Asana BioSciences, LLC.

[redacted]

ASN002

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

IND # 124113

Date: 17 Dec 2014

Amendment 1: 26 Jan 2015

Amendment 2: 30 Jan 2015

Amendment 3: 17 Mar 2015

Amendment 4: 12 Apr 2016

Amendment 5: 15 Aug 2016

Amendment 6: 24 May 2017

Rationale for the Amendment

1. Based on safety, tolerability, PK and PD considerations, the starting dose for Part B is 75 mg BID.
2. The protocol is amended to include additional dose cohorts in Part B of the study which include: myelofibrosis (MF) including primary MF (PMF), post-polycythemia vera (post-PV) MF, or post-essential thrombocythemia (post-ET) MF; Peripheral T-cell lymphoma (PTCL) and chronic lymphocytic leukemia (CLL). A full rationale for the inclusion of these subjects is found in Section **6.1**.
3. The protocol is amended to in Part A of the study to evaluate the safety and tolerability of ASN002 when co-administered with a meal. Currently ASN002 is administered under fasted conditions. A single dose study in healthy subjects indicated that co-administration with a meal increased systemic exposure by about 80% compared to fasted conditions. The first dose level at which the effect of a meal on safety, tolerability and pharmacokinetics will be evaluated will at least one dose lower than the highest dose evaluated when ASN002 was administered under fasted conditions.
4. Correction of errata from Amendment 05
5. Update of contact information

Summary of Changes

Modifications	Location
An additional 3 disease-specific cohorts, of 14 subjects each, were added in Part B to evaluate preliminary efficacy in Peripheral T-Cell Lymphoma (PTCL), Myelofibrosis (MF) and Chronic Lymphocytic Leukemia (CLL).	
• The medical and scientific rationale for including subjects with PTCL, MF and CLL was added.	Section **6.1**
• The study objectives were modified to allow for the additional cohorts o Additional cohorts added to the primary objective for Part B. o Additional exploratory biomarker objectives were added for pharmacodynamic biomarkers	Synopsis, Section **7.3**
• Additional biomarker assays were added to correlate with any observed clinical activity in DLBCL, MF and CLL.	Synopsis, Section **7.3**, Section **11.3.1**, Section **14**, and **Table 9**
• Forty-two subjects were added to Part B of the study in the additional cohorts of PTCL, MF, and CLL, 14 in each cohort.	Synopsis, Section **8.2**
• Additional efficacy/outcome measurements were added to define the efficacy endpoints for MF, and CLL.	Synopsis, Section **8.6**, Section **11.1.1.3** and Section **11.1.1.4**, Section **15.6.1**, and **Table 2**
• Additional entry criteria were added to support enrollment of subjects with MF, and CLL.	Synopsis, Section **9.1** (10f-n)
• Removed the restriction for subjects with extensive bone marrow involvement to allow for the enrollment of subjects with CLL.	Synopsis, Section **9.1** (10a)
• Previous treatment with JAK inhibitors is allowed for subjects with MF, as this is a standard treatment.	Synopsis, Section **9.2** (16)
• Modifications to the Study Procedures Section were made in accordance to the protocol amendment requirements.	Section **10**
• The study schema was updated to reflect the additional cohorts.	**Figure A**

The Schedule of Assessment Tables were changed to accommodate changes to the study design	
• The interval for Disease Assessments in solid tumors was increased to every 12 weeks after Week 24.	**Table 1**
• An additional Schedule of Assessments Table and PK/PD Table for Part B were added.	**Table 2** and **Table 4**
• The pharmacokinetic (PK), Vital signs, and electrocardiogram (ECG) assessments timepoints were reduced in Part B.	**Table 2** and **Table 4**
• The requirement for Liver Function Testing (LFT) on Days 4 and 11 of Cycle 1 was removed in Part B.	**Table 2**
• Footnotes to the Schedule of Assessments and Cycle 1 Serial Assessments Tables were updated to reflect the changes to the protocol.	**Table 1 - Table 4**
Additional changes to the entry criteria	
• The entry criterion for total bilirubin was lowered to 1.5x the upper limit of normal, as an additional safety measure for a Phase 1 clinical trial.	Synopsis, Section **9.1** (6b)
• The entry criterion for creatinine was expanded to allow calculated creatinine clearance of > 45 ml/min as qualification for the study.	Synopsis, Section **9.1** (6c)
• The interval from prior chemotherapy was modified to include prior oral tyrosine kinase inhibitors. The interval for TKIs is 2 weeks or 5 half-lives, whichever is longer.	Synopsis, Section **9.2** (1)
• Reduced the accepted dose of corticosteroids to a level of 10 mg/day of prednisone or equivalent. Avoids the needs for tapering steroids prior to start of study treatment.	Synopsis, Section **9.2** (7)
• Revised the exclusion of subjects with a known bleeding diathesis, to clarify exclusion based on safety risks.	Synopsis, Section **9.2** (8)
• Revised the PK parameters for Part B of the study.	Synopsis, Section **15.7**, **Table 2**, **Table 4**
Additional changes to the protocol	
• Based on the safety and tolerability data, the starting dose for subjects with lymphoma is 75 mg twice daily. A table for dose modifications was added for Part B	Synopsis, Section **6.4.2**, Section **8.3.2**, **Table 7**
• The summary of risks and benefits was updated with the most recent human data.	Section **6.3**
• Additional cohorts to explore the pharmacokinetic profile of ASN002 in a fed rather than fasted state were added.	Synopsis, Section **6.4.2**, Section **8.3.1**, **Figure A**, and **Table 6**

• The overall survival efficacy variable was corrected to Time to Progression (TTP).	Synopsis Section **15.6.3**
• Biomarkers for C-reactive protein (CRP, beta microglobulin, and Interleukin-10 were removed as these cytokines are part of the inflammation panel.	Synopsis, Section **7.3**, Section **11.3**, and Section **14**
• The total number of subjects enrolled increased from approximately 100 to approximately 148, including early terminations.	Synopsis, Section **8.2**
• The requirements for dose modification in Part B were clarified to indicate that the observed toxicity must be considered drug-related.	Section **8.3.3**
• The dosing schedule for subjects receiving once daily versus twice daily dosing was clarified	Synopsis, Section **8.4**, **Table 1**, and **Table 2**
• The interval for disease assessments was extended for subject with solid tumors to once every 12 weeks after 24 weeks of therapy for subject convenience and to reduce radiation exposure.	Section **10.3.2**
• Concomitant use of medications that affect gastric pH was changed to allow for the use of H2 antagonists as well as antacids within a 2-10-hour window after administration of ASN002	Section **10.6.2**
• Objective outcome measures for solid tumors and lymphoma were added to the efficacy section	Section **11.1.1.1** and **11.1.1.2**
• Assays for CD 69 and CD 86 were removed	Synopsis, Section **11.3**
• The table of PK variables was revised	**Table 11**
Administrative changes	
• The contact information for the CRO was removed. CRO contact information is contained in a separate study manual.	Section **1**
• Abbreviations were added to the List of Abbreviations to support changes to the protocol.	Section **0**
• Additional literature references were added to support the enrollment of subjects with PTCL, MF and CLL	Section **25**
• Minor corrections of errata from Amendment 05	Throughout the protocol
• Headers and tables have been renumbered as appropriate to support the changes to the protocol.	Throughout the protocol

1 SPONSOR CONTACT INFORMATION

Asana BioSciences, LLC	Name	Telephone and Email Address
[redacted]	PPD [redacted]	Office: PPD [redacted] E-mail: PPD [redacted]
[redacted]	PPD [redacted]	Office: PPD [redacted] E-mail: PPD [redacted]
[redacted]	PPD [redacted]	Office: PPD [redacted] E-mail: PPD [redacted]
[redacted]	PPD [redacted].	Telephone: PPD [redacted] E-mail: PPD [redacted]

A list of other key study personnel will be provided separately for your reference.

2 SYNOPSIS

Name of Sponsor/Company: Asana BioSciences, LLC	
Name of Investigational Product: ASN002	
Name of Active Ingredient: ASN002	
Title of Study: 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	
Study period: Estimated date first subject enrolled: March 31, 2015 Estimated date last subject completed: March 31, 2018	**Phase of development: Phase ½**
Objectives: **Primary:** 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) and mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), myelofibrosis (MF), and chronic lymphocytic leukemia (CLL).	

Secondary:

Part A and B:

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

Exploratory:

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**)
- 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 a panel of selected cytokines including inflammatory mediators associated with STAT.

Number of subjects (planned): A total of 148 evaluable subjects are estimated for the study with the distribution as follows:

Part A: Approximately 64 subjects (up to 6 subjects per dose level, with and without food)

Part B: Approximately 84 subjects in 6 groups of 14 each. The groups are patients diagnosed with relapsed/refractory DLBCL, MCL, FL, PTCL, MF, and CLL.

Assuming a 10% early termination rate, the total number of subjects is approximately163.

Study center(s): Approximately 3-15 study centers located in the United States and Latin America

Study Design:

This study is an open-label, non-randomized uncontrolled, multicenter, dose escalation, and cohort expansion study in subjects with histologically or cytologically confirmed advanced malignancies (including solid tumors, lymphomas, MF and CLL for which no standard therapy exists. The study will be conducted in 2 parts:

Part A: Patients with either advanced solid tumors or lymphoma for which no standard therapy exists. Standard 3+3 design in which subjects will be dosed for 28 days, either twice daily or once daily. Dose finding may include dosing with or without food Section **8.4** of the protocol provides detailed instructions on dosing for twice daily and once daily dosing. After assessment of safety, subjects will be eligible to continue study for a maximum number of 12 additional cycles of 28-day treatment as long as they do not meet criteria for withdrawal.

Part B: Expansion cohorts of 14 subjects each with DLBCL, FL MCL, PTCL, MF and CLL treated with the recommended dose of 75 mg BID.

Parts A and B will include a screening period (up to 28 days) and a treatment period for up to 12 months. Following the 28-day DLT assessment period in Part A and throughout Part B, treatment can continue as long a subject demonstrates at least stable disease, or until a subject experiences an intolerable adverse event (AE) or disease progression, withdraws consent or until termination of the study by the sponsor. At the end of treatment, a post-treatment period of 4 weeks will commence that concludes with an end-of-study visit.

Diagnosis and inclusion/exclusion criteria:

Inclusion criteria:

1. Written informed consent obtained prior to any study-related procedure being performed;
2. Male or female subjects at least 18 years of age at the time of consent;
3. ECOG Performance Status 0-2;
4. Radiographically evaluable tumor by 2014 Lugano Classification recommendations (lymphomas) or RECIST 1.1 (advanced solid tumors);
5. Recovered from the reversible effects of prior antineoplastic therapy (with the exception of alopecia and

Grade 1 neuropathy). Screening blood counts of the following:

a. Absolute neutrophil count ≥ 1000/μL

b. Platelets ≥ 75,000/μL

c. Hemoglobin ≥ 8 g/dL (with transfusion support);

6. Screening chemistry values of the following:

a. Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤ 3.0 × upper limit of the normal reference range (ULN)

b. Total bilirubin ≤ 1.5 × ULN

c. Creatinine ≤ 1.5 × ULN, or a calculated creatinine clearance of > 45 ml/min;

7. At screening, life expectancy of at least 3 months;
8. Subject is willing and able to comply with all protocol required visits and assessments;
9. Male and female subjects of child-bearing potential must agree to use medically acceptable methods of birth control throughout the study and for thirty (30) days after the last dose of study medication.
10. Subjects must have one of the following disease characteristics

(Part A only)

a. Histologically or cytologically confirmed metastatic and/or advanced solid tumors or lymphomas for which no standard therapy exists, or who are not eligible for standard treatment. Subjects must have received at least one prior therapy for their malignancy;

Lymphoma (Part A or B)

a. Histologically confirmed DLBCL/MCL/FL/PTCL on the basis of excisional lymph node or biopsy;

b. Diagnosis of relapsed/refractory DLBCL/MCL/FL/PTCL defined as 1) recurrence of disease after a CR, or 2) PR, SD at completion of treatment regimen preceding entry into study.

c. Subjects must not be candidates for standard therapy.

d. Subjects who have not received SCT must be ineligible to receive SCT.

Primary Myelofibrosis (Part B only)

e. Confirmed diagnosis of PMF, post-PV MF, or post-ET MF according to the 2008 WHO criteria

f. High risk or intermediate-2 risk or symptomatic intermediate -1 risk as defined by Dynamic International Prognostic Scoring System (DIPSS), See **Appendix D**.

g. Palpable splenomegaly at least 5 cm below the left costal margin.

h. Known JAK2 mutational status.

i. Refractory/relapsed disease or intolerant to prior JAK2 therapy in the judgement of the investigator.

Chronic Lymphocytic Leukemia (Part B only)

j. Confirmed diagnosis of B-cell CLL, according to International Workshop on Chronic Lymphocytic Leukemia (IWCCL)

k. Measurable disease defined as lymphocytosis> 5,000/uL, or at least one palpable or CT measurable lesion (> 2.0 cm), or quantifiable bone marrow involvement.

l. Active disease requiring treatment as defined by IWCLL consensus criteria

m. Relapsed/refractory disease following prior treatment with at least 2 and no more than 4 prior regimens, which may include chemotherapy, an approved anti-CD20 antibody with or without maintenance therapy, and an approved targeted agent, unless patients are ineligible to receive such agents.

<u>Exclusion criteria</u>:

1. Have received prior standard chemotherapy regimens within 4 weeks of Day 1, for targeted kinase inhibitors, an interval of 5 half-lives or at least 2 weeks whichever is longer.

2. Have received prior treatment with monoclonal antibodies within 6 weeks of first dose of Day 1;
3. Have had major surgery within 30 days prior to the start of Day 1;
4. Received any investigational treatment within 4 weeks prior to the start of study medication;
5. Have had an infection requiring the use of parenteral antibiotics within 14 days prior to the start of Day 1;
6. Have known central nervous system metastasis or CNS lymphoma;
7. Is receiving corticosteroids (>10 mg prednisone daily or equivalent);
8. Has known bleeding diathesis that could be considered a safety concern;
9. Has a history of other malignancy within the 3 years prior to screening, except adequately treated basal cell or squamous cell carcinoma of the skin, or carcinoma in-situ;
10. Has difficulty swallowing medications, or known history of malabsorption syndrome;
11. Has a serious concurrent medical condition, such as:
    a. History of congestive heart failure New York Heart Association (NYHA) class III or IV or uncontrolled hypertension at screening
    b. 12-Lead electrocardiogram (ECG) abnormalities considered by the investigator to be clinically significant or QTcF $\geq$ 450 milliseconds, regardless of clinical significance, at screening. Abnormal ECG may be confirmed with one repeat assessment. For subjects with QTcF$\geq$450 msec on initial ECG, the mean of the two QTcF assessments will determine eligibility;
    c. Myocardial infarction, angioplasty, or cardiac stent placement within the last 6 months.
    d. HIV infection
    e. Known Hepatitis B or C infection. Subjects at high risk for Hepatitis B or C infection should have serology testing to rule out infection;
    f. A medical condition requiring the therapeutic use of anticoagulants;
    g. Condition or situation which may put the patient at significantly increased risk, may confound the study results, or may interfere significantly with subject's participation in the study;
12. Known hypersensitivity to ASN002 or its excipients;
13. Prior participation, i.e., receipt of study medication, in this study;
14. Any condition that, in the opinion of the investigator, would impair the subject's ability to comply with study procedures;
15. Female subjects that are pregnant or lactating.
16. Part B only: Prior treatment with SYK or JAK inhibitors, except for MF patients who have received prior JAK inhibitor.

Investigational product, dosage and mode of administration: ASN002 administered orally. Planned doses are 10, 20, 30, 40, 50, 75, and 100 mg q12h. Cohorts of subjects have been added to explore q24 h dosing, at 80 mg and 120 mg once daily. The initial qd dose will not exceed the total daily dose of the highest well tolerated bid dose. The initial dose taken with food will not exceed 75% of the highest tolerated dose. ASN002 is available in 5-mg, 20-mg, and 50-mg strength tablets.

Duration of study: Parts A and B will include a screening period (up to 28 days) and a treatment period up to 12 months. A subject with no DLTs may have the opportunity to continue treatment at the discretion of the investigator and sponsor. If the subject is not a candidate for, or chooses not to participate in additional treatment, an end-of-study visit will take place followed by a 4-week post-treatment period.

Criteria for evaluation:

Assessment of PK variables: For Parts A, the following single-dose PK parameters for ASN002 will be derived from the concentration-time data of ASN002 after the first dose administration in the fasted state:

- C_{max}: peak plasma concentration

- t_{max}: the time to reach the peak plasma concentration
- $AUC_{0-\infty}$: area under the plasma concentration-time curve from time zero to infinity
- AUC_{0-t}: area under the plasma concentration-time curve from time zero to the last sample with a quantifiable concentration
- AUC_{0-24}: area under the plasma concentration-time curve from time zero to 24 hours
- λ_z: terminal elimination rate constant
- $t_{½}$: terminal elimination half-life

For Part A, the following PK parameters for ASN002 will be calculated after multiple dosing on Day 15:

- C_{max}: peak plasma concentration
- t_{max}: the time to reach the peak plasma concentration
- $AUC_{0-12:}$ area under the plasma concentration-time curve from time zero to 12 hours for bid dosing cohorts,
- $AUC_{0-24:}$ area under the plasma concentration-time curve from time zero to 24 hours for qd dosing cohorts
- CL/F: Total clearance following oral administration
- Vd/F: Volume of distribution at terminal phase following oral administration

For Part B, PK parameters, such as CL/F and other parameters as appropriate, will be determined via population PK analysis

Assessment of efficacy variables:

- Assessment of efficacy will be in accordance with
  - the 2014 Lugano Classification for lymphoma (ref *JCO September 20, 2014 vol. 32 no. 27 3059-3067*), or
  - RECIST 1.1 for advanced solid tumors, or as applicable
  - The International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) response criteria for myelofibrosis
  - International Workshop on Chronic Lymphocytic Leukemia for CLL guidelines, 2008

Assessment of safety: Safety will be assessed by AEs, vital signs, 12-lead ECG, physical examination, and laboratory safety assessments.

Criteria for DLT:

All adverse events unless they have been determined to be not related to study drug will be taken into consideration in determining dose limiting toxicity. During Phase 1, the MTD will be determined based on DLTs occurring during the first 28 days plus any rest period if applicable (i.e. Cycle 1). NCI-CTCAE version 4.03 will be the basis for the descriptive terminology and grading of adverse events. DLT are as follows:

Non-hematologic DLT is defined as:

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.
- Asymptomatic Grade 3 electrolyte abnormalities which can be corrected by optimal supplementation.

Hematologic DLT is defined as:

- ≥Grade 4 neutropenia or thrombocytopenia that lasts more than 7 days after the last dose of study drug.

- Febrile neutropenia
- ≥Grade 3 thrombocytopenia in the presence of bleeding

Assessment of pharmacodynamic parameters:

- Lymphoma
  - Inhibition of phosphorylation of S6, STAT3, $SYK^{Tyr525/526,}$ ERK
  - DLBCL molecular subtyping.
  - Changes from baseline in a panel of markers of inflammation (**Appendix C**)
- MF
  - Changes from baseline in JAK (V617F) mutant allele burden
  - Changes from baseline in a panel of markers of inflammation
- CLL
  - Changes from baseline in BCL2 expression
  - Changes in the status of chromosome 17p
  - Changes from baseline in a panel of markers of inflammation

Statistical methods:

Analysis Populations:

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.

The PK population will include all subjects who receive at least 1 dose of ASN002 and have sufficient plasma concentration data to facilitate the calculation of PK parameters.

The PD population will include all subjects who have a baseline and a post dose assessment of the PD parameters, where a change from baseline is determined.

Efficacy Population (EP) will include all subjects who have an evaluable screening and post-dose tumor assessment.

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.

PK Analyses:

The PK parameters will be derived by non-compartmental analysis for Part A and by population PK analysis for Part B. PK variables including concentrations and parameters will be summarized using descriptive statistics.

Efficacy Analyses:

Evaluation of response rate and survival rate: Responses will be listed by tumor type and dose level.

In Part B, the overall response rate (ORR), time to progression (TTP) and progression free survival (PFS) will be reported for each lymphoma histology, MF, and CLL.

Evaluation of time on treatment: The time from the start of study treatment to the discontinuation or completion of study treatment at each dose level will be summarized descriptively.

All efficacy summaries will be performed by dose level and Parts A and B, separately and combined, if appropriate.

Safety Analyses:

Assessment of safety will be based on the incidence of AEs, AEs resulting in discontinuation, and serious adverse events (SAEs) in each dose level. AEs will be graded using the NCI CTCAE v4 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries of AEs will be provided showing the

number and percentage of subjects who experienced at least 1 AE. These summaries will be presented by dose level, system organ class, and preferred term. The occurrence of AEs will also be tabulated by severity and relationship to study medication. SAEs and AEs resulting in discontinuation will be summarized separately. Vital sign measurements, clinical laboratory results, and ECG findings will be summarized by dose level and time point using descriptive statistics or frequency distributions.

Maximum Tolerated Dose: The MTD is one dose level below that at which at least two subjects in a cohort of up to 6 subjects experience DLTs during the first 28 days.

All safety summaries will be performed by dose level and Parts A, and B, separately and combined, if appropriate.

Sample Size Consideration:

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.

3 SCHEDULE OF ASSESSMENTS

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							X---------X					
Pharmacokinetic Sample		X	X[j]	X[j]		X[j]		X	X[j]	X[j]		X[jk]					
Pharmacodynamic Sample		X				X		X				X[l]					
Adverse Events		X----------X[l]															
Concomitant Medications	X----------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 **Table 10** 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 Days 1	2	8	15	22	Subsequent Cycles[a] Days 1	15	22	End of Treatment[b]	30-day Follow Up
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----------										----------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 **Table 10** 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. See **Table 4** for additional details.
[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 4: 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

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5 LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Table 5: Abbreviations and Specialist Terms

Abbreviation or specialist term	Explanation
ADL	Activities of Daily Living
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ALP	Alkaline Phosphatase
BCR	B-Cell Receptor
bid	Twice daily
CFR	Code of Federal Regulations
CI	Confidence interval
CLL	Chronic Lymphocytic Leukemia
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CRP	C – Reactive Protein
CV	Cardiovascular
CYP	Cytochrome P450
DHHS	Department of Health and Human Services
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose-limiting toxicity
EC_{50}	One half maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ELN	European LeukemiaNet
ET	Essential Thrombocytopenia
FDA	Food and Drug Administration
FIH	First in Human
FL	Follicular Lymphoma
GALT	Gut-Associated Lymphoid Tissue
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hERG	Human Ether-a-go-go Related Gene
HEL	Human Erythroleukemia
HSNTD	Highest Non-Severely Toxic Dose
IB	Investigator Brochure
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IND	Investigational New Drug

Abbreviation or specialist term	Explanation
IRB	Institutional Review Board
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
IWG-MRT	International Working Group-Myeloproliferative Neoplasms Research and Treatment
JAK	Janus kinase
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamics, Progressive Disease
PET	Positron Emission Tomography
PK	Pharmacokinetics
PP	Per Protocol
PR	Partial Response
PTCL	Peripheral T-cell Lymphoma
PV	Polycythemia Vera
qd	Once daily
QTc	Corrected QT interval
QTcF	Fridericia's correction of QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SMP	Safety Management Plan
SCT	Stem Cell Transplant
STD_{10}	Severely Toxic Dose in 10% of animal species
SYK	Spleen tyrosine kinase
TEAE	Treatment-Emergent Adverse Event
TBIL	Total bilirubin
TNM	Tumor, Nodes, Metastasis
US	United States
Units of Measure	
g	Gram
kg	Kilogram
mg	Milligram
mL	Milliliter
µM	Micromole
nM	Nanomole

6 INTRODUCTION

6.1 Background

Spleen tyrosine kinase (SYK) and Janus kinase (JAK) are tyrosine kinases that play important roles in the pathogenesis of various types of lymphomas, myeloproliferative disorders and many types of solid tumors (**1-3**). Inhibition of these targets has been shown to suppress tumor growth in various preclinical and/or clinical studies. Most B-cell malignancies are driven by the B-cell receptor (BCR) pathway and SYK plays a critical role in this pathway by initiating and amplifying the signal from the receptor. A number of small molecule inhibitors of SYK or Bruton's tyrosine kinase (downstream target of SYK) have been shown to suppress the growth of tumor cells in these malignancies (**4**). SYK is therefore an attractive target for the development of therapies for BCR-mediated lymphomas and leukemias.

The JAK kinases (JAK1, JAK2, JAK3 and TYK2) are required for the physiologic signaling through the cytokines and growth factor receptors that intrinsically lack kinase activity **(5,6).** JAK kinases, upon stimulation with factors such as erythropoietin, granulocyte–macrophage colony stimulating factor, IL-3, IL-5, thrombopoietin, and growth hormone, phosphorylate signal transducers and activators of transcription (STAT1 -5) family proteins which are translocated to the nucleus and activate various downstream target genes involved in cytokine and growth factor response. JAK kinases play a significant role in myeloproliferative neoplasms, lymphomas, various solid tumors, and inflammatory conditions. The role of JAK kinases in myeloproliferative diseases has been well validated and ruxolitinib (Jakafi®) is the standard of care for primary myelofibrosis (**7**). Another JAK inhibitor, tofacitinib (Xeljanz®), is an approved drug for rheumatoid arthritis (**8**). JAK inhibitors are also being investigated in the clinic for their efficacy in various lymphomas (**9**, **10**).

ASN002 is an orally bioavailable, potent dual inhibitor of SYK and JAK kinases with 50% inhibitory concentrations (IC_{50} values) of 5-46 nM in biochemical assays. The compound showed antiproliferative activity in a broad panel of cell lines representing both solid and leukemia/lymphoma tumor types. When evaluated in an in vivo multiple myeloma xenograft model, ASN002 caused strong inhibition of tumor growth during the treatment period. There was a significant improvement in median days to incidence of hind limb paralysis in mice treated with ASN002 in a human Erythroleukemia (HEL) model, which is driven by $JAK2^{V617}$ mutation. These preclinical data provide a strong rationale for the evaluation of ASN002 in patients with lymphomas which include mantle cell lymphoma (MCL), diffuse large B cell lymphoma (DLBCL) and follicular lymphoma (FL), and potentially in certain types of solid tumors.

6.1.1 Peripheral T-cell Lymphomas

Peripheral T/NK-cell Lymphomas are an uncommon and heterogeneous group of non-Hodgkin's lymphomas (NHL) that originate from mature, post-thymic (peripheral) T cells or mature natural killer (NK) cells. They represent 10%-15% of all NHL. They are characterized by an aggressive clinical course with inferior outcomes to those of aggressive B-cell lymphomas and the overall 5-year disease-free survival usually is less than 30% (**11**, **12**).

The standard first-line therapy still consists of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or a CHOP-like regimen. Response to first-line regimes is usually poor. After 1st-line failure, treatment options are limited and guidelines suggest enrolling patients in clinical trials.

Four agents received accelerated approval in the US for the treatment of relapsed/refractory peripheral T-cell Lymphomas (PTCL). Two HDAC inhibitors: Istodax® (romidepsin) and Beleodaq® (belinostat), the folate analogue pralatrexate (Folotyn®) and the CD30-directed antibody-drug conjugate brentuximab vedotin (Adcetris®), approved for ALCL only. However, clinical benefit based on patient reported outcome or survival is yet to be demonstrated and there is no consensus on standard treatment for PTCL.

Signaling pathways of therapeutic interest in PTCL include SYK and JAK. Mutations in JAK3 have been seen in natural killer (NK)-cell/T-cell lymphomas, and activation of the JAK/STAT signaling pathway has been described in PTCL (**13**,**14**). SYK expression was assessed in specimens from 141 patients with PTCL diagnosed by WHO criteria (**15**). This study demonstrated that SYK is overexpressed in the majority of PTCLs. suggesting that SYK merits further evaluation as a candidate target for pharmacologic inhibition in patients with PTCL. Together, this data provides a strong rationale for the treatment of PTCL with an inhibitor of SYK and JAK.

6.1.2 Myelofibrosis

Primary myelofibrosis, essential thrombocythemia and polycythemia vera are clonal hematopoietic stem cell disorders, in which the JAK2 V617F mutation is detected in more than 95% of PV patients and in approximately 50% of patients with ET and MF. The JAK-STAT pathway dysregulation, regardless of JAK2 mutational status, is a key pathologic feature of myeloproliferative disorders (MPD) (**16**, **17**). The role of JAK kinases in MPD has been well validated and ruxolitinib (Jakafi®) is the standard of care for primary myelofibrosis (**18**, **19**). However, not all patients respond to ruxolitinib, others experience progression of disease while on treatment, and some have to discontinue treatment due to toxicities (**20**). Treatment options

for MF patients remain very limited. Novel JAK inhibitors are under clinical investigation in this disease.

ASN002 produces a dose-dependent inhibition of phospho-STAT5, the downstream target of JAK1 and JAK3, as demonstrated in a PK-PD study in rats. The compound was also tested in a human Erythroleukemia (HEL) model, which is driven by JAK2V617 mutation, showing a significant improvement in median days to incidence of hind limb paralysis in treated mice. There is therefore a strong rationale for the evaluation of ASN002 in myelofibrosis.

6.1.3 Chronic Lymphocytic Leukemia

Chronic Lymphocytic Leukemia (CLL), as most B-cell malignancies, is driven by the B-cell receptor (BCR) pathway, and spleen tyrosine kinase (SYK), a non-receptor protein tyrosine kinase, plays a critical role in this pathway by initiating and amplifying the signal from the receptor (**21**). The SYK pathway has been clinically validated as a target for CLL therapy through the BTK inhibitor, ibrutinib (Imbruvica®) (**22**, **23**). However, ibrutinib, despite remarkable responses in CLL, does not eradicate the malignant clone and patients who do not respond or become resistant have a dismal prognosis.
Other pathways are being recognized as relevant in CLL biology, including STAT5A/B and STAT3, thus making JAK inhibition a potentially valid target (**24**, **25**). ASN002, a potent dual SYK and JAK inhibitor with potent anti-proliferative activity in B-cell lymphoma models, has demonstrated anti-proliferative activity in ibrutinib and idelalisib resistant cells lines. There is therefore a strong rationale for testing ASN002 in patients with CLL.

6.2 Summary of Nonclinical Studies

Nonclinical studies necessary to support clinical studies have been performed and are summarized below. Further information can be obtained from the Investigator Brochure (IB).

ASN002 showed potent inhibition of SYK and JAK kinases in biochemical assays with an IC_{50} range of 5-46 nM. In mechanistic cell-based studies involving IL-6 and IgE stimulation, ASN002 strongly blocks the SYK and JAK family kinase signaling pathways. The compound inhibited the proliferation of a broad range of lymphoma and solid tumor cell lines including H929, Pfeiffer, SUDHL6 and OCI-Ly10. In a multiple myeloma model (H929), ASN002 exhibited significant efficacy in inhibiting tumor growth (>95% at 90 mg/kg dose). It also delayed the onset of hind limb paralysis in the human erythroleukemia (HEL) model by nearly 33%, compared to vehicle.

ASN002 exhibits a medium to rapid rate of oral absorption, moderate to good oral bioavailability and short T1/2 in pre-clinical species. It exhibits good permeability characteristics and does not

appear to be a Pgp substrate in vitro. It is moderately bound to plasma protein and exhibits good metabolic stability in vitro. Limited metabolism may occur via 2C8, 2D6 and 3A4 pathways. Glucuronidation does not appear to be a pathway for metabolism of ASN002. ASN002 does not appear to have significant inhibitory activity on any of the CYP450 isozymes evaluated, which suggest a low potential for drug-drug interactions. Adequate systemic exposure was observed at the NOAEL in the 28-day GLP toxicology studies in both rat and dog.
The results of the mutagenicity studies suggest the genotoxic potential of ASN002 would be low. Safety pharmacology studies suggest no adverse effects on the cardiovascular (CV), CNS or respiratory systems. Decreased systolic, mean, and pulse blood pressure were observed in the dog, but the effects were reversible and can be easily monitored in the clinic.

In both the rat and dog 28-day toxicity studies, NOAELs were demonstrated. The primary toxicities in bone marrow and lymphoid tissue and were reversible. In dogs, the bile duct and gall bladder were additional target organs. One would expect hematologic changes before significant toxicity in the bile duct or gall bladder.

6.3 Summary of Clinical Studies and Known Risks and Benefits

This is the first study in humans. There are no known clinical benefits associated with ASN002.
As of 09 February 2017, a total of 27 patients had been treated in Part A of this study at doses of 10 – 75 mg twice daily (22 patients), and 80 mg once daily (5 patients). Nineteen patients have solid tumors and 8 have non-Hodgkins' lymphomas of various histologies. Accrual and clinical evaluation of ASN002 is ongoing.

At the cut-off date, 21 patients discontinued treatment, mostly (13/21) due to disease progression.
Overall 24 patients (89%) experienced at least one treatment-emergent adverse event (TEAE), and drug-related TEAEs occurred in 44% of patients. Considering TEAE of all causality, the most commonly involved system organ classes, were gastrointestinal disorders (52% of patients), general disorders and administrative site conditions (44%), nervous system disorders (37%), infections and infestations (30%), and investigations, psychiatric and skin disorders (22% each) Infections and infestations, including events of any severity and causality, appear more common at higher doses, with 1/10 patients (10%) at doses ≤60 mg daily compared with 7/17 (41%) of patients at doses ≥80 mg daily experiencing infectious events. This finding is not unexpected based on experience with other JAK inhibitors.

Individual TEAE occurring in > 10% of subjects, regardless of causality, were chills (5 patients, 19%); anemia, headache, pyrexia, and vomiting (4 patients each, 15%); abdominal pain,

constipation, diarrhea, nausea, small intestine obstruction, fatigue, dehydration, dizziness, anxiety and alopecia, (3 patients each, 11%).
Eleven patients (41%) developed serious adverse events (SAE) and 5 died on study, none of these events were considered to be related to study medication.

No clinically significant abnormalities were noted on ECGs during the study, as of the data cutoff. Hematologic changes, expected based on the preclinical toxicology studies, have usually been mild to moderate at the dose levels tested, but severe anemia, neutropenia, lymphopenia and thrombocytopenia has been observed. Post-treatment white blood cell counts tended to return towards baseline, indicating reversibility of myelosuppression.

Of note, a patient diagnosed with mantle cell lymphoma experienced elevation of the lymphocytosis within a week of initiation of ASN002, per investigator suggestive of lymphocyte 'redistribution'.

Mild abnormalities were noted on liver and renal function tests; however, no systematic shifts suggesting a clear treatment effect were noted. Acute kidney injury has been reported in patients with extensive retroperitoneal lymph node or kidney involvement by lymphoma. None were considered related to study drug.

Evidence of clinical activity was reported in a patient diagnosed with peripheral T-cell lymphoma who experienced reduction of pruritus within a week after initiation of ASN002 80mg QD and for a patient diagnosed with follicular lymphoma (75 mg BID) who experienced reduction in measurements of lymphadenopathy of 43%.

In summary, ASN002 has been relatively well tolerated at the doses up to 75 mg BID (150 mg daily) and the safety profile is in line with that expected based on preclinical data.

Patients developed adverse events, including serious adverse events, which were generally expected given their underlying advanced cancers and lymphomas.

Detailed information on ASN002 clinical data, a description of the nonclinical safety risks and guidance to the Investigators are provided in the Investigator Brochure.

6.4 Rationale

6.4.1 Rationale for Study

The primary objectives of this first-in-human study are to evaluate the safety and tolerability of escalating doses of ASN002 including dose-limiting toxicities (DLTs) and the maximum tolerated dose (MTD), if possible, in subjects with relapsed/refractory lymphoma, and advanced

solid tumors (see **8.5.3** for the definitions of MTD). Preliminary antitumor activity will be evaluated based on the radiographic assessments of response.

Rule-based design (3+3) will be used in the dose escalation component (Part A). This method is commonly used in Phase 1 oncology clinical trials for cytotoxic agents and molecularly targeted agents (**26**). The starting dose will be 10 mg administered every 12 hours. The subsequent cohorts will be treated on increasing dose levels that have been predetermined in the study protocol.

The pharmacokinetic (PK) properties of ASN002 will be evaluated after single and multiple dose administrations at different dose levels. Every 12-hour administration was chosen based on the data from the nonclinical studies.

In Part B, 6 additional cohorts with approximately 14 subjects each will be assigned in disease-specific cohorts (DLBCL, MCL, FL, PTCL, MF, and CLL) to obtain further safety and efficacy data for subsequent development decisions on ASN002. Cohort expansion after determination of the MTD is commonly used in Phase 1 oncology study designs.

Subject with a response to treatment of complete response (CR), partial response (PR) or stable disease (SD) may continue ASN002 treatment until progression of disease (PD) or an intolerable adverse event (AE), withdraw of consent, or until termination of the study by the sponsor.

6.4.2 Rationale for Initial Dose and Schedule

Based on the ICH S9 Guidance (**27**), an acceptable clinical starting dose for an oncology drug is 1/10 the severely toxic dose in 10% of the animals (STD_{10}) in rats, or 1/6 the highest nonseverely toxic dose (HNSTD) in dogs. The NOAEL and HNSTD are considered approximate in these studies.

The non-clinical pharmacology, ADME, safety pharmacology and toxicology of ASN002 have been comprehensively evaluated. For systemic toxicity of ASN002, the NOAEL in the 28-day rat and dog toxicity studies were determined to be 20 mg/kg/day and 15 mg/kg/day, respectively. Based on the recommended body surface area conversion method, the rat and dog NOAEL equate to human equivalent doses of 3 mg/kg and 8 mg/kg, respectively. The proposed starting dose of 20 mg per day (dosed as 10 mg bid) is approximately 1/10 of the human equivalent dose (3 mg/kg) based on the NOAEL in the most sensitive species, i.e., rat, and lower than ICH S9 recommended 1/6 of the highest non-severely toxic dose. Asana BioSciences believes that, considering the intended patient population, the 10-mg bid dose represents a safe starting dose for human exposure.

Preliminary pharmacokinetic analysis of data from cohorts 1-6, and 4a- suggest a half-life at least 12-14 hours. Therefore, once daily dosing of ASN002 are being evaluated in parallel cohorts. Since no DLTs have been identified at the 75 mg BID cohort (150 mg total daily dose) and escalation has continued at 100 mg BID, the first QD regimen was 80 mg QD. Additional doses that are being evaluated include 120 mg QD. Patients will be accrued into these cohorts after safety assessment of the previous cohort during the DLT phase is completed, similar to that for the BID regimen. Since co-administration with a low-fat meal increased ASN002 AUC by about 80% compared to administration under fasted conditions, future cohorts may evaluate safety and tolerability of ASN002 when administered immediately after a light meal. The first dose level at which this evaluation will occur will not be greater than 75% of the highest dose administered under fasted conditions.

6.4.3 Rationale for Recommended Part B Dose

The safety review committee met on May 18, 2017 to review and discuss clinical experience and key safety data. It was agreed that the recommended dose for Part B of the study will be 75 mg BID in patients with hematologic malignancies and that enrollment in Part B can proceed. The selection of the recommended dose was supported by the observation of SAE / DLT (Pneumonia) of a NHL patient at a dose of 100 mg BID, the observed cumulative hematologic toxicity in patients enrolled at a dose of 120mg QD and the SAE (Pneumonitis) observed in a NHL patient at Cycle 2 considered possibly related to ASN002.

At the recommended dose of 75 mg BID good systemic exposure and inhibition of serum biomarkers of inflammation can be observed. In NHL patients, treatment duration for more than 6 months without dose limiting toxicities and evidence of clinical activity is observed.

6.4.4 Rationale for Additional Dose Finding in Advanced Solid Tumors

The SRC also noted that the dose limiting toxicity (Pneumonia) at 100 mg BID and the Cycle 2 SAE (Pneumonitis) at 120 mg QD were reported only in NHL patients, while patients with solid malignancies enrolled at 120mg QD were dosed up to 4 cycles without need for dose reduction.

The SRC agreed to continue dose finding for patients with solid malignancies to further characterize safety, PK and PD in this study population.

6.4.5 Rationale for the Evaluation of ASN002 with Food

Co-administration of ASN002 with a standardized low fat meal increased systemic exposure by about 80% in healthy subjects in a previous study. Future cohorts may evaluate safety and tolerability when ASN002 is administered immediately after a meal. The starting dose level at which the effect of a meal on safety, tolerability and pharmacokinetics will be evaluated will be

at least one dose lower than the highest dose evaluated when ASN002 was administered under fasted conditions

7 OBJECTIVES

7.1 Primary Objectives

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).

7.2 Secondary Objectives

Part A and B:

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

7.3 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**)
- 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.

8 INVESTIGATIONAL PLAN

8.1 Study Design

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.

The study design is illustrated in **Figure A**. The Schedule of Assessments for all parts of the study is located in **Table 1** and **Table 2.**

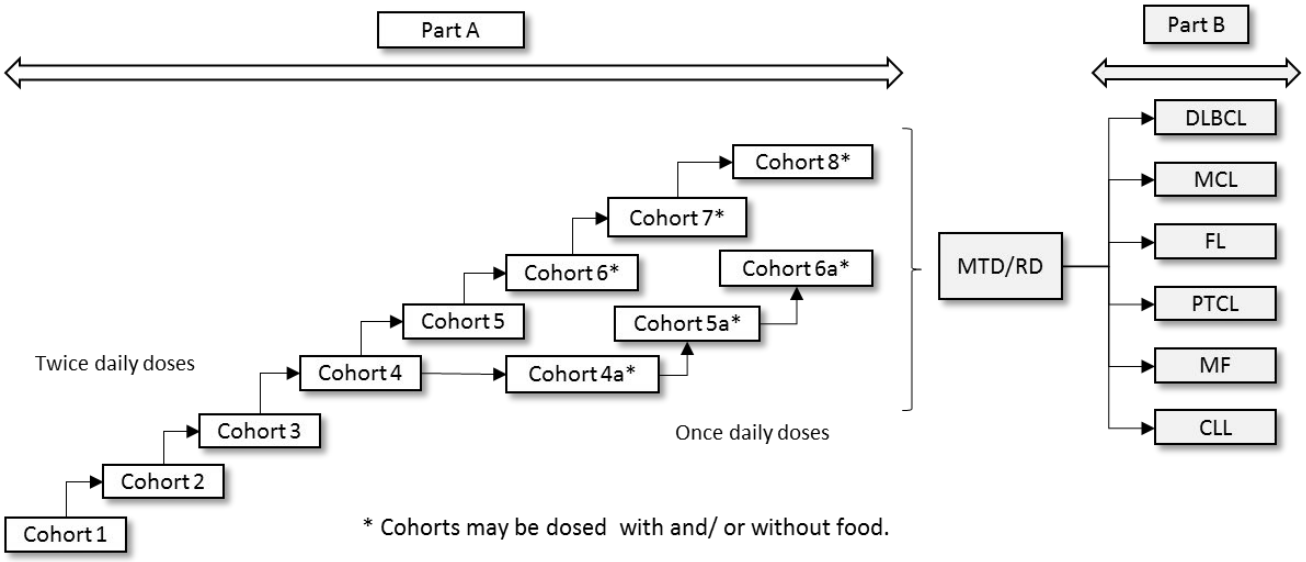

Figure A: Study Schema

8.2 Number of Subjects

Approximately 148 evaluable subjects will be enrolled in the study

Part A: Approximately 64 subjects which includes 40 subjects currently enrolled and an additional 24 subjects in cohorts dosed in fasted or fed states.

Part B: Eighty-four subjects in 6 groups of 14 each. The 6 groups are patients diagnosed with relapsed/refractory DLBCL, MCL, FL, PTCL, MF, and CLL.

Assuming a 10% early termination rate, the total number of subjects is approximately 163.

8.3 Selection of Doses

8.3.1 Part A (Dose Escalation)

Dose escalation will commence with dose level 1 (10 mg every 12 hours). Subsequent planned dose levels in Part A include: 20, 30, 40, 50, 75 and 100 mg administered every 12 hours or, 80, 120, and 150 mg every 24 hours. These planned dose levels may be modified based on data obtained throughout the course of study conduct. If an MTD is not identified after completion of the highest scheduled dosing cohort (either bid or qd) dose escalation may continue in

increments of ≤ 50% until the MTD is identified. The doses for twice daily and the single daily doses are found in **Table 6**.

The PK of ASN002 may be evaluated when administered with food. Up to 6 subjects per dose cohort may receive ASN002 after consuming a light meal. Subjects receiving ASN002 with food will receive no more than 75% of the highest dose that is deemed safe and well tolerated.

Table 6: Twice Daily and Once Daily Dosing Cohorts

Twice Daily Dose Cohorts		Single Daily Dose Cohorts	
1	10 mg	N/A	
2	20 mg	N/A	
3	30 mg	N/A	
4	40 mg	4a[a]	80 mg
5[a]	50 mg	5a[a]	120 mg
6[a]	75 mg	6a[a]	150 mg
7[a]	100 mg		

[a] Cohorts may be administered ASN002 with and/or without food.
Dose escalation may continue in increments of ≤ 50% until the MTD is identified

8.3.2 Part B (Cohort Expansion)

Based on the safety and tolerability data from Part A, the initial dose for Part B is 75 mg BID for subjects with hematologic malignancies, including lymphoma, CLL and MF. Dose adjustments for individual subjects may be made based on observed toxicity per Section **8.3.3**.

8.3.3 Dose Modifications

Part A

No dose reductions are permitted in Part A. If a subject experiences a DLT during Cycle 1, the subject should be discontinued from the study.

At the end of Part A, if the subject is receiving a sub-MTD dose, the dose may be escalated to the MTD in consultation with the Medical Monitor and Sponsor.

If a subject experiences an AE meeting DLT criteria after Cycle 1, dosing with ASN002 will be interrupted. If the AE resolves within 7 days to CTCAE grade ≤ 1, the subject may resume dose administration at the same dose or at a lower dose level as agreed between the sponsor and investigator. If the AE does not resolve to CTCAE grade ≤ 1 within 7 days or if the DLT reoccurs, the subject must be discontinued from the study.

Part B

During Part B of the study, dose interruption (of up to 7 days) and modification for an AE meeting the criteria for DLT is allowed. For a drug-related toxicity, the dose should be immediately interrupted and supportive care provided until the AE resolves to ≤ Grade 1. After the AE resolves to ≤ Grade 1, retreatment at a lower dose may be considered upon agreement between the investigator and Sponsor medical monitor. If the toxicity recurs after re-challenge at a lower dose, study treatment should be discontinued. In the absence of > Grade 1 drug-related toxicity after at least 4 weeks of study treatment, subjects may be considered for intra-patient escalation to a higher dose that has been declared safe, in agreement with the investigators and Sponsor. The decision on possible escalation to a higher dose will be made on a case by case basis.

Guidelines for dose modification for patients starting at 75 mg BID are listed in **Table 7**.

Table 7: Dose Modifications for Part B

Dose Level	mg (BID)
-1	50
Recommended dose	75
+1	100

8.4 Study Drug Administration

ASN002 will be provided as 5-mg, 20-mg, and 50-mg tablets for oral administration. All study medication supplies will be provided by Asana BioSciences, LLC. The subject should be instructed to take the study drug at the same time, either once or twice daily.

All study drugs will be administered orally every 12 or 24 hours, as assigned, on an empty stomach (either 1 hour before or 2 hours after a meal or snack) with approximately 240 mL of water (unless the patient is participating in a cohort in which co-administration with food is required). On study days in which there is a single PK sample, the subject should fast for at least 2 hours prior to collection of the PK sample. On study days with multiple PK samples, the subject should fast overnight (at least 8 hours prior to study drug administration) and remain fasting for 2 hours after study drug administration. The date and time of the dose(s) taken prior to or on PK sampling days will be collected by the study site or via a diary card provided to the subject.

Subjects receiving the twice daily dosing schedule will receive a single dose on Day 1 and skip the evening dose. On Day 2, twice daily dosing cohorts will begin twice daily dosing. Subjects assigned to the once daily dosing schedule will have a single dose on Day 1 and will skip the Day 2 dose. All other Day 2 study procedures should be completed per protocol except study

drug dosing. On Day 3, subjects assigned to once daily dosing will begin continuous once daily dosing. The effect of co-administration of ASN002 with a meal may be evaluated. Patients enrolling in this cohort will take their medication immediately after a meal

8.4.1 Missed or Vomited Doses

Should the subject forget to take the study drug, s/he should take the study drug as soon as s/he remembers up to 2 hours after the planned dosing time. Thereafter, the forgotten dose should not be taken. Vomited doses should not be retaken.

8.4.2 Duration of Treatment

The subject may continue to receive treatment with ASN002 in the absence of progressive disease or intolerable toxicity for up to 12 months.

Further details regarding the study drug can be found in Section **16**

8.5 Procedures and Criteria for Dose Escalation

8.5.1 Safety Review Committee

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.

The overall safety will be evaluated after each cohort based on the safety data from the first 28 days of treatment. The safety data will include medical history, all AEs, concomitant medications, vital signs, electrocardiogram (ECG) findings, and laboratory data.

The safety review committee will be comprised of the following members: sponsor representatives including the clinical pharmacologist, medical adviser, chief medical officer, clinical manager; site investigators from active sites; CRO representatives including the medical monitor, pharmacovigilance medical monitor. Other representatives may be included as needed.

8.5.2 Dose Escalation Criteria

Dose escalation will continue until the MTD, a plateau of ASN002 plasma concentration has been identified, or until the planned highest dose level is reached (refer to section **8.3.1**).

Initially, 3 subjects will be treated at the same dose level. There will be at least a 24-hour interval between the administrations of the first dose of the study drug for each subject.

After a minimum of 3 subjects in each cohort have completed cycle 1 of treatment and the safety review has been performed, 3 new subjects can be enrolled at the next higher dose level, in the absence of DLT. No intra-subject dose escalation is permitted during the dose escalation phase.

If 1 of the first 3 subjects experiences a DLT, an additional 3 subjects will be enrolled at the same dose level. The dose escalation will be stopped if 2 or more subjects among a cohort of 3 or 6 subjects experience a DLT. Three additional subjects will be entered to the previous lower dose level cohort, if only 3 subjects were treated in that cohort.

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.

Dose escalation can also be stopped based on the PK data if a plateau in ASN002 plasma concentration versus the dose curve is observed prior to reaching the MTD. Subsequent development decisions regarding the therapeutic doses of ASN002 for future studies will be considered in the evaluation of PK data.

8.5.3 Dose-Limiting Toxicity (DLT) Definitions

During Phase 1, the MTD will be determined based on DLT occurring during the first 28 days plus any rest period if applicable (i.e. Cycle 1). All adverse events unless they have been determined to be not related to study drug will be taken into consideration in determining DLT. NCI-CTCAE version 4.03 will be the basis for the descriptive terminology and grading of adverse events. DLT are defined as follows:

Non-hematologic DLT is defined as:

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.
- Asymptomatic Grade 3 electrolyte abnormalities which can be corrected by optimal supplementation.

Hematologic DLT is defined as:

≥ Grade 4 neutropenia or thrombocytopenia that lasts more than 7 days after the last dose of study drug;

Febrile neutropenia;

≥ Grade 3 thrombocytopenia in the presence of bleeding;

See section **12.4** for assessments of intensity criteria.

8.6 Definitions of Response to ASN002

8.6.1 Relapsed/Refractory Lymphomas

The 2014 Lugano Classification will be used to document disease response or progression in subjects with DLBCL, MCL, FL, or PTCL (**28**).

8.6.2 Solid Tumors

The RECIST 1.1 criteria will be used to document disease response or progression in subjects with advanced/metastatic solid tumors (**29**).

8.6.3 Myelofibrosis

The International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria will be used to document disease response or progression in subjects with myelofibrosis (**30**)

8.6.4 Chronic Lymphocytic Leukemia

The International Workshop on Chronic Lymphocytic Leukemia (**31**) will be used to document disease response or progressions in subjects with CLL. For patients with persistent lymphocytosis, a partial response in all other measures will be defined as a partial response with lymphocytosis (**33**).

8.6.5 Clinical Disease Progression

Clinical disease progression can be characterized by loss of appetite, weight loss, change in bone pain/worsening bone pain, increased use of analgesics, cachexia/decrease in performance scale (e.g., an increase in the subject's ECOG score) and other symptoms of progressive neoplastic disease.

The investigator will evaluate the integrated results of all these parameters and based on this evaluation will decide if a subject has clinical progression.

9 SELECTION AND WITHDRAWAL OF SUBJECTS

9.1 Subject Inclusion Criteria

In order to be eligible to participate in the study, subjects must meet the following criteria:

1. Written informed consent obtained prior to any study-related procedure being performed;
2. Male or female subjects at least 18 years of age at the time of consent;
3. ECOG Performance Status 0-2;
4. Radiographically evaluable tumor by 2014 Lugano Classification recommendations (lymphomas) or RECIST 1.1 (advanced solid tumors);
5. Recovered from the reversible effects of prior antineoplastic therapy (with the exception of alopecia and Grade 1 neuropathy). Screening blood counts of the following:
    a. Absolute neutrophil count ≥ 1000/μL,
    b. Platelets ≥ 75,000/μL,
    c. Hemoglobin ≥ 8 g/dL (with transfusion support);
6. Screening chemistry values of the following:
    a. Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤ 3.0 × upper limit of the normal reference range (ULN),
    b. Total bilirubin ≤ 1.5 × ULN,
    c. Creatinine ≤ 1.5 × ULN;
7. At screening, life expectancy of at least 3 months;
8. Subject is willing and able to comply with all protocol required visits and assessments;
9. Male and female subjects of child-bearing potential must agree to use medically acceptable methods of birth control throughout the study and for thirty (30) days after the last dose of study medication.
10. Subjects must have one of the following disease characteristics

(Part A only)

a. Histologically or cytologically confirmed metastatic and/or advanced solid tumors or lymphomas for which no standard therapy exists, or who are not eligible for standard treatment. Subjects must have received at least one prior therapy for their malignancy;

(Part A or B only)

Lymphomas

b. Histologically confirmed DLBCL/MCL/FCL/PTCL on the basis of excisional lymph node or extranodal tissue biopsy;

c. Diagnosis of relapsed/refractory DLBCL/MCL/FL/PTCL defined as 1) recurrence of disease after a CR, or 2) PR, SD at completion of treatment regimen preceding entry into study. Subjects must have received at least one regimen of treatment for lymphoma.
d. Subjects must not be candidates for standard therapy.
e. Subjects who have not received SCT must be ineligible to receive SCT.

(Part B only)
Primary Myelofibrosis

f. Confirmed diagnosis of PMF, post-PV MF, or post-ET MF according to the 2008 WHO criteria (30),

g. High risk or intermediate-2 risk or symptomatic intermediate-1 risk as defined by Dynamic International Prognostic Scoring System (DIPSS), see **Appendix D**

h. Palpable splenomegaly at least 5 cm below the left costal margin,

i. Known JAK2 mutational status,

j. Refractory/relapsed, or intolerant to prior JAK2 therapy in the judgement of the investigator.

Chronic Lymphocytic Leukemia

k. Confirmed diagnosis of B-cell CLL, according to the International Workshop on Chronic Lymphocytic Leukemia (IWCCL) (31)

l. Measurable disease defined as lymphocytosis> 5,000/uL, or at least one palpable or CT measurable lesion (> 2.0 cm), or quantifiable bone marrow involvement.

m. Active disease requiring treatment as defined by IWCLL consensus criteria

n. Relapsed or refractory disease or intolerant to a maximum of 2 prior systemic therapies. One of the prior regimens must have included a purine analog and/or an alkylating agent.

9.2 Subject Exclusion Criteria

Subjects who meet any of the following criteria will not be eligible to participate or continue further in the study:

1. Have received prior standard therapy regimens within 4 weeks of Day 1;

2. Have received prior treatment with monoclonal antibodies within 6 weeks of first dose of Day 1;
3. Have had major surgery within 30 days prior to the start of Day 1;
4. Received any investigational treatment within 4 weeks prior to the start of study medication;
5. Have had an infection requiring the use of parenteral antibiotics within 14 days prior to the start of Day 1;
6. Have known central nervous system metastasis or CNS lymphoma;
7. Is receiving corticosteroids (>10 mg prednisone daily or equivalent);
8. Has known bleeding diathesis that could be considered a safety concern;
9. Has a history of other malignancy within the 3 years prior to screening, except adequately treated basal cell or squamous cell carcinoma of the skin, or carcinoma in situ;
10. Has difficulty swallowing medications, or known history of malabsorption syndrome;
11. Has a serious concurrent medical condition, such as:
    a. History of congestive heart failure New York Heart Association (NYHA) class III or IV,
    b. 12-Lead ECG abnormalities considered by the investigator to be clinically significant or QTcF $\geq$ 450 milliseconds at screening. Abnormal values may be confirmed from one additional assessment. For subjects with QTcF $\geq$ 450 on initial screening ECG, the mean of the two QTcF assessments will be used to determine eligibility;
    c. Myocardial infarction, angioplasty, or cardiac stent placement within the last 6 months,
    d. HIV infection,
    e. Known Hepatitis B or C infection. Subjects at high risk for Hepatitis B or C infection should have serology testing to rule out infection;
    f. A medical condition requiring the therapeutic use of anticoagulants
    g. Condition or situation which may put the subject at significantly increased risk, may confound the study results, or may interfere significantly with the subject's participation in the study
12. Known hypersensitivity to ASN002 or its excipients;
13. Prior participation, i.e., receipt of study medication, in this study;
14. Any condition that, in the opinion of the investigator, would impair the subject's ability to comply with study procedures;
15. Subjects that are pregnant of lactating;

16. Part B only:Prior treatment with SYK or JAK inhibitors, except for subjects with myelofibrosis treated with a JAK inhibitor.

9.3 Subject Discontinuation Criteria

Study discontinuation will occur when a subject who signed informed consent ceases participation in the study. Subjects can be discontinued from the study for one of the following reasons:

- An adverse event;
- Progression of disease;
- Death;
- A protocol violation (reason must be specified, for example: lack of compliance, use of a prohibited concomitant medication, failure to meet inclusion/exclusion criteria after study entry, etc.);
- Withdrawal of consent by the subject (reason must be specified);
- The subject was "lost to follow-up";
- Other reasons (reason must be specified, for example: the subject moved, investigator decision, sponsor decision to terminate study, etc.).

A subject is free to withdraw his consent and discontinue participation in the study at any time. The investigator must withdraw any subject from the study if the subject requests to be withdrawn. Any subject who withdraws consent as a result of an adverse event, regardless of intensity or investigator's opinion, must be reported as a discontinuation due to adverse event.
If a subject discontinues from the study, all end of treatment procedures should be conducted as detailed in **Table** 1 or **Table 2**. The date a subject discontinues ASN002, and the reason for discontinuation will be recorded in the source documentation and electronic Case Report Form (eCRF). If a subject has an ongoing adverse event, the event will be followed until resolution or stabilization for at least 30 days after the last dose of ASN002. If a subject refuse to complete any of the specified End of Treatment procedures, this information will be recorded in the source documentation. A subject who discontinues from the study will not be allowed to re-enter the study.

When a subject is "lost to follow-up" (i.e., fails to return for study visits), a reasonable effort will be made to contact the subject:

1. to determine the reason for the failure to return and these contacts will be recorded in the source documents;
2. to follow up on any ongoing AEs from the previous visits;
3. to recover any unused ASN002.

The subject should be identified as "lost to follow up" in the eCRF, as appropriate.

9.3.1 Replacement Procedures

During Part A, a subject who prematurely discontinues from the study before completing 28 days of the dose escalation component for reasons other than DLT, or has demonstrated significant non-compliance with ASN002 dosing, may be replaced at the discretion of the sponsor. 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.

10 VISIT PROCEDURES

10.1 Screening

The Schedule of Assessments to be performed during the study are detailed in **Table** 1 - **Table 4**

10.1.1 Subject Screening

Investigators will maintain a screening log of all potential study subjects. This log will include limited information about the potential subject (screening identification (ID), date of consent, initials, date of birth, sex, race and ethnicity), the outcome of the screening process, and the date of the outcome. Investigators will provide information about the study to subjects who appear to meet the criteria for participation in the study.

After obtaining informed consent, the full assessment of eligibility will be conducted according to the Schedule of Assessments in **Table** 1 or **Table 2**. Results of tests performed that would ordinarily be performed according to the standard of medical care, may be used for screening purposes if obtained within the screening period. Once the subject has fulfilled all entry criteria, a subject ID will be assigned.

Subjects who do not meet eligibility criteria may be re-screened at the discretion of the sponsor. Any subject who is re-screened will be assigned a new screening ID number and will be required to repeat all screening procedures unless approved in advance by the sponsor.

For those subjects who are screened for the study but are considered ineligible or are never entered into the study (i.e., do not receive study medication), the following eCRF data will be collected: date of informed consent, demographic information, AEs, and reason for non-participation (e.g., inclusion and/or exclusion criteria not met, withdrawal of consent, etc.).

10.2 Cycle 1

All study assessments will be conducted in accordance with the Schedule of Assessments in **Table** 1 - **Table 4**, as applicable to the study part assignment. During visits when multiple PK

samples are collected, the following "priority order" will be in effect when more than 1 assessment is required at a particular time point:

- PK blood sampling will take priority over all study procedures except ASN002 dose administration. Pre-dose samples should be obtained immediately (within 1 hour) prior to dose administration.
- Safety assessments (e.g., vital signs, 12-lead ECG, AE questioning) may be performed within 15 minutes of the protocol specified time point.

10.2.1 Day 1

The subject should arrive at the investigational site after an overnight fast of at least 8 hours. The investigator will confirm the subject's eligibility for the study and ensure the subject's condition has not changed since the screening assessments. The subject will have the following procedures performed on Day 1:

- Obtain hematology, serum chemistry, liver function tests, urinalysis, and pregnancy test (if applicable) if not done within 72 hours prior to Day 1 (**Table 10)**;
- Perform physical examination within 72 hours of Day 1 (Section **12.10**), including ECOG PS and measurement of the spleen by manual palpation in subjects with MF;
- Review study entry criteria to confirm eligibility (Section **9**);
- Obtain baseline MPN-SAF form completed for MF subjects only;
- Obtain pre-dose PK/PD samples (Section **13.1**), ECG tracing (Section **12.9**), and vital signs including weight (Section **12.8**) according to the schedule in **Table 3** or **Table 4**, as applicable;
- If dosing is to occur in the presence of food, a light meal will be administered prior to dosing. ASN002 should be administered within 15 minutes of consumption of the light meal.
- Administer assigned dose of ASN002 with approximately 240 mL of water;
- Obtain post-dose PK/PD samples, ECG tracings, and vital signs according to the schedule in **Table** 3 or **Table 4**, as applicable;
- Observe for adverse events;
- Record any changes in concomitant medications since the last visit

10.2.2 Day 2

- Obtain a l PK sample (Section **13.1**), ECG tracing (Section **12.9**), and vital signs (Section **12.8**) according to the schedule in **Table 3** or **Table 4** (as applicable).
- Assess for AEs and changes to concomitant medications.
- If dosing is to occur in the presence of food, a light meal will be administered prior to dosing. ASN002 should be administered within 15 minutes of consumption of the light meal.
- Dispense ASN002 for dosing at home, if the subject is assigned to a bid dosing regimen.

- Hold dosing if the subject is participating in a QD cohort.
- Provide Diary card to the subject, and provide instructions for completion

10.2.3 Day 3

For subjects in the QD dosing cohorts only
The subject will arrive at the study site in the morning in a fasted state prior to taking the study drug.

- Obtain a pre-dose PK sample (Section **13.1**), ECG tracing (Section **12.9**), and vital signs (Section **12.8**) according to the schedule in **Table** 3; prior to study drug administration;
- If dosing is to occur in the presence of food, a light meal will be administered prior to dosing. ASN002 should be administered within 15 minutes of consumption of the light meal.
- Administer assigned dose of ASN002 with approximately 240 mL of water after PK sample is collected;
- Dispense ASN002 for dosing at home;
- Fast may be broken approximately 2 hours after dosing;
- Assess for AEs and changes to concomitant medications.

10.2.4 Day 4, and 11 (± 1 day)

Part A only

- Obtain blood sample for liver function tests (**Table 10**);
- Assess for AEs and changes to concomitant medications.

10.2.5 Day 8 (± 1 day)

The subject will arrive at the study site in the morning in a fasted state prior to taking the study drug.

Part A

- Obtain a trough level PK sample and PD sample prior to study drug administration (**Table** 3 or **Table 4**, as applicable);
- Obtain clinical laboratory assessments as described in **Table** 1, or **Table 2** (as applicable) and **Table 10**; Perform ECG; Obtain vital signs (Section **12.8**);
- Assess ASN002 treatment compliance (Section **10.7**);

- Observe for adverse events, and record any changes in concomitant medications since the last visit;
- If dosing is to occur in the presence of food, a light meal will be administered prior to dosing. ASN002 should be administered within 15 minutes of consumption of the light meal.
- Administer ASN002 with approximately 240 mL of water;
- Dispense ASN002 for dosing at home, if indicated;
- Fast may be broken approximately 2 hours after dosing for subjects who remain fasted.

Part B assessments

- Obtain MPN-SAF form completed for MF subjects only;
- Vital signs and ECG are not required on Day 8, 15 and 22 in Part B
- Treatment compliance occurs at the end of Cycle 1

10.2.6 Day 15 (± 1 day)

Subjects will arrive at the study site in the morning of Day 15 after an overnight fast of at least 8 hours. The following procedures will be performed.

- Obtain PK/PD samples according to Section **13.1** and **Table** 3 or **Table 4**, as applicable;
- Perform physical examination (Section **12.10**);
- Obtain clinical laboratory assessments as described in **Table** 1, **Table 2**, and **Table 10**
- Obtain vital signs according to **Table** 3;
- Obtain ECG tracing according to **Table** 3;
- Assess ASN002 treatment compliance;
- Observe for adverse events, and record any changes in concomitant medications since the last visit;
- If dosing is to occur in the presence of food, a light meal will be administered prior to dosing. ASN002 should be administered within 15 minutes of consumption of the light meal.
- Administer ASN002 with approximately 240 mL of water;
- Dispense ASN002 for dosing at home, if indicated;
- Fast may be broken approximately 2 hours after dosing.

Part B assessments

- Obtain MPN-SAF form completed for MF subjects only

10.2.7 Day 16 (± 1 day)

For subjects in the QD dosing cohorts only

- Obtain a trough level PK sample (Section **13.1**), ECG tracing (Section **12.9**), and vital signs (Section **12.8**) according to the schedule in **Table** 3;
- If dosing is to occur in the presence of food, a light meal will be administered prior to dosing. ASN002 should be administered within 15 minutes of consumption of the light meal.
- Administer assigned dose of ASN002 with approximately 240 mL of water;
- Fast may be broken approximately 2 hours after dosing;
- Assess for AEs and changes to concomitant medications.

10.2.8 Day 22 (± 1 day)

The subject should arrive at the study site in the morning of Day 22 in a fasted state of at least 2 hours. The following procedures will be performed.

- Obtain a trough level PK sample prior to study drug administration;
- Obtain clinical laboratory assessments as described in **Table** 1 or **Table 2** (as applicable) and **Table 10**;
- Obtain vital signs (Section **12.8**);
- Perform ECG
- Assess ASN002 treatment compliance (Section **10.7**);
- Observe for adverse events, and record any changes in concomitant medications since the last visit;
- If dosing is to occur in the presence of food, a light meal will be administered prior to dosing. ASN002 should be administered within 15 minutes of consumption of the light meal.
- Administer ASN002 with approximately 240 mL of water;
- Dispense ASN002 for dosing at home;
- Fast may be broken approximately 2 hours after dosing.

Part B assessments

- The MPN-SAF form (completed for MF subjects only) may be completed at home if the Day 22 laboratory assessments are not performed. Day 22 laboratory assessments may be omitted.

10.2.9 Day 28

Day 28 is considered the end of Cycle 1 and the DLT assessment period. No site procedures are scheduled for Day 28. The subject should return to the study site the following day for the beginning of the next cycle. All scheduled follow up assessments must be completed prior to the initiation of subsequent ASN002 dosing.

10.3 Subsequent Cycles (± 3 days)

10.3.1 Day 1

- Perform clinical laboratory assessments according to **Table 1** or **Table 2** (as applicable) and **Table 10**, if not performed within 3 days of Day 1;
- Review disease status, if an assessment was performed (Section **11.1.1**);
- Perform physical examination (Section **12.10**) including vital signs, weight, ECOG PS. Determine if the subject should continue ASN002;
- Obtain pre-dose PK/PD sample (Section **14.1**) and **Table** 3 or **Table 4**, as applicable);
- Assess ASN002 treatment compliance (Section **10.7**);
- Observe for adverse events, and record any changes in concomitant medications since the last visit;
- Dispense additional ASN002 and subject diary.

Part B assessments

- Obtain MPN-SAF form completed weekly for MF subjects only
- Spleen length should be assessed by manual palpation every 4 weeks for the first 24 weeks and every 12 weeks thereafter of the study (MF subjects only);

10.3.2 Day 15 (± 2 days)

- Obtain clinical laboratory assessments as described in **Table 1** and **Tabel 10**
- Obtain vital signs (Section **12.8**);
- Obtain PK sample as specified in **Table 4**
- Observe for adverse events, and record any changes in concomitant medications since the last visit;
- Schedule radiographic evaluation of the subject's disease status to be conducted and evaluated prior to the end of the cycle, if appropriate;
  - For DLBCL, MCL, FL, and PTCL schedule every 12 weeks (end of Cycle 3, 6, 9, etc.).
  - For advanced solid malignancies schedule every 8 weeks (end of Cycle 2, 4, 6, etc.) for the first 24 weeks, and then every 12 weeks thereafter.
  - For MF schedule MRI (preferred) or CT of abdomen on week 24
  - For CLL schedule every 8 weeks for the initial 24 weeks and every 12 weeks thereafter (CT scan for chest/abdomen/pelvis recommended if previously abnormal and otherwise with a CR).
- Schedule a bone marrow aspirate and biopsy for CLL subjects in case of CR or cytopenias of uncertain origin.
- Obtain MPN-SAF form completed weekly for MF subjects only

10.4 End of Treatment

The following assessments should be performed within 1 week of last dose of ASN002.

- Perform physical examination (Section **12.10**);
- Obtain vital signs, including weight (Section **12.8**);
- Obtain ECOG performance status (**Appendix B**);
- Obtain ECG (Section **12.9**);Perform clinical laboratory tests **Table 1** or **Table 2** (As applicable) and **Table 10**, including pregnancy test if applicable;
- Observe for adverse events, and record any changes in concomitant medications since the last visit;
- Perform disease assessment (Section **11.1.1**);
- Assess medication compliance (Section **10.7**);
- Obtain all unused medication for reconciliation and destruction.
- Obtain MPN-SAF form completed weekly for MF subjects only
- Obtain PK samples (Part B only, **Table 2**)

10.5 30-Day Follow-up

The following assessments should be performed at the follow-up visit.

- Perform physical examination (Section **12.10**);
- Obtain vital signs, including weight (Section **12.8**);
- Perform clinical laboratory tests (**Table 10**);
- Follow up on all AEs ongoing at the End of Treatment visit.

10.6 Prior and Concomitant Medications

Any concomitant therapy with the exceptions noted in Section **10.6.1** that are considered necessary for the subject's welfare may be given at the discretion of the investigator. The investigator will authorize the therapy after consideration of the clinical situation, the potential for masking symptoms of a more significant underlying event, and whether the use of the therapy will compromise the outcome or validity of the study.

Any concomitant therapy used while the subject is in the study must be recorded in the source documents and eCRF. The medication name, dosage, date, and indication for use must be recorded. The Medical Monitor should be notified in advance of (or as soon as possible after) any instances in which prohibited therapies are or need to be administered.

Any changes to ongoing concomitant medications or the addition of new medications must be recorded in the source documents and eCRF.

Upon entering the study, each subject will be instructed to report the use of any medication to the investigator. Subjects will also be instructed about the importance of not taking any medication (including over-the-counter medications) without consulting the investigator.

10.6.1 Prohibited Medications

The following medications will be prohibited during the study:

- Chemotherapy, radiotherapy, immunotherapy, or investigational treatments are not allowed with concomitant use of ASN002;
- Use of localized palliative radiation for pre-existing lesions for pain control may be approved after discussion with the sponsor. The radiation field must not include any target or non-target lesions, and progressive disease must be ruled out as the underlying requirement for palliative radiotherapy.
- Therapeutic doses of anticoagulants.

10.6.2 Concomitant Use of Drugs that may Affect Gastric pH

The use of antacids and H2 antagonists should be considered in place of proton pump inhibitors in patients receiving ASN002. Aluminum, magnesium, or calcium-based antacids and H2-antagonists should be taken in a window of 2-10 hours after administration of the actual dose of ASN002. Refer to **Table 8** for examples of concomitant medication that may affect gastric pH.

Table 8: Examples of H2 antagonists, and Proton Pump Inhibitors

H2 antagonists	Proton Pump Inhibitors	Antacids
cimetidine	esomeprazole	Aluminum-based antacids
omeprazole	lansoprazole	Magnesium-based antacids
nizatidine	pantoprazole	Calcium-based antacids
ranitidine	rabeprazole	
The examples provided are not an exhaustive list of possible drugs that may affect gastric pH. The investigator is responsible for assessing all concomitant medications that may have effects on gastric pH.		

10.7 Treatment Compliance

Study drug compliance will be calculated weekly during Cycle 1. In subsequent cycles, compliance will be calculated on Day 1 prior to receiving additional ASN002. Subjects taking too much or too little study drug should be re-educated on the proper use of study drug. Repeated non-compliance (less than 80% or greater than 100%) should be evaluated by the investigator for the need to withdraw the subject.

Compliance can be assessed using the following formula:

(Number of tablets taken/number of tablets required per protocol) * 100 = % compliance
Accidental or intentional overdoses should be reported to the sponsor/designee promptly (refer to Section **12.6.1**).

10.8 Blinding and Randomization

The study is an open-label, non-randomized study.

11 ASSESSMENT OF EFFICACY

11.1 Primary Efficacy Variable

11.1.1 Disease Response

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.

11.1.1.1 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.

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
- Time to Tumor Progression (TTP)
- Progression-free Survival (PFS)
- PFS rate at week 24

11.1.1.2 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.

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

11.1.1.3 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 (**31**).

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

11.1.1.4 CLL

The response in patients with CLL will be evaluated according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (**32**); 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 (**33**).

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

11.2 Secondary Efficacy Variables.

11.2.1 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance status will be assessed according to the schedule of assessments in **Table** 1 or **Table 2**. Changes from baseline will be evaluated. Refer to **Appendix B** for further information.

11.3 Exploratory Markers

11.3.1 Assessment of Biomarkers

A panel of biological markers will be assessed to determine the effect of ASN002 on both SYK and JAK/STAT pathways in the disease process. Biomarkers for this study are shown in **Table 9**. Some of these markers include the following:

Lymphomas and solid tumors, changes from baseline in the following biomarkers

- Phopsho-STAT3, Phospho-S6, Phospho-SYK 525/526, Phospho-ERK
- DLBCL molecular subtype (GCB, ACB) (baseline only)
- Inflammation panel (**Appendix C**).

Myelofibrosis

- Changes in JAK (V617F) mutant allele burden.
- Inflammation panel (**Appendix C**).

CLL

- Changes in BCL2 expression
- Changes in the status of chromosome 17p.
- Inflammation panel (**Appendix C**).

Table 9: Pharmacodynamic Assessments

	Solid Tumors, and Lymphoma	MF	CLL
Phospho-STAT 3	X	X	X
Phospho-S6	X	X	X
Phospho-SYK 525/526	X	X	X
Phospho-ERK	X	X	X
Inflammation panel	X	X	X
JAK (V617F) allele		X	
BCL2 expression			X
Chromosome 17p del.			X
Molecular subtyping	DLBCL only		

Additional details regarding specimen ascertainment may be found in the Laboratory Manual.

12 ASSESSMENT OF SAFETY

12.1 Definitions

12.1.1 Adverse Events

An adverse event (AE) is any unfavorable or unintended change in body structure (signs), body function (symptoms), laboratory result (e.g., chemistry, ECG, X-ray, etc.), or worsening of a preexisting condition associated temporally with the use of the study medication whether or not considered related to the study medication. AE will be captured once a subject has signed the informed consent. AEs include:

- Changes in the general condition of the subject;
- Subjective symptoms offered by or elicited from the subject;
- Objective signs observed by the investigator or other study personnel;

- All concurrent diseases that occur after the start of the study, including any change in severity or frequency of pre-existing disease;
- All clinically relevant laboratory abnormalities or physical findings that occur during the study.

A treatment-emergent adverse event (TEAE) is any condition that was not present prior to treatment with study medication but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

All AEs, including any observed or volunteered problems, complaints, signs or symptoms must be recorded on the AE page of the eCRF, regardless of whether the AE is considered related to ASN002. This would include AEs resulting from concurrent illness, reactions to concurrent medication use, or progression of disease states (excluding the disease under study). A condition present at baseline that worsens after initiation of study treatment will be captured as an AE; the onset date will be the date the event worsened. The AE should be recorded in standard medical terminology when possible. The reporting of AEs should include a definitive diagnosis. Reporting of a list of signs or symptoms should only occur when no definitive diagnosis can be made.

12.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that:

- Results in death;
- Is immediately life-threatening (there is an immediate risk of death from the AE as it occurred; this does not include an AE that had it occurred in a more serious form may have caused death);
- Results in or prolongs an inpatient hospitalization (Note: a hospitalization for elective or pre-planned surgery, procedure, or drug therapy does not constitute an SAE);
- Results in permanent or substantial disability (permanent or substantial disruption of one's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect (in offspring of a subject using the study medication regardless of time to diagnosis);
- Is considered an important medical event.

Important medical events are defined as events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the other serious outcomes. Examples of important medical events include allergic bronchospasm

requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

12.2 Monitoring Adverse Events

At each visit, subjects will be queried regarding any AEs that have occurred since the last visit. Subjects will be asked to volunteer information concerning AEs with a non-leading question such as, "How do you feel?" Study site personnel will then record all pertinent information in the source documents and the eCRF. The study drug compliance record should also be reviewed to detect non-compliance.

Any AEs identified on the subject's diary will be reported in the appropriate eCRF module.

12.3 Relationship to Study Drug

The degree of "relatedness" of the AE to the study medication must be described using the following scale:

- **Not related** indicates that the AE is definitely not related to the study medication;
- **Possibly related** indicates that a direct cause and effect relationship between study medication and the AE has not been demonstrated, but there is evidence to suggest there is a reasonable possibility that the event was caused by the study medication;
- **Probably related** indicates that there is evidence suggesting a direct cause and effect relationship between the AE and the study medication.

12.4 Intensity Assessment

An assessment of intensity grade will be made using the NCI CTCAE version 4.03 (refer to **Appendix A**), which includes the following descriptors:

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 activities of daily living (ADL);

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL;

Grade 4: Life-threatening consequences; urgent intervention indicated;

Grade 5: Death related to the AE.

For those AEs not directly referenced in CTCAE, the investigator should use clinical judgment in assessing the intensity of such events using the above categories as a guide. For a continuous episode of an AE with variable intensity, the greatest intensity should be recorded for the AE.

12.5 Reporting Adverse Events and Serious Adverse Events

12.5.1 Reporting Adverse Events

Throughout the study, AEs will be documented on the source document and on the appropriate page of the eCRF whether or not considered treatment-related. This includes any new signs, symptoms, injury or illness, including increased severity of previously existing signs, symptoms, injury, or illness. Conditions existing prior to screening will be recorded as part of the subject's medical history. The investigator is responsible for assessing the relationship of AEs to the study medication; relationship will be classified as not related, possibly related, or probably related.

All AEs will be collected by the investigator from the time of signing the informed consent through 30 days after the last dose of ASN002; this includes any AEs that are ongoing at the time of completion/termination of the study. All ongoing AEs must be followed until resolution or for 30 days after the subject's last study visit, whichever comes first.

12.5.2 Reporting Serious Adverse Events

Any SAE, including death resulting from any cause, which occurs to any subject participating in this study, must be reported according to the Safety Management Plan within 24 hours of first becoming aware of the SAE. SAEs will be collected by the investigator from the time of signing the informed consent through 30 days after the last dose of study medication. SAEs that occur within 30 days, following cessation of the study treatment, or within 30 days, following premature discontinuation from the study for any reason, must also be reported within the same timeframe. Any SAE that is felt by the investigator to be related to the study medication must be reported regardless of the amount of time since the last dose received. Follow-up information collected for any initial report of an SAE must also be reported to the sponsor within 24 hours of receipt by the investigator.

All SAEs will be followed until resolution, stabilization of condition, or until follow-up is no longer possible.

In the event discussion is necessary regarding treatment of a subject, call the Medical Monitor

All SAEs should be entered into the eCRF within 24 hours of knowledge of the event. If the eCRF is not available, report the SAE via telephone, fax or e-mail using the information from the Study Reference Manual or Section 1

The sponsor will determine the reporting time frame to regulatory authorities in compliance with local and regional law. If so, the sponsor (or the sponsor's representative) will report the event to the appropriate regulatory authorities. The investigator will report SAEs to the institutional review board (IRB) per their IRB policy.

12.5.2.1 Follow-up Procedures for Serious Adverse Events

To fully understand the nature of any SAE, obtaining follow-up information is important. Whenever possible, relevant medical records such as discharge summaries, medical consultations, reports of radiographic studies, and clinical laboratory reports should be obtained. In the event of death, regardless of cause, all attempts should be made to obtain the death certificate and any autopsy report, if performed. These records should be reviewed in detail, and the investigator should comment on any event, lab abnormality, or any other finding, noting whether it should be considered a serious or non-serious AE, or whether it should be considered as part of the subject's history. In addition, all events or other findings determined to be SAEs should be identified on the follow-up SAE form and the investigator should consider whether the event is related or not related to study drug. All events determined to be non-serious should be reported on the eCRF.

12.6 Special Reporting Situations

12.6.1 Overdose

Study drug overdose is any accidental or intentional use of study drug in an amount higher than the dose indicated per protocol for a given subject. Study drug compliance (see section **10.7**) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be noted on the study medication eCRF.

All AEs associated with an overdose should both be entered on the Adverse Event eCRF and reported using the procedures detailed in section **12.5.2**, Reporting of Serious Adverse Events, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the SAEs reporting procedures and in

an expedited manner, but should be noted as non-serious on the form and the Adverse Event eCRF.

12.6.2 Pregnancy

All pregnancies in subjects receiving ASN002 or in the sexual partners of subjects receiving ASN002 must be reported within 24 hours of knowledge of the event according to SAE reporting procedures.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (e.g., congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form. Spontaneous miscarriages should also be reported and handled as SAEs.

Subjects should be instructed to immediately notify the investigator of any pregnancies.

12.7 Clinical Laboratory Determinations

The investigator will review all abnormal lab results for clinical significance. Any abnormal clinical laboratory test result meeting the investigator's criteria for clinical significance will be recorded as an AE or SAE as appropriate (see section **12.1.1**, Adverse Events, and section **12.1.2**, Serious Adverse Events).

Clinical laboratory parameters that will be measured in this study are listed in **Table 10.**

Table 10: Clinical Laboratory Tests

Hematology	Comprehensive Metabolic Panel	Urinalysis
Hemoglobin	Glucose	Specific gravity
Hematocrit	Sodium	pH
Red blood cell	Potassium	Glucose
White blood cell (WBC)	Calcium	Protein
Platelets	Chloride	Ketones
WBC Differential	Carbon dioxide	Bilirubin
Reticulocyte count	Phosphorus	Urobilinogen
	Blood urea nitrogen	Nitrite

Hematology	Comprehensive Metabolic Panel	Urinalysis
Lipid Panel	Creatinine	Blood*
Total cholesterol	Uric acid	Leukocytes*
Triglycerides	Lactate dehydrogenase (LDH)	Reflex microscopic evaluation, if abnormal or clinically indicated.
Liver Function Tests	Albumin	
ALP	Total protein	
AST		
ALT	**Pregnancy test**	
Gamma-glutamyl transferase (GGT)	Serum or urine pregnancy testing is required at screening and within 72 hours of Day 1 of every cycle for females of childbearing potential.	
TBIL (direct bilirubin reflex if elevated)		
* Microscopic examination will be performed if blood or leukocytes are detected by dipstick		

12.8 Vital Signs

Vital sign measurements will be recorded in source documents and conducted at the times indicated in **Table 1 - Table 4**, as appropriate. These parameters include systolic and diastolic blood pressure, and pulse rate. Blood pressure and pulse readings will be taken after the subject has been seated or recumbent for 5 minutes. Oral body temperature will be collected at Visit 1 only, unless clinically indicated.

The investigator will review all vital sign values for clinical significance. Additional vital signs will be obtained when clinically indicated. Any additional relevant data obtained by the investigator during the course of the study will be supplied to the sponsor.

12.9 Electrocardiogram

A 12-lead ECG recording will be conducted at the times indicated in **Table 1 - Table 4**. The subject should rest in a semi-recumbent position for at least 5 minutes before the recording is conducted. Lead position will be that of a standard 12-lead ECG; no additional or special lead placements will be necessary. The ECG record should include 10 seconds of 12-lead data. A copy of the tracing and report must be filed in the subject's records.

The investigator will review all ECG results for clinical significance.

Refer to the site operations manual for further information.

12.10 Physical Examination

A complete physical examination 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. Subjects with MF will have splenic measurements by palpation. The screening physical examination will also include a measurement of body height and weight.

Follow up physical examinations may be brief problem-focused examinations and review of systems. Additional weight measurements will be performed as indicated. Any abnormal clinically significant findings on follow up examination will be recorded as AEs on the eCRF.

All examinations will be performed by a physician or health professional listed on the Form FDA 1572 and licensed to perform physical examinations. The investigator will review all physical examination findings for clinical significance.

13 ASSESSMENT OF PHARMACOKINETICS

13.1 PK Sample Collections

PK assessments for the ASN002 parent compound will be performed for all subjects participating in Parts A and B of the study. Samples of venous blood will be obtained according to the study site procedures and collected at the times indicated in **Table 1 - Table 4**, as appropriate. Samples collected within the specified windows will not be considered protocol deviations; however, every attempt will be made by the study site personnel to collect samples at the specified times. The exact sample collection times will be recorded in the eCRF to the nearest minute.

Individual venipunctures for each time point may be performed or an indwelling catheter may be used. If an indwelling catheter is used, the catheter should be kept patent according to institutional standards. If using an indwelling catheter for PK/PD samples, care should be taken to waste an appropriate amount of blood to avoid contaminating the PK/PD sample with anticoagulant or saline. Procedures for processing the blood samples will be provided in the site Laboratory Manual.

All sample collection and freezing tubes will be clearly labeled in a manner that identifies the study, the subject or accession number, and the collection nominal time. Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing.

13.2 Sample Storage and Shipment

All PK plasma samples will be stored frozen until they are shipped to the central laboratory. Prior to shipping, the samples will be packed into thermal insulated containers and packed in sufficient dry ice to assure they remain frozen, and are protected from breakage during shipment. Samples will be shipped by courier with appropriate documentation to identify the samples. The samples will be divided into 2 shipments, each containing 1 aliquot of plasma for each time point. After receipt of verification that the first shipment was received by the central laboratory, the second shipment will be processed.

Refer to the site Laboratory Manual for further information regarding sample storage and shipment requirements.

13.3 PK Analytical Methodology

A validated liquid chromatography-tandem mass spectrophotometry (LC-MS/MS) method will be used for the determination of concentration of the ASN002 from the plasma samples. Details of the method validation and sample analysis will be included in the final analytical report.

14 ASSESSMENT OF PHARMACODYNAMICS

14.1 PD Sample Collection

Blood samples will be collected according to the schedule in **Table 1- Table 4**, and analyzed to assess

- Inhibition of phosphorylation of S6, STAT3, $SYK^{Tyr525/526}$; and ERK;
- DLBCL molecular subtyping may be conducted on archived tumor if the subtyping has not been done as standard of care.
- Change from baseline in a panel of markers of inflammation (see **Appendix C**)
- Change from baseline in JAK (V617F) mutant allele burden in subjects with MF
- Change from baseline in BCL2 and chromosome 17p in subjects with CLL.

Due to specimen shipping considerations, only U.S. sites will collect PD samples to determine the inhibition of phospho-proteins.

Refer to the Study Laboratory Manual for further information regarding sample collection and shipments.

15 STATISTICAL CONSIDERATIONS AND METHODS

This section outlines the statistical methodology and principles which will be used for data analysis in this study. A separate statistical analysis plan (SAP) will further describe the details regarding statistical methods and will govern the analysis. Where differences occur between the protocol and the SAP, the SAP will take priority.

15.1 Determination of Sample Size

Part A: A traditional 3+3 design will be used. Including the 40 subjects currently enrolled in dose cohorts ranging from 10 – 100 mg BID and 80 and 120 mg QD, up to an additional 4 cohorts will be tested under fed conditions. It is anticipated that a total of 64 subjects may be enrolled in Part A. 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.

15.2 Subject Populations

The following populations will be considered in the statistical analysis of the study:

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, B and C.
PK population: The PK population will include all subjects who receive at least 1 dose of ASN002 and have sufficient plasma concentration data to facilitate the calculation of PK parameters as determined by the pharmacokineticist.

Efficacy Population (EP) will include all subjects who have an evaluable screening and post-dose tumor assessment.

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.

15.3 Subject Disposition

The number and percentage of subjects included in each study population will be summarized by dose level and overall. Subjects excluded from the safety and efficacy (EP or PP) populations or PK populations will be listed by dose level.

The number and percentage of subjects completed and discontinued during the treatment periods will be presented for each dose level and overall. Reasons for discontinuation from the treatment period as recorded on the eCRF will be summarized (number and percentage) by dose level and overall for all treated subjects.

15.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics, including sex, age, age group, race, height, and weight, and baseline values (e.g., clinical stage, ECOG performance status), will be summarized by dose level and overall, for all populations, using descriptive statistics. All baseline characteristics and medical information will also be summarized by dose level using descriptive statistics. The descriptive summaries will include frequency tables for all categorical response variables and number, mean, standard deviation, minimum, and maximum for all continuous variables.

15.5 Safety Analyses

Safety variables include AEs, concomitant medications, laboratory parameters, vital signs, ECG parameters, and physical examinations. For each safety parameter, the last assessment made prior to the first dose of study drug will be used as the baseline.
All safety summaries will be performed by dose level and Part A and B, separately and combined, if appropriate.

15.5.1 Prior, Concomitant, and Post Medications

The current version of WHO Drug at the initiation of protocol conduct will be used to classify prior and concomitant medications by therapeutic class. Prior medication will be defined as any medication taken prior to the first dose of study drug. Concomitant medication is defined as any medication taken between the date of first dose of study drug and the date of last dose of study drug. Any medications taken after the last dose of study drug will be considered as post medications.

Prior, concomitant, and post medication use will be summarized descriptively by the number and percentage of subjects in each dose level receiving each medication within each therapeutic class. Multiple use of the same medication by a subject will be counted only once.

15.5.2 Study Drug Exposure

Exposure to study drug for the Safety Population will be summarized in terms of treatment duration, which will be calculated as the number of days from the date of first study drug taken to the date of last dose taken, inclusively. Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for treatment duration will be presented for each dose level.

15.5.3 Measurement of Treatment Compliance

Descriptive statistics for study drug compliance will be presented by dose level for each period, as well as for the whole treatment period of the study.

15.5.4 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA, version 17.0 or higher) will be used to code AEs.

An AE (classified by preferred term) that started during the treatment period will be considered a TEAE if it was not present prior to the first dose of study drug, or was present prior to the first dose of study drug but increased in intensity during the treatment period. If more than 1 AE is reported prior to the first dose of study drug and coded to the same preferred term, then the AE with the least intensity will be used as the benchmark for comparison to the AEs occurring during the treatment period which were also coded to that preferred term. Any AE present prior to the first dose of study drug that increases in intensity during the treatment period will be re-entered with a new start date of the date of increased intensity. An AE that occurs more than 30 days after the last dose of study drug will not be counted as a TEAE.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs will be tabulated by system organ class, preferred term, and dose level. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term.

The incidence of TEAEs by severity and relationship to study drug will be summarized by system organ class, preferred term, and dose level. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug respectively. The incidence of TEAEs will also be summarized by preferred term and dose level and sorted by decreasing frequency. SAEs and AEs leading to premature discontinuation of study drug will be summarized by preferred term and dose level, and sorted by decreasing frequency for dose level.

Descriptive statistics (the number and percentage) for subjects reporting TEAEs will be tabulated by system organ class, preferred term, and dose level. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term.

The incidence of TEAEs by severity and relationship to study drug will be summarized by system organ class, preferred term, and dose level. If more than 1 AE is coded to the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to the study drug respectively. The incidence of TEAEs will also be summarized by preferred term and dose level and sorted by decreasing frequency. SAEs and AEs leading to premature discontinuation of study drug will be summarized by preferred term and dose level, and sorted by decreasing frequency for dose level.
Listings will be presented for subjects with AEs, subjects with SAEs, subjects with AEs leading to discontinuation, and death. All safety summaries will be performed by dose level and Parts A, and B, separately and combined, if appropriate.

15.5.5 Vital Signs

Descriptive statistics for vital signs (e.g., systolic and diastolic blood pressure, pulse rate, temperature, and body weight) and their changes from baseline at each visit and at the end of study will be presented by dose level.

15.5.6 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values in International System of Units (SI units) and changes from baseline at each assessment time point will be presented by dose level for each clinical laboratory parameter.

15.5.7 Electrocardiogram

Descriptive statistics for ECG parameters (e.g., heart rate, PR interval, QRS interval, QT interval, and QTc interval) at baseline and changes from baseline at each assessment time point will be presented by dose level. QTc interval will be calculated using both Bazett [$QTcB = QT/(RR)^{1/2}$] and Fridericia [$QTcF = QT/(RR)^{1/3}$] corrections; and if RR is not available, it will be replaced with 60/HR in the correction formula.

15.5.8 Physical Examination

Clinically significant changes from the screening and/or Day 1 physical examinations will be captured as AEs, and analyzed according to the criteria in Section **15.5.4**.

15.6.1 Evaluation of Disease Status

15.6.1.1 DLBCL, MCL, FL, PTCL

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.

15.6.1.2 Advanced Solid Malignancies

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.

15.6.1.3 Myelofibrosis

The frequency of response and type of response according to IWG-MRT response criteria for subjects with MF will be evaluated.

15.6.1.4 CLL

The frequency of response, and type of response according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia (32), will be evaluated. For patients with persistent lymphocytosis, a partial response in all other measures will be defined as a partial response with lymphocytosis (33). Duration of response and the PFS rate at week 24 will also be evaluated.

15.6.1.5 Evaluation of Performance Status

The ECOG performance status and the changes from baseline will be presented with frequency tables at each dose level.

15.6.2 Evaluation of Time on Treatment

The time from the start of study treatment to the discontinuation or completion of study treatment at each dose level will be summarized descriptively.

15.6.3 Evaluation of Time to Progression

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. The time to progression will be analyzed using the Kaplan-Meier method. The number and percent of subjects progressed, number and percent of subjects censored, and median time to progression along with its 95% confidence interval will be presented by dose level and combined.

15.6.4 Evaluation of Progression Free Survival

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. The number and percent of subjects progressed, number and percent of subjects censored, and median time to progression along with its 95% confidence interval will be presented by dose level and combined. The Kaplan-Meier survival curves will be presented by dose level and combined.

15.7 Pharmacokinetic Analyses

15.7.1 Calculation of Pharmacokinetic Variables

For Part A, PK variables for the ASN002 parent compound will be estimated from the plasma concentration data using standard non-compartmental methods. Actual sample times (hours, relative to the corresponding administration time) rounded to 2 decimal digits and negative pre-dose times set to zero, will be used in the computation of the PK variables, rather than scheduled times. Refer to Section **15.7.3** for the handling of missing values.

For Part B, PK analysis for the parent compound will be performed using a population PK method. The population PK analysis plan will be described separately and the results will be reported separately.

The definition for each PK variable is summarized in **Table 11**

Table 11: Pharmacokinetic Variables for Part A

Variable	Definition
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve from time 0 to infinity after first dose only
AUC_{0-t}	Area under the plasma concentration versus time curve from time 0 to the time of last measured concentration (C_t)
AUC_{0-24}	Area under the plasma concentration versus time curve from time 0 to 24 hours

Variable	Definition
$AUC_{0-\infty}$	Area under the plasma concentration versus time curve from time 0 to infinity after first dose only
AUC_{0-t}	Area under the plasma concentration versus time curve from time 0 to the time of last measured concentration (C_t)
AUC_{0-24}	Area under the plasma concentration versus time curve from time 0 to 24 hours
AUC_{0-12}	Area under the plasma concentration versus time curve from time 0 to 12 hours
C_{max}	Observed maximum plasma concentration; the highest concentration observed after a dose
t_{max}	The time to reach the peak plasma concentration
CL/F	Total clearance following oral administration
Vd/F	Volume of distribution at terminal phase following oral administration
λ_z	Terminal elimination rate constant, calculated as the negative slope of the ln-linear portion of the terminal plasma concentration-time curve
$t_{½}$	Terminal half-life, calculated as $\ln(2)/\lambda_z$

15.7.2 Analysis of Pharmacokinetic Results

The PK variables will be summarized using descriptive statistics by dose level. Mean, median, standard deviation, coefficient of variance, and range will be reported for each variable.

Part A and Part B data may be combined for PK/pharmacodynamic (PD) analysis. This will be described in a separate PK/PD analysis plan.

15.7.3 Handling of Missing Values

For PK analyses, plasma concentrations below the limit of quantification (BLQ) will be set to zero in the computation of mean concentration values; however, BLQ concentrations between 2 non-BLQ concentrations will be set to missing. For the computation of PK variables, the BLQ concentrations prior to the first measurable concentration will be set to zero and other BLQ concentrations will be set to missing.

15.8 Pharmacodynamic Analyses

The actual values and the changes from baseline for the PD variables will be summarized using descriptive statistics by dose level. mean, median, standard deviation, coefficient of variance, and range will be reported for each PD variable.

15.9 Protocol Deviations

A list of subjects with protocol deviations will be compiled based on entry criteria deviations as well as deviations from study conduct and assessments. Prior to database lock, an evaluation of subjects with protocol deviations will be performed to assess the appropriateness of their inclusion into the various analyses.

15.10 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.

15.11 Statistical Software

Statistical analyses will be performed using version 9.2 (or higher) of SAS® (SAS Institute, Cary, NC).

16 STUDY DRUG MATERIALS AND MANAGEMENT

16.1 Study Drug Identity

ASN002 5-mg, 20-mg, and 50 mg oral tablets will be manufactured and supplied by Kashiv Pharma, LLC, for Asana BioSciences, LLC.

16.2 Study Drug Packaging and Labeling

ASN002 5-mg, 20-mg, and 50 mg tablets will be supplied in high density polyethylene bottles. The bottles will have a foil induction seal and child-resistant screw cap. Each bottle will be minimally labeled with a single-panel label containing the protocol number, name of the product and dosage form/strength, contents, lot number, dosing directions, storage directions, appropriate cautionary statements, and sponsor name and address.

16.3 Study Drug Storage

All study drugs will be provided by Asana BioSciences, LLC. Study drug must be stored in an appropriate, secure area (e.g., a locked cabinet in a locked room) at room temperature [25°C (77°F)], with excursions permitted to 15°C-30°C (59°F-86°F).

16.4 Study Drug Preparation

Not applicable

16.5 Study Drug Accountability

The principal investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for and that dispensed study drug is recorded in the drug accountability source records. Drug accountability will be verified by the monitor during site visits.

The principal investigator will not supply the study drug to any person except those named as sub-investigators on Form FDA 1572, designated staff reflected on the Delegation of Authority Log, and consented subjects in this study. Study drug may not be relabeled or reassigned for use by other subjects.

16.5.1 Study Drug Handling and Disposal

All unused study drug that was dispensed to the subject will be returned to the site for reconciliation and assessment of compliance. The site must account for all study drug received, dispensed, and returned including study drug that was accidentally or deliberately destroyed. Any discrepancies between the actual and expected returned study drug counts should be documented. The site will destroy all study medication returned by the subject after it has been verified by the clinical monitor. At the end of the study, all unused drug supplies will be destroyed according to local standards. A copy of the Standard Operating Procedure or documented process for drug destruction will be filed in the Investigational Site File.

17 DIRECT ACCESS TO SOURCE DATE/DOCUMENTS

17.1 Source Documents

Source documents include but are not limited to original documents, data and records such as hospital/medical records (including electronic health records), clinic charts, lab results, subject diaries, data recorded in automated instruments, microfilm or magnetic media, and pharmacy records, etc. At a minimum, all data required to be collected by the protocol should have supporting source documentation for entries in the eCRF, unless the protocol specifies that data can be recorded directly on/in the eCRF or other device.

17.2 Study Monitoring

A representative of Asana BioSciences, LLC will meet with the investigator and his/her staff prior to the entrance of the first subject to review study procedures and methods of recording study data.

After enrollment of the first subject, an Asana BioSciences, LLC representative will be assigned to periodically monitor each investigator site for study progress and to verify that standards of Good Clinical Practice (GCP) and/or ICH guidelines were followed. The investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms and other study related documents are readily available for review.

17.3 Audits and Inspections

The investigator shall permit audits and inspections by the sponsor, its representatives and members of regulatory agencies. The investigator should immediately notify the sponsor of an upcoming Food and Drug Administration (FDA) or other regulatory agency inspection.

17.4 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The investigator shall permit members of the IRB/IEC to have direct access to source documents.

17.5 Data Recording and Documentation

All data recordings and source documentation (including electronic health records) must be made available to the sponsor (or designee), FDA, and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

18 QUALITY CONTROL AND QUALITY ASSURANCE

Steps to assure the accuracy and reliability of data include the selection of qualified principal investigators and appropriate study centers, review of protocol procedures with the principal investigators and associated personnel prior to start of the study, and periodic monitoring visits conducted by the sponsor or sponsor representative. Significant and/or repeated non-compliance will be investigated and remedial action instituted when appropriate. Failure to comply with remedial actions may result in investigator site termination and regulatory authority notification.
The sponsor or its designee will utilize qualified monitors to review and evaluate activities conducted at investigator sites.

The data will be entered into the clinical study database and verified for accuracy, following procedures defined by the sponsor (or designee). Data will be processed and analyzed following procedures defined by the sponsor (or designee).

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the

19 ETHICS

19.1 Ethics Review

Approval by the IRB/IEC prior to the start of the study will be the responsibility of the investigator. A copy of approval documentation will be supplied to Asana BioSciences, LLC along with a roster of IRB members that demonstrates appropriate composition (a Department of Health and Human Services [DHHS] Assurance Number will satisfy this requirement).

The study protocol, the informed consent form, advertisements, materials being provided to subjects and amendments (if any) will be approved to IRB/IECs at each study center in conformance with ICH E6, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The investigator is responsible for supplying the IRB/IEC with a copy of the current IB, as well as any updates issued during the study. During the course of the study, the investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC. At the conclusion of the study, the investigator will submit a final report or close out report to the IRB/IEC and provide a copy to Asana BioSciences, LLC.

Any amendment to this protocol will be provided to the investigator in writing by Asana BioSciences, LLC. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the investigator, has been received by Asana BioSciences, LLC. Where the protocol is amended to eliminate or reduce the immediate risk to the subject, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment and approval obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the subject, and must be immediately reported to Asana BioSciences, LLC.

The investigator will be responsible for supplying updated safety and/or study information to study subjects as it becomes available.

19.2 Ethical Conduct of the Study

The study will be conducted in accordance with ICH-GCP and all applicable regulations including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable local laws and regulations. This may include an inspection by the sponsor representative and/or regulatory authority representatives at any time. In accordance

with any applicable local regulations, the sponsor or designee will obtain approval from the appropriate regulatory agency prior to a site initiation of the study in the country or jurisdiction.

19.3 Subject Information and Consent

The principal investigator will ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. A subject must also be notified that he is free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

Each subject must voluntarily sign and date the informed consent form (and other locally required documents) prior to the performance of any study-related activity. The consent form must be approved by both the reviewing IRB/IEC and by the sponsor prior to use.

The consent form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.

The consent form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. For data verification purposes, authorized representatives of the sponsor, a regulatory authority or an IRB/IEC may require direct access to source data relevant to the study, including the subjects' medical history.

The consent process shall be recorded in source documents. Signed copies of the informed consent will be given to the subject and originals will be placed in the investigator study files. For Latin America sites, per local regulations, an original signed copy of the informed consent form will be given to the subjects.

20 DATA COLLECTION

Data that is not captured directly via an electronic device or instrument will be collected from source documents and entered into an eCRF within an electronic data capture (EDC) system. EDC security features will include the requirement for a unique user ID and password for each individual who make entries, reviews or makes changes to the data.

The investigator will be responsible for ensuring data is electronically captured or that it is entered into the eCRF in a timely manner relative to the subject visit. The investigator will

ensure the accuracy and completeness of all subject data specified in the protocol. Upon study completion, the data collected in the eCRF will be provided to each study site in portable document format (PDF).

21 REPORTING AND PUBLICATION

All data generated in this study are the property of Asana BioSciences, LLC. An integrated clinical and statistical report will be prepared at the completion of the study. Publication of the results by the investigator will be subject to mutual agreement between the investigator and Asana BioSciences, LLC.

22 INVESTIGATOR OBLIGATIONS

22.1 Regulatory Documents

The investigator is responsible for creating and/or maintaining all study documentation required by 21 CFR 50, 54, 56 and 312, ICH E6 section 8, as well as any other documentation defined in the protocol or the Investigator Agreement. The investigator must maintain the documentation relating to this study and permit Asana BioSciences, LLC or a member of a regulatory agency access to such records.

The investigator must provide the following key documents to Asana BioSciences, LLC prior to the start of the study:

- A completed and signed Form FDA 1572. If during the course of the study any information reported on the Form FDA 1572 changes, a revised Form FDA 1572 must be completed and returned to Asana BioSciences, LLC for submission to the FDA. For studies executed outside the United States, documentation required by the governing regulatory authority may be substituted for the Form FDA 1572;
- A fully executed contract;
- The Investigator's Statement page in this protocol signed and dated by the investigator and any subsequent amendment signature pages;
- The IB acknowledgment of receipt page;
- Curricula vitae for the principal investigator and all sub-investigators listed on Form FDA 1572, including a copy of each physician's license (if applicable);
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals or shorter intervals defined by the IRB/IEC. All subsequent modifications must be submitted and approved by the IRB, as described in section **19.1**;
- A copy of the IRB/IEC-approved informed consent form;
- A list of IRB/IEC members or DHHS Assurance Number;

- Laboratory certifications and normal ranges (if local labs are required by the protocol);
- Financial Disclosure Forms will be completed and signed by the investigator and all sub-investigators listed on Form FDA 1572. Investigator site staff that submitted an initial financial disclosure are also responsible for informing Asana BioSciences, LLC of any changes to their initial financial disclosure form throughout the duration of the study, and for up to1 year after the completion of the study.

A complete list of required regulatory documents will be supplied by Asana BioSciences, LLC or its representative.

22.2 Delegation of Responsibilities and Adequate Resources

The investigator should have adequate time to conduct the study properly and should have an adequate number of qualified staff to assist with the conduct of the study. The investigator shall delegate tasks only to individuals qualified by education, training and experience to perform the delegated tasks. The investigator or sub-investigator shall have direct oversight of or be easily accessible to all personnel with delegated activities. A log documenting delegation of responsibilities will be maintained throughout the study. The investigator is responsible for ensuring all delegated staff have been properly trained on the protocol and their assigned study responsibilities.

22.3 Medical Care of Study Subjects

The investigator and/or a qualified sub-investigator shall be responsible for the subjects' medical care. Any unrelated medical condition discovered during the course of the study should be communicated to the subject so that they may seek appropriate medical care. The investigator will report all AEs as required by the protocol (section **12.5**). The investigator will inform study subjects of new information regarding the study drug as it becomes available.

22.4 Use of Investigational Materials

The investigator will acknowledge that the study drug supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the principal investigator or sub-investigators listed on Form FDA 1572 (or other regulatory document, depending on region). Study drug must be stored in a safe and secure location. At study initiation, a representative from Asana BioSciences, LLC or designee will inventory the study drug at the site. The investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The investigator is responsible for monitoring subject's use of the study drug to ensure compliance with the protocol. All unused ASN002 will be destroyed

at the investigational site, according to institutional standards after reconciliation by the clinical monitor. It is the investigator's responsibility to ensure that subjects return their medication.

22.5 Retention of Records

Federal and local regulations require that the investigator retain a copy of all regulatory documents and records that support the data for this study (e.g., informed consents, laboratory reports, source documents, study drug dispensing records) for whichever of the following is the longest period of time:

- A period of 2 years following the final date of approval by the FDA or other regulatory agency of the study drug for the purposes that were the subject of the investigation; or
- A period of 5 years following the date on which the results of the investigation were submitted to the FDA or other regulatory agency in support of, or as part of, an application for a research or marketing permit for the study drug for the purposes that were the subject of the investigation.
- Longer retention times may be required by individual local, or national regulatory authorities. The investigator is responsible to understanding and complying with all retention requirements.

Asana BioSciences, LLC will notify investigators once one of the above 3 timeframes has been satisfied.

If the investigation does not result in the submission of the data in support of, or as part of, an application for a research or marketing permit, records must be retained according to applicable local and national governmental authority regulation.

If the investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Asana BioSciences, LLC must be notified in writing of the name and address of the new custodian. Study records should not be destroyed without consultation with Asana BioSciences, LLC.

22.6 Subject Confidentiality

All subject records submitted to Asana BioSciences, LLC or its designee will be identified only by initials and code number. Subjects' names are not to be transmitted to Asana BioSciences, LLC. The investigator will keep a Master Subject List on which the ID number and the full name, address, and telephone number of each subject are listed. It is the investigators' responsibility to inform study subjects that representatives of the sponsor, FDA, or other

regulatory agencies may review all records that support their participation in the study. The investigator will adhere to all privacy laws to which he/she is subject.

22.7 Clinical Trials Registration

The Sponsor will be responsible for entering information on the www.ClinicalTrials.gov website. Information on investigator name and site information may be disclosed as part of this posting.

23 TERMINATION OF STUDY

The sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

24 PROTOCOL SIGNATURE PAGE

24.1 Asana BioSciences, LLC

PPD

PPD

24.2 Investigator Signature

I agree to conduct the study in accordance with the protocol and with all applicable government regulations and International Conference on Harmonisation/Good Clinical Practice guidances.

_____ ____/____/____

Investigator's Signature Date

_____

Typed Name of Investigator

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Appendix A NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE V4.03)

A printed copy of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (publication date: June 14, 2010) will be provided in the site operations manual. This document is also available on the NCI website: http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

Appendix B EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all 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

As published in Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982; 5(6):649-655.

Appendix C PANEL OF PHARMACODYNAMIC MARKERS OF INFLAMMATION

Human Inflammation MAP® v. 1.0					
#	Analyte	Short Name	#	Analyte	Short Name
1	Beta-2-Microglobulin	B2M	25	Tumor Necrosis Factor beta	TNF-beta
2	C-Reactive Protein	CRP	26	Brain-Derived Neurotrophic Factor	BDNF
3	Von Willebrand Factor	vWF	27	Eotaxin-1	
4	Alpha-2-Macroglobulin	A2Macro	28	Factor VII	
5	Ferritin	FRTN	29	Intercellular Adhesion Molecule 1	ICAM-1
6	T-Cell-Specific Protein RANTES	RANTES	30	Interleukin-1 alpha	IL-1 alpha
7	Tissue Inhibitor of Metalloproteinases 1	TIMP-1	31	Interleukin-1 beta	IL-1 beta
8	Tumor necrosis factor receptor 2	TNFR2	32	Interleukin-1 receptor antagonist	IL-1ra
9	Vascular Cell Adhesion Molecule-1	VCAM-1	33	Interleukin-12 Subunit p40	IL-12p40
10	Granulocyte-Macrophage Colony-Stimulating Factor	GM-CSF	34	Interleukin-12 Subunit p70	IL-12p70
11	Interferon gamma	IFN-gamma	35	Interleukin-15	IL-15
12	Interleukin-10	IL-10	36	Interleukin-17	IL-17
13	Interleukin-18	IL-18	37	Interleukin-23	IL-23
14	Interleukin-2	IL-2	38	Matrix Metalloproteinase-3	MMP-3
15	Interleukin-3	IL-3	39	Matrix Metalloproteinase-9	MMP-9
16	Interleukin-4	IL-4	40	Stem Cell Factor	SCF
17	Interleukin-5	IL-5	41	Vascular Endothelial Growth Factor	VEGF
18	Interleukin-6	IL-6	42	Alpha-1-Antitrypsin	AAT
19	Interleukin-7	IL-7	43	Fibrinogen	
20	Interleukin-8	IL-8	44	Haptoglobin	
21	Macrophage Inflammatory Protein-1 alpha	MIP-1 alpha	45	Vitamin D-Binding Protein	VDBP
22	Macrophage Inflammatory Protein-1 beta	MIP-1 beta			
23	Monocyte Chemotactic Protein 1	MCP-1			
24	Tumor Necrosis Factor alpha	TNF-alpha			

Appendix D: DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS)

Prognostic Variable	0 Points	1 Point	2 Points
Age (years)	≤ 65	> 65	
WBC (x 10^9 / L	≤ 25	> 25	
Hemoglobin (g / dL)	≥ 10		< 10
Peripheral blood blasts	< 1	≥ 1	
Constitutional symptoms	No	Yes	

DIPSS score	DIPSS risk category
0	Low
1-2	Intermediate – 1
3-4	Intermediate – 2
5-6	High