INDUCERS

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
broccoli brussel sprouts chargrilled meat insulin methylcholanthrene modafinil nafcillin beta-naphthoflavone omeprazole tobacco	phenobarbital rifampin	rifampin	rifampin secobarbital	carbamazepine norethindrone NOT pentobarbital prednisone rifampin	dexamethasone rifampin	ethanol isoniazid	HIV Antivirals: efavirenz nevirapine barbiturates carbamazepine efavirenz glucocorticoids modafinil nevirapine oxcarbazepine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's wort troglitazone

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Source: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007).
Available at: http://medicine.iupui.edu/clinpharm/ddis/main-table/ (accessed 07 March 2018).

APPENDIX H – BASELINE DISEASE ASSESSMENTS ACCORDING TO 2018 IWCLL GUIDELINES

Below is a summary of the baseline disease assessments per 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].

Diagnostic test	**Clinical Trial**
Tests to Establish the Diagnosis	
• Complete blood count and differential count	Always
• Immunophenotyping of peripheral blood lymphocytes	Always
Assessments Prior to Treatment	
• History and physical, performance status	Always
• Complete blood count and differential count	Always
• Marrow aspirate and biopsy	Desirable
• Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always
• Infectious disease status	Always
Additional Tests Prior to Treatment	
• Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always
• Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	Desirable
• *TP53* mutation	Always
• IGHV mutational status	Always
• Serum ß$_2$-microglobulin	Always
• CT scan of chest, abdomen, and pelvis	Desirable

Abbreviations: FISH, fluorescence in situ hybridization.
* conventional karyotyping in peripheral blood lymphocytes (with specific stimulation) may be useful prior to therapy if established methodology is available.

APPENDIX I – PATIENT DOSING DIARY

PATIENT ID:_____PATIENT INITIALS:_____ ASSIGNED COHORT/DOSE:_____GROUP _____

CYCLE ___	DATE (DD MMM YYYY)	TIME OF DOSING __ __: __ __ AM	# and STRENGTH of CAPSULES TAKEN					Ibrutinib Dose	COMMENTS (Document missed dose/reason; document vomiting after dosing and time)
			1 mg	4 mg	16 mg	*25 mg*	*100 mg*	_____ mg	
Example:	*01 Jan 2017*	*09:24*	***0***	***2***	***0***	***1***	***0***	*420*	*Vomited 2 hrs after dosing*
WEEK 1									
Day 1									
Day 2									
Day 3									
Day 4									
Day 5									
Day 6									
Day 7									
WEEK 2									
Day 1									
Day 2									
Day 3									
Day 4									
Day 5									
Day 6									
Day 7									
WEEK 3									
Day 1									
Day 2									
Day 3									
Day 4									
Day 5									
Day 6									
Day 7									
WEEK 4									
Day 1									
Day 2									
Day 3									
Day 4									
Day 5									
Day 6									
Day 7									