DOCUMENT: Statistical Analysis Plan

PROTOCOL: ASN002-101

A PHASE 1/2, OPEN-LABEL, UNCONTROLLED, MULTIPLE-DOSE ESCALATION, COHORT EXPANSION STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PRELIMINARY EFFICACY OF ASN002 IN RELAPSED/REFRACTORY LYMPHOMA, MYELOFIBROSIS, CHRONIC LYMPHOCYTIC LEUKEMIA AND ADVANCED SOLID TUMORS

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ABBREVIATIONS

α	Significance level
AE	Adverse event
CR	Complete response
CRF	Case Report Form
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EP	Efficacy population
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NE	Non-evaluable
NR	No response
PD	Progressive disease or Pharmacodynamics
PFS	Progression-free Survival
PK	Pharmacokinetics
PP	Per-protocol
PR	Partial response or interval between the P wave and the QRS complex
q12H	Every 12 hours
QRS	Quasi-random signal
QT	QT interval
QTcB	QT interval, Bazett's formula
QTcF	QT interval, Frederica's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Interval between heart beats
SAE	Serious adverse event
SAF	Safety
SD	Stable Disease or Standard Deviation
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TTP	Time to Tumor Progression
WHO	World Health Organization

DEFINITIONS OF TERMS

Part A	Part A, the dose escalation component of this study, will evaluate the safety and tolerability of ASN002 (study drug) including dose-limiting toxicities (DLT) and to determine the maximum tolerated dose (MTD).
Part B	Part B, the cohort expansion component of this study, will evaluate the safety, tolerability, and preliminary efficacy of ASN002 in subjects with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), myelofibrosis (MF), and chronic lymphocytic leukemia (CLL).
Safety population	The safety population will include all subjects who take at least 1 dose of study medication. Safety analyses will be conducted using the safety population. The safety population will apply to Parts A and B.
Efficacy population	The efficacy population (EP) will include all subjects who have an evaluable screening and post-dose tumor assessment. The EP will be used as the supportive analysis population for efficacy endpoints.
PP population	The Per Protocol (PP) population will include all EP subjects without major protocol violations. The PP population will be used as the primary analysis population for efficacy.
Treatment Cohort	There are nine treatment cohorts planned for Part A of this study: Treatment Cohort 1 – 10 mg ASN002 q12H Treatment Cohort 2 – 20 mg ASN002 q12H Treatment Cohort 3 – 30 mg ASN002 q12H Treatment Cohort 4 – 40 mg ASN002 q12H Treatment Cohort 5 – 50 mg ASN002 q12H Treatment Cohort 6 – 75 mg ASN002 q12H Treatment Cohort 7 – 100 mg ASN002 q12H Treatment Cohort 4a – 80 mg q24H Treatment Cohort 5a –120 mg q24H
Treatment-emergent	Symptoms or conditions with onset after the first administration of ASN002.

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used in summarizing and analyzing the safety, tolerability, and efficacy data from Protocol ASN002-101. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

Pharmacokinetic analyses and reporting are not included in this analysis plan.

2 STUDY OBJECTIVE(S), TREATMENTS, AND ENDPOINT(S)

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objectives of this study are:

Part A:

- To evaluate the safety and tolerability of ASN002 including dose-limiting toxicities (DLTs) and to determine the maximum tolerated dose (MTD).

Part B:

- To evaluate the safety, tolerability, and preliminary efficacy of ASN002 in subjects with relapsed/refractory diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), myelofibrosis (MF), and chronic lymphocytic leukemia (CLL).

2.1.2 Secondary Objectives

Part A and B:

- To evaluate the pharmacokinetic (PK) profile of ASN002 after single and multiple doses.

2.1.3 Exploratory/Pharmacodynamic Objectives

Parts A and B:

- To evaluate the effects of ASN002 on Phospho-STAT3, Phospho-S6, Phospho-SYK 525/526, Phospho-ERK, and a panel of markers of inflammation (Appendix C of Protocol Amend 6).
- Evaluate the response to therapy based on DLBCL molecular subtype [germinal center B-cell like (GCB) or activated B-cell (ACB)].
- To evaluate the effects of ASN002 on JAK (V617F) mutant allele burden in subjects with MF.
- To evaluate the effects of ASN002 on BCL2, and chromosome 17p.

2.2 Treatment Comparisons

The dose escalation component (Part A) of this study will identify – based on safety and tolerability – a dose of ASN002 to be evaluated within the cohort expansion component of the study (Part B). In Part B, eligible subjects will enroll into one of the six disease-specific cohorts (DLBCL, FL, MCL, PTCL, MF and CLL) and receive the dose of ASN002 identified in Part A.

2.3 Study Endpoints and Evaluations

2.3.1 Efficacy

2.3.1.1 Primary Efficacy Variable

The primary efficacy variable for this study is disease response to ASN002. It is expected that the investigator will choose the most appropriate method for radiographic assessment of the individual subject's disease status. Subjects with a diagnosis of lymphoma are expected to undergo CT (for non-FDG-avid lymphoma), or PET-CT (for FDG-avid lymphoma) for their efficacy evaluation. Subjects with advanced or metastatic solid tumors are expected to undergo CT with contrast (unless medically contraindicated) or MRI for their efficacy evaluation.

For patients with MF spleen measurement will be performed by palpation and by MRI (preferred) or CT scan.

For patients with CLL a baseline CT scan of chest/abdomen/pelvis and a bone marrow aspirate and biopsy are desirable.

If Part B is not completed, only listings will be generated for descriptive summary of efficacy.

DLBCL, MCL, FL, and PTCL

The International Conference on Malignant Lymphoma (ICML) Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (2014 Lugano Classification) will be used to determine the stage of subjects with lymphoma, and the response to treatment.

For cohorts that have at least 5 subjects at the recommended Part B dose of 75 mg BID, the following endpoints will be used to determine the response to treatment with ASN002 in subjects with lymphomas:

- Objective Response Rate
- Duration of Response
- Time to Tumor Progression (TTP)
- Progression-free Survival (PFS)
- PFS rate at week 24

For cohorts with less than 5 subjects at the recommended Part B dose of 75 mg BID, efficacy will be summarized in a descriptive manner for those subjects who have at least stable disease per protocol criteria.

Advanced Solid Malignancies

The Tumor, Nodes, Metastasis (TNM) staging system developed by the American Joint Committee on Cancer (AJCC) will be used to record the subject's clinical stage. Disease response will be assessed using the RECIST 1.1 criteria.

For cohorts that have at least 5 subjects at the recommended Part B dose of 75 mg BID, the following endpoints will be used to determine the response to treatment with ASN002 in subjects with solid tumors:

- Objective Response Rate
- Duration of Response

- TTP
- PFS
- PFS rate at week 24

For cohorts with less than 5 subjects at the recommended Part B dose of 75 mg BID, efficacy will be summarized in a descriptive manner for those subjects who have at least stable disease per protocol criteria.

Myelofibrosis

The International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) response criteria will be used to evaluate the response to treatment with ASN002. If less than 5 subjects were enrolled at the recommended Part B dose of 75 mg BID, efficacy will be summarized in a descriptive manner for those subjects who have at least stable disease per protocol criteria.

The following endpoints will be used to determine the response to treatment with ASN002 in subjects with MF:

- Splenic response rate at week 24
- Clinical improvement rate at week 24
- Symptom response evaluated using the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) tool
- rate of RBC transfusion through week 24

CLL

The response in patients with CLL will be evaluated according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia with the exception that lymphocytosis will not be the sole criterion for disease progression. For patients with persistent lymphocytosis, a partial response in all other measures will be defined as a partial response with lymphocytosis.

If less than 5 subjects were enrolled at the recommended Part B dose of 75 mg BID, efficacy will be summarized in a descriptive manner for those subjects who have at least stable disease per protocol criteria.

The following endpoints will be used to determine the response to treatment with ASN002 in subjects with CLL:

- Objective Response Rate
- Duration of Response
- TTP
- PFS
- PFS rate at week 24

2.3.1.2 Secondary Efficacy Variables

- Eastern Cooperative Oncology Group (ECOG) performance status – ECOG performance status will be assessed in accordance with the schedule of assessments (Section 3.2). Change from baseline in ECOG performance status will be evaluated for each post-baseline assessment.

2.3.1.3 Exploratory Efficacy Variables

The exploratory pharmacodynamics variables for efficacy are:

- Inhibition of phosphorylation of S6, STAT3, SYK 525/526, and ERK.
- Inhibition of the basal B-cell surface activation markers, CD69 and CD88.
- Change from baseline in JAK (V617F) in ML patients.
- Change from baseline in BCL and chromosome 17p in CLL patients.
- Reduction of CRP, β2-microglobulin, and IL-10.
- Change from baseline in a panel of markers of inflammation (see Appendix C of the Study Protocol for the panel of markers).

2.3.2 Safety Evaluations

The primary objective of part A of the study is to evaluate the safety and tolerability of ASN002 including DLTs and to determine the MTD. This will be accomplished by evaluation of the safety and occurrence of DLTs at each dose level.

All adverse events (AEs), unless they have been determined to be not related to study drug, will be taken into consideration in determining a DLT. NCI CTCAE version 4.03 will be used to grade AEs. A DLT is defined as follows:

Non-hematologic DLT
Any grade ≥ 3 AE, with the following exceptions: symptomatic adverse events such as nausea, vomiting and diarrhea will not be considered dose limiting if they can be reduced to less than grade 3 within 72 hours with standard supportive measures such as antiemetics and antidiarrheals.

Hematologic DLT
- A grade ≥ 4 neutropenia or thrombocytopenia that lasts more than 7 days after the last dose of study drug;
- Febrile neutropenia;
- A grade ≥ 3 thrombocytopenia in the presence of bleeding.

If one of the first 3 patients treated at a given dose level develops a DLT, up to 3 additional patients are to be treated at that dose level. If at least 2 patients treated at a given dose level develop DLT, dose escalation is to be stopped, and the penultimate dose level will be considered the MTD.

The MTD is defined as a dose level immediately below that at which ≥ 2 of 6 subjects experience a DLT. Subjects considered to be evaluable for the MTD determination are the subjects who have received the study drug for 28 days or who have discontinued the study drug earlier than 28 days because of a DLT.

The safety evaluations used to define tolerability and determine DLTs will include the following:

- Adverse events (AEs), monitored from the time the subject signs the consent form until 30 days after the last dose of ASN002;
- Prior, concomitant, and post medication use;
- Extent of exposure to study drug;
- Study drug compliance;
- Clinical laboratory tests (hematology, lipid panel, liver function, comprehensive metabolic panel, urinalysis, pregnancy [if applicable]);
- Vital signs;
- 12-lead Electrocardiogram (ECG);
- Physical examination.

3 STUDY DESIGN

3.1 Overall Study Design and Treatment Groups

This study will be performed at approximately 3 to 15 study centers located in the United States and Latin America.

The study is an open-label, non-randomized, uncontrolled, multicenter, dose escalation, cohort expansion and extension study with single and multiple-dose PK in subjects with relapsed/refractory lymphomas, MF, CLL. and advanced/metastatic solid tumors for which no standard therapy exists. The study will be conducted in 2 parts:

Part A: Evaluation of the safety and tolerability of escalating multiple doses of ASN002;

Part B: Cohort expansion of 6 identified disease-specific cohorts (DLBCL, MCL, FL, PTCL, MF and CLL) from Part A to further evaluate the safety, tolerability and antitumor activity of multiple doses of ASN002.

Parts A will be a “3+3” dose escalation scheme beginning with dose level 1 at a dose of 10 mg every 12 hours. Subjects will receive a single dose of ASN002 on Day 1, followed by every 12 or 24 hours, as assigned, dosing beginning on Day 3. The dose of ASN002 will be escalated to identify DLTs, and the MTD. If an MTD is not identified by the last scheduled cohort, dose escalation will continue in less than or equal to 50% increments until the MTD is identified. If supported by the PK profile, transition to once daily dosing may be considered. The starting dose of the once daily (qd) dosing cohorts will not exceed the total daily dose of the highest twice daily dose that is considered safe and well tolerated. Daily dosing cohorts may include doses beginning at 60 mg QD. Additional dose escalation may be performed for the qd dose cohorts, if the MTD is not identified by the 100 mg qd dose.

The study design includes a screening period (up to 28 days), and a DLT observation period of 28 days (Cycle 1). A subject with no DLTs during Cycle 1 will have the opportunity to continue to receive ASN002, at the discretion of the investigator. Subjects that are not able to complete Cycle 1 for reasons other than DLT will be replaced. Subjects participating in Parts B who discontinue from the study due to non-compliance or protocol violations may be replaced at the discretion of the Sponsor. Subjects may

receive treatment with ASN002 in the absence of intolerable toxicity or disease progression for up to 12 months. If the subject is not a candidate for or chooses not to participate in additional treatment cycles, an end of treatment visit will be performed. A follow-up visit will be performed at least 30 days after the last dose of study medication.

In Part A of the study, after the Safety Review Committee (SRC) has met and agreed to dose escalation, up to 3 additional subjects may be allowed in a lower cohort to gather additional PK, PD and safety data. The inclusion of these subjects will be based on agreement with members of the SRC and the Sponsor

Part B will be an expansion of the MTD cohort into 6 disease-specific groups to evaluate preliminary clinical anti-tumor activity. Each cohort will contain up to 14 subjects with DLBCL, MCL, FL, PTCL, MF, and CLL. Subjects may receive treatment with ASN002 in the absence of intolerable toxicity or disease progression for up to 12 months.

3.2 Summary of Scheduled Events

Table 1: Schedule of Assessments (Part A)

Study Procedure	Screening D (-28 to -1)	Cycle 1 Days										Subsequent Cycles[a]				End of Treatment[b]	30-Day Follow-up
		1	2	3	4	8	11	15	16	22	28	1	15	22	28		
Informed Consent	X										End of Cycle 1				End of Cycle		
Eligibility Screening	X																
Demographics	X																
Medical History	X																
Physical Examination[c]	X	X						X				X				X	X
Disease History & Stage	X																
Vital signs[d]	X	X	X	X		X		X	X	X		X	X			X	X
Height[e] and weight	X	X										X				X	X
ECOG PS	X	X										X				X	
12-lead ECG	X	X[f]	X	X		X		X[f]	X	X						X	
Pregnancy test, if applicable	X	X										X				X	
Serum Chemistry[g]	X	X				X		X		X		X	X			X	X
Liver Function Tests[g]	X	X			X	X	X	X		X		X	X			X	X
CBC with Diff and Platelets[g]	X	X				X		X		X		X	X			X	X
Urinalysis[g]	X	X										X				X	
Disease Assessment[h]	X													X		X	
Medication Administration		X	X[i]	X	X----------							X---------					
Pharmacokinetic Sample		X	X[j]	X[j]		X[j]		X	X[j]	X[j]		X[j,k]					
Pharmacodynamic Sample		X				X		X				X[l]					
Adverse Events		X----------															
Concomitant Medications	X----------																
Dispense Drug Diary			X									X					
Medication Compliance						X		X		X		X				X	

[a] Subsequent cycles should begin within 3 days of either Day1, or the previous cycle. Subjects may continue to receive additional cycles of ASN002 in the absence of intolerable or severe toxicity or disease progression. All safety laboratory and radiographic evaluations for continued dosing must be completed prior to evaluation by the investigator.
[b] End of Treatment Visit should take place < 1 week from the last dose of study medication.
[c] Complete physical examination will be conducted at screening and end of treatment. Other examinations may be brief, problem-focused examinations and review of systems.
[d] Vital signs will consist of heart rate, blood pressure, and temperature. Day 3 and Day 16 apply to QD dosing cohorts only.
[e] Height to be obtained at baseline only.
[f] Refer to the Schedule of Assessments Table for Day 1, and Day 15. Day 3 and Day 16 apply to QD dosing cohorts only.
[g] Laboratory assessments may be drawn up to 72 hours in advance of the scheduled visit for patient convenience. Refer to Error! Reference source not found. for a complete list of required safety laboratory assessments. Labs need not be repeated on day 1 cycle 1 if baseline data were obtained within the preceding 72 hours.
[h] Subjects will be evaluated based on malignancy-specific requirements. Evaluations may be completed up to one week prior to the nominal visit.
2014 Lugano Classification (every 12 weeks ± 1 week) or
RECIST 1.1 for advanced solid tumors every 8 weeks for the first 24 weeks, and every 12 weeks thereafter after the initiation of treatment with ASN002.
[i] In the QD dosing cohorts, the Day 2 dose should be omitted. All other assessments should be performed.
[j] PK samples are to be drawn as trough samples prior to study drug administration.
[k] Cycle 2, Day 1 only, prior to dose administration.
[l] 30-day follow up for Adverse Events may be conducted as a telephone contact.

Table 2: Schedule of Assessments (Part B)

Study Procedure	Screening D (-28 to -1)	Cycle 1					Subsequent Cycles[a]			End of Treatment[b]	30-day Follow Up
		Days									
		1	2	8	15	22	1	15	22		
Informed Consent	X										
Eligibility Screening	X										
Demographics	X										
Medical History	X										
Physical Examination[c]	X	X					X			X	X
Disease History & Stage	X										
Vital signs[d]	X	X			X		X			X	X
Height[e] and weight	X						X			X	X
ECOG PS	X	X					X			X	
12-lead ECG	X	X					X			X	
Pregnancy test, if applicable	X									X	
Serum Chemistry[g]	X	X		X	X		X	X		X	X
Liver Function Tests[g]	X	X		X	X		X	X		X	X
CBC with Diff and Platelets[g]	X	X		X	X		X	X		X	X
Urinalysis[h]	X						X				
Disease Assessment[i]	X								X		
MPN-SAF (MF subjects only)[j]		X		X	X	X	X	X	X	X	
Medication Administration		X----------							----------X		
Pharmacokinetic Samples		X[k]	X[l]	X[l]	X[l]		X[l]	X[l]		X[m]	
Pharmacodynamic Samples		X			X		X				
Adverse Events		X----------							----------X[n]		
Concomitant Medications	X----------										
Dispense Drug Diary		X					X				
Medication Compliance							X			X	

[a] Subsequent cycles should begin within 3 days of either Day1, or the previous cycle. Subjects may continue to receive additional cycles of ASN002 in the absence of intolerable or severe toxicity or disease progression. All safety laboratory and radiographic evaluations for continued dosing must be completed prior to evaluation by the investigator.
[b] End of Treatment Visit should take place < 1 week from the last dose of study medication.
[c] Complete physical examination will be conducted at screening and end of treatment. Other examinations may be brief, problem-focused examinations and review of systems. Physical exam includes spleen measurement for subjects with MF.
[d] Vital signs will consist of heart rate, blood pressure, and temperature.
[e] Height to be obtained at baseline only.
[f] Refer to the Schedule of Assessments Table for Day 1, and Day 15.
[g] Laboratory assessments may be drawn up to 72 hours in advance of the scheduled visit for patient convenience. Refer to Error! Reference source not found. for a complete list of required safety laboratory assessments. Labs need not be repeated on day 1 cycle 1 if baseline data were obtained within the preceding 72 hours. Part B: Day 22 laboratory assessments may be omitted.
[h] Urinalysis is conducted on Day 1, and then as clinically indicated.
[i] Subjects will be evaluated based on malignancy-specific requirements. Evaluations may be completed up to one week in advance of the nominal time to accommodate scheduling.
Lymphoma: every 12 weeks by 2014 Lugano Classification.
MF: MDS-SAF questionnaire to be done weekly, spleen measurement by PE every 4 weeks for the first 24 weeks and then every 12 weeks, spleen measurement by MRI/CT to be done at baseline and on week 24.
CLL: every 8 weeks during the first 24 weeks and every 12 weeks thereafter by IWCLL criteria (and updates). A CT scan of chest/abdomen/pelvis is recommended if previously abnormal and otherwise in case of CR, a bone marrow aspirate/biopsy is recommended in case of CR or cytopenia of uncertain cause.
[j] The MPN-SAF questionnaire will be completed weekly while on-study.On Day 22, and during subsequent cycles a form for completion at home should be given to the subject.
[k] PK timepoints for Day 1 will be collected at predose, 2, 4 and 6 hours.
[l] Predose PK samples are to be drawn as trough samples prior to study drug administration. A trough PK sample will be drawn on Day 1 of Cycle 3, 6, 9 and 12.
[m] Two PK samples are requested at the end of treatment. The first may be drawn with other safety laboratory assessments.The second optional sample is drawn 2-3 hours later.
[n] 30-day follow up for Adverse Events may be conducted as a telephone contact.

Table 3: Cycle 1 Serial Assessments (Part A)

Day	Nominal Time[a] (hours)	Windows	Assessments[b]			
			PK Sample	PD Sample	ECG	VS
Day 1	Predose	Up to -60 minutes	X	X	X	X
	0.5	(± 5 mins.)	X			
	1.0		X		X	X
	2.0		X	X	X	X
	4.0	(± 15 mins.)	X		X	X
	8.0	(± 1 hr)	X			
	12.0		X		X	X
Day 2	24 h post-day 1 dose	± 1 hr from 1st dose	X		X	X
Day 3[c] **(QD cohorts only)**	48 h post-Day 1 dose	± 2 hr from 1st dose	X		X	X
Day 8	Predose	N/A	X	X	X	X
Day 15	Predose	Up to -60 minutes	X	X	X	X
Day 15	0.5	(± 5 mins.)	X			
	1.0		X		X	X
	2.0		X	X	X	X
	4.0	(± 15 mins.)	X		X	X
	8.0	(± 1 hr)	X			
	12.0		X		X	X
Day 16 **(QD cohort only)**	24 h post-Day 15 dose		X		X	X
Day 22	Pre-dose	N/A	X		X	X
Cycle 2, Day 1	Pre-dose	N/A	X	X		X

[a] The actual time of all assessments will be recorded in source documents and on the eCRF

[b] The priority of assessments for the procedures is (1) PK/PD, (2)ECG, (3)VS

[c] Only subjects in single daily dose cohorts require PK on Day 3 and 16.

Table 14: PK/PD Assessments (Part B)

Day	Nominal Time[a] (hours)	Windows	Assessments	
			PK Sample	PD Sample[b]
Day 1	Predose	N/A	X	X
	2. 0	± 15 mins	X	X
	4.0	± 15 mins	X	
	6.0	± 30 mins	X	
Day 2	Predose	N/A	X	
Day 8	Predose	N/A	X	
Day 15	Predose	N/A	X	X
	2.0	± 15 mins.	X	X
Cycle 2, Day 1	Predose	N/A	X	X
	2.0	± 15 mins.	X	X
Cycle 2, Day 15	Predose	N/A	X	
Day 1, Cycle 3, 6, 9 and 12	Predose	N/A	X	
End of Treatment	N/A	N/A	X	
	2-3 (optional)	± 15 mins.	X	

[a] The actual time of all assessments will be recorded in source documents and on the eCRF
[b] In Part B of the study, only selected sites will be collecting the PD samples for phospho-proteins

4 SAMPLE SIZE CONSIDERATIONS

Part A:
A traditional 3+3 design will be used to identify the MTD. In addition to the 40 subjects enrolled in the previous amendments, an additional 24 subjects may be enrolled and dose in either fed or fasted states. A total of 64 subjects will be enrolled into the Part A dose escalation phase of the study. No randomization will be performed for Part A.

Part B: A sample size of 84 subjects (14 each in DLBCL, MCL, FL, PTCL, MF, and CLL) will be enrolled. The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative. A total of 14 patients will be accrued in each cohort. The null hypothesis will be rejected if at least 3 responses are observed in 14 subjects. This design yields a type I error rate of 0.02 and power of 0.9 when the true response rate is 0.4.

5 ANALYSIS POPULATIONS

5.1 Safety Population

The safety population includes all subjects who receive at least 1 dose of study medication. Safety analyses will be conducted against the safety population. The safety population will apply to Parts A and B.

5.2 Efficacy Population (EP)

The efficacy population (EP) will include all subjects who have an evaluable screening and post-dose tumor assessment. The EP will be used as the supportive analysis population for summaries and analyses of the efficacy endpoints. No EP will be reflected if Part B is not completed for at least one indication.

5.3 Per-Protocol (PP) Population

The PP population includes all EP subjects without major protocol deviations. The PP population will be used as the primary analysis population for efficacy summaries and analyses. No PP will be reflected if Part B is not completed for at least one indication.

6 CONSIDERATIONS FOR DATA ANALYSIS

6.1 Programming Environment

All analyses will be conducted using SAS® version 9.3.

6.2 Strata and Covariates

There are no other planned strata or covariates for the analysis of this study.

6.3 Subgroups

There are no planned subgroup analyses.

6.4 Multiple Comparisons and Multiplicity

There are no planned adjustments for multiple hypothesis testing.

6.5 Significance Level

Unless otherwise specified, all statistical analyses will be conducted using a one-sided significance level (α) of 0.05 and one-sided hypothesis testing.

6.6 Statistical Notation and Methodology

Unless stated otherwise, the term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous data and frequencies (counts and percentages) for categorical data. Unless otherwise noted, all data collected during the study will be included in subject data listings and will be sorted by study component (i.e., Part A, and Part B), dosing cohort, subject number, and date/time within each subject.

7 DATA HANDLING METHODS

7.1 Missing Data

7.1.1 Date Values

The missing component(s) of incomplete dates (e.g. start and/or stop dates of AE, concomitant medication, medical history) will be assumed as the most conservative value possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations, etc. If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components. For determination of treatment-emergent status, the start date will be imputed as the date of the first dose of study drug.

Date imputation will only be used for computational purposes such as treatment-emergent status, etc. Actual data values, as they appear in the original CRFs, will be presented in the subject data listings.

7.1.2 Non-Date Values

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been enrolled. There will be no imputation for missing data.

7.2 Visit Windows

The screening assessments and the treatment/post-treatment assessments will be partitioned into the following two visit windows:

- A screening window, beginning on Day -28 and ending on Day -1.
- A treatment window, beginning on Day 1 of Cycle 1 and ending on the Study Day (see Section 7.3) corresponding with the End of Treatment visit.

Subject visits for all parts of the study (i.e., Part A, and Part B) will be presented according to the nominal visit as obtained upon the CRF. All values will be included in the subject data listings.

7.3 Data Derivations

Day 1 will be the date corresponding to the first administration of study drug.

Baseline values will be considered as the last non-missing assessment prior to the first administration of study drug (ASN002). Pre-dose assessments of ECG, vital signs, and the samples for pharmacokinetics (PK) and pharmacodynamics (PD) on Day 1 of Cycle 1 will be considered the baseline assessment for

each of these respective study procedures. Assessments performed on Day 1 of Cycle 1 for all other study procedures will be assumed to have been performed prior to administration of ASN002. Unless otherwise specified, change from baseline calculations for a treatment window assessment will be the applicable treatment window assessment minus the baseline assessment.

For a given date within the treatment window, Study Day will be computed as the given date minus Day 1 of Cycle 1 plus 1 day (i.e., Study Day = Date – Day 1 of Cycle 1 + 1). For a given date within the screening window, Study Day will be computed as the given date minus Day 1 of Cycle 1 (i.e., Study Day = Date – Day 1 of Cycle 1).

For a given entry upon the Drug Log Form of the eCRF, total dose of ASN002 administered for the entry will be calculated as:

Total dose of ASN002 for entry (mg) = Total Daily Dose (mg/day) * (Stop Date – Start Date + 1).

Furthermore, for a given date which lies between (non-inclusive) the Start Date and Stop Date, partial total dose of ASN002 for the entry can be calculated by substituting the given date for either the Stop Date or Start Date within the above formula.

For each visit over the treatment window and overall, total dose of ASN002 will be calculated as the cumulative sum of the total dose and partial total dose of ASN002 administered over the entries to the Drug Log Form pertaining to the visit (or, overall). An entry to the Drug Log Form will pertain to a given visit, if: (1) the Start Date of the entry is earlier than the date corresponding to the visit; and, (2) the Stop Date of the entry falls after the date corresponding to the immediately preceding visit.

Expected total dose of ASN002 to be administered – for, a Drug Log Form entry, a visit, or overall – will be calculated similarly, with the daily dose corresponding to the assigned treatment cohort substituted in lieu of Total Daily Dose within the above formula.

8 STUDY POPULATION

Unless otherwise stated, all study population analyses will be performed against the Safety Population.

8.1 Subject Enrollment

Subject enrollment will be summarized as the number and percentage for each analysis population (EP, PP, and Safety) by treatment cohort and overall (all treatment cohorts combined). The denominators for calculating percentages will be based on the number of subjects in each analysis population by treatment cohort and overall.

Enrollment information will be provided in a data listing by subject.

8.2 Subject Disposition

Subject disposition will be summarized by treatment cohort and overall. The number and percentage of subjects who are still on treatment on this study or who have rolled over to the extension study, and the number and percentage of subjects discontinued from the study will be presented by reason for discontinuation. The denominators for calculating the percentages will be based on the number of subjects in the analysis population by treatment cohort and overall.

Discontinued subjects will be provided in a data listing by subject.

8.3 Protocol Deviations

Major protocol deviations are defined to be those deviations that could potentially bias either efficacy or safety summaries of the study. Subjects associated with major protocol deviations will be identified prior to database lock.

Major deviations from the clinical protocol may include, but are not limited to:

- Subjects that were administered at least one dose of ASN002 and who did not satisfy the inclusion/exclusion criteria.
- Subjects meeting conditions for withdrawal that were not withdrawn.
- Subjects that received a prohibited concomitant medication.
- Repeated non-compliance in administration of study drug, as monitored by the study site at the assessment timepoints shown within Table 1 of Section 3.2, where non-compliance is less than 80% or greater than 105% of expected administration of study drug.

The number and percentage of subjects with major deviations and the number of deviations will be summarized by type of violation and overall. Summaries will be provided by treatment cohort and overall. The denominators for calculating percentages will be based on the number of subjects in the analysis population for each treatment cohort and overall.

Major protocol deviations will be provided in a data listing by subject.

8.4 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria deviations will be provided in a data listing by subject.

8.5 Demographic Characteristics

Subject demographics at screening: gender; age; ethnicity; height; weight; and, race, will be summarized by treatment cohort and overall.

Gender, ethnicity, and race will be summarized as the number and percentage (n, %) of subjects within each category by treatment cohort and overall. Denominators used in the calculation of percentages will be based on the number of subjects in the analysis population for each treatment cohort and overall.

Age, weight, and height will be summarized as a continuous variable using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by treatment cohort and overall.

Demographic characteristics will be provided in a data listing by subject.

8.6 Clinical Stage

Subject clinical stage at study entry will be summarized by diagnosis type (Lymphoma or Solid Tumor). For subjects with Lymphoma diagnosis, the summary of clinical stage will include stratification on the following factors: FDG avidity status; Lymphoma type; and, Lugano Stage at study entry. For subjects with Solid Tumor diagnosis, clinical stage will be summarized by TNM Stage at study entry. Summaries will present the number and percentage of subjects by treatment cohort and overall. Denominators used in the calculation of percentages will be based on the number of subjects in the analysis population for each treatment cohort and overall.

Clinical stage will be presented in a data listing by subject.

8.7 Prior Antineoplastic Therapy

Prior antineoplastic cancer therapy will be reported in a data listing by subject.

8.8 Medical History

Medical history (excluding prior antineoplastic cancer therapy) will be provided in a data listing by subject.

9 EFFICACY ANALYSIS

The PP population and EP will be used for summaries and analyses of the efficacy variables described below.

All efficacy results for each lymphoma type will be calculated and presented separately. Efficacy results for solid tumor patients will be shown in listings, and parameters will be shown in text and text tables by range only.

If Part B is not completed for at least one indication, efficacy parameters will only be reported as individual patient listings for summary descriptive reporting in the CSR.

9.1 Evaluation of Disease Status

9.1.1 DLBCL, MCL, FL, PTCL

For cohorts that have at least 5 subjects at the recommended Part B dose of 75 mg BID, the frequency of responders according to the 2014 Lugano Classification for subjects with lymphoma will be evaluated at each dose level and for each lymphoma subgroup in Part B. Differences in response to therapy based on the molecular subtypes of DLBCL will be explored.

Assessments will be made after every two 28-day cycles of therapy, i.e., starting just before Day 1 of cycle 3 and then just before each odd-numbered cycle, for solid tumor patients and after every 3 cycles, i.e., just before Day 1 of cycle 4 and then just before cycles 7, 10, and 13, etc, for lymphoma patients.

In Part B, response to treatment will be analyzed using the binomial test for each of the disease-specific cohorts (DLBCL, MCL, FL, PTCL, MF and CLL). The dichotomous classifications to be assessed in each binomial test are disease responders versus non-responders. Responders will be considered as subjects with 2014 Lugano Classifications given by Complete Response (CR) or Partial Response (PR), and non-responders as subjects with 2014 Lugano Classifications given by No Response (NR) or Stable Disease (SD), or Progressive Disease (PD). For each binomial test, the null hypothesis is that the rate of disease responders is 5% and the one-sided alternative hypothesis is that the rate of disease responders is greater than 5%. The null hypothesis will be rejected if the p-value is less than 0.05 (i.e., using a one-sided significance level of 0.05).

Summaries for best disease response will be provided by treatment cohort for subjects diagnosed with lymphoma using frequencies (counts and percentages). For Part B, the estimated rate of disease responder and the p-value from the binomial test will be provided by disease-specific cohort (DLBCL, MCL, FL, PTCL, MF and CLL).

Response to treatment will be provided in a data listing by subject.

9.1.2 Advanced Solid Malignancies

For cohorts that have at least 5 subjects at the recommended Part B dose of 75 mg BID, the frequency of responders according to modified RECIST 1.1 criteria for subjects with advanced solid malignancies will be evaluated at each dose level. The changes from baseline in overall assessment of CR, PR, SD and PD will be reported. The frequency of disease assessment to treatment will be provided in a data listing by subject.

9.1.3 Myelofibrosis

For cohorts that have at least 5 subjects at the recommended Part B dose of 75 mg BID, the frequency of response and type of response according to IWG-MRT response criteria for subjects with MF will be evaluated. The frequency of disease assessment to treatment and type of response (e.g. every 2 months, and spleen volume) will be provided in a data listing by subject.

9.1.4 Chronic Lymphocytic Leukemia

For cohorts that have at least 5 subjects at the recommended Part B dose of 75 mg BID, the frequency of response, and type of response according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia, will be evaluated. For patients with persistent lymphocytosis, a partial response in all other measures will be defined as a partial response with lymphocytosis. Duration of response and the PFS rate at week 24 will also be evaluated.

9.1.5 Evaluation of Performance Status

For cohorts that have at least 5 subjects at the recommended Part B dose of 75 mg BID, the ECOG performance status and the changes from baseline will be presented with frequency tables at each dose level.

The ECOG performance status will be assessed according to the Schedule of Assessments (see Section 3.2). ECOG scores – numeric scale, range from 0 to 5, inclusive – will correspond to the ECOG responses, as shown within Appendix B of the Study Protocol. For a given treatment window ECOG assessment, change from baseline (CFB) in ECOG will be calculated as the difference between the treatment window ECOG assessment and baseline ECOG (i.e., CFB in ECOG = treatment window ECOG – baseline ECOG).

Summaries for absolute and CFB in ECOG will be provided by visit and treatment cohort using frequencies (counts and percentages) for each study component separately and combined.

Absolute and CFB in ECOG will be provided in a data listing by subject.

9.2 Evaluation of Time to Treatment

The time (days) on treatment, beginning with the date of first administration of study drug and ending with the date of discontinuation or completion of study treatment, will be provided by treatment cohort using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum.

Time on treatment will be provided in a data listing by subject.

9.3 Evaluation of Time to Progression

For cohorts that have at least 5 subjects at the recommended Part B dose of 75 mg BID, the time to disease progression (radiographic or clinical) will be calculated as the number of days from the date of the

first dose of study medication to the date the progression is observed or death due to tumor progression in the absence of previous documented PD. For subjects who have not progressed at the end of the study, the time to progression will be censored at the last assessment, unless the subject dies due to disease progression.

9.4 Evaluation of Progression-free Survival

For cohorts that have at least 5 subjects at the recommended Part B dose of 75 mg BID, PFS will be calculated as the number of days from the date of the first dose of study medication to the date progression is observed, or death from any cause. PFS will be analyzed using the Kaplan-Meier method.

9.5 Exploratory Efficacy Variables

9.5.1 Panel of Biomarkers

Serum concentrations of the biomarkers Phospho-S6, Phospho-STAT3, Phospho-SYK 525/526, Phospho -ERK, basal B-cell surface activation markers, CD69, CD88, and the panel of markers of inflammation (see Appendix C of the Study Protocol), including CRP, β2-microglobulin, and IL-10, will be collected pre-dose on Day 1 of Cycle 1 (baseline assessment) and at the visits/timepoints indicated within the within the Schedule of Assessments (see Section 3.2). For each biomarker and post-baseline assessment, change from baseline (CFB) in the biomarker will be calculated as the difference between the post-dose assessment and the baseline value (i.e., CFB in biomarker = post-dose biomarker value – baseline biomarker value).

Summaries for absolute and CFB for each biomarker will be provided by visit/timepoint and treatment cohort using descriptive statistics (n, mean, standard deviation, median, coefficient of variance, minimum, and maximum).

Absolute and CFB for each biomarker will be provided in a data listing by subject.

10 SAFETY ANALYSIS

Unless stated otherwise, all safety analyses will be performed on the Safety Population.

10.1 Adverse Events

Treatment emergent adverse events (TEAE) will be classified into a standardized terminology using the Medical Dictionary for Regulatory Activities (MedDRA, version 17.0 or higher) system organ classifications and preferred terms. All summaries of the incidence of treatment-emergent adverse events will be provided using the Safety Population by treatment cohort and overall. Although a preferred term or system organ class may be reported more than once for a subject, each subject will only be counted once in the incidence count for that preferred term or system organ class. Summaries of the following types will be provided:

- Summary of treatment-emergent adverse events;
- Summary of treatment-emergent adverse events by MedDRA system organ class and MedDRA preferred term;
- Summary of treatment-emergent adverse events by MedDRA system organ class, MedDRA preferred term, relationship to study drug, and intensity;

- Summary of serious treatment-emergent adverse events leading to discontinuation from the study by MedDRA preferred term, sorted alphabetically by system organ class and preferred term;
- Summary of treatment-emergent adverse events leading to discontinuation from the study by MedDRA preferred term, sorted alphabetically by system organ class and preferred term.

These summaries will present the number and percentage of subjects reporting an adverse event for each classification level. The denominators for calculating the percentages will be based on the number of exposed subjects in the Safety population (i.e., study drug was administered) in the treatment cohort summarized.

Listing of subject dropouts due to AEs prior to post-dose tumor assessment will be generated. All adverse events, serious adverse events and deaths, and adverse events leading to discontinuation from the study will also be provided in data listings by subject.

10.2 Treatment Exposure

The duration of exposure (days) to study drug, total dose of ASN002, and average dose of ASN002 will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) by treatment cohort. Duration of exposure will be calculated as the difference between the date of last administration of study drug and the date of first administration of study drug plus 1 day.

Exposure data including study drug bottle assignment, date and time of study drug administration at study site visits, diary dispense/return dates, and study drug log data will be provided in separate data listings by subject.

10.3 Prior, Concomitant, and Post-Treatment Medications

Medication usage will be coded using the World Health Organization (WHO) Drug Dictionary. Medication use will be presented for the Safety population by WHO Drug Anatomical/Therapeutic/Chemical (ATC) category and WHO Drug preferred name. Medication use summaries will be presented for prior medication use (prior to first administration of study drug), concomitant medication use (between the date of first administration of study drug, but not beyond the date of the last administration of study drug), and post medication use (superseding the date of last administration of study drug). Summaries will be provided by treatment cohort and overall. Medications with partial start and/or stop dates, which cannot be definitely categorized as prior, concomitant, or post-treatment medications will be considered concomitant.

All summaries will present the number and percentages of subjects using each medication by treatment cohort. The denominators for percentages will be the number of subjects in the analysis population for the treatment cohort summarized.

Prior, concomitant, and post medications will be provided in separate data listings by subject.

10.4 Laboratory Evaluations

Absolute and change from baseline values for continuous hematology panel, lipid panel, comprehensive metabolic panel, and urinalysis parameters will be summarized by analyte, assessment (see Section 3.2), and treatment cohort using descriptive statistics (mean, median, SD, minimum, maximum, and number of subjects). Categorical laboratory evaluations will also be summarized by analyte as the number and percentage of subjects at each possible analyte level. The denominators for percentages will be the number of subjects in the analysis population for the treatment cohort summarized. The following analytes will be considered for all summary tables described within this section: hemoglobin, total white

blood cell (WBC), WBC differential, platelets, alkaline phosphatase (ALP), ALT, AST, bilirubin, creatinine, total cholesterol, and triglycerides.

Shifts relative to baseline will be evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 criteria and presented by analyte, assessment, and treatment cohort. Summaries will contain the numbers and percentages of subjects with sufficient data to evaluate new Grade 1 abnormalities (i.e., normal at baseline) and shifts of one Grade higher relative to baseline.

Data listings for laboratory parameters and shifts will be presented by subject.

10.5 Vital Signs

Vital sign measurements (blood pressure, heart rate, temperature [Visit 1 only]), height (Screening Visit only), and weight will be provided in a data listing by subject.

10.6 Pregnancy Test

Serum or urine pregnancy testing is required at screening and within 72 hours of Day 1 of every Cycle for females of childbearing potential. Results of pregnancy tests will be provided in a data listing by subject.

10.7 Electrocardiograms

For QTcF intervals, the proportion of QTcF above the upper limit of normal – both ≥ 450 msec and ≥ 481 msec will be considered as upper limits of normal QTcF – and change from baseline > 30 msec and > 60 msec will be presented. Denominators for percentages will be the number of subjects in the analysis population for the treatment cohort summarized.

ECG data will be displayed in a data listing by subject.

10.8 Physical Examinations

A complete physical examination (PE) will be performed at the Screening and End of Treatment visits. The examination will include an assessment of the following: general appearance, skin, head and neck (including eyes, ears and throat), thorax, lymph nodes, thyroid, musculoskeletal/extremities (including spine), cardiovascular, lungs, abdomen and neurological systems. The screening exam will also include a measurement of body height and weight. The investigator will review all PE findings for clinical significance. Findings from the screening PE will be recorded as Medical History. Except for the screening PE, only changes from the previous PE will be recorded. Clinically significant changes from the screening PE will be captured as AEs, and analyzed according to the criteria in Section 10.1.

A data listing, comprised of status of whether or not each assessment was conducted and date of each assessment, for physical examinations will be presented by subject.

11 OTHER ANALYSES

11.1 Dose Escalation Safety Analyses

The study will include multiple safety analyses for the dose escalation component (Part A). Each treatment cohort is viewed as a separate safety analysis, insofar as the safety review committee will decide whether the dose escalation will continue to the next planned (or intermediate) dose level, if additional subjects will be added to the current dose level, or if the dose escalation will be stopped. The safety review committee can also terminate the study due to safety concerns. Each review will be conducted with the latest available data.

A data listing of dose-limiting toxicities (DLTs) for Part A will be presented by subject.

11.2 Pharmacokinetic and Pharmacodynamic Analysis

Pharmacokinetic (PK) analysis will be included in a separate analysis plan.

Part A and Part B may be combined for population PK/PD analysis. This analysis will be included in a separate population PK/PD analysis plan.

12 INTERIM ANALYSIS

An interim analysis is not applicable to this study. As this is an open-label study, appropriate analyses will be conducted on an ongoing basis.

13 END-OF-STUDY-ANALYSIS

A final analysis will be conducted after the last patient completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

14 SUMMARY OF CHANGES FROM THE PROTOCOL

No changes from the protocol were made in this analysis plan.

15 REFERENCES

[1] Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. *J Clin Oncol*. 2014; 32(27): 3059-3068.

[2] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45(2): 228-247.