# Clinical Protocol

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| Study Title: | A Phase I/II Dose-Escalation and Expansion Study of the Selective PKC-β Inhibitor MS-553 in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma |
| Protocol Number: | MS-553-103 |
| Investigational Drug: | MS-553 |
| Sponsor: | MingSight Pharmaceuticals Inc. |
| | [redacted] |
| | San Diego, CA 92131 |
| | [redacted] |
| Indication: | Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma |
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| Protocol Version 8.1 | Amendment 6.1/ 16 June 2023 |

**Protocol Signature Page**

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Protocol Number: MS-553-103

This protocol has been approved by MingSight Pharmaceuticals, Inc. The following person is authorized on behalf of MingSight to approve this protocol and the signature below documents approval.

[redacted]

[redacted]

Date

[redacted]

MingSight Pharmaceuticals

# INVESTIGATOR'S AGREEMENT

Protocol Number: MS-553-103

Protocol Version 8.1: Amendment 6.1 / 16 June 2023

**I have read this protocol in its entirety, and I agree to all aspects.**

- I agree to implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- I have read and agree to comply with the Investigator obligations stated in this protocol. Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of subjects.
- I have read and understand the MS-553 Investigator's Brochure.
- I agree to conduct in person or to directly supervise the trial.
- I agree to ensure that all that assist me in the conduct of the study are aware of their obligations.
- I agree to maintain all information supplied by MingSight Pharmaceuticals Inc. in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

[redacted]

Printed Name of Investigator

[redacted]

Signature of Investigator

[redacted]

Date

## SYNOPSIS

**Name of Sponsor/Company:** MingSight Pharmaceuticals, Inc.

**Name of Investigational Product:** MS-553

**IND Number:** 135339

**Title of Study:** A Phase I/II Dose-Escalation and Expansion Study of the Selective PKC-β Inhibitor MS-553 in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

**Phase:** I/II

**Comparator:** None

**Number of Subjects:** Approximately 153

**Study Sites:** Up to approximately 15 sites

**Study Design:**

**Single agent MS-553 cohorts (A-series):**

This is a Phase I/II multi-center, open-label study of MS-553 in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL). The first part of the study, the dose escalation portion **(Cohort A1**), will determine the safety of MS-553 and the maximum tolerated dose (MTD) or initial recommended Phase 2 dose (RP2D) of MS-553 monotherapy. After the MTD or initial RP2D is identified, an expansion cohort ("**Expansion Cohort A2**") of approximately 25 patients with refractory or relapsed CLL/SLL who (a) have failed at least two prior lines of therapies, or (b) have either acquired clinical and/or molecular resistance to a BTK inhibitor (i.e., BTK and/or PLCG2 mutation) after achieving initial response to a BTK inhibitor will be enrolled.

In addition, an **optional expansion cohort** ("**Expansion Cohort A3**") of approximately 25 patients with aggressive lymphoma, including Richter's transformation, diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL) may be enrolled. At least 15 patients in this cohort shall be MCL patients.

[redacted]
additional patients will be enrolled in Cohort A2 to allow testing of two dose levels before a final RP2D can be declared.

The two dose schedules, designated as dose schedule 1 (DS1) and dose schedule 2 (DS2), are as follows:

Dose Schedule 1 (DS1)

| | MS-553 Oral Daily Dose |
|---|---|
| Week 1 | 150 mg BID |
| Week 2 | 200 mg BID |
| Week 3 and beyond | 250 mg BID |

Dose Schedule 2 (DS2)

| | MS-553 Oral Daily Dose |
|---|---|
| Cycle 1 and beyond | 225 mg BID |

Twenty of the 40 additional patients will be treated with DS1 and the other 20 patients with DS2. The patients will be allocated to either dose schedule in alternate fashion according to the sequence of their enrollment. For example, the first enrolled patient will be allocated to DS1, the second patient to DS2, the third patient to DS1, the fourth to DS2, and so on.

The optional expansion cohort (Cohort A3) will be closed to accommodate the new dose testing plan.

**Combination Cohorts**

[redacted]

**Combination Cohorts with acalabrutinib (B-series)**

As soon as the MTD or initial RP2D is declared for MS-553 monotherapy in Cohort A1, MS-553 will be evaluated in combination with acalabrutinib.

**Cohort B1.**The first part of the study will be a determination of MTD or initial RP2D of MS-553 when combined with acalabrutinib in treatment experienced CLL/SLL patients who are BTK inhibitor naïve, eligible for standard of care treatment with a BTK inhibitor as a single agent and who have had no more than 2 previous lines of treament regimens. The number of patients in the dose escalation will range from 3 to approximately 12 patients, and start with a MS-553 dose of 150 mg BID in the first dose level. Once the MTD or initial RP2D of MS-553 is known for the combination, two expansion cohorts (B2 and B3) will be started to further evaluate the safety of the combination regimens, as well as to assess early evidence of anti-tumor activity as described below.

**Cohort B2.** Once the MTD/ intial RP2D is established in Cohort B1 for MS-553 in combination with acalbrutinib, an expansion cohort will be opened. This cohort will evaluate MS-553 in combination with acalabrutinib in treatment experienced CLL/SLL patients who are BTK inhibitor naïve, are eligible for treatment with a BTK inhibitor as a single agent, and who have had no more than 2 previous lines of treatment regimens. Approximately 20 patients will be

enrolled in Cohort B2 to further confirm the safety of the combination and assess early evidence of anti-tumor activity.

**Cohort B3.** Once the MTD/initial RP2D is established in Cohort B1, Cohort B3 will be opened in parallel to Cohort B2 to evaluate MS-553 in combination with acalabrutinib in treatment experienced CLL/SLL patients who are BTKi naïve, have received no more than 2 prior lines of therapies and have TP53 abnormalities (including 17p deletion and P53 mutations). Once this cohort is open, all patients with TP53 abnormalities who are also naïve to BTK inhibitors will be preferentially enrolled in Cohort B3, rather than Expansion Cohorts B2. Approximately 10 treatment experienced CLL/SLL patients, eligible for standard of care acalabrutinib will be enrolled in Cohort B3 to further confirm the safety of the combination and assess early evidence of anti-tumor activity.

**Combination Cohorts with venetoclax and rituximab (C-series)**

As soon as the MTD or initial RP2D is declared for MS-553 monotherapy in Cohort A1, MS-553 will be evaluated in combination with venetoclax and rituximab.

**Cohort C1.** The first part of the study will be a determination of the MTD or initial RP2D of MS-553 in combination with venetoclax and rituximab in treatment experienced CLL/SLL patients eligible for standard of care venetoclax and rituximab, who are naïve to prior Bcl-2 inhibitor treatment and who have had no more than 2 prior lines of treatment regimens. The number of patients in dose escalation will range from 3 to approximately 12 patients, and start with a MS-553 dose of 150 mg BID.

**Cohort C2**. Once the MTD or initial RP2D of MS-553 is known for the combination of venetoclax, rituximab, and MS-553, an expansion cohort will be initiated. Treatment experienced CLL/SLL patients who are eligible for standard of care venetoclax and rituximab, who are naïve to prior Bcl-2 inhibitor treatment and have had no more than 2 previous lines of treatment regimens can be enrolled. Approximately 20 patients will be enrolled to further confirm the safety of the combination and assess early evidence of anti-tumor activity.

**Objectives:**

**Series A Cohorts**

**Primary**

- Evaluate the safety of MS-553 monotherapy in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic leukemia (SLL) whose disease relapsed after or was refractory to at least two prior lines of therapies with the following exceptions:
    - Patients with a 17p deletion who have already received venetoclax, or
    - Patients who have a *TP53* mutation (prior therapy is not required for these patients), or
    - Patients who have either acquired clinical and/or molecular (e.g., BTK or PLCG2 mutation) resistance to a BTK inhibitor.

- Determine the MTD or the initial RP2D of MS-553 monotherapy.

**Secondary**

- Evaluate the clinical activity of MS-553 in patients with relapsed or refractory CLL/SLL who:
  - Have failed at least two prior lines of therapies, or
  - Have either acquired clinical and/or molecular (e.g., BTK or PLCG2 mutation) resistance to a BTK inhibitor.
- Evaluate pharmacokinetics in patients receiving MS-553.

Pursuit of the secondary objectives should not jeopardize the primary objective, which is safety.

**Exploratory**

[redacted]

**Series B Cohorts**

**Primary**

- Evaluate the safety of MS-553 in combination with acalabrutinib in patients with CLL/SLL.
- Determine the MTD or the initial RP2D of MS-553 in combination with acalabrutinib.

**Secondary**

- Evaluate the clinical activity of MS-553 in combination with acalabrutinib in patients with CLL/SLL.
- Evaluate pharmacokinetics in patients receiving MS-553 and acalabrutinib.

Pursuit of the secondary objectives should not jeopardize the primary objective, which is safety.

**Exploratory**

- [redacted]
- [redacted]

**Series C Cohorts**

**Primary**

- Evaluate the safety of MS-553 in combination with venetoclax and rituximab in treatment experienced CLL/SLL.
- Determine the MTD or the initial RP2D of MS-553 in combination with venetoclax and rituximab.

**Secondary**

- Evaluate the clinical activity of MS-553 in combination with venetoclax and rituximab in patients with CLL/SLL.
- Evaluate pharmacokinetics in patients receiving MS-553 in combination with venetoclax and rituximab.

Pursuit of the secondary objectives should not jeopardize the primary objective, which is safety.

**Exploratory**

- [redacted]
- [redacted]

**Endpoints:**

**Primary Endpoints**

- Safety
    - Incidence of dose-limiting toxicities and treatment-emergent adverse events (TEAE) requiring study drug discontinuation. Assessments for DLT and TEAE will occur during Cycle 1 for Cohort A1, and the protocol defined DLT evaluation periods for Cohort B1 and Cohort C1 (See Section 0 and 3.3.4). TEAE will be assessed throughout the course of the trial. The primary endpoint will be the rate of DLT and TEAE requiring study drug discontinuation in the respective DLT evaluation periods of Cohort A1, Cohort B1, and Cohort C1.
- MTD or initial RP2D as monotherapy, as well as in combination with either acalabrutinib or venetoclax and rituximab.

**Secondary Endpoints**

- Objective response rate (ORR), with overall response defined as best response of complete response (CR), CR with incomplete marrow recovery (CRi), partial response

(PR), or PR with lymphocytosis (PRwL) according to the 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) Response Criteria, with modifications for treatment-related lymphocytosis.

- Duration of response (DoR), defined as time from first documentation of response to first documentation of progressive disease (PD) per 2008 IWCLL, first new therapy including allogeneic transplantation, or death due to any cause.
- Progression free survival (PFS), defined as time from first dose of study treatment to the first documentation of PD, first new therapy (excluding allogeneic transplantation), or death due to any cause.
- Overall survival (OS), defined as time from first dose of study treatment to death due to any cause.
- Disease control rate (DCR) defined as the percentage of patients who have achieved CR, Cri, PR, PRwL and stable disease (SD). Duration of stable disease, with stable disease defined as at least 6 months from the start of MS-553 monotherapy to first documentation of progressive disease (PD) in relapsed and refractory CLL/SLL patients.
- Pharmacokinetics of MS-553 monotherapy, as well as the small molecule agents used in combination, acalabrutinib, or venetoclax.

**Overview of Exploratory Endpoints**

- Serum plasma, blood, and tissue biomarker assays will be used to assess:

**See Section 2.6 for a more detailed discussion of samples and endpoints by Cohort.**

**Study Design and Methodology:**

This is a Phase I/II, multi-center, open-label study of single agent MS-553, as well as MS-553 in combination with acalabrutinib or venetoclax and rituximab in treatment experienced CLL or SLL patients.

The study will consist of 3 cohorts. Cohort A will evaluate MS-553 monotherapy, Cohort B will evaluate MS-553 in combination with acalabrutinib and Cohort C will evaluate MS-553 in combination with venetoclax and rituximab.

**Cohort A**

Patients will be treated in 28-day cycles. Patients who discontinue treatment for progressive disease and/or use of other CLL/SLL therapy will be followed for survival every 24 weeks (± 7 days) for up to 3 years. Patients who discontinue treatment for reasons other than progressive disease, use of other CLL/SLL therapy, death, or withdrawal of consent will have response assessments every 12 weeks (± 7 days) until progressive disease occurs. Thereafter they will be followed for survival every 24 weeks (± 7 days) for up to 3 years. All patients will discontinue survival follow-up upon completion of 3 years of survival follow-up, withdrawal of consent, death, or study closure, whichever is the earliest.

Cohort A1 will follow a conventional "3+3" patient enrollment scheme for the dose escalation part of the study. Patients will be dosed with MS-553 by mouth twice daily at an initial dose (dose level 0, DL 0) of 100 mg BID daily in 28-day cycles. MS-553 shall be taken with food.

| Dose Level | Dose |
|---|---|
| **0** | 100 mg BID |
| **1** | 200 mg BID |
| **2** | 250 mg BID |
| **3** | 300 mg BID |
| **4+** | TBD* mg BID |

*To be determined

After completion of dose level 3 (DL 3), the dose escalation of MS-553 can continue in 50 mg BID increments (or lower if an intermediate dose is introduced) until a MTD is reached. Or, the Safety Review Committee and/or the Sponsor may declare an initial RP2D, if further dose escalation is not warranted prior to reaching MTD. Furthermore, in order to facilitate initial RP2D determination, select cohort(s) may be expanded up to 10 patients total in a cohort to assess the safety and clinical activity of MS-553 provided that the dose does not exceed the MTD and the Safety Review Committee, upon reviewing the safety and tolerability, efficacy, and available PK and PD data, agrees.

During the dose escalation period, intra-patient dose escalation will be permitted at the discretion of the study investigators and after discussion with the medical monitor and Sponsor, if the following criteria are met:

1. The next higher dose for the regimen has been demonstrated to be safe by at least 3 patients and all 3 patients complete one cycle without experiencing any dose limiting toxicity (DLT).

2. The patient who will receive the higher dose has not experienced a DLT and has also completed at least 2 cycles of therapy at the current dose.
3. Intra-patient dose escalation can be increased by only one dose level at a time.

After the MTD or initial RP2D is identified, an expansion cohort ("**Expansion Cohort A2**") of approximately 25 patients with refractory or relapsed CLL/SLL who (a) have failed at least two prior lines of therapies, or (b) have acquired clinical and/or molecular resistance of a BTK inhibitor (i.e., BTK and/or PLCG2 mutation) after achieving initial response to a BTK inhibitor will be activated.

In addition, an **optional expansion cohort (Cohort A3)** of approximately 25 patients with aggressive lymphoma, including Richter's transformation, DLBCL and MCL, can be activated simultaneously with the activation of the two expansion cohorts. At least 15 patients in this cohort shall be MCL patients.

Patients in the expansion cohorts will be treated at the MTD (or initial RP2D).

All patients will continue to be monitored for approximately 30 days ( +7 days) after treatment discontinuation for development of any late treatment emergent adverse events. Any such late adverse events will be considered in the determination of the maximum tolerated dose/initial RP2D and dose schedule to be taken forward into the expansion phase of the study.

[redacted]
additional patients will be enrolled in Cohort A2 to further testing two dose levels before a final RP2D can be declared.

The two dose schedules designated as dose schedule 1 (DS1) and dose schedule 2 (DS2) are as follows:

Dose Schedule 1 (DS1)

| | MS-553 Oral Daily Dose |
|---|---|
| Week 1 | 150 mg BID |
| Week 2 | 200 mg BID |
| Week 3 and beyond | 250 mg BID |

Dose Schedule 2 (DS2)

| | MS-553 Oral Daily Dose |
|---|---|
| Cycle 1 and beyond | 225 mg BID |

Twenty of the 40 additional patients will be treated with DS1 and the other 20 patients with DS2. The patients will be allocated to either dose schedule in alternate fashion according to

the sequence of their enrollment. For example, the first enrolled patient will be allocated to DS1, the second patient to DS2, the third patient to DS1, the fourth to DS2, and so on.

The optional expansion cohort (Cohort A3) will be closed to accommodate the new dose testing plan.

[redacted]

**Cohort B**

**Cohort B1.** Once the MTD or initial RP2D is established in A1, Cohort B1 will be initiated. A conventional "3+3" patient enrollment scheme will be followed during this dose escalation Cohort B1. The dose escalation will enroll from 3 to approximately 12 patients. The initial MS-553 dose will be 150 mg BID. Treatment experienced CLL/SLL patients who are BTK inhibitor naïve, eligible for standard of care treatment of a BTK inhibitor as a single agent, and who have had no more than 2 previous lines of treatment regimens, will be enrolled for combination treatment with MS-553 and acalabrutinib. Patients will be dosed with MS-553 by mouth twice daily and acalabrutinib as per the Prescribing Information.

At least two dose levels are planned for Cohort B1. The dosing schedule and DLT evaluation periods are described in the table below.

| MS-553 Dose Levels | Dosing Schedule | DLT Evaluation Period |
|---|---|---|
| 150 mg BID | In 28-day cycles | Cycle 1 |
| 200 mg BID | In 28-day cycles | Cycle 1 |

MTD determination, DLT and safety assessments will follow the general principles outlined in Cohort A1. Initial RP2D of MS-553 for the combination is expected to be reached before the dose escalation reaches 250 mg BID, the high dose level of MS-553 under testing as a single agent therapy. Intermediate dose levels (i.e., at 25 mg increment) or lower dose levels may also be evaluated as determined by the Investigators, the Safety Review Committee and Sponsor until the MTD or initial RP2D for the combination is determined.

**Cohort B2.** After the MTD or initial RP2D is identified in Cohort B1, an expansion cohort of approximately 20 treatment experienced CLL/SLL patients who are BTK inhibitor naïve, eligible for standard of care treatment of a BTK inhibitor as a single agent, and who have had no more than 2 previous lines of treatment regimens will be enrolled at the initial RP2D.

**Cohort B3.** In parallel with Cohort B2, an expansion cohort with treatment experienced CLL/SLL patients with TP53 abnormalities (including 17p deletion and P53 mutations), who are eligible for standard of care acalabrutinib will be enrolled. Approximately 10 patients will be enrolled for dosing with MS-553 and acalabrutinib to further confirm the safety of

the combination and assess early evidence of anti-tumor activity. Once this cohort is open, patients with TP53 abnormalities will be preferentially enrolled in Cohort B3, rather than Expansion Cohort B2.

**Patients in Cohort B1, B2, and B3.** Patients will be treated in 28-day cycles until the combination is no longer tolerated or progressive disease. All patients will continue to be monitored for approximately 30 days ( +7 days) after treatment discontinuation for development of any late treatment emergent adverse events. Any adverse events noted only in patients enrolled in Cohort B1 within the DLT evaluation period will be considered in the determination of the maximum tolerated dose/initial RP2D and dose schedule to be taken forward into the expansion phase of the study.

Patients who discontinue combination treatment for progressive disease and/or use of other CLL/SLL therapy will be followed for survival every 24 weeks (± 7 days) for up to 3 years. Patients who discontinue treatment for reasons other than progressive disease, use of other CLL/SLL therapy, death, or withdrawal of consent will have response assessments every 12 weeks (± 7 days) until progressive disease occurs. Thereafter they will be followed for survival every 24 weeks (± 7 days) for up to 3 years. All patients will discontinue survival follow-up upon completion of 3 years of survival follow-up, withdrawal of consent, death, or study closure, whichever is the earliest.

**Cohort C**

**Cohort C1.** Once the MTD or initial RP2D is established in A1, Cohort C1 will be initiated. A conventional "3+3" patient enrollment scheme will be followed during this dose escalation Cohort C1. The dose escalation will enroll from 3 to approximately 12 patients. The initial MS-553 dose will be 150 mg BID. Treatment experienced CLL/SLL patients eligible for standard of care venetoclax and rituximab, who are naïve to prior Bcl-2 inhibitor treatment and who have had no more than 2 prior lines of treatment regimens are eligible for this cohort. Starting from Cycle 1, patients will be dosed with MS-553 by mouth twice daily and rituximab according to standard of care, and as outlined in Section 5.2.3.3. Beginning with Cycle 3, venetoclax dosing once daily by mouth will be initiated with weekly dose escalations from 20 mg to 400 mg over 5 weeks per its prescribing information.

At least two dose levels are planned for Cohort C1. The dosing schedule and DLT evaluation periods are described in the table below.

| **Dose level** | **Cycle 1** | **Cycle 2** | **Cycle 3** | **Cycle 4+** | **DLT Period(s)** |
|---|---|---|---|---|---|
| 150 mg BID | 150 mg BID | 150 mg BID | 150 mg BID | 150 mg BID | Cycle 1 through 4 |
| 200 mg BID | 200 mg BID | 200 mg BID | 200 mg BID | 200 mg BID | Cycle 1 through 4 |

Initial RP2D of MS-553 for the combination is expected to be reached before the dose escalation reaches 250 mg BID, the high dose level of MS-553 under testing as monotherapy. Intermediate dose levels (i.e. at 25 mg increment) or even lower dose levels may also be evaluated as determined by the Investigators, the Safety Review Committee and Sponsor until the MTD or initial RP2D for the combination is determined.

**Cohort C2.** After the MTD or initial RP2D is identified for the combination of MS-553, venetoclax and rituximab, an expansion cohort of approximately 20 patients will be initiated. Treatment experienced CLL/SLL patients, eligible for standard of care venetoclax and rituximab, who are naïve to prior Bcl-2 inhibitor treatment and who have had no more than 2 prior lines of treatment regimens are eligible for this cohort to further confirm the safety of the combination and assess early evidence of anti-tumor activity. Venetoclax will be initiated on Cycle 3 following the administration of MS-553 and rituximab combination for two cycles. For this reason, the DLT evaluation period for the triplet combination is extended to 4 cycles of therapy in order to include ramping up of the venetoclax dose that is introduced in Cycle 3.

**Patients in Cohort C1 and C2**

Patients will be treated in 28-day cycles provided they continue to tolerate the drug, have no evidence of progression, and do not meet any of the criteria for discontinuation. All patients will continue to be monitored for approximately 30 days (+7 days) after treatment discontinuation for development of any late treatment emergent adverse events. Any adverse events noted during the DLT evaluation periods will be considered in the determination of the maximum tolerated dose/initial RP2D and dose schedule to be taken forward into the expansion phase of the study.

Patients who discontinue treatment for progressive disease and/or use of other CLL/SLL therapy will be followed for survival every 24 weeks (± 7 days) for up to 3 years. Patients who discontinue treatment for reasons other than progressive disease, use of other CLL/SLL therapy, death, or withdrawal of consent will have response assessments every 12 weeks (± 7 days) until progressive disease occurs. Thereafter they will be followed for survival every 24 weeks (± 7 days) for up to 3 years. All patients will discontinue survival follow-up upon completion of 3 years of survival follow-up, withdrawal of consent, death, or study closure, whichever is the earliest.

**Dose limiting toxicity, Dose Adjustments and Management of DLTs**

**Cohort A1**

At least 3 patients will be enrolled at starting dose level 0 (100 mg BID for Cohort A1, MTD/initial RP2D level -1 for Cohort B1). During the first cycle of any dose level, if $\leq$1 DLT is observed, then escalation to the next higher dose level will follow the 3+3 design and proceed when 3/3 or 5/6 patients have completed one 28-day treatment cycle without a DLT. If at least 1 of 3 patients experiences a DLT at any dose level, the cohort will be expanded to 6 patients. If ≥ 2/3 or ≥ 2/6 patients experience a DLT within a cohort, the MTD will be considered to have been exceeded. No additional patients will be enrolled in that cohort, and dose escalation will stop. If at least 3/3 or 5/6 patients have completed one 28-

day treatment cycle at the previous dose level without a DLT, then that dose may be accepted as the MTD. At Sponsor discretion, additional patients may be enrolled into a cohort where ≤ 1 patient develops a DLT to obtain additional safety, PK, PD, and/or efficacy data.

If greater than 1/6 patients experience a DLT at DL 1, then 100 mg BID may be declared the MTD, or intermediate dose levels and/or alternative dosing schedules may be evaluated upon review of safety, pharmacodynamic, and/or pharmacokinetic data.

**Cohort B1**

In Cohort B1, at least 3 patients will be enrolled at starting dose level of 150 mg BID. The general principles of dose escalation and DLT evaluation rules described in Cohort A1 are applicable to Cohort B1.

**Cohort C1**

In Cohort C1, at least 3 patients will be enrolled at starting dose level of 150 mg BID. The dosing rules for Cohorts A1 and B1 will be similarly applied to Cohort C1. For the dose levels of MS-553 up to and including 225 mg BID, the DLT evaluation period will be through Cycle 4 (16 weeks). During the DLT evaluation period, if ≤ 1 DLT is observed, then escalation to the next higher dose level will follow the 3+3 design and proceed when 3/3 or 5/6 patients have completed four treatment cycles without a DLT. If at least 1 of 3 patients experiences a DLT at any dose level, the cohort will be expanded to 6 patients. If ≥2/3 or ≥2/6 patients experience a DLT within a cohort, the MTD will be considered to have been exceeded. At Sponsor discretion, additional patients may be enrolled into a cohort where ≤ 1 patient develops a DLT to obtain additional safety, PK, PD, and/or efficacy data.

**Determination of DLT for dosing Cohorts A1**

Each dose cohort will include a minimum of 3 evaluable patients for assessment of DLT. In order to be considered evaluable for DLT, patients must meet at least one of the following criteria:

1. Complete one 28-day cycle and receive at least 75% of MS-553 intended doses in Cycle 1
2. Discontinue due to DLT

During the DLT evaluation period for each cohort, non-evaluable patients who discontinue treatment before one cycle is complete for reasons other than study drug-related toxicities (e.g., progressive disease, non-compliance), or do not receive at least 75% of MS-553 doses, will be replaced with additional patients enrolled at the same dose level. After a DLT is resolved or reversed to ≤ Grade 1, the study drug may continue at a lower dose level at the discretion of the investigator.

A decision on dose escalation to the next dose level will be based on evaluation of the clinical safety profile and may also include evaluation of MS-553 exposure in treated patients. After the completion of each cohort, safety and PK data (if available) will be

reviewed and a decision on dose escalation will be determined by the Investigators, the Safety Review Committee, and the Sponsor.

After completion of each dose escalation cohort, the Safety Review Committee (SRC) will review clinical safety and tolerability data as well as PK data available at the time for all patients in order to confirm dose escalation to the next dose level. Based on the SRC's review, a cohort may be expanded, or an intermediate or a lower-than-planned dose level or an alternative dosing schedule may be evaluated.

**Determination of DLT for dosing Cohort B1**

Each dose cohort will include a minimum of 3 evaluable patients for assessment of DLT. In order to be considered evaluable for DLT, patients must meet at least one of the following criteria:

1. Complete one 28-day cycle and receive at least 75% of MS-553 intended doses in Cycle 1;
2. Discontinue due to DLT

During the DLT evaluation period for each cohort, non-evaluable patients who discontinue treatment before the DLT evaluation period is complete for reasons other than study drug-related toxicities (e.g., progressive disease, non-compliance), or do not receive at least 75% of MS-553 doses, will be replaced with additional patients enrolled at the same dose level. After a DLT is resolved or improved to $\leq$ Grade 1, the study drug may continue at a lower dose level at the discretion of the investigator.

A decision on dose escalation to the next dose level will be based on evaluation of the clinical safety profile and may also include evaluation of MS-553 exposure in treated patients. After the completion of each cohort, safety and PK data (if available) will be reviewed and a decision on dose escalation will be determined by the Investigators, the Safety Review Committee, and the Sponsor.

After completion of each dose escalation cohort, the SRC will review clinical safety and tolerability data as well as PK data available at the time for all patients in order to confirm dose escalation to the next dose level. Based on the SRC's review, a cohort may be expanded, or an intermediate (i.e., at 25 mg increment) or a lower-than-planned dose level or an alternative dosing schedule may be evaluated.

**Determination of DLT for dosing Cohort C1**

Each dose cohort will include a minimum of 3 evaluable patients for assessment of DLT. In order to be considered evaluable for DLT, patients must meet at least one of the following criteria:

1. Complete the first four consecutive 28-day cycles and receive at least 75% of MS-553 intended doses in these cycles
2. Discontinue due to DLT

During the DLT evaluation periods for Cohort C1, non-evaluable patients who discontinue treatment before the DLT evaluation periods are complete for reasons other than study drug-related toxicities (e.g., progressive disease, non-compliance), or do not receive at least 75% of MS-553 doses, will be replaced with additional patients enrolled at the same dose level. After a DLT is resolved or reversed to $\leq$ Grade 1, the study drug may continue at a lower dose level at the discretion of the investigator.

A decision on dose escalation to the next dose level will be based on evaluation of the clinical safety profile and may also include evaluation of MS-553 exposure in treated patients. After the completion of each cohort, safety and PK data (if available) will be reviewed and a decision on dose escalation will be determined by the Investigators, the SRC, and the Sponsor.

After completion of each dose escalation cohort, the SRC will review clinical safety and tolerability data as well as PK data available at that time for all patients to confirm dose escalation to the next dose level. Based on the SRC's review, a cohort may be expanded, or an intermediate (i.e., at 25 mg increment) or a lower-than-planned dose level or an alternative dosing schedule may be evaluated.

**Safety**

For Cohort A1, assessments for DLT and TEAE will occur during Cycle 1. For Cohort B1, assessments for DLT and TEAE will occur during Cycle 1 for dose levels up to and potentially including 225 mg BID. For Cohort C1, assessments for DLT and TEAE will occur from Cycle 1 through Cycle 4 for dose levels up to and potentially including 225 mg BID. TEAE will be assessed during the course of the trial. The primary safety endpoint will be the rate of DLT and TEAE requiring study drug discontinuation in the DLT evaluable period.

Toxicities will be defined using NCI CTCAE v5.0 criteria.

**Efficacy**

Response assessments will be made by the individual investigators. Response for CLL will be evaluated according to 2008 criteria published by IWCLL. Because of the well-documented lymphocytosis not associated with disease progression that occurs with BCR signaling inhibitors such as BTK inhibitors, progressive lymphocytosis in the absence of other signs of disease progression (e.g., splenomegaly, enlarging lymph nodes, disease-related constitutional symptoms) will not be considered disease progression. Isolated lymphocytosis in the context of what would otherwise be a PR is defined as a PR with lymphocytosis (noted as PR-L, PR+L, or PRwL in literature). Response criteria in the SLL patients and aggressive lymphoma patients will be based on the International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017).

Initial evaluation of the efficacy endpoints related to response will incorporate the data from the first 9 cycles of treatment. Any patient who receives at least one cycle of study therapy is evaluable for response. Patients who have stable disease or a response by 9 cycles and continue treatment after 9 cycles will have response assessments including CT scans of the chest, abdomen, and pelvis (and neck if involved), preferably every 12 weeks, or as

clinically indicated until disease progression. Patients who do not have a response by 9 cycles but who have stable disease are eligible to stay on study treatment for up to a total of 24 cycles, with continual re-evaluation for response at subsequent visits during this time period. For patients who continue to have stable disease after 24 cycles or have a response after 9 cycles therapy, drug therapy can continue until disease progression.

**Exploratory**

[redacted]

**Correlative Science**

Pharmacokinetic, pharmacodynamic, and exploratory analyses will be coordinated by MingSight.

**Specimens to be collected for correlative science studies include:**

**Cohort A:**

**Pre-treatment**

[redacted]

**During Treatment**

[redacted]

9. Plasma for pharmacokinetic analysis.
10. Blood for pharmacodynamic PKC-β biomarker analysis.

[redacted]

**At disease progression in patients with response**

[redacted]

**Cohort B:**

**Pre-treatment**

[redacted]

**During Treatment**

[redacted]

5. Plasma for pharmacokinetic analysis.

[redacted]

7. Blood for pharmacodynamic PKC-β biomarker analysis.

[redacted]

**At disease progression in patients with response**

[redacted]

**Cohort C:**

**Pre-treatment**

[redacted]

**During Treatment**

[redacted]

4. Plasma for pharmacokinetic analysis.

[redacted]

6. Blood for pharmacodynamic PKC-β biomarker analysis.

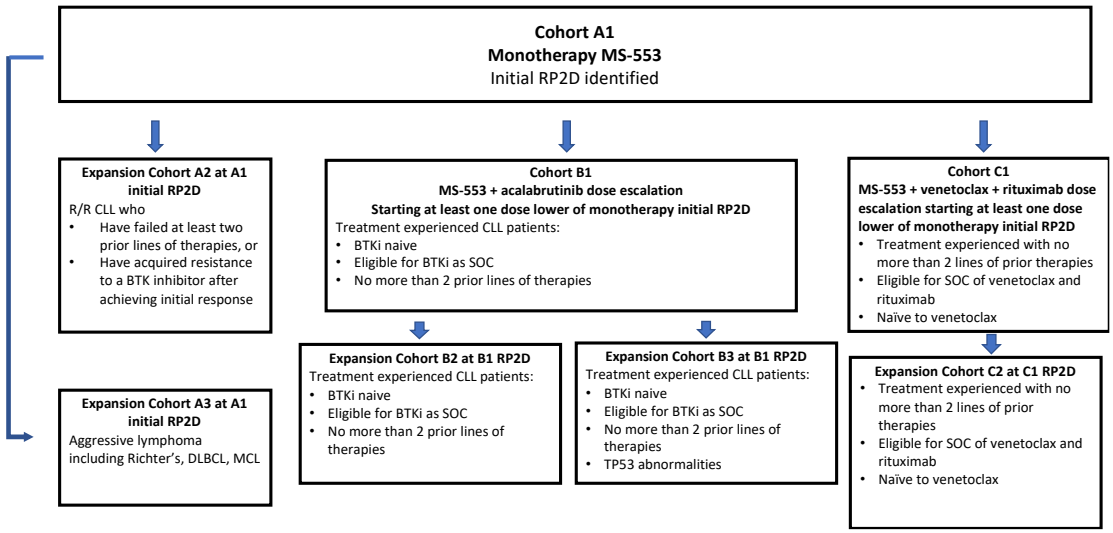
[redacted]

**At disease progression in patients with response**

[redacted]

Please refer to Section 6.3.2 for more detailed description and schedule of correlative science sample collections.

**Study Schema**




**Diagnosis and main criteria for inclusion:**

[redacted]

**Inclusion Criteria:** To be eligible for inclusion in the **dose escalation cohorts** or **expansion cohorts** in this study, patients must meet all of the following criteria:

1. Age 18 years or older.
2. Diagnosis of CLL or SLL:
   a. History of histologically documented CLL or SLL that meets IWCLL diagnostic criteria according to the 2008 guidelines, and
   b. Indication for treatment as defined by the 2008 IWCLL guidelines, or the need for disease reduction prior to allogeneic transplantation.
3. Cohort specific inclusion requirements:

   **Cohort A1 (MS-553 monotherapy)**

Relapsed after, or refractory to, progressing after at least two prior lines of therapies with the following exceptions:

a. Patients with a 17p deletion who have already received venetoclax; or

b. Patients who have *TP53* mutation (prior therapy is not required) which shall be confirmed [redacted] at screening for enrollment. [redacted] or

c. Patients with clinical and/ or molecular (e.g., BTK and/or PLCG2 mutation) resistance after achieving initial response to a BTK inhibitor.

- For patients without clinical resistance, molecular resistance (i.e., BTK and/or PLCG2 mutation) shall be confirmed [redacted] at screening for enrollment.

**Cohort A2 (MS-553 monotherapy)**

Relapsed/refractory CLL/SLL patients who have:

a. Failed at least two prior lines of therapies, or

b. Developed clinical and/or molecular (i.e., BTK and/or PLCG2 mutation) resistance after achieving an initial response to a BTK inhibitor.

- For patients without clinical resistance, molecular resistance (i.e., BTK and/or PLCG2 mutation) shall be confirmed [redacted] assay at screening for enrollment.

**Cohort A3 (MS-553 monotherapy)**

See Inclusion Criterion #4 below.

**Cohort B1, B2 (MS-553 in combination with acalabrutinib)**

Treatment experienced patients with no more than two prior lines of therapies, who

a. Are naïve to prior BTK inhibitor treatments, and

b. Are eligible for single agent BTK inhibitor.

**Cohort B3 (MS-553 in combination with acalabrutinib)**

Treatment experienced patients receiving no more than two prior lines of therapies, who:

a. Are naïve to prior BTK Inhibitor treatments,

b. Are eligible for single agent BTK inhibitor, and

c. Have 17p deletion or *TP53* mutation which shall be confirmed [redacted] at screening for enrollment. ([redacted]

[redacted]

**Cohort C1, C2 (triple regimen of MS-553 + rituximab + venetoclax)**

Treatment experienced patients receiving no more than 2 prior lines of treatment regimens, who:

a. Are naïve to prior Bcl-2 inhibitor treatments, and

b. Are eligible for venetoclax in combination with rituximab.

4. For inclusion in the Cohort A3, patients must meet both of the following diagnostic criteria instead of inclusion criterion #2 or #3:
   a. Diagnosis of aggressive lymphoma, explicitly comprising Richter's Transformation of CLL/SLL to Diffuse Large B-Cell Lymphoma (DLBCL); Activated B-cell (ABC) or non-Germinal Center B-cell (GCB) DLBCL not transformed from CLL/SLL, or MCL. Other histologies may be included after discussion with and approval of the study principal investigator and Sponsor medical monitor.
   b. Additionally, patients with MCL, or de novo ABC or non-GCB DLBCL patients must have received at least two lines of prior therapy and MCL patients must have failed at least a BTK inhibitor. Patients with Richter's transformation have no such restriction on the use of prior therapy.
5. WHO/ECOG performance status ≤ 2.
6. Meet laboratory parameters (see Exclusion Criteria).
7. In the opinion of the investigator, all of the following criteria are met:
   a. Have life expectancy ≥ 2 months
   b. Are willing to undergo all study-related evaluations and procedures, and
   c. Have ability to understand and willingness to execute a written informed consent document.

**Exclusion Criteria:** Patients who meet any of the following criteria are not eligible for this study.

1. Current or past transformation of CLL/SLL to prolymphocytic leukemia (PLL), non-Hodgkin lymphoma, or Hodgkin lymphoma.
   a. Patients being considered for inclusion in the optional expansion cohort A3 (aggressive lymphoma) are not excluded on the basis of transformed lymphoma, but must meet the definition of aggressive lymphoma outlined in the inclusion criteria for Cohort A3.
2. Active and uncontrolled autoimmune cytopenia(s).
3. Any of the following prior therapies within 14 days prior to Cycle 1 Day 1:

a. Major surgery

b. Corticosteroids greater than 20 mg / day prednisone (or equivalent), unless used by inhalation, topical, or intra-articular routes, or unless necessary for premedication before and/or after iodinated contrast dye. Higher doses, and more prolonged courses of steroids are permitted under certain circumstances after discussion with the medical monitor and/or Sponsor including, but not limited to, the following:

   i. Treatment of disease-related autoimmune hemolysis or autoimmune thrombocytopenia;

   ii. Symptomatic relief of lymphadenopathy – preferably after completion of Cycle 1;

   iii. Symptomatic relief of B symptoms – after completion of Cycle 1;

   iv. Treatment of GVHD – please discuss with medical monitor;

   v. Short courses (up to 14 days) if needed for any intercurrent condition such as acute exacerbation of any non-disease-related condition (e.g., arthritis, asthma, COPD) including steroid dose modification required for adrenal insufficiency.

c. Cytotoxic chemotherapy or biologic therapy, with the exception of BCR pathway kinase inhibitors for which only a 24-hour wash out prior to Cycle 1 Day 1 is required.

4. Failure to recover:

   a. From clinically relevant toxicity to Grade 1 or less from prior chemo or radiotherapy or biologic therapy with the exception of alopecia, atrial fibrillation or hypertension that developed during treatment with a BTK inhibitor.

   b. to Grade 2 or less for atrial fibrillation or hypertension that occurred as a consequence of treatment with a BTK inhibitor.

5. CNS leukemia/lymphoma – including history of treated CNS disease even if the patient is asymptomatic.

6. Inadequate bone marrow function / hematopoietic reserve, except in the case of documented bone marrow involvement, evidenced as:

   a. Absolute Neutrophil Count (ANC) $< 1 \times 10^9$/L

   b. Platelet count $< 30 \times 10^9$/L

7. Inadequate liver or renal function as specified below:

   a. Serum total bilirubin > 2 x ULN (upper limit of normal), or > 3 x ULN in case of liver involvement with CLL/SLL, or serum total bilirubin > 3 x ULN in patients with documented history of Gilbert's disease and normal direct bilirubin.

b. AST or ALT > 2.5 x ULN, or > 5 x ULN if CLL/lymphoma is present in the liver

c. Estimated GFR < 30 mL/min.

8. For Cohort B patients, active treatment with strong CYP3A inhibitors, CYP3A inducers or proton pump inhibitors, unless medication can be stopped prior to enrollment in the study.

9. For Cohort C patients, active treatment with strong and moderate CYP3A inhibitors, strong CYP3A inducers, or strong P-gp inhibitors, unless medication can be stopped prior to enrollment in the study.

[redacted]

[redacted]

12. Receiving treatment with medications that are known to be strong inducers, inhibitors or sensitive substrates of CYP3A4/5 or medications with risk for QT prolongation that cannot be discontinued prior to study entry (at least 48 hours prior to the start of Cycle 1 Day 1 dosing). For any exceptions, discussion with medical monitor and/or Sponsor is needed. Weak or moderate inhibitors may be used with caution, except as otherwise specified in Exclusion Criteria. Examples of these medications are listed in Appendix 3.

13. Clinically significant cardiac diseases, including any of the following:

a. History or presence of ventricular tachyarrhythmia

b. Presence of unstable/uncontrolled atrial fibrillation **is exclusionary**. Patients with stable atrial fibrillation (rate controlled pharmacologically) are eligible provided that they do not meet any other exclusion criteria. Patients whose atrial fibrillation occurred as a consequence of treatment with a BTK inhibitor may be eligible for the study provided that the patient is asymptomatic and on a stable dose of medication for rate control, and only after discussion with the medical monitor.

c. Unstable angina pectoris or acute myocardial infarction within 3 months prior to start of study drug.

d. NYHA functional class III or IV heart failure

e. Baseline QTcF interval of > 480 msec. Prior QTc prolongation due to prior medication no longer on board is not exclusionary. A family history of QTc interval prolongation by itself is not exclusionary provided that the patient's QTc is not prolonged. For those with prolonged QTc interval due to bundle branch block, patient may be eligible after documentation of a "corrected value" ≤480 msec and confirmation by cardiologist that patient is asymptomatic and that no other

cardiac conduction or cardiac abnormality is present that would pose any safety issue for the patient.

*Note:* As the eligibility criteria specify the QT interval corrected by the method of Fridericia (QTcF), any correction for widened QRS should be sure to include a cube-root corrected R-R interval. Please discuss/consult with a cardiologist if there are any questions.

14. History of another malignancy that in the opinion of the investigator limits survival to less than 2 years.

[redacted]

17. Gastrointestinal dysfunction, including motility or malabsorption syndromes or inflammatory bowel disease which could limit absorption of MS-553.
18. Known HIV positivity, or active hepatitis B or C infection with detectible viral nucleic acid in the blood.
19. Severe systemic infections requiring intravenous antibiotics within the two weeks prior to initiation of MS-553.
20. Any other life-threatening illness, medical condition, laboratory abnormalities, or therapies that in the opinion of the investigator could compromise the safety of the patient or interfere with analysis of study endpoints.
21. Women who are lactating or pregnant.
22. Women of child-bearing potential or male partners of women of child-bearing potential who will not agree to use highly effective method of contraception throughout the entire study period and for a minimum of 3 months after the last dose of study drug. Highly effective contraception methods include:
    a. Total abstinence *or*
    b. Male or female sterilization *or*
    c. Combination of any two of the following:
        i. Use of oral, injected or implanted hormonal methods of contraception
        ii. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        iii. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

    Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or

tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

Women of child-bearing potential who will not agree to the following are ineligible for the study:

- Refrain from breastfeeding and donating oocytes or blood during the course of the study and for 3 months after the last dose of study drug, and
- Ongoing pregnancy testing during the course of the study and at the end of treatment visit.

23. Men who will not agree to the following are ineligible for the study:

- Refrain from donation or blood during the course of the study and for 3 months after the last dose of study drug, **and**
- Completely abstain from sexual contact, or must always use a latex or synthetic condom during any sexual contact until 3 months after the last dose of study drug, or have prior documentation of surgical sterilization.

**Investigational product, dosage and mode of administration in all Cohorts in A, B, C:**
MS-553 is administered orally, twice daily, in 28-day cycles. Dose levels include 100, 150, 200, 225, 250 and 300 mg.

**Cohort B:** Standard of care acalabrutinib will be administered according to the Full Prescribing Information in combination with MS-553.

**Cohort C:** Standard of care rituximab will be administered beginning in Cycle 1, according to the Full Prescribing Information, in combination with MS-553 for two cycles. Beginning in Cycle 3, venetoclax will be started and the dose escalated from 20 mg to 400 mg over five (5) weeks in combination with rituximab and MS-553.

**Duration of treatment:** Patients may continue receiving study drug provided they continue to tolerate the drug, have no evidence of progression, do not meet any of the criteria for discontinuation, and the patients' participation in the study has not ended. The anticipated median treatment duration is unknown.

**Reference therapy, dosage and mode of administration:**

Not applicable.

**Statistical methods:**

Summary statistics will be provided for all endpoints. Statistics will be reported according to intention-to-treat (ITT), per-protocol, and per-dose-level. The safety summary statistics will include any patient who received at least one dose of study drug.

Patient characteristics will be described and summarized for each dose level and in total.

Because disease-relevant pharmacodynamics biomarkers are not yet established, and some limited toxicity and pharmacokinetic data in healthy subjects exists, dose escalation will be guided by toxicity.

There is no formal hypothesis to be tested in this study; therefore, no predefined sample size calculation has been made for the efficacy or exploratory endpoints.

The protocol details dose modifications (i.e., reductions, interruptions) that may be warranted as a consequence of drug-related toxicities. At a starting dose level of 100 mg BID (Dose Level 0), no dose reduction is anticipated as monotherapy. If unacceptable toxicity presents during Cycle 1 at Dose Level 0 then the patient will be instructed to discontinue treatment with MS-553. If a patient experiences potential drug-related toxicity, the appropriate dose modification may be implemented until the toxicity has adequately resolved or improved to Grade 1. If unacceptable toxicity presents, then the patient will be instructed to discontinue treatment with MS-553.

Formal stopping criteria are specified in Section 7.13. Since the study is unblinded, the Precision Oncology medical monitor, the Safety Review Committee, the relevant MS-553-103 Investigator(s), and the Sponsor will closely review available safety and PK data on an ongoing basis throughout the dose escalation and dose expansion segments of the open-label study.

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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

**Table 1: Abbreviations**

| Abbreviation or Specialist Term | Definition |
|---|---|
| AE | Adverse Event |
| ALT | Alanine aminotransferase/glutamic pyruvic transaminase/SGPT |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT |
| AUC | Area under the curve |
| BCR | B-cell receptor |
| BID | bis in die/twice a day |
| BTK | Bruton's Tyrosine Kinase |
| CBC | Complete Blood Count |
| CK | Creatine Phosphokinase |
| CI | Confidence Interval |
| CLL | Chronic lymphocytic leukemia |
| $C_{max}$ | Maximum (peak) concentration of drug |
| $C_{min}$ | Minimum (peak) concentration of drug |
| CR | Complete Response |
| CT | Computed Tomography |
| CTC | Circulating Tumor Cells |
| CTCAE | Common Terminology Criteria Adverse Events |
| DLT | Dose Limiting Toxicity |
| DoR | Duration of Response |
| DLBCL | Diffuse Large B-cell Lymphoma |
| ECG | Electrocardiogram |
| EOT | End of Treatment |
| FFPE | Formalin-Fixed Paraffin-Embedded |
| GCB | Germinal Center B-Cell |

| Abbreviation or Specialist Term | Definition |
|---|---|
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| ICH | International Council for Harmonization |
| IRB | Institutional Review Board |
| IWCLL | International Workshop on Chronic Lymphocytic Leukemia |
| LDH | Lactate Dehydrogenase |
| [redacted] | [redacted] |
| MAD | Multiple Ascending Dose |
| MCL | Mantle Cell Lymphoma |
| MRD | Minimal Residual Disease |
| MTD | Maximum Tolerated Dose |
| NGS | Next-generation sequencing |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |
| PFS | Progression Free Survival |
| PK | Pharmacokinetics |
| PKC | Protein Kinase C |
| PLCG2 | Phospholipase C gamma 2 |
| PR | Partial Response |
| PRwL | Partial Response with lymphocytosis |
| QD | Quaque die/ once a day |
| QTCF | QT interval, corrected by Fridericia method |
| RP2D | Recommended Phase 2 Dose |
| SAD | Single Ascending Dose |
| SAE | Serious Adverse Event |
| SD | Stable Disease |
| SLL | Small lymphocytic lymphoma |

| Abbreviation or Specialist Term | Definition |
|---|---|
| SRC | Safety Review Committee |
| TBD | To be determined |
| TEAE | Treatment Emergent Adverse Event |
| TLS | Tumor Lysis Syndrome |
| TP53 | Tumor Protein P53 |
| $T_{max}$ | Time to reach maximum (peak) concentration of drug |
| $t_{1/2}$ | Terminal half-life |
| WBC | White Blood cells |
| WHO | World Health Organization |

# 1. INTRODUCTION

## 1.1. Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is the most common leukemia in United States adults, accounting for about one third of all new cases of leukemia as well as one third of all leukemia deaths.[1] CLL as a cancer is defined by an excess of clonal, abnormal B lymphocytes, accumulation of which was historically believed to be solely (at least in early stage disease) due to evasion of apoptosis, although we now know that that there is a significant proliferative component to CLL[2,3] frequently in the protective and nurturing microenvironment of hematopoietic tissues, such as the bone marrow and lymph node.

Traditionally, therapy for CLL has consisted of a sequence or combination of cytotoxic chemotherapy and monoclonal antibody immunotherapy. Response rates for front line chemo-immunotherapy therapy are good, and can exceed 90%, but relapse is inevitable and CLL is therefore currently considered an incurable disease. Patients who relapse after initial chemo-immunotherapy at present have limited treatment options outside the context of a clinical trial, and responses to agents in second line and beyond are often fair at best. Furthermore, the molecular biology—and hence the clinical course— varies significantly among patients, and of patients with poor-risk genetic features no currently approved therapies seem to produce durable and robust responses. With a view to improve response rates and response durability among all patients, including high-risk patients, and with an increased understanding of the mechanisms of CLL, recent clinical work has shifted toward targeted therapy with small molecules and engineered antibodies: there have been a number of successes in targeting key points in B-cell receptor (BCR) signaling and the NF-κB cascade, as well as various cell-surface markers, especially CD20.

### 1.1.1. B Cell Receptor (BCR) Signaling Inhibitors

Because activated BCR signaling seems to be a *sine qua non* of CLL, much work has been devoted to targeting components of this pathway. The BCR complex itself is a transmembrane immunoglobulin molecule partnered with a CD79 heterodimer. Ligation of the BCR results in phosphorylation of an intracytoplasmic domain of CD79, which then signals through multiple pathways, notably through BTK (Bruton's Tyrosine Kinase), PLCG2, and PI3K. Upregulation of genes involved in these pathways has been observed in CLL and represent targets.[4] In fact, targeting BTK as a component of the BCR pathway has shown enormous promise in multiple clinical trials and has led to FDA approval of the first-in-class BTK in both the upfront and relapsed setting. [5,6]

However, because of tumor heterogeneity, genomic instability, and historic experience with other targeted agents, it is not surprising that CLL would develop resistance mutations in response to prolonged monotherapy with a BTK inhibitor. A recent report of 3 patients who had progressed on ibrutinib utilized next-generation sequencing techniques to look for mutations arising from exposure to the BTK inhibitor.[7] Investigators discovered two mutations in BTK and one constitutive gain-of-function mutation in PLCG2, a substrate of BTK. We have subsequently identified additional mutations in PLCG2 among ibrutinib-treated patients.

### 1.1.2. Protein Kinase C and PKC-β

Immediately downstream of PLCG2 lies Protein Kinase C beta (PKC-β), at the confluence of the BCR pathway, the NF-κB cascade, and the RAS/RAF/MEK/ERK pathway; PKC-β is thus a critical downstream effector in BCR signaling. In healthy B lymphocytes, PKC-β is important in the transduction of normal BCR signals. However, it has been well-demonstrated that constitutive activation of BCR signaling plays a key role in the maintenance of the CLL cell,[8] and as a consequence of this it stands to reason that PKC-β therefore occupies a position of both considerable import and opportunity. By acting immediately downstream of the BTK and PI3K components of the BCR signaling pathway, modulation of PKC-β has the potential to bypass mechanisms of resistance effected by mutations in these genes, and targeting PKC-β in this patient population is a rational and highly promising strategy.

PKC-β, encoded by the gene *PRKCB*, is a member of a large family of protein kinases responsible for phosphorylation of serine and threonine residues of downstream effector proteins; PKC-β is, like the other two other members of the "conventional" protein kinase C subfamily PKC-α and PKC-γ, activated by the second messengers diacylglycerol and $Ca^{2+}$, whereas members of the novel subfamily (PKC delta, eta, epsilon, and theta) require only diacylglycerol.[9] While PKC family proteins are present across many cell types, normal and malignant B lymphocytes express only a few of these at a significant level, including PKC-β and PKC-δ. PKC-β is exceptional among the others, however, for being much more highly expressed in CLL cells compared to normal B cells: *PRKC-β* mRNA transcripts are up to 8 fold higher in some CLL cells than in normal B cells in our unpublished observations, and others have shown that the protein product exists as a higher proportion of total cellular protein compared to normal B cells. [10] This is likely reflective of the combination of high levels of BCR signaling in CLL compared to normal B cells and the critically of PKC-β within this network. Not surprisingly, the previously mentioned study and others have shown that *in vitro* inhibition of PKC-β has a detrimental effect on CLL cell survival. [10-12] Indeed, *TCL1tg*, PKC-β null mice even failed to develop leukemia. [13] Other forms of PKC likely also play a part in the signal transduction that sustains CLL: the delta form of PKC (PKC-δ) has also been shown to interact with PI3K in CLL cells and inhibition of PKC-δ enhanced apoptosis of CLL cells, but not normal B cells. [14]

### 1.1.3. PKC in the Microenvironment

PKC inhibition appears to have relevance beyond the tumor cell itself, extending also into the microenvironment. Experiments with *Prkcb* knockout mice demonstrated the importance of PKC-β and subsequent NF-κB signaling in the microenvironment: CLL-like leukemia cells from *TCL1tg* mice would not engraft in *Prkcb-/- mice* whereas wild-type mice succumbed to disease. [15]

The possibility that systemic inhibition of PKC even in non-tumor tissues could provide additional benefit thus provides further rationale for the use of PKC inhibitor in CLL. Separate from this, we have found that the PKC inhibitor sotrastaurin also activates GSK-β via dephosphorylation in the 2-5 μM range with subsequent decrease in B-catenin levels with concomitant decrease in Myc, Cyclin D1, and Mcl-1 expression. Given that previous studies have demonstrated that the WNT/β- catenin levels are active in CLL and also have frequent

mutations, pursuing PKC inhibitors as therapeutic agents targeting WNT is worthwhile and may provide a pharmacodynamic endpoint to study the effect of this therapy in vivo.

### 1.1.4. Autoimmunity

Besides the role of PKC-ß in transducing the overactive BCR signals in CLL cells, the PKC family of kinases has been shown to be crucial to the regulation and normal function of both normal T cell and B cell lymphocytes, and their contribution to autoimmune diseases. The three isoforms, PKC-θ, PKC-α and PKC-β, appear to be most important for lymphocyte function. PKC-θ is downstream of the T cell receptor complex and is required for effector T cell activation, function, survival, and autoimmune stimulation. Interestingly, PKC-θ negatively regulates the function of regulatory T cells and therefore inhibition of PKC-θ enhances the function of regulatory T cells. PKC-α plays a non- redundant role and collaborates with PKC θ in T effector cell activation and function. As in CLL, PKC-β plays a key role in B cell activation, function, survival, and the dysfunction seen in autoimmunity.

Interestingly, inhibition of PKC-δ, in contrast to other isoforms, appears to have the potential to induce autoimmune disease in B cells. Previous PKC inhibiting compounds (e.g., enzastaurin, sotrastaurin) inhibit PKC-δ as well as PKC-ß. MS-553, a novel PKC-ß inhibitor lacks PKC-δ inhibition while selectively inhibiting PKC-ß and to slightly lesser extent PKC-α and PKC-θ. These features of MS-553 effectively combine to downregulate autoimmune stimulation of B and T cells while enhancing the function of regulatory T cells. Avoidance of autoimmunity is key, because complications related to enhanced T cell function including fatal pneumonitis and colitis have been reported with other kinase inhibitors in CLL and lymphoma.

## 1.2. MS-553

MS-553 (chemical name: ((2S,5R)-2,5-dimethyl-4-((tetrahydro-2H-pyran-4- yl)methyl)piperazin-1-yl)(3-(5-fluoro-2-methylpyrimidin-4-ylamino)-6,6-dimethylpyrrolo[3,4-c]pyrazol-5(1H,4H,6H)-yl)methanone) is a selective inhibitor of PKC activity. It has a molecular weight of 500.6 g/mol and is orally bioavailable in humans. For clinical testing it can be formulated with high purity to GMP standards. MS-553 is an investigational product and has not been approved for marketing in any country.

### 1.2.1. Mechanism of Action

Nonclinical pharmacology studies have demonstrated that MS-553 is a potent, ATP-competitive and reversible inhibitor of several classical PKC enzyme isoforms with a Ki =5.3 nM for recombinant PKC-β and a Ki = 10.4 nM for recombinant PKC-α. It also is a potent inhibitor of the novel isoform PKC-θ with an IC50 = 25.6 nM. MS-553 does not inhibit PKC-δ (IC50 > 1000 nM). Additionally, screening a broad panel of protein kinases reveals that MS-553 is very selective against kinases other than PKC.

MS-553 has been shown to be efficacious in several cell lines and a xenograft model of diffuse large B cell lymphoma that are driven by chronic activation of BCR-NFκB signaling due to CD79 mutation. In addition, several nonclinical studies also demonstrated that MS-553 is effective in

autoimmune disease models of lupus, rheumatoid arthritis, multiple sclerosis, and uveitis. For more information on the pharmacology see the MS-553 Investigator's Brochure (IB).

### 1.2.2. Safety Pharmacology

A core battery of safety studies performed in nonhuman animals (rat; dog) indicated no undesirable pharmacodynamics effects of MS-553 on physiological functions in relation to exposure in the therapeutic range and above. No functional changes in vital organs or systems which are likely to be of importance in clinical testing of MS-553 were identified.

[redacted]

### 1.2.3. Metabolism and Drug-Drug Interaction Potential

[redacted]

### 1.2.4. Summary of Clinical Experience with MS-553

MS-553 has been explored in single ascending dose (SAD) (protocol 2014-04-001) and multiple ascending dose (MAD) (protocol MS-553-102) studies in healthy human volunteers. MS-553 has not been studied in patients with cancer or other immune system diseases.

The Phase 1 SAD study evaluated doses ranging from 25 mg to 400 mg. Pharmacokinetic (PK) data from this study demonstrated that MS-553 was rapidly absorbed into systemic circulation with a $T_{max}$ of 2-4 hours and was rapidly eliminated with a mean apparent terminal half-life (t ½)

of 10-14 hours. The t ½ did not appear to be dose dependent. The inter-subject variability in exposure measures ($C_{max}$ and AUC) and the t ½ appears to be low. Increases in dosage led to mostly dose proportional increases in exposure. The PK behavior of MS-553 was similar when administered in either a fed or a fasted condition. While food did not change the PK profile of MS-553, gastrointestinal side effects decreased substantially when MS-553 is taken with food, as demonstrated in the MAD study.

In the SAD study, MS-553 was well tolerated; AEs were either mild or moderate and were observed predominantly in the highest active dose group (400 mg). The most frequently observed adverse events were nausea (9 subjects, 19% of subjects who received active drug), vomiting (4 subjects, 8% of subjects who received active drug), visual disturbance (4 subjects, 8% of subjects who received active drug), dizziness/vertigo (4 subjects, 8% of subjects who received active drug) and headache (3 subjects, 6% of subjects who received active drug). All AEs were transient and resolved. Refer to the IB for additional details.

[redacted]

In the MAD study, MS-553 was well tolerated and all AEs were either moderate or mild. The most frequent observed AEs were headache (9 subjects, 37.5% of subjects receiving active drug), nausea (3 subjects, 12.5% of subjects receiving active drug), visual disturbance (3 subjects, 12.5% of subjects receiving active drug), neck pain (3 subjects, 12.5% of subjects receiving active drug), abdominal pain (3 subjects, 12.5% of subjects receiving active drug) and dizziness (2 subjects, 8.3% of subjects receiving active drug). All AEs were transient and resolved. Refer to the IB for additional details.

# 2. OBJECTIVES AND ENDPOINTS

## 2.1. Cohort A Objectives

### 2.1.1. Primary Objective

The primary objective of Cohort A is to:

- Evaluate the safety of MS-553 monotherapy in patients with CLL/SLL whose disease relapsed after or was refractory to at least two prior lines of therapies with the following exceptions:
  - Patients with a 17p deletion who have already received venetoclax, or
  - Patients who have *TP53* mutation (prior therapy is not required for these patients), or
  - Patients who have either acquired clinical and/ or molecular (e.g., BTK or PLCG2 mutation) resistance to a BTK inhibitor.
- Determine the MTD or the initial RP2D of MS-553 monotherapy.

### 2.1.2. Secondary Objective

The secondary objective of Cohort A is to:

- Evaluate the clinical activity of MS-553 in patients with relapsed or refractory CLL/SLL who
  - Have failed at least two prior lines of therapies, or
  - Have either acquired clinical and/ or molecular (e.g., BTK or PLCG2 mutation) resistance to a BTK inhibitor.
- Evaluate pharmacokinetics in patients receiving MS-553.

Pursuit of the secondary objective should not jeopardize the primary objective, which is safety.

### 2.1.3. Exploratory Objectives

Exploratory objectives of Cohort A include the following:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

## 2.2. Cohort B Objectives

### 2.2.1. Primary Objective

The primary objective of Cohort B is to:

- Evaluate the safety of MS-553 in combination with acalabrutinib in patients with CLL/SLL.
- Determine the MTD or the initial RP2D of MS-553 in combination with acalabrutinib.

### 2.2.2. Secondary Objectives

The secondary objectives of Cohort B are to:

- Evaluate the clinical activity of MS-553 in combination with acalabrutinib in patients with CLL/SLL.
- Evaluate pharmacokinetics in patients receiving MS-553 in combination with acalabrutinib.

Pursuit of the secondary objectives should not jeopardize the primary objective, which is safety.

### 2.2.3. Exploratory Objectives

Exploratory objectives of Cohort B include the following:

- [redacted]
- [redacted]

## 2.3. Cohort C Objectives

### 2.3.1. Primary Objective

The primary objectives of Cohort C are to:

- Evaluate the safety of MS-553 in combination with venetoclax and rituximab in patients with CLL/SLL.
- Determine the MTD or the initial RP2D of MS-553 in combination with venetoclax and rituximab.

### 2.3.2. Secondary Objectives

The secondary objectives of Cohort C are to:

- Evaluate the clinical activity of MS-553 in combination with venetoclax and rituximab in patients with CLL/SLL.
- Evaluate pharmacokinetics in patients receiving MS-553 in combination with venetoclax and rituximab.

Pursuit of the secondary objectives should not jeopardize the primary objective, which is safety.

### 2.3.3. Exploratory Objectives

Exploratory objectives of Cohort C include the following:

- [redacted]
- [redacted]

## 2.4. Primary Endpoints

The primary endpoints of this study include:

- Safety
  - The incidence rate of dose-limiting toxicities (DLT) and treatment-emergent adverse events (TEAE) requiring study drug discontinuation. Assessments for DLT and TEAE will occur during Cycle 1 for Cohort A1, and during the protocol defined DLT periods for Cohort B1 and Cohort C1 (see Sections 0 and 3.3.4). TEAE will be assessed throughout the course of the trial. The primary endpoint will be the rate of DLT and TEAE requiring study drug discontinuation in the respective DLT evaluation periods of Cohort A1, Cohort B1, and Cohort C1.
- MTD or initial RP2D as monotherapy, as well as in combination with either acalabrutinib or venetoclax and rituximab.

## 2.5. Secondary Endpoints

Secondary endpoints in this study are related to clinical activity. These include the following:

- Objective response rate (ORR), with overall response defined as best response of complete response (CR), CR with incomplete marrow recovery (CRi), partial response (PR), or PR with lymphocytosis (PRwL) according to the 2008 International Workshop on Chronic Lymphocytic Leukemia Response Criteria (IWCLL) with modifications for treatment-related lymphocytosis.
- Duration of response (DoR), defined as time from first documentation of response to first documentation of progressive disease (PD) per 2008 IWCLL, first new therapy including allogeneic transplantation, or death due to any cause.
- Progression free survival (PFS), defined as time from first dose of study treatment to the first documentation of PD, first new therapy excluding allogeneic transplantation, or death due to any cause.
- Overall survival (OS), defined as time from first dose of study treatment to death due to any cause.
- Disease control rate (DCR) defined as the percentage of patients who have achieved CR, CRi, PR, PRwL and stable disease (SD). Duration of stable disease with stable disease defined as at least 6 months from the start of MS-553 monotherapy to first

documentation of progressive disease (PD) in relapsed and refractory CLL/SLL patients.

- Pharmacokinetics of MS-553 monotherapy, as well as the small molecule agents used in combination, acalabrutinib, or venetoclax.

## 2.6. Exploratory Endpoints

**Cohort A:**

[redacted]

**Cohort B:**

Samples: For Cohort B, the samples being collected in this study **for the measurement of exploratory endpoints are**:

[redacted]

**Cohort C:**

Samples: For Cohort C, the samples being collected in this study **for the measurement of exploratory endpoints are**:

[redacted]

# 3. INVESTIGATIONAL PLAN

## 3.1. Overview of Study Design

This is a Phase I/II multi-center, open-label study of single agent MS-553, as well as MS-553 in combination with acalabrutinib or venetoclax and rituximab in treatment experienced CLL/SLL patients.

The study will consist of 3 cohorts. Cohort A will evaluate MS-553 monotherapy, Cohort B will evaluate MS-553 in combination with acalabrutinib, and Cohort C will evaluate MS-553 in combination with venetoclax and rituximab. A schema of the three cohorts is shown in Figure 1 in Section 3.1.4.

[redacted]

### 3.1.1. Cohort A: MS-553 Monotherapy

The first part of the study, the dose escalation portion (Cohort A1), will determine the safety of MS-553 and the MTD or initial RP2D. After the initial RP2D is identified, an expansion cohort (Cohort A2) will be started at the MTD or initial RP2D, enrolling approximately 25 patients with relapsed/refractory CLL/SLL who (a) have failed at least two prior lines of therapies, or (b) have either acquired clinical and/or molecular resistance to a BTK inhibitor (i.e., BTK and/or PLCG2 mutation) after achieving initial response to a BTK inhibitor. In addition, an optional expansion cohort (Cohort A3) of approximately 25 patients with aggressive lymphoma, including Richter's transformation, DLBCL and MCL will be enrolled. At least 15 patients in Cohort A3 shall be MCL patients.

[redacted] additional patients will be enrolled in Cohort A2 to further testing two dose levels before a final RP2D can be declared.

The two dose schedules designated as dose schedule 1 (DS1) and dose schedule 2 (DS2) are as follows:

Dose Schedule 1 (DS1)

| | MS-553 Oral Daily Dose |
|---|---|
| Week 1 | 150 mg BID |
| Week 2 | 200 mg BID |
| Week 3 and beyond | 250 mg BID |

Dose Schedule 2 (DS2)

| | MS-553 Oral Daily Dose |
|---|---|
| Cycle 1 and beyond | 225 mg BID |

Twenty of the 40 additional patients will be treated with DS1 and the other 20 patients with DS2. The patients will be allocated to either DS1 or DS2 in alternating fashion, according to the sequence of their enrollment. For example, the first enrolled patient will be allocated to DS1, the second patient to DS2, the third patient to DS1, the fourth to DS2, and so on.

The optional expansion cohort (Cohort A3) will be closed to accommodate the new dose testing plan.

[redacted]

### 3.1.2. Cohort B: MS-553 in combination with acalabrutinib

As soon as the MTD or initial RP2D is declared for MS-553 monotherapy in Cohort A1, MTD or initial RP2D of MS-553 in combination with acalabrutinib will be evaluated at an MS-553 starting dose of 150 mg BID (Cohort B1) in treatment experienced CLL/SLL patients who are BTK inhibitor naïve, eligible for standard of care treatment with a BTK inhibitor as a single agent and who have had no more than 2 previous lines of treament regimens. The number of patients in the dose escalation will range from 3 to approximately 12 patients. Once the MTD or initial RP2D is known for the combination (Cohort B1), two expansion cohorts (B2 and B3) will be started in parallel to further evaluate the safety of the combination regimens, as well as to assess early evidence of anti-tumor activity.

One of the expansion cohorts (Cohort B2) will evaluate MS-553 in combination with acalabrutinib in treatment experienced CLL/SLL patients who are BTK inhibitor naïve, are eligible for treatment with a BTK inhibitor as a single agent, and who have had no more than 2 previous lines of treatment regimens. Approximately 20 patients will be enrolled in Cohort B2 to further confirm the safety of the combination and assess early evidence of anti-tumor activity.

The other expansion cohort (Cohort B3) will evaluate MS-553 in combination with acalabrutinib in treatment experienced CLL/SLL patients who have received no more than 2 prior lines of therapy and have TP53 abnormalities (including 17p deletion and P53 mutations). Once this cohort is open, all patients with TP53 abnormalities who are also naïve to BTK inhibitors will be preferentially enrolled in Cohort B3, rather than Expansion Cohorts B2. Approximately 10 treatment experienced CLL/SLL patients eligible for standard of care acalabrutinib will be enrolled in Cohort B3 to further confirm the safety of the combination and assess early evidence of anti-tumor activity.

### 3.1.3. Cohort C: MS-553 in combination with venetoclax and rituximab

As soon as the MTD or initial RP2D is declared for MS-553 monotherapy in Cohort A1, MS-553 will be evaluated in combination with venetoclax and rituximab at the starting dose of 150 mg BID in treatment experienced CLL/SLL patients who are eligible for standard of care venetoclax and rituximab, naïve to prior Bcl-2 inhibitor treatment, and have had no more than 2 prior lines of treatment regimens. The number of patients in dose escalation will range from 3 to approximately 12 patients per dose group.

Once the MTD or initial RP2D is known for the combination (Cohort C1), one expansion cohort will be initiated to further evaluate the safety of the combination regimen, as well as to assess early evidence of anti-tumor activity. This cohort (Cohort C2) will enroll treatment experienced CLL/SLL patients who are eligible for standard of care venetoclax and rituximab, naïve to prior Bcl-2 inhibitor treatment and have had no more than 2 previous lines of treatment regimens. Approximately 20 patients will be enrolled to further confirm the safety of the combination and assess early evidence of anti-tumor activity.

### 3.1.4. Study Design Schematic

**Figure 1: Study Schema**

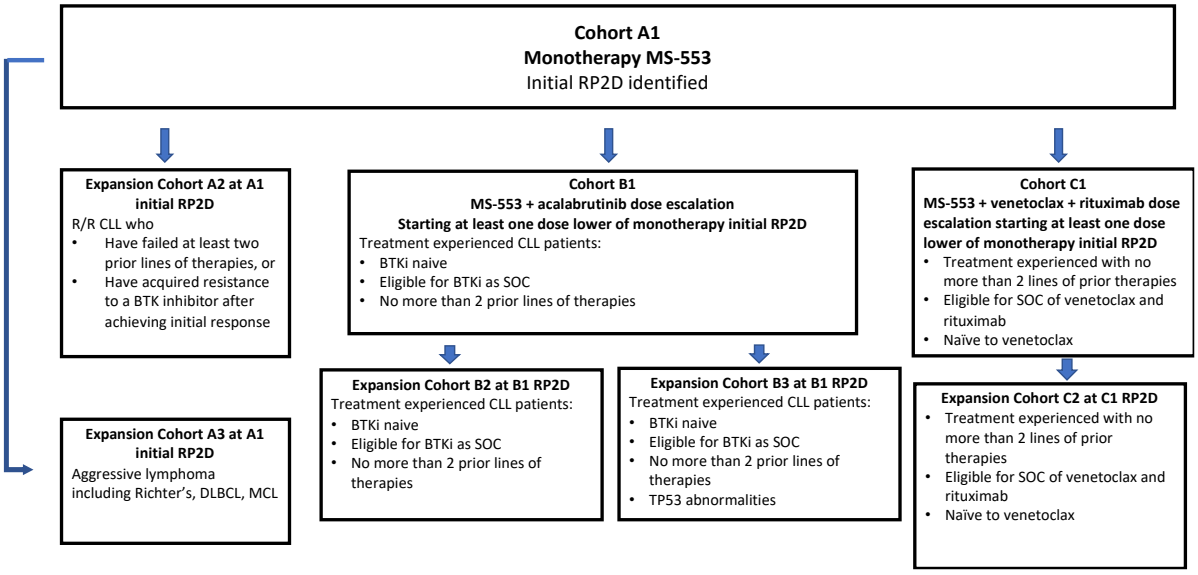



Figure 1: Cohort schema including dose escalation for monotherapy and each of the combinations as well as subsequent expansion cohorts.

## 3.2. Treatment Duration

Patients will be treated in 28-day cycles. Patients on this study may continue receiving study drug provided they continue to tolerate the drug, have no evidence of progression, do not meet any of the criteria for discontinuation, and the patient's participation in the study has not ended. The anticipated median treatment duration is unknown. Patients who have discontinued treatment for progressive disease and/or who have started another anticancer therapy or an investigational

product, will be followed for survival every 24 weeks (± 7 days) for up to 3 years (follow up can include clinic visit, chart review or telephone contact). Patients who discontinue treatment for reasons other than progressive disease, use of other anticancer therapy or an investigational product, death, or withdrawal of consent will have response assessments every 12 weeks (± 7 days) until progressive disease occurs. Thereafter they will be followed for survival every 24 weeks (± 7 days) for up to 3 years. All patients will discontinue survival follow-up upon completion of 3 years of survival follow-up, withdrawal of consent, death, or study closure, whichever is the earliest. The Sponsor reserves the right to discontinue the study for clinical or administrative reasons at any time.

## 3.3. Dose Escalation

### 3.3.1. Dose Escalation: Monotherapy Cohort A1

The study will be conducted as a limited 3+3 phase 1 dose escalation study with potential expansion cohorts. Clinical safety data in healthy volunteers suggest very few toxicities at 100 to 200 mg BID for up to 14 days. A conservative starting dose of 100 mg BID has been chosen and will be escalated according to Table 2 below:

**Table 2: Monotherapy Dose Levels**

| Dose Level | Dose |
|---|---|
| **0** | 100 mg BID |
| **1** | 200 mg BID |
| **2** | 250 mg BID |
| **3** | 300 mg BID |
| **4+** | TBD* mg BID |

*To be determined

A conventional “3+3” patient enrollment scheme will be followed during the dose escalation part of the study. Patients will be dosed with MS-553 by mouth twice daily at an initial dose (dose level 0, DL 0) of 100 mg BID daily in 28-day cycles. MS-553 shall be taken with food.

At least 3 patients will be enrolled at starting dose level 0 (100 mg BID).

After completion of dose level 3 (DL 3), the dose escalation of MS-553 can continue in 50 mg BID increments (or lower if an intermediate dose level is introduced) until a MTD is reached. Or the Safety Review Committee and/or the Sponsor may declare an initial RP2D, if further dose escalation is not warranted prior to reaching MTD. Furthermore, in order to facilitate initial RP2D determination, select cohort(s) may be expanded up to 10 patients total in a cohort to assess the safety and clinical activity of MS-553 provided that the dose does not exceed the MTD and the Safety Review Committee, upon reviewing the safety and tolerability, efficacy, and available PK and PD data, agrees. The DLT period is defined in this cohort as 28 days.

### 3.3.2. Dose Escalation: General Principles

During the first cycle of any dose level, if ≤1 Dose Limiting Toxicity (DLT; as defined in Section 3.3.1) is observed, then escalation to the next higher dose level will follow the 3+3 design and proceed when 3/3 or 5/6 patients have completed one 28-day treatment cycle without a DLT. If at least 1 of 3 patients experiences a DLT at any dose level, the cohort will be expanded to 6 patients. If ⩾2/3 or ⩾2/6 patients experience a DLT within a cohort, the MTD will be considered to have been exceeded. No additional patients will be enrolled in that cohort, and dose escalation will stop. If at least 3/3 or 5/6 patients have completed one 28-day treatment cycle at the previous dose level without a DLT, then that dose may be accepted as the MTD. At Sponsor discretion, additional patients may be enrolled into a cohort where ≤ 1 patient develops a DLT to obtain additional safety, PK, PD, and/or efficacy data.

If greater than 1/6 patients experience a DLT at DL 1, then 100 mg BID may be declared the MTD, or intermediate dose levels and/or alternative dosing schedules may be evaluated upon review of safety, pharmacodynamic, and/or pharmacokinetic data.

Each dose cohort will include a minimum of 3 evaluable patients for assessment of DLT. In order to be considered evaluable for DLT, patients must meet at least one of the following criteria:

1. Complete dosing through the DLT period and receive at least 75% of MS-553 intended doses during that time.
2. Discontinue due to DLT

During the DLT evaluation period, non-evaluable patients who discontinue treatment before DLT period is complete for reasons other than study drug-related toxicities (e.g., progressive disease, non-compliance) or do not receive at least 75% of MS-553 intended doses in the DLT period, will be replaced with additional patients enrolled at the same dose level. After a DLT is resolved or reversed to ≤ Grade 1, the study drug may continue at a lower dose level at the discretion of the investigator.

A decision on dose escalation to the next dose level will be based on evaluation of the clinical safety profile, and may also include evaluation of MS-553 exposure in treated patients. After the completion of each cohort, safety and PK data (if available) will be reviewed and a decision on dose escalation will be determined by the Investigators, the Safety Review Committee, and the Sponsor.

During the dose escalation period, intra-patient dose escalation will be permitted at the discretion of the study investigators and after discussion with the medical monitor and Sponsor, if the following criteria are met:

1. The next higher dose for the regimen has been demonstrated to be safe by at least 3 patients and all 3 patients complete one cycle without experiencing any DLT.
2. The patient who will receive the higher dose has not experienced a DLT and has also completed at least 2 cycles of therapy at their current dose.
3. Intra-patient dose escalation can be increased only by one dose level at a time.

After completion of each dose escalation cohort, the SRC will review clinical safety and tolerability data as well as PK data available at the time for all patients in order to confirm dose escalation to the next dose level. Based on the SRC's review, a cohort may be expanded, or an intermediate or a lower-than-planned dose level or an alternative dosing schedule may be evaluated.

All patients will continue to be monitored for approximately 30 days ( +7 days) after treatment discontinuation for development of any late treatment emergent adverse events. Any such late adverse events will be considered in the determination of the MTD/initial RP2D and dose schedule to be taken forward into the expansion phase of the study.

[redacted] While the MTD was not reached, an initial RP2D was identified. [redacted] the SRC reviewed all available efficacy, safety, PK and PD data of Cohort A1 and some Cohort A2 patients and agreed on an updated RP2D with a ramp-up dosage regimen as shown in Table 3 below.

**Table 3: Initial Recommended Phase 2 Dose**

| **MS-553** | **Oral Daily Dose** |
|---|---|
| Weeks 1 to 4 (Cycle 1) | 150 mg BID |
| Weeks 5-8 (Cycle 2) | 200 mg BID |
| Weeks 9 and beyond (Cycle 3+) | 250 mg BID |

[redacted]

The two new dose schedules are designated as dose schedule 1 (DS1) and dose schedule 2 (DS2) are as follows:

Dose Schedule 1 (DS1)

| | MS-553 Oral Daily Dose |
|---|---|
| Week 1 | 150 mg BID |
| Week 2 | 200 mg BID |
| Week 3 and beyond | 250 mg BID |

Dose Schedule 2 (DS2)

| | MS-553 Oral Daily Dose |
|---|---|
| Cycle 1 and beyond | 225 mg BID |

Twenty of the 40 additional patients will be treated with DS1 and the other 20 patients with DS2. The patients will be allocated to either DS1 or DS2 in alternating fashion, according to the sequence of their enrollment. For example, the first enrolled patient will be allocated to DS1, the second patient to DS2, the third patient to DS1, the fourth to DS2, and so on.

The optional expansion cohort (Cohort A3) will be closed to accommodate the new dose testing plan.

### 3.3.3. Dose Escalation: Combination Cohort B1

Once the MTD or initial RP2D is established for the monotherapy Cohort A1, enrollment in Cohort B1 will begin at 150 mg BID. The principles outlined in Section 3.3.2 will be followed for the Dose Escalation for the combination regimens. One or more 3+3 dose escalation cycles may be undertaken to determine an initial RP2D for MS-553 for each combination expansion cohorts. At least two dose levels are planned for Cohort B1. The dosing schedule and DLT evaluation periods are described in the table below.

**Table 4: Dosing Schedule and DLT Evaluation Periods for Cohort B1**

| MS-553 Dose Levels | Dosing Schedule | DLT Evaluation Period |
|---|---|---|
| 150 mg BID | In 28-day cycles | Cycle 1 |
| 200 mg BID | In 28-day cycles | Cycle 1 |

MTD determination, DLT and safety assessments will follow the general principles outlined in Cohort A1. Initial RP2D of MS-553 in the combination therapy is expected to be reached before the dose escalation reaches 250 mg BID, the high dose level of MS-553 monotherapy under testing. Intermediate dose levels (i.e. at 25 mg increment) or lower dose levels may also be evaluated as determined by the Investigators, the SRC and Sponsor until the MTD or initial RP2D for the combination is determined.

### 3.3.4. Dose Escalation: Combination Cohort C1

Once the MTD or initial RP2D is established for the monotherapy (Cohort A1), enrollment in Cohort C1 will begin. Starting with cycle 1, patients will be dosed with MS-553 by mouth twice daily beginning at 150 mg BID, and rituximab will be started according to standard of care, and as outlined in Section 5.2.3.3. Beginning with Cycle 3, venetoclax dosing once daily by mouth will be initiated with weekly dose escalations from 20 mg to 400 mg over 5 weeks.

At least two dose levels are planned for Cohort C1. The dosing schedule and DLT evaluation periods are described in the table below.

**Table 5: Dosing Schedule and DLT Evaluation Periods for Cohort C1**

| Dose level | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4+ | DLT Period(s) |
|---|---|---|---|---|---|
| 150 mg BID | 150 mg BID | 150 mg BID | 150 mg BID | 150 mg BID | Cycle 1 through 4 |
| 200 mg BID | 200 mg BID | 200 mg BID | 200 mg BID | 200 mg BID | Cycle 1 through 4 |

MTD determination, DLT and safety assessments will follow the general principles outlined in Cohort A1. Initial RP2D of MS-553 in the combination therapy is expected to be reached before or when the dose escalation reaches 250 mg BID, the high dose level of MS-553 under testing as monotherapy. Intermediate dose levels (i.e., at 25 mg increment) or lower dose levels may also be evaluated as determined by the Investigators, the Safety Review Committee and Sponsor until the MTD or initial RP2D for the combination is determined.

### 3.3.5. Dose Limiting Toxicity Definition

Dose limiting toxicities (DLT) occurring during DLT period appropriate for the cohort will be used to determine which dose of MS-553 will be examined in expansion cohorts. Toxicities will be assessed utilizing the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0) in Appendix 4.

Dose limiting toxicities (DLT) are defined as any of the following treatment-emergent events occurring from Cycle 1 Day 1 (after administration of MS-553) through the end of the DLT period (unless the event is determined to be unrelated to the drug):

1. Death
2. Hematologic toxicities:
   - Grade 4 neutropenia for $\geqslant$ 7 days
   - Grade 3 febrile neutropenia: absolute neutrophil count (ANC) <1000/mm$^3$ and single temperature >38.3°C (101°F) or a sustained temperature $\geqslant$38°C (100.4°F) for > 1 hour
   - Grade 4 thrombocytopenia $\geqslant$ 14 days (patients with baseline platelet count of $\geqslant$ 50 x 10$^9$/L)
   - Grade 4 thrombocytopenia $\geqslant$ 28 days (patients with baseline platelet count < 50 x 10$^9$/L)
   - $\geqslant$ Grade 3 thrombocytopenia associated with $\geqslant$ Grade 2 hemorrhage
   - New $\geqslant$ Grade 3 anemia requiring transfusion in a patient previously transfusion-independent.
3. Nonhematologic toxicities:
   - Any other $\geqslant$ Grade 3 toxicity not reversed to any one of the following three conditions in 7 days with appropriate intervention: a) baseline; b) $\leq$ Grade 1; or c) a status considered to be controlled by the Safety Review Committee (For example, isolated $\geqslant$ Grade 3 laboratory toxicity [e.g., electrolyte abnormalities] not associated with clinical signs or symptoms and is reversed to Grade 2 with appropriate intervention in 7 days is not considered a DLT.)
   - Any treatment-related adverse event (TEAE) requiring >25% of doses of scheduled study drug to be withheld during the DLT period.

All patients will continue to be monitored for approximately 30 days (+7 days) after treatment discontinuation for development of any late treatment emergent adverse events. Any such late adverse events will be considered in the determination of the MTD/initial RP2D and dose schedule to be taken forward into the expansion phase of the study.

## 3.4. Dose Expansion Cohorts

Dose expansion cohorts will be initiated after determination of the MTD or initial RP2D for monotherapy or combination treatment.

### 3.4.1. Expansion Cohort A2: Monotherapy

A dose expansion cohort ("**expansion cohort A2**") of approximately 25 patients with refractory or relapsed CLL/SLL who (a) have failed at least two prior lines of therapies, or (b) have either acquired clinical and/or molecular (e.g., BTK and/or PLCG2 mutation) resistance to a BTK inhibitor after achieving an initial response will be activated, and enrolled at the initial RP2D or the highest dose level at which fewer than 2/6 patients have completed the first cycle without experiencing DLT (e.g., the MTD).

[redacted] an additional 40 patients will be enrolled in Cohort A2 to further testing two dose levels before a final RP2D can be declared.

#### 3.4.1.1. Optional Expansion Cohort A3: Monotherapy

In addition, an optional expansion cohort of approximately 25 patients with aggressive lymphoma, including Richter's Transformation, DLBCL and MCL, can be enrolled simultaneously once activated. At least 15 patients in this cohort shall be MCL patients.

The optional expansion cohort A3 will be closed to accommodate testing two dose schedules in Cohort A2.

### 3.4.2. Expansion Cohorts B: Combination with Acalabrutinib

[redacted]

#### 3.4.2.1. Expansion Cohort B2

Once the MTD/initial RP2D is established in Cohort B1 for MS-553 in combination with acalabrutinib, an expansion cohort will be opened. This cohort will evaluate MS-553 in combination with acalabrutinib in treatment experienced CLL/SLL patients who are BTK inhibitor naïve, are eligible for standard of care treatment with a BTK inhibitor as a single agent, and who have had no more than 2 previous lines of treatment regimens. Approximately 20 patients will be enrolled in Cohort B2 to further confirm the safety of the combination and assess early evidence of anti-tumor activity.

#### 3.4.2.2. Expansion Cohort B3

Once the MTD/initial RP2D is established in Cohort B1, Cohort B3 will be opened in parallel to Cohort B2 to evaluate MS-553 in combination with acalabrutinib in treatment experienced CLL/SLL patients who are BTK inhibitor naïve, have TP53 abnormalities (including 17p deletion and P53 mutations), and have had no more than 2 previous lines of therapy. Once this cohort is open, all patients with TP53 abnormalities who are also naïve to BTK inhibitors will be preferentially enrolled in Cohort B3, rather than Expansion Cohorts B2. Approximately 10 treatment experienced CLL/SLL patients eligible for standard of care acalabrutinib will be enrolled in Cohort B3 to further confirm the safety of the combination and assess early evidence of anti-tumor activity.

### 3.4.3. Expansion Cohorts C: Combination of Venetoclax and Rituximab

[redacted]

#### 3.4.3.1. Expansion Cohort C2

Once the MTD or initial RP2D is established in Cohort C1 for the combination of venetoclax, rituximab and MS-553, an expansion Cohort C2 will be initiated. Treatment experienced CLL/SLL patients who are eligible for standard of care venetoclax and rituximab, naïve to prior Bcl-2 inhibitor treatment and have had no more than 2 previous lines of treatment regimens can be enrolled. Approximately 20 patients will be enrolled to further confirm the safety of the combination and assess early evidence of anti-tumor activity.

## 3.5. Safety Review Committee

The SRC will monitor the safety of all patients in the dose escalation segment. The Committee will receive all available demographics, PK, and safety data (including, but not limited to, lab and ECG results, physical exam findings, vital signs, adverse events) for all patients dosed within a given cohort in order to make a decision regarding dose escalation to the next dose level. Based on the SRC's review, a dose escalation cohort may be expanded or an intermediate or a lower-than-planned dose level may be evaluated. The SRC will include the Sponsor representatives, the medical monitor, and Principal Investigators.

A separate Safety Management Plan outlines the roles and responsibilities for those involved in the collection and processing of Serious Adverse Events (SAEs), and pregnancies for this clinical study.

## 3.6. Remaining on Treatment

Patients will remain on treatment with MS-553 until disease progression, initiation of other anti-cancer therapy or investigational drug product, patient refusal of treatment or revocation of consent, or death due to any cause.

## 3.7. Response Assessment

Response data will be collected at screening and on day 1 of every cycle beginning with the first treatment visit and ending at the end of treatment visit, which should occur 30 (+ 7 days) after the last dose of study drug, if the condition of the patient permits, or up to the start of other anti-cancer therapy or investigational drug product(s), whichever is sooner. Patients who discontinue treatment for reasons other than progressive disease, use of other anticancer therapy or an investigational drug product, death, or withdrawal of consent will undergo response assessments every 12 weeks (± 7 days) until progressive disease occurs.

Response data consists of a combination of interviews, physical exams, labs, and scans. Not all labs and scans will be obtained at each time point. See Section 6.2 and Appendix 1 for complete details.

# 4. PATIENT POPULATION

CLL is most commonly a disease of the elderly, with a median age at diagnosis of 71, but disease has been witnessed in adults of all ages. This study is targeted at CLL adults of any age who meet the inclusion criteria for the cohort to which the patient is enrolled.

[redacted]

## 4.1. Inclusion Criteria

To be eligible for inclusion in the **dose escalation cohorts or expansion cohorts** in this study, patients must meet all of the following criteria:

1. Age 18 years or older.
2. Diagnosis of CLL or SLL:
    a. History of histologically documented CLL or SLL that meets IWCLL diagnostic criteria according to the 2008 guidelines, and
    b. Indication for treatment as defined by the 2008 IWCLL guidelines, or the need for disease reduction prior to allogeneic transplantation.
3. Cohort specific inclusion requirements:

    **Cohort A1 (MS-553 monotherapy)**

    Relapsed after, or is refractory to, progressing after at least two prior lines of therapies with the following exceptions:

    a. Patients with a 17p deletion who have already received venetoclax; or
    b. Patients who have *TP53* mutation (prior therapy is not required) which shall be confirmed [redacted] at screening for enrollment. [redacted] or
    c. Patients with clinical and/ or molecular (e.g., BTK and/or PLCG2 mutation) resistance after achieving initial response to a BTK inhibitor.
        - For patients without clinical resistance, molecular resistance (i.e., BTK and/or PLCG2 mutation) shall be confirmed [redacted] at screening for enrollment.

    **Cohort A2 (MS-553 monotherapy)**

    Relapsed/refractory CLL/SLL patients who have:

    a. Failed at least two prior lines of therapies, or

b. Developed clinical and/or molecular (i.e., BTK and/or PLCG2 mutation) resistance after achieving an initial response to a BTK inhibitor

- For patients without clinical resistance, molecular resistance (i.e., BTK and/or PLCG2 mutation) shall be confirmed [redacted] at screening for enrollment.

**Cohort A3 (MS-553 monotherapy)** See Inclusion Criterion #4 below

**Cohort B1, B2 (MS-553 in combination with acalabrutinib)**

Treatment experienced patients with no more than two prior lines of therapies, who

a. Are naïve to prior BTK inhibitor treatments, and

b. Are eligible for single agent BTK inhibitor

**Cohort B3 (MS-553 in combination with acalabrutinib)**

Treatment experienced patients with no more than two prior lines of therapies, who

a. Are naïve to prior BTK inhibitor treatments, and

b. Are eligible for single agent BTK inhibitor, and

c. Have 17p deletion or TP53 mutation which shall be confirmed [redacted] at screening for enrollment. [redacted]

**Cohort C1, C2 (triplet regimen of MS-553 + rituximab + venetoclax)**

Treatment experienced patients receiving no more than 2 prior lines of treatment regimens, who

a. Are naïve to prior Bcl-2 inhibitor treatments, and

b. Are eligible for venetoclax in combination with rituximab.

4. For inclusion in the Cohort A3, patients must meet both of the following diagnostic criteria *instead of* inclusion criterion #2or #3:

   a. Diagnosis of aggressive lymphoma, explicitly comprising Richter's Transformation of CLL/SLL to Diffuse Large B-Cell Lymphoma (DLBCL); Activated B-cell (ABC), or non-GCB DLBCL not transformed from CLL/SLL, or MCL. Other histologies may be included after discussion with and approval of the study principal investigator and Sponsor medical monitor.

   b. Additionally, patients with MCL or de novo ABC or non-GCB subtype DLBCL patients must have received at least two lines of prior therapy and MCL patients must have failed at least a BTK inhibitor. Patients with Richter's transformation have no such restriction on the use of prior therapy.

5. WHO/ECOG performance status $\leqslant$ 2.

6. Meet laboratory parameters (see Exclusion Criteria).
7. In the opinion of the investigator, all of the following criteria are met:
    a. Have life expectancy $\geqslant$ 2 months
    b. Are willing to undergo all study-related evaluations and procedures, and
    c. Have ability to understand and willingness to execute a written informed consent document.

## 4.2. Exclusion Criteria

Patients who meet any of the following criteria are not eligible for this study.

1. Current transformation of CLL/SLL to PLL, non-Hodgkin lymphoma, or Hodgkin lymphoma.
    d. Patients being considered for inclusion in the optional expansion cohort (aggressive lymphoma) are not excluded on the basis of transformed lymphoma but must meet the definition of aggressive lymphoma outlined in the inclusion criteria for Cohort A3.
2. Active and uncontrolled autoimmune cytopenia(s).
3. Any of the following prior therapies within 14 days prior to Cycle 1 Day 1:
    a. Major surgery
    b. Corticosteroids greater than 20 mg / day prednisone (or equivalent), unless used by inhalation or topical route, or unless necessary for premedication before and/ or after iodinated contrast dye. Higher doses, and more prolonged courses of steroids are permitted under certain circumstances after discussion with the medical monitor and/or Sponsor including, but not limited to, the following:
        i. Treatment of disease-related autoimmune hemolysis or autoimmune thrombocytopenia;
        ii. Symptomatic relief of lymphadenopathy – preferably after completion of Cycle 1;
        iii. Symptomatic relief of B symptoms – after completion of Cycle 1;
        iv. Treatment of GVHD – please discuss with medical monitor;
        v. Short courses (up to 14 days) if needed for any intercurrent condition such as acute exacerbation of any non-disease-related condition (e.g., arthritis, asthma, COPD) including steroid dose modification required for adrenal insufficiency.
    c. Cytotoxic chemotherapy or biologic therapy, with the exception of BCR pathway kinase inhibitors for which only a 24-hour wash out prior to Cycle 1 Day 1 is required.
4. Failure to recover:

a. From toxicity to Grade 1 or less from prior chemo- or radiotherapy or biologic therapy with the exception of alopecia, atrial fibrillation or hypertension that developed during treatment with a BTK inhibitor.

b. To Grade 2 or less for atrial fibrillation or hypertension that occurred as a consequence of treatment with a BTK inhibitor.

5. CNS leukemia/lymphoma – including history of treated CNS disease even if the patient is asymptomatic.

6. Inadequate bone marrow function / hematopoietic reserve, except in the case of documented bone-marrow involvement, evidenced as:

   a. Absolute Neutrophil Count (ANC) < 1 x $10^9$/L

   b. Platelet count < 30 x $10^9$/L

7. Inadequate liver or renal function as specified below:

   a. Serum total bilirubin > 2 x ULN (upper limit of normal), or > 3 x ULN in case of liver involvement with CLL/SLL, or serum total bilirubin > 3 x ULN in patients with documented history of Gilbert's disease and normal direct bilirubin.

   b. AST or ALT > 2.5 x ULN, or > 5 x ULN if CLL/SLL is present in the liver.

   c. Estimated GFR < 30 mL/min.

8. For Cohort B patients, active treatment with strong CYP3A inhibitors, CYP3A inducers or proton pump inhibitors, unless medication can be stopped prior to enrollment in the study.

9. For Cohort C patients, active treatment with strong and moderate CYP3A inhibitors, strong CYP3A inducers, or strong P-gp inhibitors unless medication can be stopped prior to enrollment in the study.

[redacted]

[redacted]

12. Receiving treatment with medications that are known to be strong inducers, inhibitors or sensitive substrates of CYP3A4/5 or medications with risk for QT prolongation that cannot be discontinued prior to study entry (at least 48 hours prior to the start of Cycle Day 1 dosing). For any exceptions, discussion with medical monitor and/or Sponsor is needed. Weak or moderate inhibitors may be used with caution, except as otherwise specified in Exclusion Criteria. Examples of these medications are listed in Appendix 3.

13. Clinically significant cardiac diseases, including any of the following:

    a. History or presence of ventricular tachyarrhythmia

b. Presence of unstable/uncontrolled atrial fibrillation **is exclusionary**. Patients with stable atrial fibrillation (rate controlled pharmacologically) are eligible provided that they do not meet any other exclusion criteria. Patients whose atrial fibrillation occurred as a consequence of treatment with a BTK inhibitor may be eligible for the study provided that the patient is asymptomatic and on a stable dose of medication for rate control, and only after discussion with the medical monitor.

c. Unstable angina pectoris or acute myocardial infarction within 3 months prior to start of study drug.

d. NYHA functional class III or IV heart failure

e. Baseline QTcF interval of > 480 msec. Prior QTc prolongation due to prior medication no longer on board is not exclusionary. A family history of QTc interval prolongation by itself is not exclusionary provided that the patient's QTc is not prolonged. For those with prolonged QTc interval due to bundle branch block, patient may be eligible after documentation of a "corrected value" $\leqslant$480 msec and confirmation by cardiologist that patient is asymptomatic and that no other cardiac conduction or cardiac abnormality is present that would pose any safety issue for the patient.

   *Note:* As the eligibility criteria specify the QT interval corrected by the method of Fridericia (QTcF), any correction for widened QRS should be sure to include a cube-root corrected R-R interval. Please discuss/consult with a cardiologist if there are any questions.

14. History of another malignancy that in the opinion of the investigator limits survival to less than 2 years.

[redacted]

17. Gastrointestinal dysfunction, including motility or malabsorption syndromes or inflammatory bowel disease which could limit absorption of MS-553.
18. Known HIV positivity, or active hepatitis B or C infection with detectible viral nucleic acid in the blood.
19. Severe systemic infections requiring intravenous antibiotics within the two weeks prior to initiation of MS-553.
20. Any other life-threatening illness, medical condition, or laboratory abnormalities or therapies that in the opinion of the investigator could compromise the safety of the patient or interfere with analysis of study endpoints.
21. Women who are lactating or pregnant.
22. Women of child-bearing potential or male partners of women of child-bearing potential who will not agree to use highly effective method of contraception throughout the entire

study period and for a minimum of 3 months after the last dose of study drug. Highly effective contraception methods include:

a. Total abstinence *or*

b. Male or female sterilization *or*

c. Combination of any two of the following:

    i. Use of oral, injected or implanted hormonal methods of contraception

    ii. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

    iii. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

Women of child-bearing potential who will not agree to the following are ineligible for the study:

- Refrain from breastfeeding and donating oocytes or blood during the course of the study and for 3 months after the last dose of study medication, and
- Ongoing pregnancy testing during the course of the study and at the end of treatment visit.

23. Men who will not agree to the following are ineligible for the study:

- Refrain from donation of sperm or blood during the course of the study and for 3 months after the last dose of study medication, **and**
- Completely abstain from sexual contact, or must always use a latex or synthetic condom during any sexual contact until 3 months after the last dose of study drug, or have prior documentation of surgical sterilization.

# 5. STUDY TREATMENT

## 5.1. Overall Study Design Investigational Study Drug

Detailed information about MS-553 is available in the IB and the Pharmacy Manual.

### 5.1.1. MS-553 Treatment Description

MS-553 drug product is supplied as an immediate release, round, white film-coated tablet provided in three strengths: 25 mg, 50 mg and 100 mg. The precise composition of the drug product and purpose of all ingredients are provided in the IB.

#### 5.1.1.1. Storage and Handling

MS-553 drug product drug product is packaged in white, opaque, high-density polyethylene bottles with white, opaque, polypropylene, child resistant caps. Counts of 30 tablets each for 25 mg, 50 mg and 100 mg strength tablets are provided. Each bottle will be labeled with its contents, product lot number, required storage conditions, Sponsor's address, and any specific cautionary statement such as "New Drug – Limited by Federal Law to Investigational Use." Bottles are to be stored at room temperature (15-30°C). Until dispensed to the patients, MS-553 drug product bottles should be stored in a securely locked area accessible only to authorized site personnel. The MS-553 drug product should not be repackaged into alternative containers other than the bottles in which it was supplied. Refer to the Pharmacy Manual for more specific storage and handling information.

#### 5.1.1.2. Study Drug Disposal

Used (empty) bottles and opened bottles with unused study drug supplies will be destroyed on-site by the Investigational Pharmacy Service according to the site SOP after completion of study drug accountability by the study monitor. Study drug destruction will be documented in the study's pharmacy binder. Unopened bottles will be returned to MingSight Pharmaceuticals Inc. or destroyed per the site SOP.

### 5.1.2. Combination Treatment Description

Combination treatment with either acalabrutinib (B Series Cohorts) or venetoclax and rituximab (C Series Cohorts) will be according to standard of care and as described in Section 5.2.3.2 and 5.2.3.3, respectively. The combination drugs should be stored, handled and disposed of according to the Complete Prescribing Information and site standard procedures for these drugs.

## 5.2. Treatment Plan

### 5.2.1. Premedication

Appropriate anti-emetic drugs per institutional standard should be administered upon initiation of MS-553.

### 5.2.2. Administration Instructions

MS-553 should be taken orally with food at approximately the same time each day. Patients should be instructed not to bite, chew or crush the tablet. If the patient is unable to take the entire tablet, contact the medical monitor for further instructions. Refer to the Pharmacy Manual for more specific dose administration details.

### 5.2.3. Dosing Instructions and Schedule

#### 5.2.3.1. MS-553 Dosing – All Cohorts

MS-553 should be taken orally twice daily, every 12 hours ± 2 hours. At C1D1, C1D8, and C2D1, the morning dose will be administered by clinic staff. All other doses will be administered by the patient. MS-553 should be taken at approximately the same time each day. Small variations in the twelve-hour schedule are understandable, but patients should be advised to adhere to the prescribed schedule as closely as possible. Adherence to the dosing schedule will be documented in the patient chart and EDC /electronic CRF at each scheduled visit. Patients will record all at-home dosing in a patient diary. Refer to the Pharmacy Manual for more specific dose administration details.

<u>Administration Instructions: Dosing Interruptions, Missed Doses, and Vomited Doses</u>

If a dose is late but within 4 hours of its scheduled administration time it should be taken; if more than 4 hours have passed, the dose should be omitted and the patient should continue treatment with the next scheduled dose with no alteration of timing for the subsequent dose. The missed dose should be documented in the patient's diary, chart and the EDC / electronic CRF.

If vomiting occurs while taking MS-553, no re-dosing is allowed before the next scheduled dose. Treating physicians are encouraged to use prophylactic antiemetics per standard of care at their institution.

Patients should be instructed that if they miss two or more doses consecutively that they must contact the investigator or other study site personnel.

#### 5.2.3.2. Acalabrutinib Dosing – B Cohorts

For patients who are enrolled into any of the B series cohorts, acalabrutinib will be administered according to the Full Prescribing Information in combination with MS-553. As both acalabrutinib and MS-553 are substrates of P-glycoprotein (P-gp), it is recommended that acalabrutinib be taken 90 minutes (but at least 1 hour) prior to the time when MS-553 is taken to avoid potential drug-drug interaction.

#### 5.2.3.3. Venetoclax and Rituximab Dosing – C Cohorts

For patients are enrolled into any of the C series cohorts, venetoclax will be initiated after eight weeks of treatment with MS-553 and rituximab. Rituximab will be administered according to the Full Prescribing Information except the necessary changes to allow for the dosing sequence of the triple drug combination regimen. In order to reduce the risk of TLS,

venetoclax will not be administered until Cycle 3. Beginning in Cycle 3, venetoclax will be started and dose escalated in accordance with the Prescribing Information from 20 mg to 400 mg over five (5) weeks and administered in combination with rituximab and MS-533. Venetoclax should be taken with food $\geqslant$ 6 hr after the morning dose of MS-553. Venetoclax shall be administered in accordance with the Full Prescribing Information.

For patients who have achieved complete responses with the treatment of the triplet regimen of MS-553, venetoclax, and rituximab, assessments of uMRD in a central lab will be performed in a fashion consistent with IWCLL 2018 guideline. If uMRD in both peripheral blood and bone marrow is confirmed in a central lab, MS-553 may be discontinued at the discretion of the investigators after completion of venetoclax administration as defined in package label.

### 5.2.4. Concomitant and Supportive Therapy

#### 5.2.4.1. MS-553

Treating physicians are encouraged to use prophylactic antiemetics per standard of care at their institution.

Steroids in doses of up to 20 mg prednisone (or equivalent) daily are allowed for symptomatic relief of lymphadenopathy and B symptoms if needed, with preference for their administration to be delayed until after completion of Cycle 1. If steroids are needed to control lymphadenopathy-related issues, please discuss with the medical monitor/Sponsor. After completion of Cycle 1, higher dose steroids may only be used for therapeutic treatment of (1) GVHD or (2) autoimmune cytopenia after discussion with the medical monitor and/or Sponsor. Treatment with short courses of steroids is permitted for intercurrent illness as per standard of care practice.

No other direct anti-leukemia therapy is permitted.

Supportive care with blood products (prophylactic or therapeutic) and hematopoietic growth factors may be used in accordance with institutional standards. Use of myeloid or erythroid growth factor during DLT period should be discussed with the medical monitor and the study Sponsor.

#### 5.2.4.2. Acalabrutinib

Treating physicians are encouraged to use concomitant and supportive therapy for acalabrutinib per standard of care at their institution.

#### 5.2.4.3. Venetoclax

Prior to initiation of venetoclax, MS-553 and rituximab combination shall be given for two cycles to allow for debulking of tumor mass with the intent of avoiding tumor lysis syndrome (TLS). Venetoclax shall start on Cycle 3. Treating physicians should assess patient-specific factors for level of risk of TLS and provide prophylactic hydration and anti-hyperuricemics to patients prior to the first dose of venetoclax to reduce risk of TLS according to standard site procedures. After two cycles treatment of MS-553 and rituximab, restaging prior to Cycle 3 at

investigator discretion is allowed for patients who were initially high risk for TLS, to allow outpatient treatment if they now are low or medium risk.

**Table 6: Recommended TLS Prophylaxis Based on Tumor Burden in Patients with CLL/SLL**

| Tumor Burden | Prophylaxis | | Blood Chemistry Monitoring[cde] |
|---|---|---|---|
| | Hydration[a] | Anti-hyperuricemics | Frequency of Assessments |
| All LN < 5cm<br>AND<br>ALC < 25 x $10^9$/L | Oral<br>(1.5-2 L) | Allopurinol[b] | • First dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours<br>• For subsequent ramp-up doses: Pre-dose |
| Any LN ⩾ 5cm to < 10cm<br>OR<br>ALC ⩾25 x $10^9$/L | Oral<br>(1.5-2 L)<br>and consider additional intravenous | Allopurinol | • First dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours<br>• For subsequent ramp-up doses: Pre-dose<br>• For first dose of 20mg and 50mg: Consider hospitalization for patients with CrCl < 80 mL/min |
| LN ⩾ 10cm<br>OR<br>ALC ⩾ 25 x $10^9$/L<br>AND any LN ⩾ 5 cm | Oral<br>(1.5-2 L)<br>and intravenous (150-200 mL/hr as tolerated) | Allopurinol; consider rasburicase if baseline uric acid is elevated | • In hospital first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12, 24 hours<br>• For subsequent ramp-up doses, outpatient: Pre-dose, 6 to 8 hours, 24 hours |

[a.] Administer intravenous hydration for any patient who cannot tolerate oral hydration
[b.] Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax
[c.] Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d.] For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose or according to institutional standard.
[e.] A window of one hour is permitted for the post-dose labs that are due <24 hours and a two-hour window is permitted for the 24-hour post dose labs.

To reduce risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered, if clinically indicated.

#### 5.2.4.4. Anti-CD20 mAb

Consistent with the Prescribing Information of venetoclax, the anti-CD20 mAb used in the combination shall be rituximab for the relapsed/refractory CLL/SLL patients. Premedicate with acetaminophen and an antihistamine before each rituximab infusion according to institutional standard of care. Depending on the severity of any infusion-related reaction and the required

interventions, temporarily or permanently discontinue rituximab. Resume infusion according to institutional standard of care after symptoms have resolved.

Provide prophylaxis treatment for Pneumocystis jirovecii pneumonia (PCP) and herpes virus infections for patients with CLL during treatment and for up to 12 months following treatment as appropriate.

### 5.2.5. Excluded Medications

Co-administration of strong ($\geqslant$ 5-fold) inhibitors or inducers and sensitive substrates of CYP3A4/5 is prohibited and should be discontinued at least 48 hours prior to initiation of study drug. Medications with QT prolongation risk as listed in their package inserts or belong to drugs with known risk of Torsades de Pointers on crediblemeds.org should be avoided whenever possible. Refer to Appendix 3 for examples of these medications. When substitution of another medication is not feasible, discussion with the medical monitor and Sponsor will be needed. For example, the metabolism of the drug in question may be more affected by other P450 enzymes and not CYP3A4 or CYP3A5, in which case use of that drug may be approvable for use in the study. If in doubt, please discuss with the medical monitor.

Systemic steroids (not inhalation or topical) in amounts of 20 mg or higher of prednisone or equivalent per day may be permitted under certain circumstances (e.g., as pre- and post-medication for reactions to contrast agents; treatment of pre-existing disease-related autoimmune cytopenias and hemolysis; those treated for GVHD; those with an acute need for a non-disease related condition (e.g., additional steroid requirement for adrenal insufficiency or other acute condition where a short course [up to 14 days] may be required). In such circumstances of non-disease-related conditions, please discuss with the medical monitor/Sponsor regarding continuation of dosing of study drug during this period of increased steroid administration. Patients may not receive any other anticancer therapies for the current malignancy while on study prior to disease progression.

Supportive care with blood products (prophylactic or therapeutic) and hematopoietic growth factors may be used in accordance with institutional standards, however the use of myeloid or erythroid growth factor during the DLT evaluation period should be discussed with the medical monitor and the study Sponsor.

<u>Cohorts using combination with acalabrutinib (B Cohorts)</u>

Concomitant strong CYP3A inhibitors, CYP3A inducers or proton pump inhibitors are prohibited. Dose modifications should be used according to the Prescribing Information and institutional standard of care for concomitant moderate CYP3A inhibitors. Treating physicians should avoid co-administration with proton pump inhibitors. If the patient is taking antacids, patients should be advised to separate dosing by at least 2 hours of taking antacids. If the patient is taking an H2 receptor antagonist, patients should be advised to take acalabrutinib 2 hours prior to the H2 receptor antagonist.

Cohorts using combination with venetoclax (C Cohorts)

Strong and moderate CYP3A inhibitors/inducers or strong P-gp inhibitors are prohibited. As MS-553 may be a P-gp substrate, patients must avoid taking venetoclax together with MS-553 at the same time. **A six-hour interval between MS-553 and venetoclax is advised**.

## 5.3. Withdrawal Criteria

Patients will be advised that they are free to withdraw from the study at any time for any reason. A patient may be withdrawn from the study for any of the following reasons:

- Patient voluntarily discontinues study participation (consent withdrawal);
- The need to take medication which may interfere with study measurements;
- Adverse events;
- Disease progression; Exceptions may be allowed if continuing study drug beyond disease progression is needed and prior consent of the medical monitor is obtained;
- Major violation or deviation of study protocol procedures;
- Non-compliance of patient with protocol;
- Patient is unable to comply with study procedures;
- Withdrawal from the study is, in the Investigator's judgment, in the patient's best interest;
- Patient is lost to follow-up;
- Study termination by the Sponsor.

The reasons for withdrawal will be recorded on the CRF and included in the final report along with any adverse events and any necessary medical treatment.

## 5.4. Discontinued Patients

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to the Sponsor (or designee) and will be clearly documented on the appropriate electronic CRF. If a patient is discontinued from the study early, all End of Treatment visit evaluations should be performed at the time of discontinuation, if possible.

Patients who are withdrawn or discontinue early may be replaced at the discretion of the Sponsor.

# 6. STUDY PROCEDURES

A calendar of study procedures to be conducted for each patient enrolled in the study is presented in a table in Appendix 1, as Appendix 1A (A Cohorts), 1B (B Cohorts), and 1C (C Cohorts), which are also described in the text that follows.

The Investigator must document any deviation from protocol procedures and notify the Sponsor or designee.

Safety and tolerability assessments will include regular monitoring of AEs, changes from baseline in laboratory variables, physical examinations, vital signs, and safety assessments.

From the time that informed consent is obtained through the first administration of investigational drug product, the Investigator must record all SAEs, as well as any non- serious AEs related to protocol mandated procedures, on the adverse event electronic CRF. All other untoward medical occurrences observed during the Screening period, including exacerbation or changes in medical history, are to be captured on the medical history electronic CRF.

## 6.1. Description of Study Procedures

### 6.1.1. Patient Enrollment and Treatment Assignment

Patient eligibility will be established at the conclusion of the Screening evaluations. During the dose escalation phase, assignment to dose level will be sequential and as described in Section 5.2 Treatment Plan. For the dose expansion phase, patients will be dosed at the MTD or initial RP2D identified during dose escalation.

### 6.1.2. Screening Period

Screening procedures shall be performed within 28 days prior to first dose of study drug unless otherwise stated. Procedures may be conducted over multiple visits if necessary.

### 6.1.3. Informed Consent

Screening begins with the informed consent procedure. The Investigator is obliged to give the patient thorough information about the study and study related assessments, and the patient should be given ample time to consider his or her participation. All patients must sign and date the Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent form before any study procedures are performed except where noted in the protocol in relation to standard of care procedures. Optional procedures require separate patient consent either within the main or a separate informed consent form, per IRB/IEC requirements.

### 6.1.4. Disbursement of Study Medication

#### 6.1.4.1. Disbursement of MS-553 Study Medication

Patients will be dispensed the appropriate amount of MS-553. One hundred eighty (180) or 120 of the 100 mg MS-553 tablets in bottles at the 300, or 200 mg BID dose levels, respectively; one hundred twenty (120) 100 mg and sixty (60) 50 mg tablets at the 250 mg BID dose level, an

additional thirty (30) 25 mg tablets will be provided to DS1; one hundred twenty (120) 100 mg and sixty (60) 25 mg tablets at the 225 mg BID dose level (DS2); or sixty (60) 100 mg tablets at the 100 mg BID dose level. Patients will be dispensed the appropriate amount of 25 mg, 50 mg and/or 100 mg tablets of MS-553 based on their assigned dose level or dose adjustments. Additional tablets may be dispensed if necessary in the opinion of the investigator when the subsequent visit will be later than 28 days but within the 3-day window (see Appendix 1A (A Cohorts), 1B (B Cohorts), and 1C (C Cohorts). Refer to the Pharmacy Manual for more specific dispensation details.

#### 6.1.4.2. Disbursement of Acalabrutinib, Venetoclax, and Rituximab

Patients will be dispensed the appropriate amount of acalabrutinib, venetoclax, and rituximab according to the prescribing information located in the package insert. The insurance provider and/or the patient will be responsible for the cost of acalabrutinib, venetoclax, and rituximab.

### 6.1.5. Instruction to the Patient for Administration

The Investigator must instruct the patient to take the study drug per protocol, the full Prescribing Information, and institutional standard of care for the approved combination drugs. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded in the dosage administration record CRF as appropriate. Patients shall be instructed to record their doses in the provided study drug diary. Refer to the Pharmacy Manual for more detailed patient dosing instructions.

### 6.1.6. Study Drug Accountability and Treatment Compliance

At each clinic visit, patients will be asked to return any remaining study drug from the previous dosing cycle as well as all used and unused study drug containers. The designated site staff will perform accountability as per each clinical site's standard practice.

For MS-553, the study site personnel are to supervise the patients taking study drug at the study site on days in which PK samples are taken. Patients are to keep a study drug diary of the date and time the study drug was taken for doses taken at home. The study drug diaries and used study drug packaging are to be returned to study site personnel at the next study visit. Study site personnel will review the study drug diary, examine the study drug packaging, and document their findings on the appropriate e-CRF. Designated site staff must thoroughly document and re-instruct the patient when significant noncompliance is noted.

For the combination treatments, institutional standard procedures or patient diaries should be used for study drug accountability and treatment compliance recorded.

All records must be readily available for inspection by the Sponsor or its representatives and the U.S. FDA or other regulatory authorities at any time.

### 6.1.7. Dose Modifications and Dose Delay

Investigators should follow the guidelines described herein for the modification of MS-553 treatment. Any plan to deviate from these guidelines in view of patient safety must be

previously discussed with the study Sponsor and the medical monitor unless there is an urgent need for action.

All dose modifications should be based on the worst preceding toxicity. If study treatment is being held due to toxicity, scheduled visits and all safety assessments in Cycle 1 should continue to occur, even without dispensation of the study drug. Additional scheduled visits and assessments including all PK samplings may be adjusted according to the actual dosing schedule upon the agreement between the investigator, the study medical monitor, and the Sponsor.

Recommended modifications to dosing (not including dose-limiting toxicities in the first cycle) are described in Appendix 2A (MS-553 Recommended Dose Modifications and Delays for Toxicity).

A maximum of three dose reduction steps but not lower than 100 mg BID as a single agent will be allowed, after which the patient will be discontinued from study treatment if there is a need for further dose reduction. In the combination regimens of cohort B and C, dose reductions to not lower than 50 mg BID is allowed.

For patients who undergo dose interruptions (delays) due to toxicity, if the same toxicity returns after re-initiation of treatment, regardless of duration, the second re-initiation of study drug must resume at the next lower dose level. However, the dose of MS-553 that is restarted could be reduced if the investigator feels it prudent to re-challenge at a lower dose. Please refer to Appendix 2A for dose modification instructions.

Recommended modifications to dose and schedule for the combination treatments are outlined in Appendix 2B and 2C, and according to institutional standard of care.

If the patient requires a dose interruption of > 28 days from previous dose for either MS-553 or combination treatment, then the patient must be discontinued from study treatment. Patients who discontinue the treatment due to an adverse event or an abnormal laboratory value, even if not related to study drug, must be followed until resolution or stabilization of the event.

All dose changes or interruptions must be recorded in the dosage administration record CRF.

### 6.1.8. Permitted Concomitant Therapy

In general, the use of any concomitant medication/therapy, including over-the-counter (OTC) medications, deemed necessary for the care of the patient is permitted during the study, with the exception of the prohibited medications noted in Section 5.2.5 and Section 6.1.10.

Hormonal contraceptives are permitted in women of child-bearing potential (see Section 4.2). Hormonal contraceptives include any marketed contraceptive agent that includes an estrogen and/or a progestational agent. It is unknown whether MS-553 could affect the efficacy of hormonal contraceptives and therefore women of childbearing potential on study must agree to use at least two methods of contraception as outlined in the Exclusion Criteria.

The patient must be told to notify the investigator and study personnel about any new medications, including OTC and herbal supplements that he or she begins after the commencement of the study drug. All medications (other than study drug) and significant non-

drug therapies (including physical therapy and blood transfusions) administered during the study must be recorded.

See Section 5.2.4 for additional information on concomitant and supportive therapy, instructions, in particular for the combination regimens.

### 6.1.9. Permitted Concomitant Therapy to be Used with Caution

Medication that are weak or moderate (as defined by the FDA; see the link in Appendix 3) inhibitors or inducers of CYP3A4/5 are not prohibited but should be administered with caution, as they may increase or decrease MS-553 exposure. (Moderate CYP3A inhibitors are prohibited in Cohort C.) Medications that are moderate inhibitors of CYP3A will require dose modifications as outlined in Section 5.2.5 for patients on the combination with acalabrutinib (Cohort B Series). Medications that are P-gp substrates must not be taken $\leqslant$ 6 hours prior to venetoclax (Cohort C Series) as outlined in Section 5.2.3.3.

After Cycle 1, steroids at doses up to 20 mg prednisone or equivalent per day are allowed for symptomatic relief of lymphadenopathy and B symptoms, if needed.

After completion of Cycle 1, higher doses of steroids may be used for therapeutic treatment of GVHD or autoimmune cytopenia or other intercurrent illness after discussion with the medical monitor and/or Sponsor.

Systemic steroids (not inhalation or topical) in amounts of 20 mg or higher of prednisone or equivalent per day may be permitted under certain circumstances (e.g., as pre- and post-medication for reactions to contrast agents; treatment of pre-existing disease-related autoimmune cytopenia and hemolysis; those treated for GVHD; those with an acute need for a non-disease related condition (e.g., additional steroid requirement for adrenal insufficiency or other acute condition where a short course [up to 14 days] may be required). In such circumstances of non-disease-related conditions, please discuss with the medical monitor/Sponsor regarding continuation of dosing of study drug during this period of increased steroid administration.

### 6.1.10. Prohibited Concomitant Medications

Strong inhibitors or inducers of CYP3A4/5 and sensitive CYP3A4/5 substrates and compounds with known QT prolongation risk as listed in their package inserts or belong to drugs with known risk of Torsades de Pointers (TdP) on crediblemeds.org should be avoided whenever possible and should be discontinued at least 48 hours prior to initiation of study drug. Refer to Appendix 3 for examples of these medications. When substitution of another medication is not feasible, discussion with the medical monitor and Sponsor will be needed. For example, the metabolism of the drug in question may be more affected by other P450 enzymes and not CYP3A4 or CYP3A5, in such case use of that drug may be approvable for use in the study. If in doubt, please discuss with the medical monitor.

Medications that are known to cause or have the potential to cause QTc prolongation as listed in their package inserts or belong to drugs with known risk of Torsades de Pointers (TdP) on crediblemeds.org should be avoided whenever possible unless prior approval of the Sponsor or

medical monitor is provided. Those with a history of increased risk for QT prolongation (e.g., congenital long QT-syndrome, low ventricular ejection fraction, impaired hepatic or renal function that could affect drug metabolism, uncorrected electrolyte disturbances, and history of drug-related prolonged QT interval) are addressed in Exclusion Criterion #13. When substitution of another medication has been approved by the Sponsor or medical monitor, patients taking medications known to cause QT/QTc prolongation as listed in as listed in their package inserts or belong to drugs with known risk of Torsades de Pointers (TdP) on crediblemeds.org should be monitored appropriately with serial ECGs. Refer to Section 5.2.5 for the prohibited concomitant medications.

### 6.1.11. Visit Schedule

The schedule of visits including which study related procedures are to be performed and which samples are to be collected at each time point is described graphically in Appendix 1A (A Cohorts), 1B (B Cohorts), and 1C (C Cohorts).

### 6.1.12. Visit Days and Numbering

Mandatory visits include the Screening visit, C1D1, C1D8, and Day 1 (± 3 days) of subsequent cycles, and the End of Treatment (EOT) visit. Patients may be required to make visits for PK samplings. Other visits may occur as required for standard of care medical practice.

If a patient comes early to begin a new cycle (for example, coming on Cycle 3 Day 28 would be equivalent to Cycle 4 Day -1), all study related procedures including, physical exam, clinical safety laboratory, CT scans if applicable, and study drug dispensing can occur, but Day 1 of the next cycle is not renumbered.

If a patient comes late to begin a new cycle but has missed doses of study medication, the day that the study medication is resumed shall be designated Day 1 of the next cycle (i.e., the previous cycle is lengthened).

If a patient's temporary discontinuation of study medication overlaps Day 1 of a subsequent cycle, the day that the study medication is resumed shall be designated Day 1 of the next cycle (i.e., the previous cycle is lengthened). If a patient holds study drug mid-cycle but resumes before Day 1 of a subsequent cycle, the cycle days are not renumbered.

Other alterations to the visit schedule, cycle numbering, or the ± 3 day window must be discussed with the medical monitor and recorded as a protocol deviation.

## 6.2. Assessments of Safety, Efficacy, and Exploratory Endpoints

### 6.2.1. Safety

For Cohort A1, assessments for DLT and TEAE will occur during Cycle 1. For Cohort B1 and C1, assessments for DLT and TEAE will occur during defined DLT evaluation periods (see Sections 0 and 3.3.4). TEAE will be assessed during the course of the trial. The primary endpoint will be the rate of DLT and TEAE requiring study drug discontinuation in the DLT evaluable period.

Toxicities will be defined using NCI CTCAE v5.0 criteria in Appendix 4.

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the monitoring of hematology, blood chemistry, and the regular monitoring of vital signs, ECGs, and physical condition as shown in Appendix 1A (A Cohorts), 1B (B Cohorts), or 1C (C Cohorts). For details on AE collection and reporting, refer to Section 7, Adverse Events and Toxicity Management. If a patient has vision-related adverse event that is $\geqslant$ Grade 2 and deemed at least possibly related to the drug, the patient will be referred to an ophthalmologist for a typical 8-point exam including measurement of visual acuity, slit-lamp bio-microscopy, and dilated full-fundus examination of the macula, optic nerve and peripheral retina.

### 6.2.2. Efficacy

Response assessments will be made by the individual investigators. Response for CLL will be evaluated according to criteria published by 2008 IWCLL. Because of the well-documented lymphocytosis not associated with disease progression that occurs with BCR signaling inhibitors such as BTK inhibitors, progressive lymphocytosis in the absence of other signs of disease progression (e.g., splenomegaly, enlarging lymph nodes, and disease-related constitutional symptoms) will not be considered disease progression. Isolated lymphocytosis in the context of what would otherwise be a PR is defined as a PR with lymphocytosis (noted as PR-L, PR+L, or PRwL in literature). Response criteria in the SLL patients and aggressive lymphoma patients will be based on the International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017).

Initial evaluation of the efficacy endpoints related to response will incorporate the data from the first 9 cycles of treatment. Any patient who receives at least one dose of study therapy is evaluable for response. Patients who have stable disease or a response by 9 cycles and continue treatment after 9 cycles will have response assessments including CT scans of the chest, abdomen, and pelvis (and neck if involved), preferably least every 12 weeks, or as clinically indicated until disease progression. Patients who do not have a response by 9 cycles but who have stable disease are eligible to stay on study treatment for up to a total of 24 cycles, with continual re-evaluation for response at subsequent visits during this time period. For patients who continue to have stable disease after 24 cycles or have a response after 9 cycles therapy, drug therapy can continue until disease progression.

Secondary efficacy endpoints in all cohorts include overall response rate (ORR), duration of response (DoR), disease control rate (DCR), PFS, and OS. For patients achieving a response, the response duration will be measured from the time at which criteria for CR, PR, or PR with lymphocytosis is first assessed until the date at which recurrent or progressive disease or death due to disease is documented. Stable disease, a component of DCR, is defined as at least 6 months from the start of MS-553 monotherapy until to first documentation of progressive disease (PD) in relapsed and refractory CLL/SLL patients. Progression free survival will be measured as the time from the first dose of the study drug until disease progression or death from any cause. Overall survival will be measured as the time from the first dose of the study drug until death due to any cause. For the secondary efficacy endpoints of response duration, PFS, and OS, patients who have not progressed or died at the time of last known status will be censored at that time; for response duration and PFS, patients may also be censored at the time

of subsequent treatment if a prior progression is not documented. See Section 8, Statistics, for more complete details on censoring.

### 6.2.3. Pharmacokinetics and Exploratory

Flow cytometry for diagnosis will be performed at screening on both bone marrow (when available) and peripheral blood samples (all patients). Flow cytometry will be performed on blood samples at other visits at the investigator's discretion.

[redacted]

Pharmacokinetics of MS-553 and/or its metabolites will be studied. Please see table below for timing of PK assessment. The exact time of each PK draw must be accurately recorded in the source document and on respective eCRFs.

**Table 7: Schedule of PK Assessments**

| | C1D1 | C1D8 | C2D1 | C2D8 | C3D8 | C4D1 | C4D8 | C5D1 |
|---|---|---|---|---|---|---|---|---|
| Cohort A1 | X | X | | | | | | |
| Cohort A2 | | X | | X[1] | X[1] | X | | |
| Cohort A2 DS1 | | | X | | | | | |
| Cohort A2 DS2 | | | X | | | | | |
| Cohort A3 | | | Y | | | | | |
| Cohort B1 | | | | | | | | |
| ≤200 mg BID | | X | Y | | | | | |
| >200 mg BID | | X | | X[1] | X[1] | Y | | |
| Cohort B2 & B3 | | | | | | | | |
| ≤200 mg BID | | | Y | | | | | |
| >200 mg BID | | | | | | Y | | |
| Cohort C | | | | | | | | |
| C1 | | | | | Z | X | | X |
| C2 | | | | | | | | Y |

DS1: Dose Schedule 1
DS2: Dose Schedule 2
X: PK sampling timepoints: MS-553 pre-dose, and 1 hr, 2 hr, 3 hr, and 4 hr (± 5 minutes) post-dose, and 6 hr (± 10 minutes) post-dose
Y: PK Sampling timepoint: MS-553 pre-dose
Z: PK sampling time points: 1 hr, 2 hr, 3 hr, and 4 hr (± 5 minutes), and 6 hr (± 10 minutes) post-venetoclax dose
1: Patients need to return for PK blood draws.

## 6.3. Correlative Science

Correlative studies are critical to understanding toxicity and efficacy of novel targeted agents. Tightly coupling correlative studies with clinical trials can help understand best next lines of therapies for patients as well as predictors of response and mechanisms of resistance in a much more rapid manner. The samples collected and procedures performed for correlative laboratory science are an integral part of this study. Complete details of correlative science sample collection, analyses and end points are provided in the Lab Manual.

### 6.3.1. Responsibilities

MingSight will coordinate the collection and analysis of all correlative science and exploratory studies.

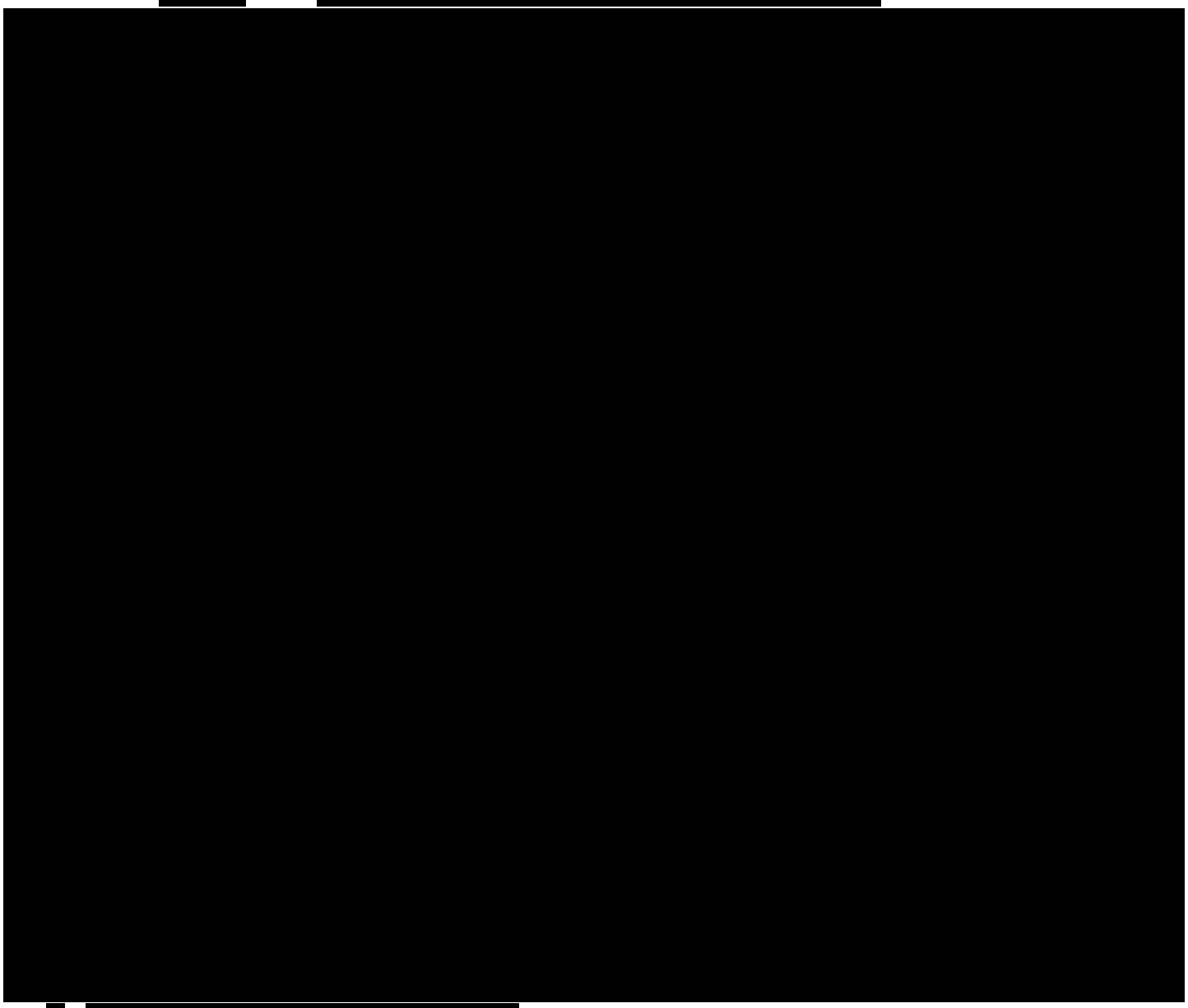
### 6.3.2. Correlative Sciences Sample Collection Overview

There are three types of samples being collected for the correlative sciences studies to be performed. They are:

[redacted]

3) Pharmacodynamic samples (PKC-β Biomarkers) for the measurement of PKC-β signalling in cells isolated from whole blood.

[redacted]



- [redacted]
- [redacted]
- [redacted]
- [redacted]ould be done every 3 cycles for three assessments after patient [redacted]

### 6.3.3. Correlative Science Studies Description

Several key study time points for correlative sample collection are planned (see Section 6.3.2). For responding patients, some samples may be collected during follow up therapy. [redacted] will be ideally collected at Cycle 1 Day 1 using the [redacted]

For Cohorts A1, A2, and B1 [redacted] will be collected immediately prior to dosing on Cycle 1 Day 1 and Cycle 1 Day 8 pre-dose and at 3 hr post-dose. For Cohort C1, PKC-β biomarker samples will be collected prior to dosing on Cycle 4 Day 1 and pre-dose and at 3 hr post-dose on Cycle 4 Day 8.

[redacted]

For all cohorts, research samples will be taken f[redacted] for CLL patients and Richter's from CLL. For all patients in Cohort A, additional research samples will be taken for [redacted]

[redacted]

# 7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

## 7.1. Dose Limiting Toxicities

Determination of DLTs occurs only during the DLT periods defined in Section 3 for Cohorts A1, B1, and C1. See Study Procedures for DLT definitions.

## 7.2. Modification or Holding of Dose for Toxicities

Doses of MS-553 can be decreased or held for toxicities for events deemed possibly, probably, or definitely related to MS-553. Refer to Section 6.1.7, Dose modifications and dose delay and Appendix 2A: MS-553 Recommended Dose Modifications and Delays for Toxicity, Appendix 2B and Appendix 2C for more information and specific guidance. The dose of MS-553 that is restarted could be reduced if the investigator feels it prudent to re-challenge at a lower dose, and if the same toxicity does not recur approximately after four weeks, the dose may be increased back to the patient's prior dose. Discussion with the medical monitor/Sponsor are needed for such dose modifications.

## 7.3. Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (FDA Guidance for Industry 1995). In addition, AEs may also represent pre- or post-treatment complications that occur as a result of protocol-specified procedures. For the purposes of this clinical study, AEs shall include events which are either new or represent detectable worsening of pre-existing conditions that occur as a consequence of participation in the clinical study. The following are expressly not considered AEs:

Pre-existing conditions

- Pre-existing conditions (documented in the medical history CRF) unless the severity, frequency, or character is exacerbated during the study period
- Hospitalization except for elective hospitalizations that had been planned for preexisting conditions that have not worsened. However, if the pre-planned hospitalization is lengthened as a result of participation in the study or if during the pre-planned hospitalization an adverse event, meeting SAE criteria, occurs then the event(s) are considered SAEs.

Abnormal laboratory results requiring treatment or that are assessed as related to the study drug are captured as AEs. If the results of the laboratory abnormality do not require treatment and is assessed as not related to the study drug, they will not be considered AEs and will be assessed as part of safety with the laboratory assessments.

## 7.4. Serious Adverse Event

The ICH topic E2 on Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting defines a serious adverse event (or experience; SAE) or reaction as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization of at least 24 hours.
- Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect (i.e., an adverse finding in a child or fetus or a subject exposed to the study medication prior to conception or during pregnancy).
- An important medical event

  NOTE: Important medical events that may not result in death, be life- threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such 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 hospitalizations, or the development of drug dependency. (FDA Guidance for Industry 1995).

  Given the unique and important perspectives of both the investigator and the Sponsor, if either considers that the event is serious, the event will be considered an SAE. Serious adverse events should be reported within 24 hours of discovery. Death is an outcome of an AE/SAE rather than an SAE itself and should be reported as the antecedent proximate cause.

Disease progression (CLL/SLL/Lymphoma) resulting in death will not be captured as an SAE but will be captured on the specific CRF.

Elective hospitalizations that had been planned for starting a new treatment or for preexisting conditions that have not worsened are not considered SAEs.

## 7.5. Definition and Grading of Toxicities

Toxicities will be defined using NCI CTCAE v5.0 criteria. All toxicities should be graded 1-5 according to the standardized scale laid out therein.

## 7.6. Causality of Adverse Events

The investigator should use his or her best judgement to identify one of the following categories for causality / relatedness of the AE to the study medication.

1. **Unrelated –** The Adverse Event is *clearly not related* to the investigational agent(s)
2. **Unlikely –** The Adverse Event is *doubtfully related* to the investigational agent(s)
3. **Possible –** The Adverse Event *may be related* to the investigational agent(s)
4. **Probable –** The Adverse Event is *likely related* to the investigational agent(s)
5. **Definite –** The Adverse Event is *clearly related* to the investigational agent(s).

## 7.7. Documentation of Adverse Events and Serious Adverse Events

### 7.7.1. Reporting Period

Adverse events (including SAEs) will be documented on the AE eCRF and monitored continuously throughout the study from the time of first dose of study drug until 30 days (+ 7 days) after the patient's last dose of study drug or until the event has resolved, stabilized, or an outcome has been reached, whichever comes first regardless of the timing of the End of Treatment visit. If the End of Treatment visit occurs prior to 30 days (± 7 days) after the date of last dose, then a toxicity assessment should be performed either in person or via telephone to capture AEs through the AE reporting period. In addition, SAEs occurring between the time of signing of informed consent form and the first dose of the study drug must be reported. SAEs related to the study drug and occurring after the end of the AE reporting period must be reported.

For patients who discontinue study drug due to a study-related AE, the reporting time period may be extended. These patients must be followed at least once a week for four weeks, and subsequently at four-week intervals until resolution or stabilization of the adverse event or laboratory abnormality, whichever comes first. Additionally, the frequency of AE monitoring will increase for patients who experience a DLT at the discretion of the investigator.

If the investigator considers it necessary to report an AE in a study patient occurring after the end of study, he or she should contact the Sponsor to determine how the AE should be documented and reported.

### 7.7.2. Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation time points during the study. All AEs and SAEs whether volunteered by the patient, discovered by study

personnel, or detected through physical or laboratory examination, or by any other means will be recorded in the patient's medical record and on the AE CRF.

Each assessment of AEs or SAEs will be described with the prescribed terminology including grade, with start and end (if applicable) dates, regulatory seriousness criteria (if applicable), suspected relationship to study drug, and any action(s) taken in response.

## 7.8. Procedures for Reporting Serious Adverse Events

All serious adverse events occurring during study participation must be reported to the Sponsor (or designee) and to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities.

### 7.8.1. Completion and Transmission of SAE Report

Once an Investigator becomes aware that an SAE has occurred in a study patient, she/he will report the information to the Sponsor (or designee) within 24 hours. The eSAE form in the EDC will always be completed as thoroughly as possible with all available details of the event and submitted to the Sponsor (or designee) within the designated time frames. If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Sponsor (or designee) of the event and completing the form. The form will be updated when additional information is received. Pertinent follow-up information is also reported within 24 hours of the site becoming aware of the updates.

The Investigator will provide an assessment of causality at the time of the initial report as described above. If the EDC system is not operational (e.g., system malfunction) at the time of the SAE, a paper SAE report may be completed and faxed to the Safety team. Paper SAE templates will be provided to the Investigator prior to study start.

[redacted]

The Sponsor will provide a list of project contacts for SAE receipt. Any event that in the opinion of the Investigator may be of immediate or potential concern for the patient's health or well-being will be reported to the Sponsor (or designee).

### 7.8.2. Regulatory Reporting Requirements for Serious Adverse Events

The Investigator must promptly report all SAEs to the Sponsor in accordance with the procedures describe above. Prompt notification of SAEs by the Investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met. The Investigator will be responsible for reporting SAEs to the IRB/IEC per local regulatory requirements.

The Sponsor (or designee) is responsible for reporting SAEs to the relevant regulatory authorities in accordance with local regulations. That is, SAEs which are "Unexpected" and classified as "Suspected Adverse Reactions" or "Adverse Reactions" will be reported.

The Sponsor (or designee) is responsible for submitting reports to the FDA of unexpected SAEs considered to be possibly related to the administration of study drug, according to 21 Code of Federal Regulations 312.32. All Investigators participating in ongoing clinical studies with the study drug will receive copies of these reports for prompt submission to their IRB/IEC. Investigators are to provide a copy of the written IRB notification for each report to the Sponsor or its designee.

An adverse event is considered “Unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that is observed in the present study.

## 7.9. Pregnancy

Pregnancy is an exclusion criterion. All patients should be instructed to immediately notify the investigator and study staff of pregnancy that occurs during the study period. Any female patient who becomes pregnant should immediately discontinue the study medication. Although pregnancy itself is not an AE, if a study patient or the partner of a study patient should become pregnant during the course of the study this should be reported on a pregnancy report form and the pregnancy should be followed to conclusion with the outcome(s) including any untoward events in mother or child reported to the study Sponsor.

## 7.10. Follow Up of Adverse Events and Serious Adverse Events

All AEs and SAEs occurring during the study are to receive appropriate medical treatment and be followed up in accordance with good medical practice until resolved or judged no longer clinically significant, or if a chronic condition, until fully characterized. Relevant follow-up information is to be provided to the Sponsor or its designee.

[redacted]

[redacted]

[redacted]

## 7.12. Management of Overdose and Toxicity

There are no specific treatments for overdose. In the case of accidental or intentional overdose of MS-553, standard supportive measures for overdose should be employed.

## 7.13. Study-wide Stopping Rule for Excessive Toxicity

To ensure patient safety, the sponsor will implement a set of study-wide stopping rules as described below.

- The sponsor shall evaluate adverse events that occur throughout the duration of therapy beyond the DLT window.
- The sponsor shall evaluate all adverse events at least quarterly throughout the study.
- [redacted]
- The study stopping rule shall be triggered if the rate of major hemorrhage events (serious or any $\geqslant$ Grade 3 bleeding or any central nervous system bleeding) is $\geqslant$ 4.2%, the rate of major hemorrhage events listed in the product label of ibrutinib.

- The study stopping rule shall be triggered if an SAE considered to be at least possibly related to the study drug results in death.
- The sponsor shall also report to the Safety Review Committee any additional serious or $\geqslant$ Grade 3 adverse events that are above reference rates in CLL patients.

Once a stopping rule is triggered, the study shall be paused for enrollment and a comprehensive safety review shall be conducted by the Safety Review Committee. After this review, the SRC will determine whether to recommend resuming treatment with appropriate safety measures.

# 8. STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

## 8.1. General Considerations

Summary statistics will be provided for all endpoints. Statistics will be reported according to intention-to-treat (ITT), per-protocol, and per-dose-level. The ITT summary statistics will include any patient who received at least one dose of study drug. As a phase I study, the ITT population also serves as the safety population.

Patient characteristics will be described and summarized for each dose level and in total.

## 8.2. Sample Size Calculations

The projected sample size was estimated on the basis of a standard 3+3 design plus a mandatory expansion cohort, plus two optional non-comparative expansion cohorts. This study is not powered to detect differences in tolerability/safety or efficacy between cohorts.

## 8.3. Dose Escalation Criteria

Because disease-relevant pharmacodynamics biomarkers are not yet established, and some limited toxicity and pharmacokinetic data in healthy subjects exists, dose escalation will be guided by toxicity.

## 8.4. Determination of Sample Size

There is no formal hypothesis to be tested in this study; therefore, no predefined sample size calculation has been made for the efficacy or exploratory endpoints.

## 8.5. Analysis Populations

### 8.5.1. Intention to Treat

The intention to treat (ITT) population shall be defined as all patients who sign the informed consent form *and* received at least one dose of study drug. This population will be used primarily for the analysis of safety data. Summary statistics for efficacy will also be performed on the ITT population.

### 8.5.2. Per Protocol Population

The per-protocol population shall be defined as all patients who received at least one dose of study drug and who within the limits of the protocol completed an entire prescribed course of treatment, terminating at disease progression or after the maximum number of cycles. Efficacy summary statistics will also be reported for this population.

### 8.5.3. Pharmacokinetic Population

The PK population shall be defined as all patients who received at least one dose of study drug and had at least one post-treatment PK sample properly collected and analyzed. Pharmacokinetic summary statistics will be reported in this population.

### 8.5.4. Pharmacodynamic Population

The population shall be defined as all patients who received at least one dose of study drug and had at least one post-treatment PD sample properly collected and analyzed. Pharmacodynamic biomarker data summary statistics will be reported in this population.

## 8.6. Demographic Data

Demographic and baseline measurements will be summarized using standard descriptive methods on the ITT population.

## 8.7. Summary Statistics

Tables of summary statistics over the foregoing analysis populations shall include the following for continuous variables: N (number in analysis set); n (number with data), mean, standard deviation, median, minimum, and maximum. 95% confidence intervals will also be presented for select continuous endpoints.

Tables of summary statistics over the foregoing analysis populations shall include the following for categorical variables: N, n, percentage, and 95% confidence intervals will also be presented for select categorical endpoints.

Analyses will be based on the observed data, unless specific methods for handling missing data are specified herein.

## 8.8. Secondary Analyses: Efficacy

ORR will be calculated along with its 95% CI based on exact method. In the analysis of ORR, patients who do not have sufficient on-study tumor assessment to characterize response will be excluded from the denominator.

[redacted]

## 8.9. Exploratory Analyses

Summary statistics and other assay-appropriate measures will be provided for all exploratory analyses ([redacted]

## 8.10. Protocol Deviations and Violations

The Investigator is responsible for ensuring that the study is conducted in accordance with the protocol. No modifications to the protocol, other than those that are deemed necessary to protect the safety, rights, or welfare of patients by the Investigator are to be made without prior, written approval by the Sponsor. The nature and reasons for the protocol deviation will be recorded where appropriate and indicated. The Sponsor must be notified of all protocol deviations. Significant protocol deviations (e.g., inclusion/exclusion criteria) will be reported to the Sponsor and to the IRB/IEC in accordance with its reporting policy.

## 8.11. Data Recording

An electronic CRF (eCRF) will be used. In some cases, direct entry of data into the eCRF will result in the eCRF being considered the source document. The eCRF will be an FDA 21 CFR part 11 compliant database.

## 8.12. Data Quality Control

Data recorded in patient eCRFs will be subjected to a quality control review. Persons responsible for any data entry, calculations and/or transcriptions will each sign and date for the work performed.

# 9. REGULATORY AND ETHICAL CONSIDERATIONS

## 9.1. Summary Statistics Regulatory and Ethical Compliance: Good Clinical Practice

This study must be implemented and carried out in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (US Code of Federal Regulations Title 21 including parts 50 and 56 concerning informed consent and IRB regulations; European Directive 2001/20/EC and 91/507/EEC), and in accordance with the ethical principles laid down in the Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

Study investigators shall have current training in Good Clinical Practice.

## 9.2. Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to patients, must be reviewed by a properly constituted IRB/IEC. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be kept in study binders on site and given to the Sponsor before study initiation. The name and occupation of the chairman and the members of the IRB/IEC must be supplied to the study Sponsor. Any amendments to the protocol, other than administrative ones, must be approved by this committee. Additionally, amendments to the protocol must be reviewed and approved by the study Sponsor prior to implementation.

The Investigator will not implement any changes to the protocol without prior written approval of an appropriate amendment by the IRB, except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study (e.g., change of monitor or telephone numbers).

The Investigator will promptly report to the IRB (per local requirements) any of the following:

- Deviations from the protocol.
- Changes to the protocol to eliminate immediate hazards to patients that were implemented without prior approval.
- All SAEs that are considered at least possibly related to study drug and are unexpected (i.e., the nature or severity is not consistent with information provided in the current IB).
- New information that may adversely affect the safety of the patients or the conduct of the study.
- Termination or completion of the study.

The Investigator will comply with the IRB requirements for periodic (at least annual) review of the study until such time as all patients have concluded participation at the Investigator's site, and with all other requirements established by the IRB and local regulations.

## 9.3. Informed Consent

The Investigator must explain to each patient (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The patient should read and consider the statement before signing and dating it and should be given a copy of the signed document. If the patient cannot read or sign the documents, oral presentation may be made or signature given by the patient's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol and must be submitted by the Investigator with it for IRB/IEC approval.

The informed consent document should timely be amended as necessary to reflect changes in the protocol over time.

## 9.4. Amendments to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by the investigator and the study Sponsor before implementation. Amendments significantly affecting the safety of patients, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC. A copy of the written approval of the IRB/IEC, must be sent to the study Sponsor.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC approval but the IRB/IEC of each center must be kept informed of such administrative changes

## 9.5. Files and Records Retention

The Investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to the Sponsor, patient files (source documentation) that substantiate entries in CRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

An Investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Local regulations may require a longer period for record retention; said local regulations will supersede this protocol. The Investigator must notify the Sponsor and obtain written approval from the Sponsor before destroying any clinical study records at any time. The Sponsor will in turn inform the Investigator of the date that study records may be destroyed or returned.

## 9.6. Publication of Results

Any formal presentation or publication of data from this trial may be published after review and comment by the Sponsor and prior to any outside submission. The Sponsor must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and twenty working days for manuscripts). These requirements acknowledge the Sponsor's responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of the Sponsor and, in accord with the trial contract and shall not permit disclosure of Sponsor's confidential or proprietary information.

Authorship, in general, will follow the recommendations of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors 2014).

The stipulation on "publication of results" will be finalized in a contract regarding this clinical study between the Institution and the Sponsor. In case of any conflicts between this protocol and the contract regarding "publication of results", the contract will prevail.

## 9.7. Disclosure and Confidentiality

The Investigator agrees to keep all information provided by the Sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by the Sponsor (Investigator's Brochure and other material) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor to the Investigator may not be disclosed to others without direct written authorization from the Sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

The stipulation on "disclosure and confidentiality" will be finalized in a contract regarding this clinical study between the Institution and the Sponsor. In case of any conflicts between this protocol and the contract regarding "disclosure and confidentiality", the contract will prevail.

## 9.8. DEFINITION OF END OF TRIAL

### 9.8.1. End of Trial Participation in a Member State of the European Union

End of trial participation in a Member State of the European Union is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (i.e., clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

### 9.8.2. End of Trial in All Other Participating Countries

End of trial in all other participating countries is defined as last subject last visit (LSLV).

# 10. REFERENCES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# 11. APPENDICES

# APPENDIX 1A: STUDY CALENDAR A COHORTS (MS-553 MONOTHERAPY)

Visit Evaluation Schedule

| **Study Cycle (28 days)** | **0** | **1** | | **2** | **3** | **4+** | | **EOT[a]** | **S/RFU[b]** |
|---|---|---|---|---|---|---|---|---|---|
| **Cycle day[i]** | **Screening[h]** | **1** | **8** | **1 (± 3 days)** | **1 (±3 days)** | **1 (±3 days)** | | **±7 days** | **Q12 wks ±7d for response or Q24 wks ±7d for survival** |
| **Study Procedure/Assessment** | | | | | | | | | |
| Study Drug Dispensation | | | | | | | | | |
| MS-553 PO BID[c] | | X | | X | X | X | | | |
| Procedures | | | | | | | | | |
| Informed Consent | ✕ | | | | | | | | |
| Confirmation of inclusion/exclusion criteria | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical History and Physical Exam | X | X | X | X | X | X | | X | X |
| Concomitant medication survey | X | X | X | X | X | X | | X | |
| Adverse Events Assessment[p] | | X | X | X | X | X | | X | |
| Vital signs; height[k]/weight | X | X | X | X | X | X | | X | X |
| WHO/ECOG Performance Status | X | X | X | X | X | X | | X | X |
| Electrocardiogram[J] | X | X | X | X | | | | | |
| [redacted] | | | | | | | | | |
| Laboratory Studies | | | | | | | | | |
| [redacted] | | | | | | | | | |
| Complete blood count with differential | X | X | X | X | X | X | | X | X |
| Serum chemistry[e] | X | X | X | X | X | X | | X | |
| Urinalysis | X | | | | | | | | |

**Continuing follow-up until disease progression, toxicity, or other withdrawal**

| **Study Cycle (28 days)** | **0** | **1** | | **2** | **3** | **4+** | | **EOT[a]** | **S/RFU[b]** |
|---|---|---|---|---|---|---|---|---|---|
| **Cycle day[i]** | **Screening[h]** | **1** | **8** | **1 (± 3 days)** | **1 (±3 days)** | **1 (±3 days)** | | **±7 days** | **Q12 wks ±7d for response or Q24 wks ±7d for survival** |
| **Study Procedure/Assessment** | | | | | | | | | |
| Urine pregnancy test[f] | X | | | | | | | | |
| HIV Ab, Hepatitis C Ab, HBsAg, anti-HBcAb | X | | | | | | | | |
| [redacted] | [redacted] | | | | | | | | |
| Interphase FISH and stimulated cytogenetics[o] | x | | | | | | | | |
| *IGHV* mutation status | X | | | | | | | | |
| Flow Cytometry[o] | X | See note l | | | | | | See note l | |
| Radiographic Studies | | | | | | | | | |
| CT scans[g] | X | | | | | X[g] | | | X |
| Exploratory (Correlative) Studies | | | | | | | | | |
| Pharmacokinetic samples | See Section 6.2.3 and Table 7 | | | | | | | | |
| Correlative sciences samples | See Section 6.3.2 and Table 8 | | | | | | | See Section 6.3.2 and Table 8 | |

**Footnotes:**

a. EOT (End of Therapy) visit; should occur 30 ± 7 days after last dose of study drug or prior to the start of a new anticancer therapy, whichever is sooner.

b. S/RFU (Safety/Response Follow Up); Patients who discontinue treatment for progressive disease and/or use of other CLL/SLL therapy will be followed for survival every 24 weeks (± 7 days) for up to 3 years. Patients who discontinue treatment for reasons other than progressive disease, use of other CLL/SLL therapy, death, or withdrawal of consent will have response assessments every 12 weeks (± 7 days) until progressive disease occurs. Thereafter they will be followed for survival every 24 weeks (± 7 days) for up to 3 years. All patients will discontinue survival follow-up upon completion of 3 years of survival follow-up, withdrawal of consent, death, or study closure, whichever is the earliest. For assessment of survival, only a review of patient chart and/or a phone call is required.

c. 100, 200, 250, 300 mg or intermediate doses PO BID according to dose level. Study staff should record clinic-administered doses in the dosing diary and patient should record home doses in the dosing diary.

[redacted]

e. Serum chemistry should include albumin, alkaline phosphatase, AST, ALT, bicarbonate, BUN, calcium, creatinine, glucose, LDH, magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid.

f. A urine pregnancy test should be performed with screening in every woman of childbearing potential prior to study entry.

g. In the CLL/SLL cohorts, CT scans of the chest, abdomen, and pelvis (and neck if involved) should occur at screening and at the post 3, post 6, and post 9 cycles of therapy assessments (i.e., at or prior to Cycle 4 Day 1, Cycle 7 Day 1, and Cycle 10 Day 1). Patients who continue with drug therapy after 9 cycles

of treatment should have CT scans, preferably every 12 weeks, or as clinically indicated until disease progression. In the aggressive lymphoma cohort, CT scans of the chest, abdomen, and pelvis (and neck if involved) should occur at screening and as clinically indicated or at a minimum of every 24 weeks while on treatment. Other image tools for response assessment may be used per RECIL 2017 for lymphomas.

h. Screening procedures shall be performed within 28 days prior to first dose of study drug. Studies performed at the study site prior to patient signing of informed consent can be utilized for screening purposes if obtained within 28 days before first dose of study drug, except in the case of *IGHV* mutation status which are permitted to have been obtained at any time prior to screening.
i. Beginning in Cycle 2, a window period of +3 days is permitted for assessments and procedures to accommodate public holidays and other emergency or unforeseen situations; however, every effort should be made to have visits correspond to Day 1 of the following cycle.
j. The ECG will be performed in triplicate at each time-point; all 3 ECG recordings should be completed within 5 minutes. Patient must rest in supine position for at least 5 minutes prior to recording an ECG. C1D1, C1D8 and C2D1 ECGs will be recorded 3 hours (± 15 minutes) following dose administration in the clinic. **ECGs should be recorded prior to any blood draw required at the same time-point** [e.g., 3 hours (± 15 minutes) post dose ECGs on C1D1 and C1D8 should be recorded prior to 3 hours post dose blood draw]. The QTc from the electrocardiogram should be recorded on the case report form.
k. Documentation of height is only required at screening. Weight should be collected at all visits.

[redacted]

# APPENDIX 1B: STUDY CALENDAR B COHORTS (ACALBRUTINIB + MS-553)

Visit Evaluation Schedule

| **Study Cycle (28 days)** | **0** | **1** | | **2** | **3** | **4+** | | **EOT[a]** | **S/RFU[b]** |
|---|---|---|---|---|---|---|---|---|---|
| **Cycle day[i]** / **Study Procedure/Assessment** | **Screening[h]** | **1** | **8 (Cohort B1 only)** | **1 (± 3 days)** | **1 (±3 days)** | **1 (±3 days)** | | **±7 days** | **Q12 wks ±7d for response or Q24 wks ±7d for survival** |
| Study Drug/SOC Treatment Dispensation for Cohort B1 and B2 | | | | | | | | | |
| MS-553 PO BID[c] | | X | | X | X | X | | | |
| Acalabrutinib PO BID[o] | | X | | X | X | X | | | |
| Procedures | | | | | | | | | |
| Informed Consent | X | | | | | | | | |
| Confirmation of inclusion/exclusion criteria | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical History and Physical Exam | X | X | X | X | X | X | | X | X |
| Concomitant medication survey | X | X | X | X | X | X | | X | |
| Adverse Events Assessment[r] | | X | X | X | X | X | | X | |
| Vital signs; height[k]/weight | X | X | X | X | X | X | | X | X |
| WHO/ECOG Performance Status | X | X | X | X | X | X | | X | X |
| Electrocardiogram[j] | X | X | X | X | | | | | |
| [redacted] | [redacted] | | | | | | | | |
| Flow Cytometry[l] | X | See note m | See note m | See note m | See note m | See note m | | See note m | |
| Laboratory Studies | | | | | | | | | |
| [redacted] | [redacted] | | | | | | | | |
| Complete blood count with differential | X | X | X | X | X | X | | X | X |
| Serum chemistry[e] | X | X | X | X | X | X | | X | |

Continue follow-up disease progression, toxicity, or other withdrawal

| **Study Cycle (28 days)** | **0** | **1** | | **2** | **3** | **4+** | | **EOT[a]** | **S/RFU[b]** |
|---|---|---|---|---|---|---|---|---|---|
| **Cycle day[i]** / **Study Procedure/Assessment** | **Screening[h]** | **1** | **8 (Cohort B1 only)** | **1 (± 3 days)** | **1 (±3 days)** | **1 (±3 days)** | | **±7 days** | **Q12 wks ±7d for response or Q24 wks ±7d for survival** |
| Urinalysis | X | | | | | | | | |
| Urine pregnancy test[f] | X | | | | | | | | |
| HIV Ab, Hepatitis C Ab, HBsAg, anti-HBcAb | X | | | | | | | | |
| [redacted] | [redacted] | | | | | | | | |
| Interphase FISH and stimulated cytogenetics[n] | X | | | | | | | | |
| *IGHV* mutation status | X[h] | | | | | | | | |
| Radiographic Studies | | | | | | | | | |
| CT scans[g] | X | | | | | X[g] | | | X |
| Exploratory (Correlative) Studies | | | | | | | | | |
| Pharmacokinetic samples | See Section 6.2.3 and Table 7 | | | | | | | | |
| Correlative Science Samples | See Section 6.3.2 and Table 8 | | | | | | | See Section 6.3.2 and Table 8 | |

**Footnotes:**

a. EOT (End of Therapy) visit; should occur 30 ± 7 days after last dose of study drug or prior to the start of a new anticancer therapy, whichever is sooner.

b. S/RFU (Safety/Response Follow Up); Patients who discontinue treatment for progressive disease and/or use of other CLL/SLL therapy will be followed for survival every 24 weeks (± 7 days) for up to 3 years. Patients who discontinue treatment for reasons other than progressive disease, use of other CLL/SLL therapy, death, or withdrawal of consent will have response assessments every 12 weeks (± 7 days) until progressive disease occurs. Thereafter they will be followed for survival every 24 weeks (± 7 days) for up to 3 years. All patients will discontinue survival follow-up upon completion of 3 years of survival follow-up, withdrawal of consent, death, or study closure, whichever is the earliest. For assessment of survival, only a review of patient chart and/or a phone call is required.

c. 100, 200, 250, or 300 mg PO BID according to dose level. Study staff should record clinic-administered doses in the dosing diary and patient should record home doses in the dosing diary.

[redacted]

e. Serum chemistry should include albumin, alkaline phosphatase, AST, ALT, bicarbonate, BUN, calcium, creatinine, glucose, LDH, magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid.

f. A urine pregnancy test should be performed with screening in every woman of childbearing potential prior to study entry.

g. In the CLL/SLL cohorts, CT scans of the chest, abdomen, and pelvis (and neck if involved) should occur at screening and at the post 3, post 6, and post 9 cycles of therapy assessments (i.e., at or prior to Cycle 4 Day 1, Cycle 7 Day 1, and Cycle 10 Day 1). Patients who continue with drug therapy after 9 cycles of treatment should have CT scans, preferably every 12 weeks, or as clinically indicated until disease progression. In the aggressive lymphoma cohort, CT scans of the chest, abdomen, and pelvis (and neck if involved) should occur at screening and as clinically indicated or at a minimum of every 24 weeks while on treatment.

h. Screening procedures shall be performed within 28 days prior to first dose of study drug. Studies performed at the study site prior to patient signing of informed consent can be utilized for screening purposes if obtained within 28 days before first dose of study drug, except in the case of *IGHV* mutation status which are permitted to have been obtained at any time prior to screening.

i. Beginning in Cycle 2, a window period of +3 days is permitted for assessments and procedures to accommodate public holidays and other emergency or unforeseen situations; however, every effort should be made to have visits correspond to Day 1 of the following cycle.

j. The ECG will be performed in triplicate at each time-point; all 3 ECG recordings should be completed within 5 minutes. Patient must rest in supine position for at least 5 minutes prior to recording an ECG. C1D1, C1D8 and C2D1 ECGs will be recorded 3 hours (± 15 minutes) following MS-553 administration in the clinic. **ECGs should be recorded prior to any blood draw required at the same time-point** [e.g., 3 hours (± 15 minutes) post dose ECGs on C1D1 and C1D8 should be recorded prior to 3 hours post dose blood draw]. The QTc from the electrocardiogram should be recorded on the case report form.

k. Documentation of height is only required at screening. Weight should be collected at all visits.

[redacted]

n. [redacted]

o. Acalabrutinib administered according to institutional standard of care. It is recommended that acalabrutinib be taken 90 minutes (but at least 1 hour) prior to the time when MS-553 is taken.

[redacted]

# APPENDIX 1C: STUDY CALENDAR C COHORTS (TRIPLET REGIMEN MS-553 + RITUXIMAB + VENETOCLAX)

Visit Evaluation Schedule

| **Study Cycle (28 days)** | **0** | **1** | | | **2** | **3** | | | | | **4+** | **EOT[a]** | **S/RFU[b]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle day[i]**<br>**Study Procedure/Assessment** | **Screening[h]** | **1** | **2** | **8[q]** | **1 (± 3 days)** | **1 (±3 days)** | **2** | **8** | **15** | **22** | **1 (±3 days)** | **±7 days** | **Q12 wks ±7d for response or Q24 wks ±7d for survival** |
| MS-553 PO BID[c, s] | | X | | | X | X | | | | | X | | |
| Venetoclax PO QD (5 week ramp up dose)[r,p] | | | | | | X | X | X | X | X | X[p] | | |
| Anti-CD20 mAb (rituximab) [p] | | X | | | X | X | | | | | X[p] | | |
| **Procedures** | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | |
| Confirmation of inclusion/exclusion criteria | X | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | |
| Medical History and Physical Exam | X | X | X | X[q] | X | X | | X | X | X | X | X | X |
| Concomitant medication survey | X | X | X | X[q] | X | X | X | X | X | X | X | X | |
| Adverse Events Assessment[o] | | X | X | X[q] | X | X | X | X | X | X | X | X | |
| Vital signs; height[k]/weight | X | X | X | X[q] | X | X | | X | X | X | X | X | X |
| WHO/ECOG Performance Status | X | X | X | X[q] | X | X | | | | | X | X | X |
| Electrocardiogram[j] | X | X | | X[q] | X | | | | | | | | |
| Flow Cytometry[l] | X | See note m | See note m | See note m | See note m | See note m | See note m | | | | See note m | See note m | |
| **Laboratory Studies** | | | | | | | | | | | | | |
| [redacted] | [redacted] | [redacted] | | | | | | | | | | | |
| Complete blood count with differential | X | X | X | X[q] | X | X | X | X | X | X | X | X | X |

| **Study Cycle (28 days)** | **0** | **1** | | | **2** | **3** | | | | | **4+** | **EOT[a]** | **S/RFU[b]** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle day[i]**<br>**Study Procedure/Assessment** | **Screening[h]** | **1** | **2** | **8** | **1 (± 3 days)** | **1 (±3 days)** | **2** | **8** | **15** | **22** | **1 (±3 days)** | **±7 days** | **Q12 wks ±7d for response or Q24 wks ±7d for survival** |
| Serum chemistry[e] | X | X | X | X[q] | X | X | X | X[r] | X[r] | X[r] | X | X | |
| Urinalysis | X | | | | | | | | | | | | |
| Urine pregnancy test[f] | X | | | | | | | | | | | | |
| HIV Ab, Hepatitis C Ab, HBsAg, anti-HBcAb | X | | | | | | | | | | | | |
| [redacted] | [redacted] | | | | | | | | | | | | |
| Interphase FISH and stimulated cytogenetics[n] | X | | | | | | | | | | | | |
| *IGHV* mutation status[h] | XX | | | | | | | | | | | | |
| **Radiographic Studies** | | | | | | | | | | | | | |
| CT scans[g] | X | | | | | X[q] | | | | | X[g] | | X |
| **Exploratory (Correlative) Studies** | | | | | | | | | | | | | |
| Pharmacokinetic samples | See Section 6.2.3 and Table 7 | | | | | | | | | | | | |
| Correlative Science samples | See Section 6.3.2 and Table 8 | | | | | | | | | | | See Section 6.3.2 and Table 8 | |

**Footnotes:**

a. EOT (End of Therapy) visit; should occur 30 ± 7 days after last dose of study drug or prior to the start of a new anticancer therapy, whichever is sooner.
b. S/RFU (Safety/Response Follow Up); Patients who discontinue treatment for progressive disease and/or use of other CLL/SLL therapy will be followed for survival every 24 weeks (± 7 days) for up to 3 years. Patients who discontinue treatment for reasons other than progressive disease, use of other CLL/SLL therapy, death, or withdrawal of consent will have response assessments every 12 weeks (± 7 days) until progressive disease occurs. Thereafter they will be followed for survival every 24 weeks (± 7 days) for up to 3 years. All patients will discontinue survival follow-up upon completion of 3 years of survival follow-up, withdrawal of consent, death, or study closure, whichever is the earliest. For assessment of survival, only a review of patient chart and/or a phone call is required.
c. 100, 200, 250, or 300 mg PO BID according to dose level. Study staff should record clinic-administered doses in the dosing diary and patient should record home doses in the dosing diary.

[redacted]

e. Serum chemistry should include albumin, alkaline phosphatase, AST, ALT, bicarbonate, BUN, calcium, creatinine, glucose, LDH, magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid.
f. A urine pregnancy test should be performed with screening in every woman of childbearing potential prior to study entry.
g. In the CLL/SLL cohorts, CT scans of the chest, abdomen, and pelvis (and neck if involved) should occur at screening and at the post 2, post 6, and post 9 cycles of therapy assessments (i.e., at or prior to Cycle 3 Day 1, Cycle 7 Day 1, and Cycle 10 Day 1). Patients who continue with drug therapy after 9 cycles of treatment should have CT scans, preferably every 12 weeks, or as clinically indicated until disease progression. In the aggressive lymphoma cohort, CT scans of the chest, abdomen, and pelvis (and neck if involved) should occur at screening and as clinically indicated or at a minimum of every 24 weeks while on treatment.
h. Screening procedures shall be performed within 28 days prior to first dose of study drug. Studies performed at the study site prior to patient signing of informed consent can be utilized for screening purposes if obtained within 28 days before first dose of study drug, except in the case of *IGHV* mutation status which are permitted to have been obtained at any time prior to screening.
i. Beginning in Cycle 2, a window period of +3 days is permitted for assessments and procedures to accommodate public holidays and other emergency or unforeseen situations; however, every effort should be made to have visits correspond to Day 1 of the following cycle.
j. The ECG will be performed in triplicate at each time-point; all 3 ECG recordings should be completed within 5 minutes. Patient must rest in supine position for at least 5 minutes prior to recording an ECG. C1D1, C1D8 and C2D1 ECGs will be recorded 3 hours (± 15 minutes) following MS-553 administration in the clinic. **ECGs should be recorded prior to any blood draw required at the same time-point** [e.g., 3 hours (± 15 minutes) post dose ECGs on C1D1 and C1D8 should be recorded prior to 3 hours post dose blood draw]. The QTc from the electrocardiogram should be recorded on the case report form.
k. Documentation of height is only required at screening. Weight should be collected at all visits.
l. Flow cytometry will be performed at screening on both bone marrow (when available) and peripheral blood samples (all patients). If a bone marrow aspirate/biopsy is performed to confirm a CR, flow cytometry should be performed on the bone marrow sample.

[redacted]

p. Venetoclax should be taken orally once daily with food and water, per the package insert ⩾ 6 hr after the morning dose of MS-553. Dosing Schedule for Ramp-Up Phase in Patients with CLL/SLL.VENETOCLAX Daily Dose is according to standard of care, starting with Cycle 3: Week 1 is as follows: 20 mg; Week 2 dose is 50 mg; Week 3 dose is 100 mg; Week 4 dose is 200 mg; Week 5 and beyond dose is 400 mg. When venetoclax is combined with rituximab, venetoclax is discontinued after 24 months of therapy (last dose on C26D28) and rituximab is discontinued after 6 cycles of administration, to ensure consistency with the standard of care.
q. CT scans can be performed prior to starting venetoclax treatment to allow for restaging, allowing outpatient therapy if TLS risk is reduced.
r. While day 9, Day 16 and Day 23 are not on the study calendar, blood chemistry monitoring at 24 hour post venetoclax dose is recommended for the first dose of 50mg for all patients (i.e., day 9) and for the subsequent ramp-up doses for high tumor burden patients (i.e., day 16 and day 23). Please refer to venetoclax package insert.

s. For patients who have achieved complete responses with the treatment of MS-553, venetoclax, and rituximab, assessments of uMRD in a central lab will be performed in a fashion consistent with IWCLL 2018 guideline. If uMRD in both peripheral blood and bone marrow is confirmed via a central lab, MS-553 may be discontinued at the discretion of the investigators after completion of venetoclax administration as defined in its package label.

[redacted]

## APPENDIX 2A: MS-553 RECOMMENDED DOSE MODIFICATIONS AND DOSE DELAYS

<table>
<tr><th colspan="2">Recommended dose modifications for MS-553 for Grade ≥3 toxicities at least possibly related to MS-553</th></tr>
<tr><th>Worst toxicity Grade* (value)</th><th>During a cycle of therapy</th></tr>
<tr><td colspan="2">Hematology</td></tr>
<tr><td>
<ul>
<li>Grade 4 neutropenia without fever (ANC <0.5 x $10^9$/L), <u>unless</u> the neutropenia was present at the time of study entry<br>and/or</li>
<li>iwCLL 2018 Grade 3 or above thrombocytopenia:</li>
</ul>
<table>
<tr><th>Grade^</th><th>Decrease in platelets† from baseline value, %</th></tr>
<tr><td>0</td><td>No change to 10</td></tr>
<tr><td>1</td><td>11-24</td></tr>
<tr><td>2</td><td>25-49</td></tr>
<tr><td>3</td><td>50-74</td></tr>
<tr><td>4</td><td>⩾75</td></tr>
</table>
^Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from baseline will be recorded as grade 5.<br><br>
†Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is <20 × $10^9$/L, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (e.g., 20 × $10^9$/L) was present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts.
</td><td>
Hold MS-553 until ANC is ≥ 0.5 x $10^9$/L and until platelets recover to Grade 2 or lower per iwCLL 2018 grading.<br><br>
If treatment delay is ≤ 7 days, restart at same dose.<br><br>
If treatment delay is > 7 days but ≤ 28 days, restart at lower dose.<br><br>
If treatment delay > 28 days, discontinue study treatment
</td></tr>
</table>

| | |
|---|---|
| Grade 3 Febrile Neutropenia (ANC <1.0 x $10^9$/L with fever) | If ANC at study entry was ≥ 1.0 x $10^9$/L:<br>• Hold MS-553 until ANC is ≥ 1.0 x $10^9$/L<br>If ANC at study entry was < 1.0 x $10^9$/L due to bone marrow involvement:<br>• Hold MS-553 until ANC returns to pretreatment level<br>If treatment delay is ≤ 7 days, restart at same dose<br>If treatment delay is >7 days but ≤ 28 days, restart at lower dose.<br>If treatment delay >28 days, discontinue study treatment |
| **Nausea, Vomiting or Diarrhea with maximal prophylaxis** | |
| Grade 3 | Hold MS-553 dosing until improved to grade 1 or baseline, then restart at lower dose level for MS-553 |
| Grade 4 | Hold MS-553 dosing until improved to grade 1 or baseline. If improves in <24 hours, restart at lower dose for MS-553<br>If grade 4 GI toxicity persists > 24 hours despite optimal use of SoC, discontinue treatment with MS-553. |
| **All other Toxicities** | |
| ≥ Grade 3 | Hold MS-553 until improved to ≤ Grade 1 or baseline. If treatment delay is < 7 days, restart at same dose or at a lower dose level upon agreement between the investigator and Sponsor. If treatment delay is >7 days but ≤ 28 days, restart at lower dose level. If treatment delay >28 days, discontinue study treatment. |

| | |
|---|---|
| [redacted] | [redacted] |
| ***Common Toxicity Criteria for Adverse Events (CTCAE Version 5.0)** | |

[redacted]

[redacted]

[redacted]

[redacted]

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## APPENDIX 2B: DOSE MODIFICATIONS OF ACALABRUTINIB

Recommended dose modifications for acalabrutinib for Grade 3 or greater adverse reactions are outlined below. Please refer to the acalabrutinib prescribing information for more specific details.

| **Event** | **Adverse Reaction Occurrence** | **Dose Modification**<br>(Starting dose = 100 mg approximately every 12 hours |
|---|---|---|
| Grade 3 or greater non-hematologic toxicities,<br>Grade 3 thrombocytopenia with bleeding,<br>Grade 4 thrombocytopenia<br>or<br>Grade 4 neutropenia lasting longer than 7 days | First and Second | Interrupt acalabrutinib dosing.<br>Once toxicity has reserved to Grade 1 or baseline, acalabrutinib may be resumed at 100 mg approximately every 12 hours. |
| | Third | Interrupt acalabrutinib dosing.<br>Once toxicity has reserved to Grade 1 or baseline, acalabrutinib may be resumed at a reduced frequency of 100 mg once daily. |
| | Fourth | Discontinue acalabrutinib |

## APPENDIX 2C: DOSE MODIFICATIONS OF VENETOCLAX AND RITUXIMAB

Dose modifications or hold of rituximab can be made by the treating physicians per institutional standard.

The recommended dosage modifications for venetoclax for adverse reactions are provided in the table below. For patients who have had a dosage interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks after completing the ramp-up phase, reassess for risk of TLS to determine if re-initiation with a reduced dose is necessary (e.g., all or some levels of the dose ramp-up schedule).

**Recommended Venetoclax Dosage Modifications for Adverse Reactions[a] in CLL/SLL**

| Adverse Reaction | Occurrence | Dosage Modification |
|---|---|---|
| **Tumor Lysis Syndrome** | | |
| Blood chemistry changes or symptoms suggestive of TLS | Any | Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at same dose. |
| | | For any blood chemistry changes requiring more than 48 hours to resolve, resume at reduced dose |
| | | For any events of clinical TLS[b], resume at reduced dose following resolution |
| **Non-Hematologic Adverse Reactions** | | |
| Grade 3 or 4 nonhematologic toxicities | 1st occurrence | Interrupt venetoclax.<br>Upon resolution to Grade 1 or baseline level, resume venetoclax at the same dose. |
| | 2nd and subsequent occurrences | Interrupt venetoclax.<br>Follow dose reduction guidelines when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician. |

| | | |
|---|---|---|
| | | |
| **Hematologic Adverse Reactions** | | |
| Grade 3 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia) | 1st occurrence | Interrupt venetoclax.<br>Upon resolution to Grade 1 or baseline level, resume venetoclax at the same dose. |
| | 2nd and subsequent occurrences | Interrupt venetoclax.<br>Follow dose reduction guidelines when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician. |
| Consider discontinuing venetoclax for patients who require dose reductions to less than 100 mg for more than 2 weeks.<br>[a]Adverse reactions were graded using NCI CTCAE version 5.0.<br>[b]Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures. | | |

The recommended dose reductions for venetoclax for adverse reactions are provided in the table below.

**Recommended Dose Reduction for Adverse Reactions for venetoclax in CLL/SLL**

| Dose at Interruption, mg | Restart Dose, mg[a] |
|---|---|
| 400 | 300 |
| 300 | 200 |
| 200 | 100 |
| 100 | 50 |
| 50 | 20 |
| 20 | 10 |
| [a]During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose. | |

[redacted]

[redacted]

# APPENDIX 3: LIST OF CO-MEDICATIONS TO AVOID

A. Strong and moderate CYP3A inhibitors, inducers and sensitive and moderately sensitive substrates

| CYP3A4 Inducers | | |
|---|---|---|
| apalutamide | macrolide antibiotics | primidone |
| bosentan | mitotane | rifabutin |
| carbamazepine | phenobarbital | rifampin |
| dexamethasone | phenylbutazone | rifapentine |
| efavirenz | phenytoin | sulfinpyrazone |
| enzalutamide | prednisone | St. John's wort |
| glucocorticoids | | |
| CYP3A4 Inhibitors | | |
| amprenavir | elvitegravir | paritaprevir |
| anastrozole | erythromycin | paroxetine |
| aprepitant | fluconazole | posaconazole |
| boceprevir | fluvoxamine | propranolol |
| canazol | grapefruit juice | quinidine |
| celavirdine | idelalisib | quinine |
| cimetidine | imatinib | ranitidine |
| ciprofloxacin | indinavir | ritonavir |
| crizotinib | itraconazole | saquinavir |
| clarithromycin | ketoconazole | sertraline |
| clotrimazole | lopinavir | telithromycin |
| cobicistat | mibefradil | tofisopam |
| cyclosporine | miconazole | troglitazone |
| dasabuvir | nefazodone | troleandomycin |
| danoprevir | nelfinavir | verapamil |
| diethyldithiocarbamate | nevirapine | voriconazole |
| diltiazem | norfloxacin | zafirlukast |
| dronedarone | ombitasvir | |
| CYP3A5 Inducers | | |
| phenobarbital | primidone | troleandomycin |
| phenytoin | rifampin | |
| CYP3A5 Inhibitors | | |
| clotrimazole | metronidazole | troleandomycin |
| ketoconazole | miconazole | |
| CYP3A Sensitive Substrates | | |
| alfentanil | everolimus | saquinavir |
| avanafil | felodipine | sildenafil |
| buspirone | ibrutinib | simvastatin |
| budesonide | indinavir | sirolimus |

| | | |
|---|---|---|
| conivaptan | lomitapide | tacrolimus |
| darifenacin | lovastatin | ticagrelor |
| darunavir | lurasidone | tipranavir |
| dasatinib | maraviroc | tolvaptan |
| dronedarone | midazolam | triazolam |
| ebastine | naloxegol | vardenafil |
| eletriptan | nisoldipine | |
| eplerenone | quetiapine | |
| CYP3A Moderate Sensitive Substrates | | |
| alprazolam | colchicine | rilpivirine |
| aprepitant | eliglustat | tadalafil |
| atorvastatin | pimozide | |

Source for CP3A information:

Tatro DS, Drug Interaction Facts: The Authority on Drug Interactions. Wolters Kluwer Health, 2012.

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers.

Web link Accessed 20 December 2019:
https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

B. Drugs that prolong QTc interval

Source for QTc drug list:
Woosley, RL and Romero, KA, www.Crediblemeds.org, QTdrugs List, Accession Date, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

Web link Accessed 23 August 2019:
https://www.crediblemeds.org/

## APPENDIX 4: NCI CTCAE V 5.0 AND IWCLL GUIDELINES (2008 & 2018)

National Cancer Institute Common Toxicity Criteria for Adverse Events v 5.0

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood (2018) 131 (25): 2745–2760.

https://doi.org/10.1182/blood-2017-09-806398

# APPENDIX 5: CLL/SLL RESPONSE ASSESSMENTS

**A. International Workshop on Chronic Lymphocytic Leukemia Guideline (2008)**

Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute Working Group 1996 guidelines Blood 2008 111:5446-5456; https://doi.org/10.1182/blood-2007-06-093906

**B. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017)** Ann Oncol. 2017 Jul; 28(7): 1436–1447. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5834038