**End of Study Definition**

The end of study is considered to be the last scheduled study assessment for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

**Study Completion Definition**

Participants will be considered to have completed the study if they: 1) die while on the study, or 2) are on study at the time of study closure.

## 5. STUDY POPULATION

Screening for eligible participants will be performed within 28 days before the first administration of the study drug. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedure(s) is allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

### 5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

1. ≥18 years of age.

2. Eastern Cooperative Oncology Group (ECOG) performance status grade of 0 or 1 (Appendix 10.6).

3. Participants must have histological documentation of disease: B-cell NHL or CLL/SLL requiring therapy (defined below for Part A and Part B).

   **Part A:**

   **B-cell NHL:** The following histologies of B-cell NHL that require systemic treatment will be enrolled, with the following disease-specific criteria:

| **Large B-Cell Lymphoma and High-grade B-cell Lymphoma (Refer to Appendix 11 for listing of histologies allowed per 2016 WHO classification)** |
|---|
| Received first-line chemotherapy and at least 1 subsequent line of systemic therapy that may or may not include autologous stem cell transplantation. |
| **Follicular Lymphoma (Including Transformed Follicular Lymphoma and Follicular Lymphoma Grade 3B)** |
| Previously treated with at least 2 prior lines of systemic therapy, including a standard anti-CD20 antibody. |
| **Mantle Cell Lymphoma or Waldenström Macroglobulinemia** |

| |
|---|
| Relapsed or progressing/nonresponsive to at least 2 prior lines of systemic therapy (prior BTK inhibitor treatment acceptable, provided discontinuation not due to disease progression). |
| **Marginal Zone Lymphoma (Including MALT Lymphoma)** |
| Previously treated with at least 2 prior lines of therapy appropriate for the individual patient's disease (eg, *H. pylori*-positive gastric MALT lymphoma must have failed prior *H. pylori* eradication therapy as one of their prior lines). |

**CLL/SLL:** CLL/SLL that meets criteria for systemic treatment per the iwCLL guidelines and is relapsed or progressing/nonresponsive after at least 2 prior systemic therapies, and no other approved therapies that would be considered more appropriate in the investigator's judgement. If the participant had prior treatments that included BTK inhibitors they must not have progressed on that line of treatment.

**Part B:** All above requirements for Part A apply. In addition, participants must have measurable disease as defined by the appropriate disease response criteria.

- **B-cell NHL:** In addition to the above requirements, participants must have measurable disease as defined by the appropriate disease response criteria (see Table 8). Specific cohorts will have malignancies with mutational status of interest, as determined by the sponsor, based on the results of the archived (or fresh) tumor biopsy obtained at screening and as reported by the study site
- **CLL or SLL:** Participants must have measurable disease

4. Hematology laboratory parameters within the following ranges. Values must be without transfusions or growth factors for at least 7 days prior to the first dose of study drug.
    a. Hemoglobin ≥8 g/dL
    b. Platelets ≥50 x $10^9$/L
    c. Absolute neutrophil count ≥0.75 x $10^9$/L
5. Chemistry laboratory parameters within the following range:
    a. Aspartate aminotransferase (AST) and ALT ≤2.5 x upper limit of normal (ULN) or <4xULN if participant has documented liver involvement with disease
    b. Serum total bilirubin <1.5× ULN. Participants with congenital bilirubinemia such as Gilbert's Syndrome may enroll if direct bilirubin is within normal range
    c. Estimated or measured glomerular filtration rate (GFR) ≥60 mL/min/(1.73 $m^2$).
6. Cardiac parameters within the following range: corrected QT interval (QTcF) ≤480 milliseconds based on the average of triplicate assessments performed as close as possible in succession (the full set of triplicates should be completed in less than 10 minutes).
7. Ejection fraction, as measured by the preferred local modality, and within normal range per local parameters.
8. Participants with B cell NHL must have tumor tissue available at baseline. This is not required for

participants with CLL.

For Part A, a fresh tumor biopsy is preferred. If a fresh biopsy is not obtained, archived tissue must be available.

For Part B, participants must have a fresh tumor biopsy, unless archived tissue obtained after the last treatment is available.

9. Women of childbearing potential (as defined in Appendix 10.5) must agree to all of the following during the study and for 30 days after the last dose of study drug:

- Use a barrier method of contraception
- Use a highly effective preferably user-independent method of contraception (see Appendix 10.5 for acceptable methods of contraception).
- Not to donate eggs (ova, oocytes) or freeze them for future use for the purposes of assisted reproduction during the study.
- Not to plan to become pregnant
- Not to breast-feed

10. A male must agree to all of the following during the study and for 90 days after the last dose of study drug:

- Wear a condom when engaging in any activity that allows for passage of ejaculate to another person.
- Not to donate sperm or freeze for future use for the purpose of reproduction.
- Not plan to father a child

In addition, the participant should be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

11. Participants must sign an ICF indicating that he or she understands the purpose of, and the procedures required for the study, and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the participant's disease.

12. Willing and able to adhere to the lifestyle restrictions specified in this protocol.

## 5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study.

1. Part A and select cohorts in Part B: Prior treatment with JNJ-64264681 or JNJ-67856633. Previously discontinued treatment with a BTK or MALT inhibitor other than JNJ-64264681 or JNJ-67856633 due to participant or doctor choice without evidence of progression or intolerable class-related toxicity will be eligible.

2. Known (active) CNS involvement.

3. Received prior solid organ transplantation.

4. Either of the following:

   - Received an autologous stem cell transplant ≤3 months before the first dose of study drug.
   - Prior treatment with allogenic stem cell transplant ≤6 months before the first dose of study drug, has evidence of graft versus host disease, or requires immunosuppressant therapy for graft versus host disease within the last 2 weeks.

5. Prior chemotherapy, targeted therapy, immunotherapy, chimeric antigen receptor T (CAR-T) cell therapy, radiotherapy (with the exclusion of palliative radiation to limited sites that do not interfere with response assessment based on a sufficient number of other sites), or treatment with an investigational anti-cancer agent or an investigational drug (including investigational vaccines) within 2 weeks before the first administration of JNJ-64264681 and JNJ-67856633. For investigational agents where the half-life is known, there should be a treatment-free window of at least 2 weeks or 5 half-lives.

6. Participant has known allergies, hypersensitivity, or intolerance to JNJ-64264681 or JNJ-67856633 or excipients (refer to the respective IBs).

7. Participant is taking long-term corticosteroids (>10 mg daily prednisone equivalents).

   - A short course (eg, >10 mg daily prednisone equivalents for less than 7 days) of corticosteroids is permitted. Inhaled or topical steroids, and adrenal replacement doses ≤10 mg daily prednisone equivalents, are permitted in the absence of active autoimmune disease.
   - If corticosteroids were used to treat immune-related adverse events associated with prior therapy, ≥7 days must have elapsed since the last dose of corticosteroid.

8. Toxicities from previous anti-cancer therapies that have not resolved to baseline levels, or to Grade <2 (except for alopecia [≥Grade 2], vitiligo [Grade 2] and peripheral neuropathy [Grade 1]).

9. History of clinically significant cardiovascular disease within the 6 months prior to the first dose of study drug including, but not limited to:

   a. Myocardial infarction
   b. Severe or unstable angina
   c. Clinically significant cardiac arrhythmias

d. Uncontrolled persistent hypertension (Grade 3 or worse)
e. Stroke or transient ischemic attack
f. Venous thromboembolic events (ie, pulmonary embolism) within 1 month prior to the first dose of study drug; uncomplicated (Grade ≤2) deep vein thrombosis is not considered exclusionary.
g. Congestive heart failure (New York Heart Association class III-IV) (Appendix 10.7)
h. Pericarditis or clinically significant pericardial effusion
i. Myocarditis
j. Endocarditis
k. Long QT syndrome

10. Clinically significant pulmonary compromise requiring supplemental oxygen use to maintain adequate oxygenation.

11. Prolonged coagulation values (prothrombin time, international normalized ratio, activated partial thromboplastin time) in the absence of direct oral anti-coagulants treatment, at screening that are clinically significant per investigator discretion, or has a history of subdural hematoma, abnormal bleeding tendency, or congenital bleeding diathesis.

12. Active liver cirrhosis of Child Pugh Class B or Class C.

13. Unable to swallow capsules or tablets or has malabsorption syndrome, disease that significantly affects gastrointestinal function, resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. If any of these conditions exist, the site should discuss with the sponsor to determine participant eligibility.

14. Evidence of active viral, bacterial, or fungal infection requiring systemic anti-infective treatment within 7 days before the first dose of study drug.

15. Participant has a known positive test result for human immunodeficiency virus or acquired immune deficiency syndrome , unless viral load is undetectable and CD4 count is above 200 on stable highly active anti-retroviral therapy (Note: see prohibited therapies in Section 6.8.3).

16. Participant has active or chronic hepatitis B or hepatitis C infection (see Appendix 10.2 and Appendix 10.8).

    Hepatitis B infection is defined by (a) a positive test for hepatitis B surface antigen (HBsAg), or (b) a test panel that is positive for anti-hepatitis B core antigen (HBc) and negative for HBsAg and hepatitis B surface antibody (anti-HBs). Appendix 10.8 describes the test panels that will not be excluded. Specifically, a test panel that is positive for anti-HBc, positive for anti-HBsAb, and negative for anti-HBsAg will be eligible; and for participants enrolled with this panel of results the treating physician should use their discretion and institutional guideline to decide whether (a) PCR based test of HBV is warranted at screening and repeated during treatment, and (b) prophylactic treatment for HBV reactivation is necessary.

    Hepatitis C infection is defined by a positive hepatitis C virus (HCV) antibody test, with subsequent confirmation with positive HCV RNA test.

17. Trauma or had major surgery (eg, entailing entry into a major body cavity, or significant blood loss or fluid shifts) within 28 days prior to the first dose of study drug. Note: Participants with planned minor surgical procedures to be conducted under local anesthesia may participate.

18. Any serious underlying medical or psychiatric condition (eg, alcohol or drug abuse, dementia or altered mental status); or any issue that would impair the ability of the participant to receive or tolerate the planned treatment at the investigational site, to understand informed consent, or due to which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, could compromise the participant's well-being) or that could prevent, limit, or confound the protocol-specified assessments.

19. Requires a prohibited medication that cannot be discontinued or substituted, or temporally interrupted during the study; see Section 6.8.3 for prohibited therapies.

20. Received a live attenuated vaccine within 1 month before the planned first dose of study drug.

21. Active autoimmune disease within the past 2 years that requires systemic immunosuppressive medications (ie, chronic corticosteroid, methotrexate, or tacrolimus).

22. Malignancy diagnosis other than the disease under study within 1 year prior to the first dose of the study drug; exceptions are squamous and basal cell carcinoma of the skin, carcinoma in situ of the cervix and any malignancy that is considered cured or has minimal risk of recurrence within 1 year of first dose of study drug in the opinion of both the investigator and sponsor's medical monitor.

**NOTE:** Investigators should ensure that all study enrollment criteria (inclusion/exclusion) have been met at screening and prior to the first dose of study drug. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed. The required source documentation to support meeting the enrollment criteria are noted in Appendix 10.3.

## 5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Refer to Section 6.8, Concomitant Therapy for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).