5. STUDY POPULATION

5.1. Inclusion Criteria

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Participants are eligible to be included in the study only if all the following criteria apply:

Inclusion Criteria for Cycle 1 Day 1

Age

1. Be between the ages of 18 and 75 years of age inclusive, at the time of signing the ICF.

Type of Participant and Disease Characteristics

2. Have an established, pathologically confirmed diagnosis of AML by World Health Organization (WHO 2022) criteria.
3. Newly diagnosed and previously untreated AML and eligible to receive intensive chemotherapy or participants who are currently receiving, intensive ("7+3") Induction regimen as specified in the protocol (see Section 6.1.2).

Organ Function

4. Have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2 at screening.
   - Have an ECOG PS 0-1 at screening if ≥65 years of age.
5. Within 10 days from Cycle 1 Day 1 of Induction treatment, an estimated creatinine clearance ≥50 mL/min as calculated with the Cockcroft Gault formula.
6. Within 10 days of treatment initiation, adequate liver function defined as:
   - Total bilirubin <1.5 × the upper limit of normal (ULN) for age or normal conjugated bilirubin (unless the participant has documented Gilbert's syndrome or the increase is related to increased unconjugated [indirect] bilirubin due to hemolysis).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <3 × ULN (unless attributed to leukemic involvement).
7. Adequate cardiac function defined as ejection fraction (EF) of ≥50% by echocardiogram or multigated acquisition (MUGA) scan.
8. Within 10 days of treatment initiation, potassium should be ≥4.0 mEq/L and magnesium ≥2.0 mg/dL. Specific dosing guidelines for Cycle 1 Day 1 and beyond are provided in Section 6.8.2.

Sex and Contraceptive/Barrier Requirements

9. If a woman of childbearing potential, must have a negative serum pregnancy test upon entry into the study and must be willing to use a highly effective method of contraception from the time of enrollment through 120 days following the last study drug dose, or per local labeling for standard of care, whichever is longest. If male, must be surgically sterile, or agree to use barrier contraception from the time of enrollment through 120 days following the last study drug dose, or per local labeling for standard of care, whichever is longest. See further detail in Section 10.4.

Informed Consent

10. Participant or participant's health care proxy is able and willing to provide written informed consent and able to follow study instructions.

Inclusion Criteria for Cycle 1 Day 8

11. White blood cell (WBC) count must be <25000/μL prior to the first dose of SNDX-5613. Participants are allowed to receive or have received cytoreduction with hydroxyurea or had leukapheresis.
12. KMT2Ar, NPM1c, or NUP98r mutations identified by local laboratory prior to the first dose of SNDX-5613.
    - For NPM1c participants enrolling in Dose Expansion, they must have at least 1 additional characteristic: be ≥60 years of age, have adverse risk genetics per ELN2022 criteria, or secondary AML.

Inclusion Criteria for Consolidation Phase

13. Achieved CR or CR_i, at the end of the Induction Phase.
14. Able to begin the Consolidation Phase within 60 days of Day 1 of the last Induction Phase Cycle, including resolution of hematologic AE (leukopenia, neutropenia, thrombocytopenia) to Grade 2 or lower.
15. All non-hematologic adverse events (AEs) excluding alopecia have resolved to ≤Grade 1.

Inclusion Criteria for Maintenance Phase

16. Maintained CR or CR_i, at the end of the Consolidation Phase.
17. ANC >1000/mm^3 and platelet count >50000/mm^3 without platelet transfusion support within 24 hours prior to the start of Maintenance Therapy.
18. Able to begin Maintenance Therapy within 60 days of Day 1 of the last Consolidation Cycle received, including resolution of hematologic AE (leukopenia, neutropenia, thrombocytopenia) to Grade 2 or lower.
19. All non-hematologic AEs excluding alopecia have resolved to ≤Grade 1.

Inclusion Criteria for Post-Transplant Maintenance Phase

20. Must not have experienced a DLT during Induction or an AE after Induction that would have met DLT criteria. See Section 6.7.
21. Between 30 to 180 days after first allogeneic HSCT
22. Successful engraftment as demonstrated by ANC ≥500/mm^3 and platelets ≥50000/mm^3 without transfusions.
23. Does not have Grade ≥2 acute graft versus host disease (GVHD).
24. Participant maintained CR or CRi.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Diagnosis of acute promyelocytic leukemia (APL), French-American-British classification M3 or WHO classification of APL with translocation, t(15;17)(q22;q12), or BCR/ABL positive leukemia (ie, chronic myelogenous leukemia in blast crisis)
2. FMS-like tyrosine kinase 3 (FLT3) mutation (ITD or TKD) AND use/plan to use FLT3-targeted therapy.
3. Clinically active central nervous system leukemia (blasts detected in CSF, radiographic or clinical signs and symptoms).
4. Any concurrent malignancy in the previous 2 years except for basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ, melanoma in situ) treated with potentially curative therapy. Concurrent malignancy must be in CR or no evidence of disease (NED) during this timeframe. For participants with prior therapy-related leukemia, primary disease must be in remission for 1 year following completion of therapy.
5. If the participant is known to be HIV-positive, the participant must have undetectable HIV viral load within the previous 6 months. If viral load testing has not been performed within the previous 6 months, it must be performed during Screening.
6. Have hepatitis B (defined as hepatitis B virus [HBV] surface antigen positive and HBV core antibody positive, with positive HBV deoxyribonucleic acid [DNA], or HBV positive core antibody alone with positive HBV DNA).
7. Have hepatitis C (defined as positive hepatitis C virus [HCV] antibody [Ab] with positive HCV ribonucleic acid [RNA]).
8. Are lactating/breast feeding or pregnant. Negative serum pregnancy tests are required during Screening and a negative serum or urine pregnancy test is required within 72 hours prior to receiving the first study drug administration, in females of

childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

9. Any of the following within the 6 months prior to study entry: myocardial infarction, uncontrolled/unstable angina, congestive heart failure (New York Heart Association Classification Class ≥II), life-threatening, uncontrolled arrhythmia, cerebrovascular accident, or transient ischemic attack.
10. Have QTcF >450 msec (average of triplicate), diagnosis or suspicion of Long QT syndrome or family history of Long QT syndrome.
11. Any gastrointestinal issue of the upper gastrointestinal tract that might affect oral drug absorption or ingestion (eg, gastric bypass, gastroparesis, unable to swallow and ingest tablet or oral solution, etc).
12. Have cirrhosis with a Child-Pugh score of B or C.
13. Have Down Syndrome.
14. Participants known to have 1 of the following genetic syndromes: Bloom syndrome, ataxia-telangiectasia, Fanconi anemia, Kostmann syndrome, Shwachman syndrome or any other known bone marrow failure syndrome.
15. History of or any concurrent condition, therapy, or laboratory abnormality that in the Investigator's opinion might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate.
16. Participants weighing <40 kg.
17. Other documented active, uncontrolled infection.
18. Have evidence of uncontrolled disseminated intravascular coagulation.

Prior/Concomitant Therapy

19. Require concomitant chemotherapy that is prohibited during the study (see Section 6.13.2), radiation therapy, or immunotherapy.
20. Use of strong CYP3A4 inducers or inhibitors (except for Itraconazole, Ketoconazole, Posaconazole, or Voriconazole).
21. Intrathecal prophylaxis is not allowed during Induction after the initial dose of SNDX-5613.

Other Exclusion Criteria

22. Have mental deficits and/or psychiatric history that may compromise the ability to give written informed consent or to comply with the study protocol.

23. Receipt of an investigational agent within 28 days of starting SNDX-5613.

5.3. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

Participants in backfill and Dose Escalation cohorts who do not receive SNDX-5613 will be replaced.