A Phase I/II Study of NMS-03592088, a FLT3, KIT and CSF1R Inhibitor, in Patients with Relapsed or Refractory AML or CMML

Sponsor:	Nerviano Medical Sciences, S.r.l.
Therapeutic Area:	Oncology
Substance Identifier:	NMS-03592088
Protocol Number:	**MKIA-088-001**
EudraCT Number:	2018-002793-47
Status:	Final
Protocol Version Number	9

Including Amended Information as per:

Amendment No.	Date	Countries	Sites
1	29 May 2019	Italy	All
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3	28 September 2020	Italy	All
NA	27 August 2021	Spain	All
4	27 August 2021	Italy	All
5	20 April 2022	Italy, Spain	All
6	21 January 2023	All	All
6.1	*17 March 2023*	*France*	*Not implemented*
6.2	31 March 2023	France	All
NA	18 October 2023	Italy, Spain, France	All
7	28 February 2024	EU Countries	All

SPONSOR REFERENCES AND APPROVAL

Sponsor Name:	Nerviano Medical Sciences, S.r.l.
Sponsor Address:	Viale Pasteur, 10 20014 Nerviano (Milan) Italy
Sponsor Representative:	PPD Nerviano Medical Sciences, S.r.l.
Sponsor Medical Expert:	PPD Nerviano Medical Sciences, S.r.l.
Sponsor Statistician:	PPD Nerviano Medical Sciences, S.r.l.

INVESTIGATOR' SIGNATURE

Title	**A Phase I/II Study of NMS-03592088, a FLT3, KIT and CSF1R Inhibitor, in Patients with Relapsed or Refractory AML or CMML**
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Version Number	**9**
Date	**28 February 2024**

I declare I'll carry out the study in accordance with the referenced protocol, the ICH E6 R2 (Good Clinical Practices), Declaration of Helsinki and in accordance to local legal and regulatory requirements.

Investigator's Name	Investigator's Title
Investigational Site Name	
Investigational Site Address	
Investigator' Signature	Date

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1. SUMMARY

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Background Information and Study Rationale

NMS-03592088 is a potent inhibitor of the kinase activity of FLT3, CSF1R and KIT showing high preclinical efficacy in target driven tumors, also in the presence of resistance mutations.

All three targets of NMS-03592088 are relevant in different settings of hematologic malignancies and solid tumors.

FLT3, CSF1R and KIT play an important role in Acute Myeloid Leukemia (AML). In particular, FLT3 is mutated in ~ 30% of AML. Midostaurin, a multikinase inhibitor with activity on FLT3, was approved as first-line therapy of FLT3-mutant AML in combination with chemotherapy and gilteritinib, a more selective FLT3 inhibitor, was approved as monotherapy for the treatment of FLT3- positive relapsed/refractory AML patients, confirming the validity of the target. In addition, a few additional selective FLT3 inhibitors are undergoing clinical development. Although the introduction of midostaurin as additional therapy for newly diagnosed FLT3-mutant AML and of gilteritinib for relapsed/refractory FLT3-mutant AML patient led to significant improvements in outcome for FLT3-mutant AML patients, the medical need, especially for older patients and patients who relapse after an initial response, remains high. In addition, the emergence of secondary FLT3 mutations during the course of therapy with FLT3 inhibitors raises new challenges toward effective therapy in this subset of AML.

c-KIT mutations are reported in 17%-46% of patients with a defined AML subtype known as core binding factor AML (CBF-AML). These patients have a higher relapse rate and shorter event-free survival/overall survival than those without c-KIT mutation.

Finally, CSF1R is expressed in AML blasts and there is emerging evidence suggesting a potential therapeutic role for CSF1R blockade in AML. CSF1R is expressed in Chronic Myelomonocytic Leukemia (CMML) and CMML cells have shown sensitivity to the drug in vitro. Therefore, CSF1R represents a putative target in this disease, which lacks an effective standard of care and thus represents a high medical need. The FLT3 pathway is also activated in a small CMML subset.

NMS-03592088**I** is the corresponding hemioxalate salt formulated for oral administration and it has been selected for clinical development in patients with hematological malignancies and solid tumors.

The compound demonstrated strong anti-proliferative activity against FLT3-dependent human tumor cell lines, harboring different types of mutation. CCI [redacted]. Notably, compared to other FLT3 inhibitors in clinical development in AML, NMS-03592088 is the most potent FLT3 inhibitor in the preclinical setting, also in the presence of drug resistance mutations. In fact, CCI [redacted] than comparators. On the contrary, it CCI [redacted]

NMS-3592088 has demonstrated antitumor activity in a KIT-dependent model, resistant to imatinib.

CCI [redacted]

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NMS-03592088 was proven to have an acceptable safety profile in preclinical models and to cross the blood brain-barrier CCI [redacted]

The potent activity of NMS-03592088 on FLT3-ITD and its mutants as well as the inhibitory activity of KIT and CSF1R along with a favorable pharmacological and safety profile support the clinical development of the compound in the proposed hematological malignancies.

This is a first in human study of NMS-03592088 focused on hematological malignancies, with a Phase I dose escalation in AML and CMML patients followed by a Phase II in FLT3mut AML patients.

As of 15 January 2023, cut-off date, the IB has been updated with safety, PK and anti-blast activity. A trend of CCI [redacted]. Full safety, PK, anti-leukemic blast activity, population PK model, exposure relationship to blasts and safety trends are presented in the IBv5 [55]. In summary, CCI [redacted] The current protocol provides exposure caps relative to safety trends to ensure reasonable dosing (see Section 9.2.1 and IBv5 [55]).

Trial Objectives and Endpoints

Primary Objective:

Phase I

- To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and the recommended Phase II dose (RP2D) of NMS-03592088 administered orally once daily for 21 consecutive days followed by 7 days of rest in a 28 day cycle (Schedule A) or once daily for 28 consecutive days (Schedule B) in adult patients with selected hematologic malignancies who have exhausted standard treatment options or for whom standard therapy is considered unsuitable.

Phase II

- To explore the antitumor activity of NMS-03592088 in FLT3-ITD mut AML.

Secondary Objectives (Phase I and II):

- To define the safety profile and tolerability of NMS-03592088;
- To evaluate pharmacokinetics (PK) of NMS-03592088 and its metabolites NMS-03593860 and NMS-03603422 in plasma and, limited to Phase I, also in urine;

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- To assess any preliminary evidence of clinical efficacy of NMS-03592088 (Phase I).

CCI [redacted]

Primary Endpoints:

<u>Phase I</u>

- Drug related first-cycle dose limiting toxicities (DLTs).

<u>Phase II</u>

- FLT3-ITD mut AML: Composite Complete Remission (CRc) Rate, i.e. Complete Remission (CR) + Complete Remission with Incomplete Hematologic Recovery (CRi), as defined by the Investigators based on the 2022 European LeukemiaNet (ELN) recommendations [6].

Secondary Endpoints (Phase I and II):

- Overall safety profile of NMS-03592088 characterized by type, frequency, severity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 5.0), timing and relationship to study therapy of adverse events, and laboratory and ECG abnormalities;
- Plasma pharmacokinetic profile and corresponding parameters of NMS-03592088 and its metabolites NMS-03593860 and NMS-03603422;
- Renal clearance and fraction of NMS-03592088 and its metabolites NMS-03593860 and NMS-03603422 excreted in urine (only Phase I);

Secondary efficacy endpoints include: Best Response by category, Overall Survival (OS), Time to Response (TTR), Duration of Response (DoR), Event-Free Survival (EFS) and Relapse-free Survival (RFS) as defined by the ELN recommendations [6, 7] and disease specific International Working Group criteria [56] and proportion of patients bridged to hemopoietic stem cell transplantation (HSCT). For AML and in Phase II only: Complete Remission (CR) Rate, Complete Remission and Complete Remission with Partial Hematologic Recovery (CR/CRh) Rate, CR/CRh/CRi rate and Overall Response Rate (ORR: CRc + CRh + MLFS + PR) as defined by

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the 2022 ELN recommendations [6][7]; rate of conversion from transfusion-dependence to transfusion-independence.

CCI [redacted]

[redacted]

Study Design and Methods

Study Design

This is an open-label Phase I/II, first-in-human (FIH), non-randomised, multi-center study to explore tolerability, safety and antitumor activity of NMS-03592088 in adult patients with selected hematologic malignancies who have exhausted standard treatment options or for whom standard therapy is considered unsuitable.

CCI [redacted]

Phase I: Dose Escalation

CCI [redacted]

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CCI

Starting Dose

CCI [redacted]

[redacted]

Dosing Schedule

CCI [redacted]

[redacted]

[redacted]

[redacted]

<u>Phase I: Dose-Escalation</u>

The dose escalation schema will be as follows:

For Schedule A, in the initial dose-escalation phase, defined as early accelerated phase, 100% dose escalations will be applied as per modified accelerated titration design [57]. The rapid escalation phase is intended to reduce the number of patients exposed to low study drug levels that might have lower probability of providing benefit to patients. The accelerated phase will stop when one patient experiences first cycle DLT or 2 patients at any dose level experience non-DLT NCI CTCAE Grade ≥2 drug-related toxicity during the first cycle.

At this point, the subsequent dose-escalation phase of the study will start and dose will be escalated by ≤ 50% incremental steps. At the time of protocol amendment #3, testing of Schedule A is ongoing with ≤50% dose increments. Since Schedule B will start while Schedule A is ongoing, a dose escalation with ≤ 50 % increments will be adopted since the beginning.

After the completion of each cohort, available safety and PK data will be reviewed and will form the basis for the next dose level decided jointly by the Investigators and the Sponsor.

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At each dose level, a minimum of 3 patients will be included.

If 0/3 patient experiences first cycle DLT, the next cohort will start one dose level higher.

If 1/3 patient experiences first cycle DLT, up to three more patients will receive the study medication at the same dose level; if 1/6 experiences first cycle DLT the next cohort will start one dose level higher.

If ≥2/3 or ≥2/6 patients experience DLTs in the first cycle of treatment, the MTD is considered to have been exceeded. At this point Sponsor and Investigators may request to evaluate three more patients at the previous dose level (if only 3 patients were previously treated at that prior dose) or to explore an intermediate dose level (not yet tested) in order to more precisely define the MTD. Evaluation of safety profile and exposure in patients treated in the study will guide the selection of the intermediate dose level.

The first two patients in each cohort should be treated with at least two weeks of delay between the first and the second patient. In absence of 1st cycle DLT in the first patient, the third patient can be enrolled at any time. In presence of 1st cycle DLT in the first patient, the third patient can be enrolled only after the second patient has completed the first cycle without DLT. In case a cohort needs to be expanded to more than three patients, the additional patients can be enrolled simultaneously.

If a patient fails to receive at least 70% of the treatment in the first cycle for reasons other than treatment-related toxicities, or if a patient is not assessed for DLTs, an additional patient must be enrolled at the same dose level. A patient may also be replaced if, under particular circumstances (e.g. due to noncompliance), the assessment of DLTs is not possible as judged jointly by the Investigators and the Sponsor.

For each dosing schedule, intra-patient dose escalation can be applied only for individual patients for whom the Investigator believes this is in the patient's best interest based on a risk/benefit evaluation and in agreement with the Sponsor. In this case, the patient should have already received 2-3 cycles of treatment at the assigned dose level with no relevant toxicities and the higher dose level applied should already be proven to be safe.

In backfill cohorts patients may be enrolled simultaneously.

Definition of Dose Limiting Toxicity (DLT):
For the purpose of this study, DLT is defined as any grade ≥3 non-hematologic toxicity occurring in the first cycle of treatment for which CCI [redacted]

Hematological adverse events will not be considered as DLTs. However, prolonged myelosuppression defined as grade 4 neutropenia (ANC<500 mm^3) for more than 21 days off therapy in the absence of evidence of active leukemia in the bone marrow or peripheral blood will be considered as a DLT.

CCI [redacted].

DLTs will be classified according to NCI CTCAE version 5.0.

Definition of MTD and RP2D
The MTD may or may not be determined and is defined as the dose level at which 0/3, 0/6 or 1/6 patients experience DLT in the first cycle of treatment with the next higher dose having at least 2/3 or 2/6 patients encountering DLT. Effectively, the MTD is the highest dose level associated with the cohort at which < 33% of patients experience a first cycle DLT. RP2D is no higher than MTD relative to dose or exposure but may be selected if MTD is not determined and is chosen based on PK, anti-blast activity, biomarkers and safety

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considerations among other features.
This dose may be the dose recommended for further investigations.

Phase I: Dose-Expansion and Backfill
For each schedule, once the MTD or MAD is identified and safety and PK data have been reviewed by the Investigators and the Sponsor and are considered adequate, a maximum of 10 additional patients will be enrolled and treated at the MTD or MAD to further characterize the safety and tolerability profile of NMS-03592088 and to better define the recommended dose and the schedule for the Phase II portion of the study. In the dose expansion and in the backfill cohorts the Sponsor may restrict the enrollment to AML FLT3 positive patients and/or to patients with specific prior lines or therapies. Up to 4 backfill cohorts of up to 14 patients each may enroll at doses and schedules no higher than RP2D or exposure equivalent and may include the following: 1) first cycle at reduced dose/exposure relative to RP2D to collect additional PK, matched PK/ECG for standard E14 update exposure/QTc, biomarkers, and anti-cancer activity followed by subsequent cycle up to RP2D or exposure equivalent; 2) food effect with first cycle no higher than RP2D or equivalent exposure followed by subsequent cycle with standard meal on day 1 of cycle 2 only. The exposure cap described above will be followed.

Phase II: Expansion Cohorts
Once the RP2D and schedule of NMS-03592088 have been selected, the exploratory Phase II portion of the study will be opened for enrollment and will consist of two parallel cohorts:

- **Cohort 1 (40 patients with a futility analysis at 10 patients)**: patients with AML FLT3 Internal Tandem Duplication (ITD) mutation as assessed by central laboratory, who have failed standard of care including venetoclax and gilteritinib based therapies. Dose and schedule will be within the defined exposure cap rule (see above). The enrollment in this cohort may be restricted to patients with specific prior lines/therapies and/or mutations, based on Sponsor decision.

- **Cohort 2 (40 patients with a futility analysis at 10 patients)**: patients with AML FLT3 Internal Tandem Duplication (ITD) mutation as assessed by central laboratory, who have failed standard of care. Dose and schedule will be within the defined exposure cap rule (see above). The cohort may be restricted to patients with specific prior lines/therapies and/or mutations, based on Sponsor decision.

The Sponsor will control the patient assignment to cohorts and may stop or pause cohorts in any phase or part of the study based on safety, efficacy or strategic reasons (***note***: while finalizing this document, the Sponsor has termporarily restricted cohort 2 to include patients with AML FLT3 Internal Tandem Duplication (ITD) mutation (as assessed by central laboratory) who have failed standard of care including intensive induction chemotherapy in first line of treatment and Gilteritinib based therapy in any line of prior treatments)

Dose modification: See Section 9.2.3.

Treatment Duration
Patients may continue on study treatment until disease progression, unacceptable toxicity, investigator decision, withdrawal of consent by the patient or other discontinuation criteria detailed in Section 10 are met.

Sample Size Determination

CCI [redacted]

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CCI

Table 1 shows the estimated 2-sided 95% CI for assumend CRc rates at interim analyses for futility.

Table 1 Estimated 95% Confidence Intervals for Assumed CRc Rates at Interim Analysis

Number of Treated Patients	Number of Patients Who Achieve Response	Observed CRc Rate (%)	Lower Bound Exact 95% CI (%)	Upper Bound Exact 95% CI (%)	Half-Width of CI (%)
10	1	10.00	0.25	44.50	22.13
10	2	20.00	2.52	55.61	26.55
10	3	30.00	6.67	65.25	29.29

Overall, considering both parts of the study, a maximum of approximately 180 patients is expected.

Statistical Methods

Descriptive statistics and patients' data listings will be used in the characterization of patients' disposition, demographic and baseline characteristics, treatment exposure and safety variables. Analyses by treatment cohort and dose schedule will be provided for treatment exposure and safety variables. Additional analyses will be performed by treatment period (ie cycle 1 vs. cycles >1), if appropriate, for adverse events, and selected hematological and biochemical tests. Adverse events, hematological and biochemical toxicity will be classified according to the NCI CTCAE (version 5.0). The MedDRA (Medical Dictionary for Regulatory Activities) dictionary (version 21.0) will be used to code the reported adverse events. The anti-tumor activity will be assessed by considering the objective tumor responses defined according to the ELN recommendations for the AML population [6, 7] whereas for CMML patients the tumor response evaluation will be made according to disease specific IWG criteria [56]. All efficacy data will be documented in individual patients' data listings. Untreated patients will be identified and described separately. For the Phase II portion of the trial a futility analysis will be performed for each cohort after at least 10 evaluable patients at the same dose level are observed for at least 3 cycles (ongoing enrollment up to 10 more treated patients may continue while analysis is being performed) such that if at least one responder (i.e. one CR or CRi) is observed then the full cohort may proceed. Time-matched, replicate ECGs and PK samples will be used to explore for concentration-corrected QT interval responses. Such analyses will be further described in a separate analysis plan.
For further details see Section 12.3.

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Interim Analysis

CCI [redacted]

Safety analysis:
During the Phase II part of the trial, the rate of drug-related toxicities namely grade 4 non-hematological adverse events, CCI [redacted] with systemic and/or bulbar impairment or prolonged grade 4 neutropenia leading to withdrawal and drug-related deaths will be monitored on an ongoing basis and sequential boundaries will be used to monitor rates of these events.

The analyses will include the first 20 treated patients of each cohort. The safety boundaries are developed using Pocock method, and they are based on a per patient count.

In addition, empirical safety stopping rules will be applied in each cohort beyond the 20 patients treated up to last treated patients.

For further details see Section 12.4.2.

Patient Selection

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study.

Inclusion Criterion for Phase I and Backfill

1) CCI [redacted]

Inclusion Criteria for Phase II

2) Patients with confirmed diagnosis of AML as defined by the 2022 ELN recommendations positive for FLT3-ITD mutation in the BM or PB as determined by central laboratory test performed at study entry. Patients with very rapidly proliferative disease who, in the opinion of the Investigator, cannot wait for the

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central laboratory results can be enrolled based on a local test performed at study entry. Patients with an allelic ratio ≥ 0.05 will be considered to have FLT3ITD-mutated disease. Patients positive for FLT3- D835 or I836 mutations will not be eligible.

3) Patients must have failed standard of care including venetoclax and gilteritinib based therapies (cohort 1) or standard of care (cohort 2).
The enrollment in each cohort may be restricted to patients with specific prior lines/therapies and/or mutations, based on Sponsor decision.

Inclusion Criteria applying to both <u>Phase I and Phase II</u>

4) Adult (age ≥ 18 years) patients

5) ECOG performance status ≤ 2

6) The interval from prior antitumor treatment to time of NMS-03592088 administration should be at least 2 weeks for any agents other than hydroxyurea.

7) All acute toxic effects (excluding alopecia) of any prior therapy must have resolved to NCI CTCAE version 5.0 Grade ≤ 1

8) Adequate hepatic function, as defined by serum transaminases (i.e., AST/ALT) ≤ 2.5 x ULN, ALP ≤ 2.5 x ULN and total bilirubin ≤ 1.5 x ULN unless abnormality considered due to Gilbert's syndrome in which case the limit is 2 mg/dL).

9) Adequate renal function, as defined by an estimated glomerular filtration rate (eGFR) ≥ 45 mL/min as calculated by the BSA-unadjusted Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, *
* (eGFR (mL/min)= eGFR (mL/min/1.73 m^2) x [BSA (m2)/1.73]

where

eGFR (mL/min/1.73 m^2) = 141 x $\min(Scr/\kappa,1)^{\alpha}$ x $\max(Scr/\kappa, 1)^{-1\ 209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if African American]

10) Patients must use highly effective contraception (for reference, see 0). Female patients must be surgically sterile or be postmenopausal or must agree to the use of highly effective contraception during the period of therapy and in the following 208 days after discontinuation of study treatment. Since NMS-03592088 has potential induction of CYP3A4, WOCBP must be advised that hormonal contraceptives might lose efficacy and must use alternate form of highly effective contraception. Male patients must be surgically sterile or must agree to use highly effective contraception during the period of therapy and in the following 118 days after discontinuation of study treatment.

11) Capability to swallow capsules intact (without chewing, crushing, or opening)

12) Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study indications or procedures

13) Signed and dated IEC or IRB-approved informed consent form indicating that the patient is aware of the neoplastic nature of his/her disease and has been informed of the procedures to be followed, the investigational nature of the therapy, potential benefits, side effects, discomforts, risks and alternative treatments.

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Patient Exclusion Criteria applying to both <u>Phase I and Phase II</u>:

The presence of any of the following will exclude a patient from study enrollment:

1) Current enrollment in another interventional clinical study unless currently only participating in the survival follow up part
2) Diagnosis of acute promyelocytic leukemia or BCR-ABL-positive leukaemia
3) Currently active second malignancy, except for adequately treated basal or squamous cell skin cancer and/or cone biopsied in situ carcinoma of the cervix uteri and/or superficial bladder cancer.
4) Patients with known leukemia involvement of CNS.
5) Hematopoietic stem cell transplantation (HSCT) within 3 months of treatment start and/or persistent non-hematologic toxicities of Grade ≥2 related to the transplant
6) Active acute or chronic graft versus host disease (GVHD) requiring immunosuppressive treatment
7) Patients with QTcF interval ≥ 480 milliseconds or with risk factors for torsade de pointes (e.g., uncontrolled heart failure, uncontrolled hypokalemia, history of prolonged QTc interval or family history of long QT syndrome). For patients receiving treatment with concomitant medications known to prolong the QTc interval, replacement with another treatment needs to be considered. If replacement or discontinuation is not clinically feasible, a careful risk/benefit evaluation should be performed prior to enrollment.
8) Pregnancy. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) within the screening period prior to start of study drug.
9) Breast-feeding or planning to breast feed during the study or within 3 months after study treatment.
10) Known hypersensitivity to any of the components of the NMS-03592088 drug product.
11) Any of the following in the previous 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis
12) Known active, life threatening or clinically significant uncontrolled systemic infection.
13) Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.
14) Active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) C infection.
15) Known active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes or gastric/intestinal resection that would impact on drug absorption.
16) Known active gastrointestinal ulcer.
17) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study or could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.
18) Known diagnosis of myasthenia gravis or any known history of MG autoantibodies at screening window

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19) Concomitant anticoagulant use that is not already stabilized therapeutically

20) Subjects under legal protection or unable to express their consent; subjects deprived of liberty; subjects who are not members or not beneficiaries of a social security scheme.

21) Signs or symptoms of myasthenia gravis or stroke during screening

22) Concomitant medications with the potential to cause de novo myasthenia gravis, worsening of myasthenia gravis or cause myasthenia gravis-like symptoms as in https://myasthenia-gravis.com/clinical/drugs-vaccines-to-avoid (also see 9.2.7.2.1 for a corresponding list)

23) Uncontrolled hypertension, atrial fibrillation or flutter, ventricular arrhythmia or receiving treatment for cardiac rhythm disorder or diabetes that is not adequately controlled

Schedule of Events

The tables and the related footnotes, reported in the next pages, summarize information on the timing of study assessments for:

Phase I (Dose Escalation and Dose Expansion): Schedule A

Phase I (Dose Escalation and Dose Expansion and Backfill): Schedule B

Phase II

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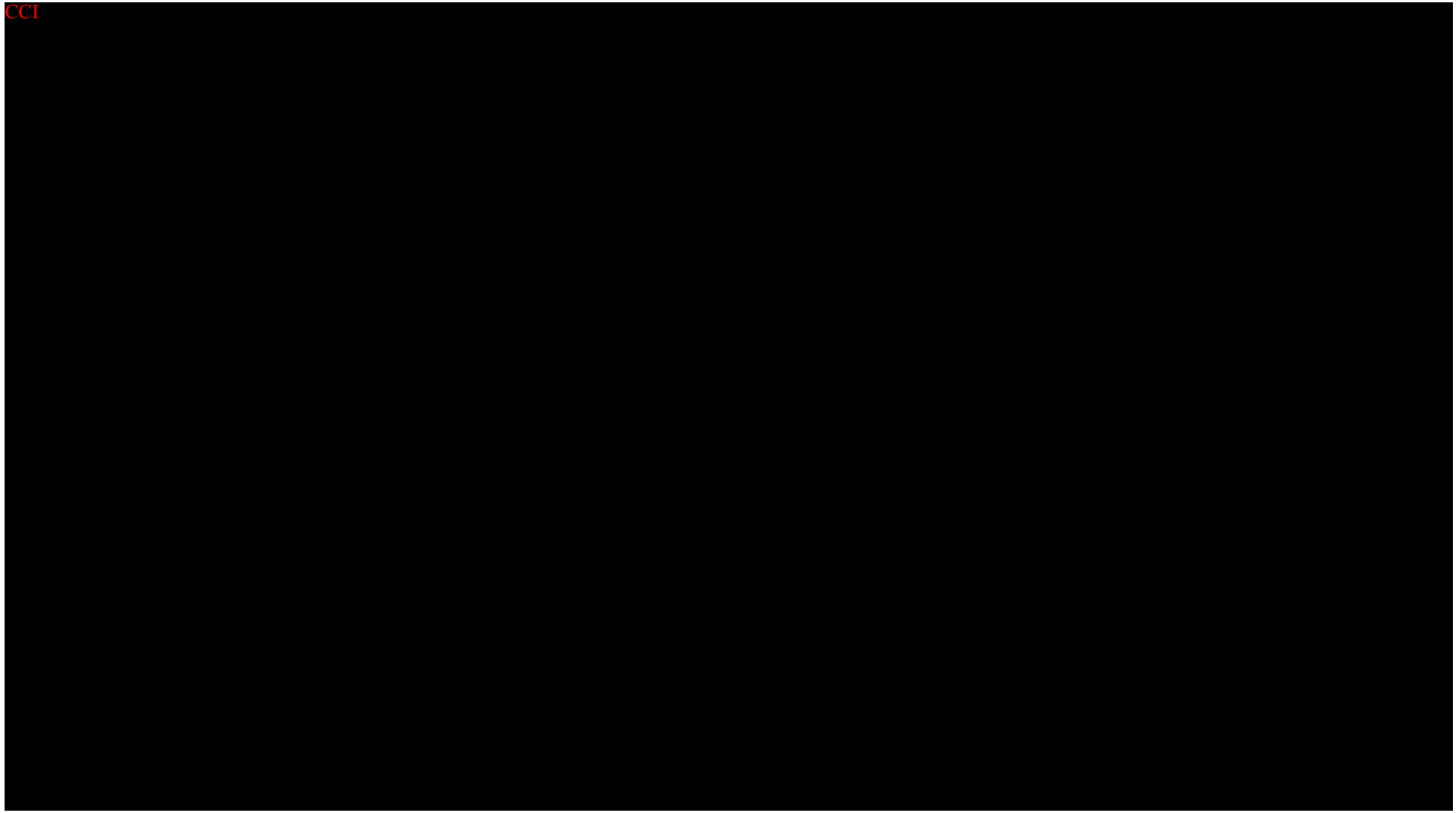

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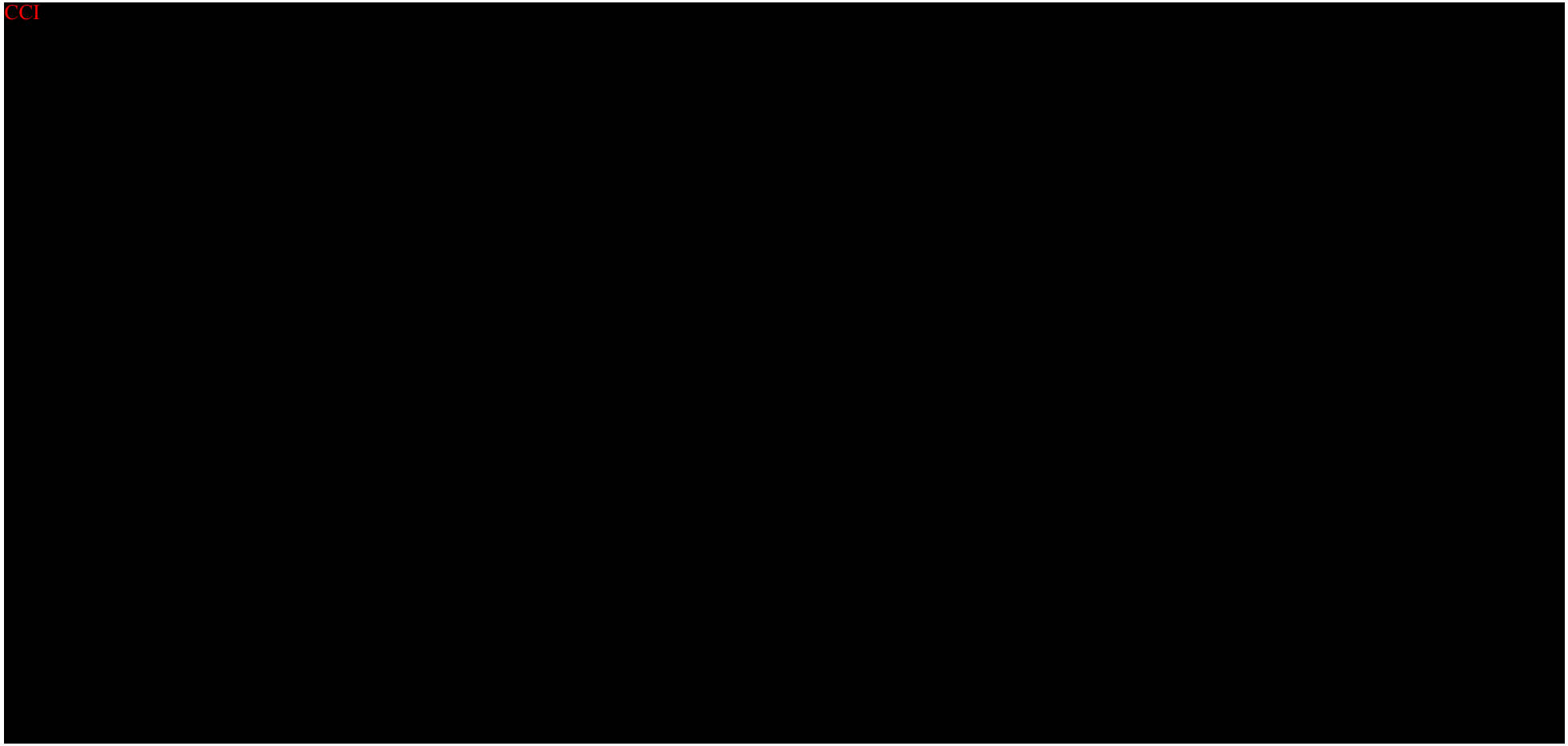

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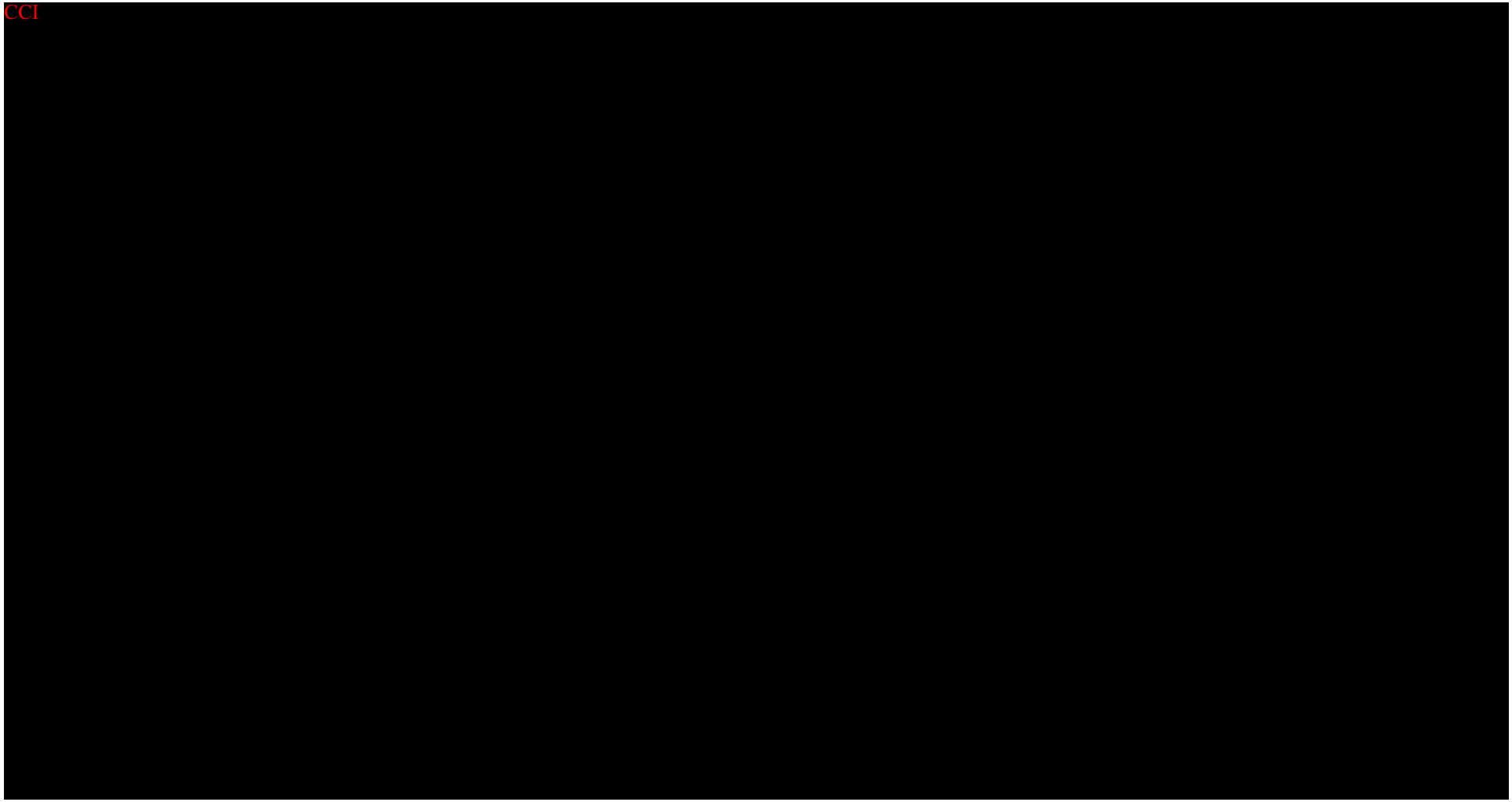

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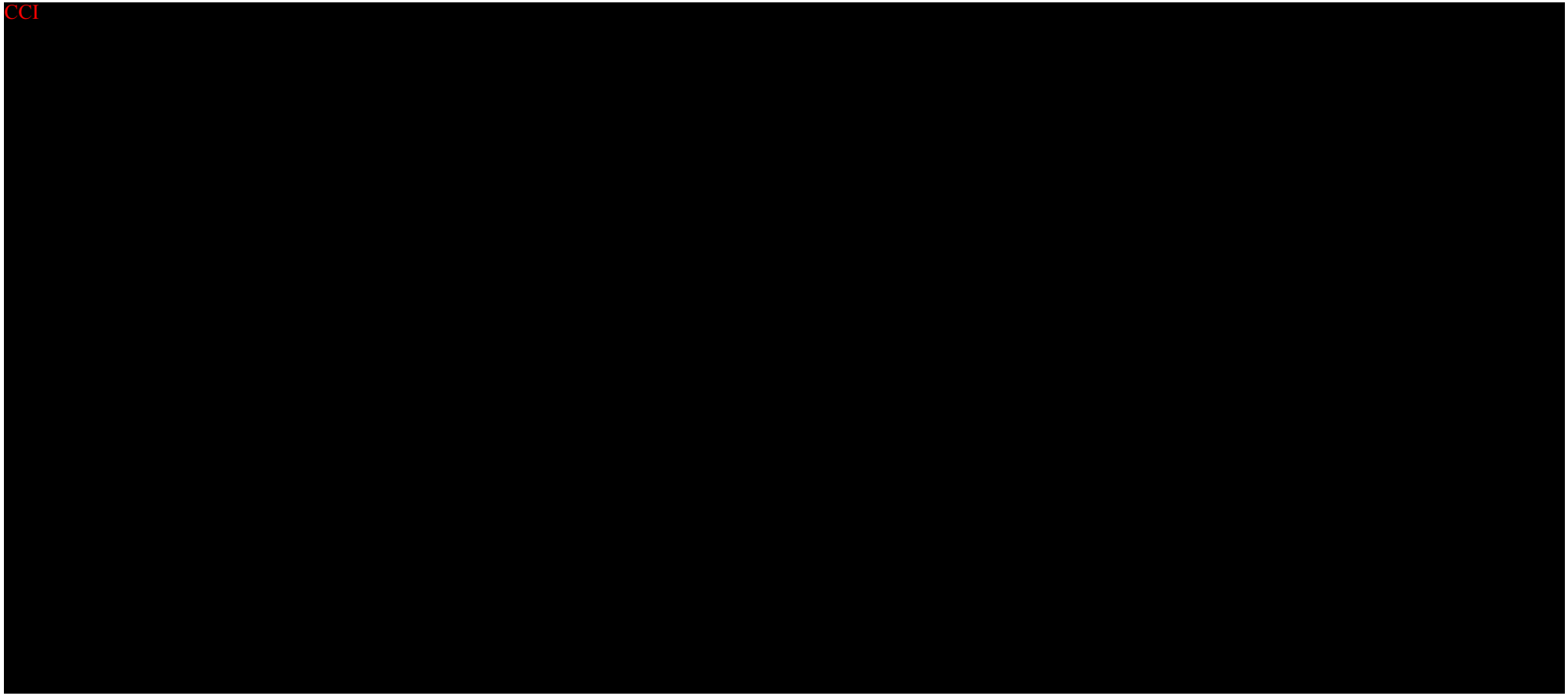

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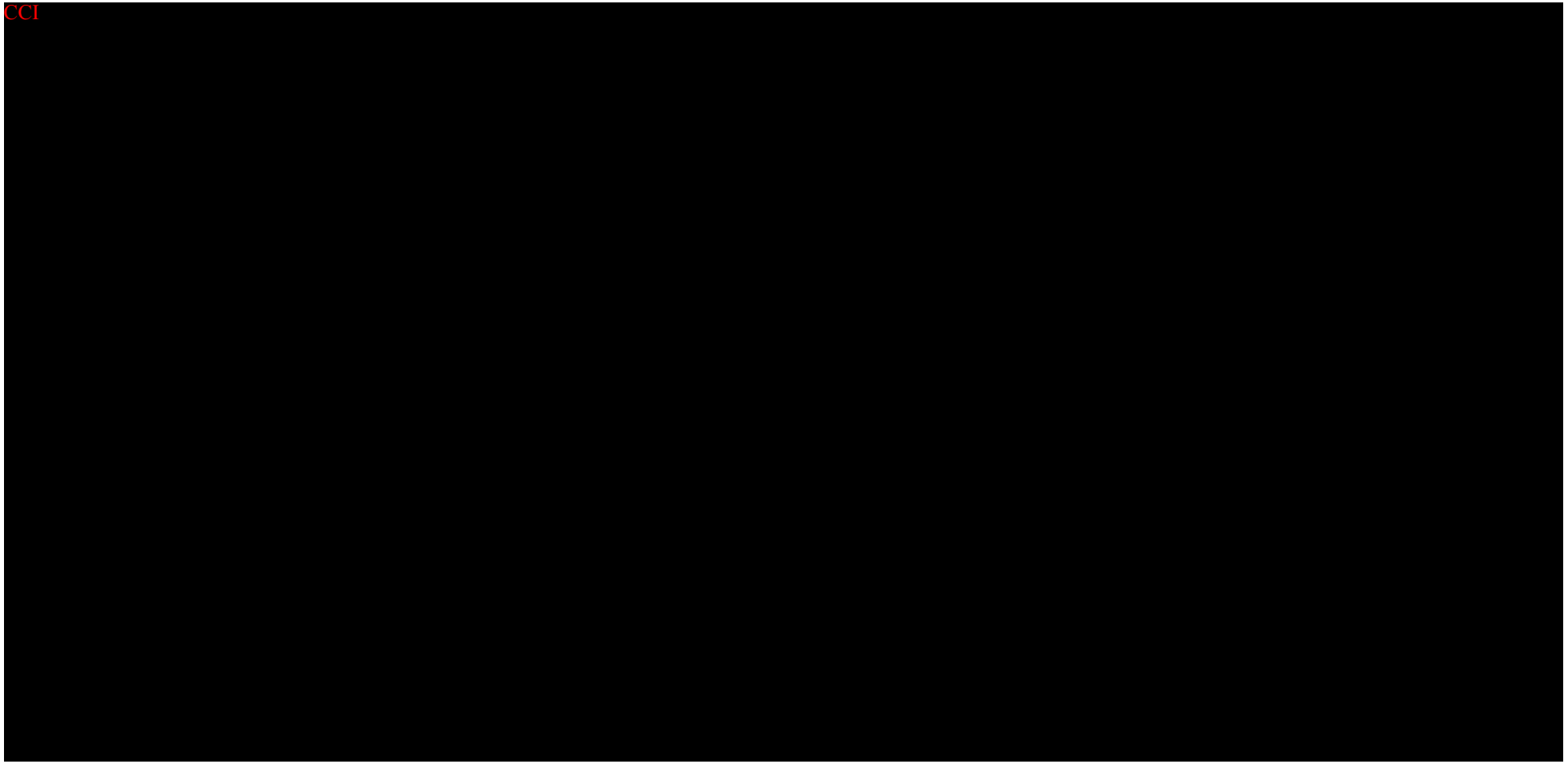

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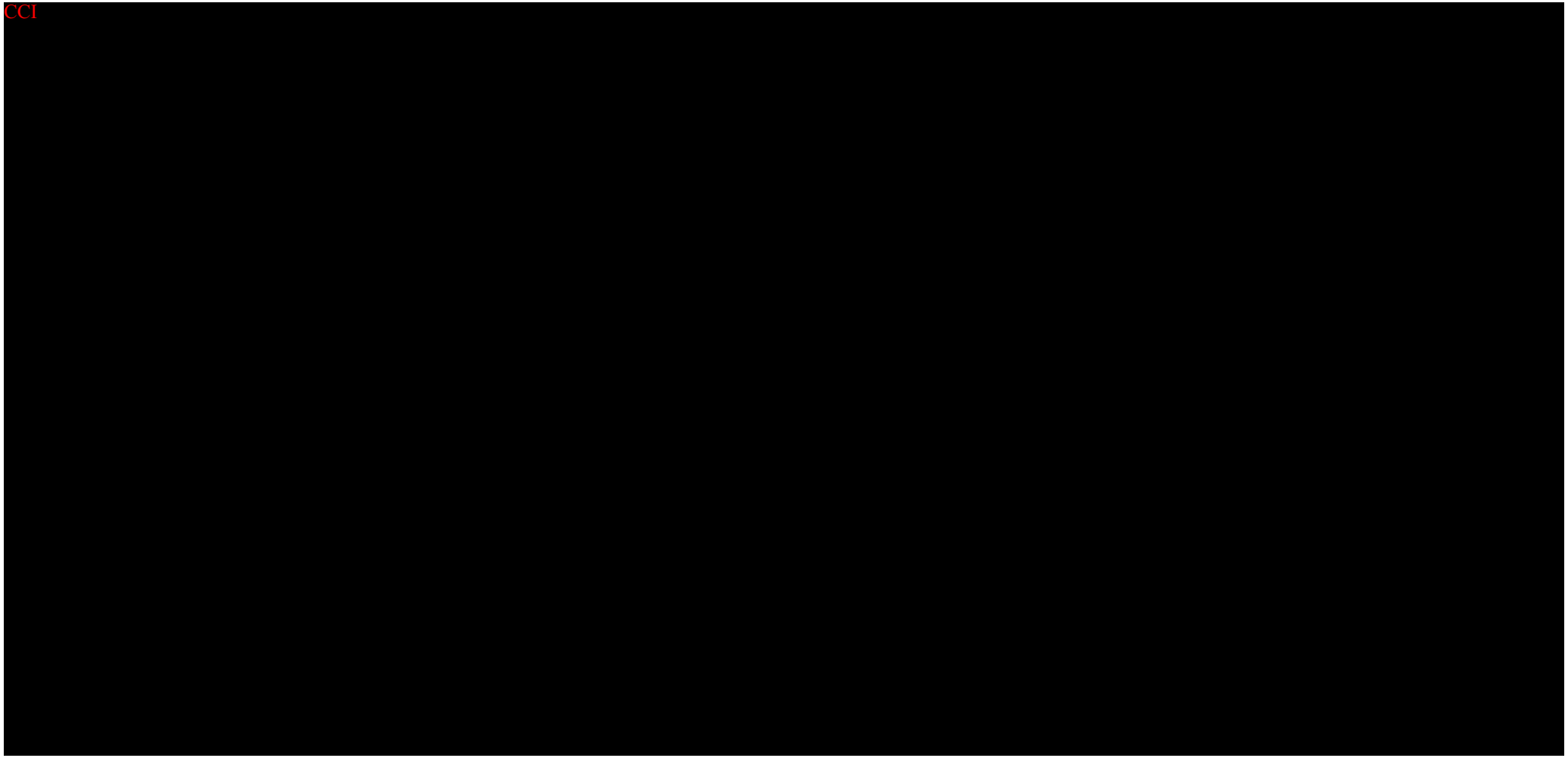

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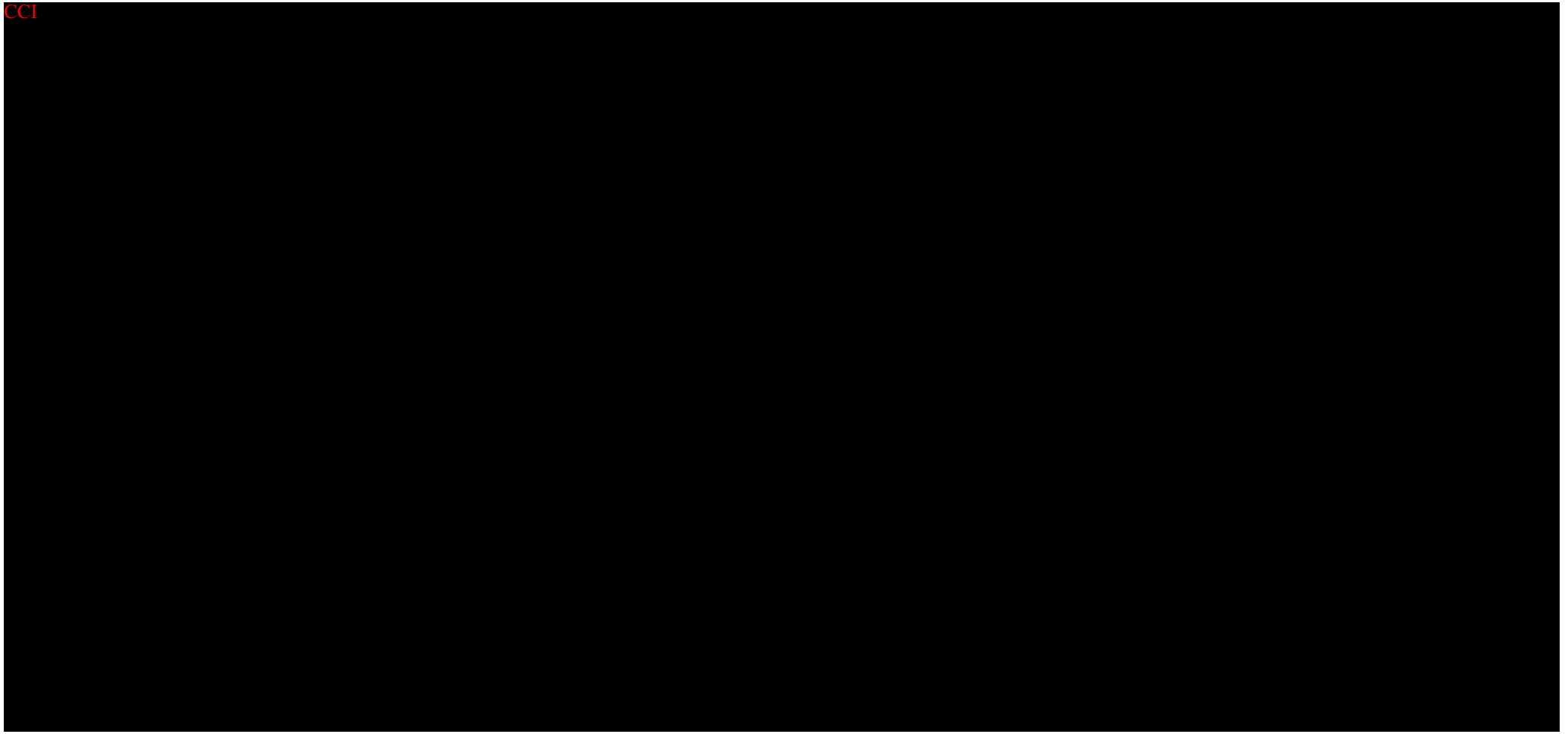

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2. ABBREVIATIONS AND DEFINITIONS OF TERMS

AchR	Acetylcholine receptor
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
AKT	AKR mouse thymoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloblastic leukemia
AST	Aspartate aminotransferase
ASXL1	Additional Sex combs Like 1
AUC	Area under the plasma concentration vs time curve up to infinite time
AUC 0-24	Area under the concentration-time curve from time zero to 24h
BCR-ABL	Breakpoint cluster region-Abelson
BM	Bone Marrow
BP	Blood pressure
BSA	Body Surface Area
CB	Clinical Benefit
CBF-AML	Core Binding Factor AML
CBR	Clinical Benefit rate
CCR	Complete Cytogenetic Remission
CE	Capillary Electrophoresis
CEBPA	CCAAT/Enhancer-Binding Protein Alpha
CDK-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	Confidence Interval
C-KIT	Stem cell factor receptor / Hardy-Zuckerman 4 feline sarcoma viral oncogene
Cmax	Maximum serum/plasma drug concentration
CMML	Chronic Myelomonocytic Leukemia
CNS	Central Nervous System
CPK	Creatine PhosphoKinase
CR	Complete Remission
CRc	Composite Complete Remission Rate
CRh	Complete Remission with Partial Hematologic Recovery
CRi	Complete Remission with Incomplete Hematologic Recovery

CSF1	Colony stimulating factor-1
CSF1R	Colony stimulating factor-1 receptor
CV	Coefficient of Variation
CYP	Cytochrome
CYP1A2, 3A4	Cytochrome P-450, 1A subfamily 2 enzyme, 3A subfamily 4 enzyme
CYP2B6	Cytochrome P-450, 2B subfamily 6 enzyme
CYP2C8, 2C9, 2C19	Cytochrome P-450, 2C subfamily 8 enzyme, 2C subfamily 9 enzyme, 2C subfamily 19 enzyme
CYP2D6	Cytochrome P-450, 2D subfamily 6 enzyme
DDI	Drug-Drug Interaction
DLT/s	Dose limiting toxicity/ies
DNA	Deoxyribonucleic Acid
DoR	Duration of Respnse
ECG	Electrocardiogram
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
ELN	European LeukemiaNet
EMD	Extramedullary disease
ES	(specific for) Spain
FACS	Fluorescence-Activated Cell Sorting
FIH	First in Human
FLT3	Fms-like tyrosine kinase 3
FR	(specific for) France
FU	Follow-up
GIST	Gastrointestinal Stromal Tumors
GLP	Good Laboratory Practices
GVHD	Graft versus host disease
Hb	Hemoglobin
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
hERG	Human ether-a-go-go-related gene
HIV	Human immunodeficiency virus
HNSTD	Highest Non-Severely Toxic Dose
HR	Hazard ratio

HSCT	Hemopoietic stem cell transplantation
IC50	Concentration for 50% inhibition
ICH E6 R2	Integrated addendum of International Conference on Harmonization E6(R1)
IEC	Independent Ethics Committee
IL-3	Interleukine-3
IRB	Institutional Review Board
IT	(specific for) Italy
ITD	Internal tandem duplication
IWG	International Working Group
JAK	Janus kinase
KIT	Tyrosine-protein kinase Kit or CD117
LDH	Lactate Dehydrogenase
MAD	Maximum Administered Dose
MAPK	Mitogen-activated protein kinase
MedRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic Leukemia-free State
MR	Marrow Response
mRNA	Messenger RNA (RiboNucleic Acid)
MTD	Maximum tolerated dose
MuSK	Muscle-specific kinase
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next Generation Sequencing
NPM1	Nucleophosmin
NOAEL	No observed adverse effect level
NOEL	No observed effect level
ORR	Overall response rate
OS	Overll survival
PB	Peripheral Blood
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PD-1	Programmed Death-1
PI3K	Phosphatidylinositol 3-kinase
PIA	Plasma inhibitory activity

PK	Pharmacokinetics
PLT	Platelets
PR	Partial Remission
QTcF	QT interval using Fridericia standard
RAF	Rapidly accelerated fibrosarcoma oncogene
RAS	Rat sarcoma oncogene
RBC	Red blood cells
RFS	Relapse-free Survival
RP2D	Recommended Phase II dose
RUNX1	Runt-related transcription factor 1
SD	Standard Deviation
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SRSF2	Serine and Arginine Rich Splicing Factor 2
STAT	Signal transducers and activators of transcription
STD10	Severely Toxic Dose in 10% of the animals
TAM	Tumor Associated Macrophage
TKD	Tyrosine Kinase Domain
TET2	Tet methylcytosine dioxygenase 2
TP53	Tumor Protein 53
TTR	Time to Response
ULN	Upper Limit of Normality
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential

3. BACKGROUND INFORMATION AND STUDY RATIONALE

3.1. INTRODUCTION

NMS-03592088 is a potent inhibitor of the kinase activity of FLT3, CSF1R and KIT. The compound is formulated for oral administration and it was selected for clinical investigation in patients with hematological malignancies and solid tumors.

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This first in human study of NMS-03592088 is a Phase I dose finding/Phase II study in patients with AML and CMML.

3.2. Disease background

Acute myeloid leukemia

Acute myeloid leukemia (AML) is the most common type of acute leukemia in adults and represents 36% of all leukemias in adults and children [1]. The American Cancer Society estimates 19,520 new cases of AML and 10,670 deaths from AML in the United States in 2018. (https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html or https://seer.cancer.gov/statfacts/html/amyl.html). Similarly, over 18,000 new cases are expected in the European Union, considering a reported crude incidence rate of 3.62 per 100,00 people [2]. AML is primarily a disease of elderly, with a median age at diagnosis of 68 years.

After many years the backbone of standard therapy for AML remains chemotherapy, a combination of cytarabine- and anthracycline-based regimens, with allogeneic stem cell transplantation for eligible candidates. Elderly patients are often unable to tolerate these regimens and carry a particularly poor prognosis. Individuals over the age of 65 are in fact more likely to present with an adverse cytogenetic-risk profile, less likely to respond to chemotherapy and often more susceptible to treatment-related toxicities. Thus, an optimal approach to elderly patients with AML has not been established.

Despite good initial response to conventional induction therapy, AML relapse is common, contributing to a 5-year survival rate of only 27.4% (https://seer.cancer.gov/statfacts/html/amyl.html).

AML is a biologically and clinically heterogeneous disease. In the majority of cases, it appears as a *de novo* malignancy in previously healthy individuals, but it can arise in patients with an underlying hematological disorder, or as a consequence of prior chemo/radiotherapy for another malignancy [3]. Regardless of its etiology, the pathogenesis of AML involves the abnormal proliferation and differentiation of a clonal population of myeloid stem cells that displace the normal hematopoietic system. Genetic mutations are

identified in more than 97% of cases, often in the absence of any large chromosomal abnormality [4, 5]. The prognostic relevance of specific mutations and karyotypes is becoming more and more recognized and is reflected in the 2017 revision [7].and in the latest 2022 revision of the AML classification of the European LeukemiaNet (ELN) [6]. Some of these mutations, such as those involving the FMS-like tyrosine kinase 3 (FLT3) gene, have an impact on disease pathophysiology, prognosis and treatment strategy.

FLT3 mutations occur in approximately 30% of AMLs, and is associated with a lower complete remission (CR) rate, higher induction death rate, increased risk of relapse, and adverse disease-free survival (DFS), event-free survival, and overall survival (OS) [8 -13]. Because of its association with poor outcomes, detection of the FLT3 mutation classifies any newly diagnosed AML as poor risk.The majority of FLT3-mutated AML patients carry an internal tandem duplication (ITD) mutation in the FLT3 gene, which leads to uncontrolled cellular proliferation, survival, and differentiation through constitutive activation of FLT3 [14].

While in the 2017 ELN recommendation the FLT3ITD allelic ratio and NPM1 mutational status were considered for ELN risk stratification that classified AML patients with wild-type NPM1 and FLT3ITD with high allelic ratio (≥ 0.5) into adverse risk cathegory [7], in the 2022 revision of the ELN recommendations [6], the FLT3-ITD allelic ratio is no longer considered in the risk classification and all AML with FLT3-ITD are now categorized in the intermediate-risk group, regardless of the allelic ratio or presence of NPM1 mutation. The rationale for this change refers to methodological issues with standardizing the assay to measure the FLT3-ITD allelic ratio, the modifying impact of midostaurin-based therapy on FLT3-ITD without NPM1 mutation, and the increasing role of MRD in treatment decisions [6].

However, the prognostic impact of the ITD of FLT3 (FLT3ITD) is reported to depend on the allelic ratio in the literature, with high FLT3ITD allelic ratio (>0.5) in the absence of a nucleophosmin (NPM1) mutation carrying a dismal prognosis [15, 16, 17].

Mutations in the tyrosine kinase domain (TKD) of FLT3 are less frequent (7%) and their prognostic relevance is less well defined) [18].

AML carrying t(8;21)(q22;q22) and inv(16)/t(16;16)(p13;q22) is classified as French-American-British (FAB) AML subtype M2 or monocytic with eosinophilic differentiation (M4Eo) by morphology and as core binding factor (CBF)-AML according to pathogenesis. CBF-AML accounts for approximately 15% of AML and frequently harbors c-KIT mutation (17~46%). c-KIT mutated CBF-AML patients usually have higher baseline white blood cell count, higher relapse rate and shorter event free survival/overall survival after conventional chemotherapy than those without c-KIT mutation.

In addition to FLT3 and NPM1 other genes such as CEBPA, RUNX1, ASXL1 and TP53 are also frequently mutated in AML and included in the ELN classification. The assessment of

their mutational status can be useful to better interpret patient outcome after treatment with NMS-03592088.

The recognition of the key role of FLT3 mutations has led to intensive research around this target, resulting in the approval of the first FLT3 inhibitor, midostaurin, in 2017. Approval was based on a randomized, double-blind, placebo-controlled trial in 717 patients with previously untreated FLT3mut AML [19]. This trial randomized patients aged 18 to 59 years to either placebo or midostaurin during induction and consolidation chemotherapy followed by continuous daily midostaurin for up to 12 cycles and demonstrated a statistically significant improvement in overall survival (OS) for patients receiving midostaurin compared with those on the placebo-containing arm (HR 0.77, p=0.016).

In addition, a more selective FLT3 inhibitor, gilteritinib, was approved in 2018 in US and 2019 in EU as monotherapy for treatment as of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation. The approval was based on results from the Phase 3 ADMIRAL trial, which investigated gilteritinib versus salvage chemotherapy in patients with relapsed or refractory FLT3 positive AML. The study showed a significantly longer overall survival (OS) in patients treated with gilteritinib (median OS 9.3 months) than those who received salvage chemotherapy (median OS 5.6 months) [20]. Additional selective FLT3 inhibitors in clinical development have reported encouraging results in AML patients [19,21,22,23]. However, activity of FLT3 selective inhibitors appears to be limited by the appearance of resistance mutations.

Although the introduction of midostaurin as additional therapy for newly diagnosed FLT3mut AML and gilteritinib for relapsed/refractory FLT mut AML patient led to significant improvements in outcomes for FLT3-mutant AML patients, the medical need, especially for older patients and patients who relapse after an initial response remains high. In addition, the emergence of secondary FLT3 mutations during the course of therapy with FLT3 inhibitors raises new challenges toward effective therapy in this subset of AML.

Chronic myelomonocytic leukemia

Chronic myelomonocytic leukemia (CMML) is a clonal hematopoietic stem cell disorder with overlapping features of myelodysplastic syndromes and myeloproliferative neoplasms. The median age at CMML diagnosis is 71-74 years, with a male preponderance. Incidence of CMML has increased in US from 0.5/100,000 to 0.6/100,000 population from 2000 to 2011 [24].

Gene mutations are seen in >90% of patients, with common abnormalities involving epigenetic regulators (TET2 and ASXL1), spliceosome components (SRSF2) and cell signaling (oncogenic RAS).

Many different prognostic models have been proposed, some of them incorporate molecular abnormalities. The Mayo Molecular Model, for example, considers the presence of nonsense or frameshift ASXL1 mutations, together with absolute monocyte count,

hemoglobin, platelet count and presence of circulating immature myeloid cells and stratifies CMML patients in 4 risk groups with median survivals from 16 months (high risk) to 97 months (low risk) [25]. Furthermore, the presence of FLT3ITD was also found in CMML patients and may represent an independent negative prognostic factor for these patients [26].

Rates of leukemic transformation vary among different series reported in literature. However, most studies quote an incidence of 20 % over 3 -5 years. [27].

Median survival post- blast transformation is short, 4.7 months, and 5-year survival is only 6%. Survival is longer with allogeneic stem cell transplant (14.4 months vs. 4.3 months for chemotherapy vs. 0.9 months for supportive care) [28].

Hypomethylating agents remain the most commonly used therapeutic intervention for CMML patients. Standard induction chemotherapy should be considered for all eligible patients who develop blast transformation. The impact of mutations on patients undergoing therapy is still unclear [29].

Therefore, the response rate and survival following therapy is suboptimal and the role of allogeneic hematopoietic cell transplantation in CMML remains controversial. Younger patients should be considered for transplant. Older patients are best suited for clinical trials [29].

3.3. Target Background

FLT3, CSF1R and KIT are members of the class III receptor tyrosine kinase family characterized by an extracellular domain with five immunoglobulin-like loops, a transmembrane region and a cytoplasmic domain containing not only the kinase domain (divided in two regions), but also an auto-inhibitory juxtamembrane (JM) domain that docks with the kinase domain to stabilize a catalytically inactive conformation.

All three targets play an important role in AML, while CSF1R and FLT3 are relevant for CMML.

FLT3 has a crucial role in normal hematopoiesis while its expression in adults is restricted to CD34+ hematopoietic stem/progenitor cells, brain, placenta, and gonads. Activation of FLT3 by FLT3-ligand promotes the normal growth of early progenitor cells. FLT3 is expressed in AML cells of most patients and mutations of the FLT3 gene are one of the most common acquired genetic lesions [30].

FLT3 mutations can be detected in ~30% of AML patients, and also in 5-10% of patients with myelodysplastic syndrome [31]. There are two types of somatic FLT3 genetic mutations: internal tandem duplications (ITDs) in the juxta-membrane domain, which are by far the most frequent, and point mutations in the activation loop of the tyrosine kinase domain. ITD mutations are any elongation or shortening of the JM domain of FLT3 due to additions or deletions of amino acids that result in the constitutive activation of FLT3. The

presence of FLT3ITD mutations is associated with a poor clinical outcome in patients with AML. Point mutations in the activation loop of the kinase domain (FLT3TKD) involve the aspartic acid D835 residue leading to an activated configuration and transformation of myeloid cells. D835 mutations are missense mutations that result in substitution of tyrosine, histidine, valine, glutamic acid or asparagine for aspartic acid at amino acid 835 of FLT3. These mutations have been reported in ~7% of patients with AML. TKD mutations, unlike ITD mutations, have an uncertain prognostic significance in AML. Both types of FLT3 mutations cause ligand-independent activation of the receptor and activation of downstream signaling pathways. Mutant FLT3 provides survival advantage to leukemic cells because it causes activation of three major intracellular signalling pathways: PI3K/AKT; RAS/RAF/MAPK and JAK/STAT [32].

In conclusion, interfering with the FLT3 signalling represents a specific and effective means of blocking tumor cell proliferation in AML. However, despite encouraging results seen with midostaurin and other agents (gilteritinib, quizartinib, crenolanib), responses to FLT3 inhibitors are usually transient due to the emergence of resistance mutations. These are point mutations in the FLT3ITD kinase domain, generally confined to the D835 and F691 residues [33,34]. The different FLT3 kinase inhibitors either approved or in development have distinct inhibitory potencies against the different resistance mutations [35,36]. In particular, the F691 mutation originally identified as one of the most frequent resistance mutations to quizartinib has also been identified in patients treated with crenolanib and gilteritinib, suggesting that this so called "gatekeeper mutation" represents a common resistance mechanism, thus resulting in an unmet medical need in the clinical setting [33, 36,37].

The FLT3 pathway may also play a role in CMML Introduction of an internal tandem duplication (ITD) mutation in the endogenous murine Flt3 locus resulted in the generation of a murine model which closely resembles human CMML [38]. Genomic analysis of a large series of primary patient samples led to the identification of a subset of FLT3ITD positive CMML [38,39,40].

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The CSF1 receptor (CSF1R) has been shown to polarize macrophages towards an immunosuppressive and tumor-promoting phenotype. Thus, the CSF1–CSF1R axis has been extensively investigated in solid tumors and is paradigmatic of the tumor-associated macrophages (TAM)–cancer cell interaction. High CSF1 or CSF1R expression levels in the tumor or peritumoral tissue have been associated with poor patient survival in different

malignancies, such as lymphoma, breast cancer, and hepatocellular carcinoma [41, 42, 43, 44].

Treatment with CSF1R has been shown to induce upregulation of circulating CSF1 ligand, which can be used as a pharmacodynamics biomarker of CSF1R inhibition [45].

CSF1R is a key regulator for monocyte differentiation from progenitors of the bone marrow and also determines monocyte activation and migration [46]. CSF1 and/or CSF1R gene are expressed in AML blasts, with a 30% of cases with co-expression of both genes and 30% of cases where neither gene is expressed [47]. Presence of CSF1R mutations is also reported as rare event in AML, mainly in the extracellular domain, that could lead to constitutive activation of the receptor. These mutations are not associated with FLT3 or c-KIT mutation [48].

Recent experimental evidence suggests a potential therapeutic role of CSF1R blockade in AML [49]), probably by interfering with microenvironmental support [43,50]. Furthermore, also CMML blasts express high level of CSF1R (A. Rambaldi, unpublished observation).

NMS-03592088 was shown to strongly inhibit CSF1R in biochemical assays (Ki= 4.5 nM) as well as in cellular assays, including cells from CMML patients, and *in vivo.*

KIT is a receptor tyrosine kinase expressed on a wide variety of cell types and normally activated by stem cell factor. Signalling by KIT plays an important role in erythropoiesis, lymphopoiesis, mast cell development and function, megakaryopoiesis, gametogenesis and melanogenesis. Hematopoietic stem cells, multipotent progenitors and common myeloid progenitors, but also early T lineage progenitors and thymocytes express high levels of KIT. KIT is mutated in 8.0% of acute myeloid leukemia (COSMIC). Oncogenic KIT mutations occur primarily in core binding factor (CBF) AML [51], which constitutes 5-8 % of all AML cases [53,54,52]. Expression levels of both KIT mRNA and proteins are much higher in CBFL, with either wild type or mutant KIT, than in leukemia cells negative for CBF rearrangement [54]. The prognostic significance of cKIT mutations remains to be established [53, 52].

NMS-03592088 inhibits wild type KIT with a Ki of 7.7 nM and has high activity against KIT activating mutations (e.g. V559D) and secondary mutations (e.g. V654A and T670I), confirmed both in cells, including KIT-mutated AML cells, and in xenograft tumors *in vivo*.

3.4. NMS-03592088

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CCI [redacted]

The following sections present a summary of the preclinical studies; detailed information is presented in the Investigator Brochure [55].

3.4.1. Pharmacology

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

3.4.2. Safety Pharmacology

CCI [redacted]

[redacted].

3.4.3. Nonclinical Pharmacokinetics

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

3.4.4. Drug-drug Interactions

CCI [redacted]

[redacted]

3.4.5. Toxicology

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

3.4.6. Study Rationale

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

4. TRIAL OBJECTIVES AND ENDPOINTS

4.1. Objectives

4.1.1. Primary Objective

Phase I

To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and the recommended Phase II dose (RP2D) of NMS-03592088 administered orally once daily for 21 consecutive days followed by 7 days of rest in a 28 days cycle (Schedule A) or once daily for 28 consecutive days (Schedule B) in adult patients with selected hematologic malignancies who have exhausted standard treatment options or for whom standard therapy is considered unsuitable.

Phase II

- To explore the antitumor activity of NMS-03592088 in FLT3-ITD mut AML.

4.1.2. Secondary Objectives (Phase I and II):

- To define the safety profile and tolerability of NMS-03592088;
- To evaluate pharmacokinetics (PK) of NMS-03592088 and its metabolites NMS-03593860 and NMS-03603422 in plasma and, limited to Phase I, also in urine;
- To assess any preliminary evidence of clinical efficacy of NMS-03592088 (Phase I).

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4.2. Endpoints

4.2.1. Primary Endpoint

Phase I

- Drug related first-cycle dose limiting toxicities (DLTs).

Phase II

- FLT3-ITD mut AML: Composite Complete Remission (CRc) Rate, i.e. Complete Remission (CR) + Complete Remission with Incomplete Hematologic Recovery (CRi), as defined by the 2022 ELN recommendations [6];

4.2.2. Secondary Endpoints (Phase I and Phase II)

- Overall safety profile of NMS-03592088 characterized by type, frequency, severity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 5.0), timing and relationship to study therapy of adverse events, and laboratory and ECG abnormalities;
- Plasma pharmacokinetic profile and corresponding parameters of NMS-03592088 and its metabolites NMS-03593860 and NMS-03603422;
- Renal clearance and fraction of NMS-03592088 and its metabolites NMS-03593860 and NMS-03603422 excreted in urine (only Phase I);
- Secondary efficacy endpoints include: Best Response by category, Overall Survival (OS), Time to Response (TTR), Duration of Response (DoR), Event-Free Survival (EFS) and Relapse-free Survival (RFS) as defined by the ELN recommendations [6, 7] and disease specific International Working Group criteria [56] and proportion of patients bridged to hemopoietic stem cell transplantation (HSCT). For AML and in Phase II only: Complete Remission (CR) Rate, Complete Remission and Complete Remission with Partial Hematologic Recovery (CR/CRh) Rate, (CR/CRh/CRi) rate and Overall Response Rate (ORR: CRc + CRh + MLFS + PR) as defined by the 2022 ELN recommendations [6]. Rate of conversion from transfusion-dependence to transfusion independence.

CCI [redacted]

[redacted]

- [redacted]
- [redacted]

CCI

5. TRIAL DESIGN AND DESIGN RATIONALE

This is an open-label Phase I/II, first-in-human (FIH), multi-centric trial in sequential cohorts of patients with relapsed or refractory hematologic malignancies who have exhausted standard treatment options or for whom standard therapy is considered unsuitable.

The study will be conducted in two parts: a Phase I dose escalation part including patients with AML and CMML and a Phase II exploratory study with interim analyses for futility and safety comprising two parallel cohorts of AML FLT3-ITD mutated patients that are more likely to respond to the drug.

NMS-03592088 will be administered as home-based treatment.

For the diagnosis and response assessment of AML patients the ELN 2017 Guidelines [7] have been followed up to the approval of amendment 6, after which ELN 2022 were implemented [6].

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Dose escalations will be decided jointly between the Investigators and the Sponsor.

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CCI [redacted]

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[redacted]

5.1. Starting Dose

CCI [redacted]

[redacted]

[redacted]

5.2. Phase I

Dosing of the drug will be based on CCI [redacted]

The dose escalation schema will be as follows.

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CCI [redacted]

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

CCI [redacted]

DLTs will be classified according to CTCAE version 5.0.

5.3.1. DLT window

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5.3.2. Patient replacement

During the first cycle of the dose-escalation part in Phase I, patients who meet any of the following criteria will not permit the DLT evaluation and therefore will be replaced:

- did not receive at least 70% of cycle study drug, unless treatment was stopped for a drug-related toxicity,
- did not undergo a first-cycle DLT assessment.

A patient may also be replaced if, under particular circumstances (e.g. due to noncompliance), the assessment of DLTs is not possible as judged jointly by the Investigators and the Sponsor.

5.4. Definition of MTD and RP2D

The MTD may or may not be determined and is defined as the dose level at which 0/3, 0/6 or 1/6 patients experience DLT in the first cycle of treatment with the next higher dose having at least 2/3 or 2/6 patients encountering DLT. Effectively, the MTD is the highest dose level associated with the cohort at which < 33% of patients experience a first cycle DLT.

RP2D is no higher than MTD relative to dose or exposure but may be selected if MTD is not determined and is chosen based on PK, anti-blast activity, biomarkers and safety considerations among other features.
This dose may be the dose recommended for further investigations.

5.5. Phase II

Once the RP2D and schedule of NMS-03592088 have been selected and communicated to sites, the exploratory Phase II portion of the study with interim analysis for futility and safety will be opened for enrollment and will consist of two parallel cohorts:

Cohort 1 (40 patients with a futility analysis at 10 patients): patients with AML FLT3 Internal Tandem Duplication (ITD) mutation as assessed by central laboratory, who have failed standard of care including venetoclax and gilteritinib based therapies. Dose and schedule will be within the defined exposure cap rule defined in section 9.2.1). The enrollment in this cohort may be restricted to patients with specific prior lines/therapies and/or mutations, based on Sponsor decision.

Cohort 2 (40 patients with a futility analysis at 10 patients): patients with AML FLT3 Internal Tandem Duplication (ITD) mutation as assessed by central laboratory, who have failed standard of care. Dose and schedule will be within the defined exposure cap rule defined in section (refer to section 9.2.1). The cohort may be restricted to patients with specific prior lines/therapies and/or mutations, based on Sponsor decision.

The Sponsor will control the patient assignment to cohorts and may stop or pause cohorts in any phase or part of the study based on safety, efficacy or strategic reasons. The sponsor have also the possibility to explore additional phase II cohorts upon protocol amendment based on restriction of patient population and/or additional dose regimens within the described cap of exposure. The same criteria for futility analysis will apply on such cohorts.

For the FLT3-ITD mutated AML group, the main endpoint in the Phase II will be the Composite Complete Remission Rate (CRc), defined as the proportion of patients who achieved a Complete Remission (CR) or Complete Remission with Incomplete Recovery (CRi). See Section 11.2 for all details.

For the safety analysis, the rate of drug-related unacceptable toxicities and drug-related deaths will be monitored on ongoing basis using sequential boundaries.

The analyses will include all treated patients of each cohort of the Phase II portion.

All details are reported in Section 12.4.2.

For statistical considerations, see Section 12.

6. PATIENT SELECTION

This clinical trial can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Patient Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study. Some specific inclusion criteria apply only to Phase I and backfill or Phase II of the study.

Phase I and backfill:

1. Patients with relapsed/refractory disease who have failed standard therapy or are unsuitable for standard treatment, with one the following confirmed diagnosis:
   - AML as defined by the European LeukemiaNet (ELN) recommendations [6, 7]. In backfill cohorts, sponsor may require specific FLT3 mutations in the BM or PB as determined by central and/or local laboratory test performed at study entry. The enrolment could also be restricted to specific prior lines/therapies.

Phase II:

2. Patients with confirmed diagnosis of AML as defined by the 2022 ELN recommendations [6] positive for FLT3-ITD mutation in the BM or PB as determined by central laboratory test performed at study entry. Patients with very rapidly proliferative disease who, in the opinion of the Investigator, cannot wait for the central laboratory results can be enrolled based on a local test performed at study entry. Patients with an allelic ratio ≥ 0.05 will be considered to have FLT3-ITD- mutated disease. Patients positive for FLT3- D835 or I836 mutations will not be eligible.
3. Patients must have failed standard of care including venetoclax and gilteritinib based therapies (cohort 1) or standard of care (cohort 2).
   The enrollment in each cohort may be restricted to patients with specific prior lines/therapies and/or mutations, based on Sponsor decision.

Both Phase I and Phase II

4. Adult (age ≥ 18 years) patients
5. ECOG performance status ≤ 2
6. The interval from prior antitumor treatment to time of NMS-03592088 administration should be at least 2 weeks for any agents other than hydroxyurea.

7. All acute toxic effects (excluding alopecia) of any prior therapy must have resolved to NCI CTCAE version 5.0 Grade ≤1
8. Adequate hepatic function, as defined by serum transaminases (i.e., AST/ALT) ≤ 2.5 x ULN, ALP ≤ 2.5 x ULN and total bilirubin ≤ 1.5 x ULN unless abnormality considered due to Gilbert's syndrome (in which case the limit is 2 mg/dL).
9. Adequate renal function, as defined by serum creatinine ≤ 1.5 x ULN and an estimated glomerular filtration rate (eGFR) ≥ 45 mL/min as calculated by the BSA-unadjusted Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, *
   * eGFR (mL/min)= eGFR (mL/min/1.73 m^2) x [BSA (m^2)/1.73]

   where

   $\text{eGFR (mL/min/1.73 m2)} = 141 \times \min(\text{Scr}/\kappa,1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] x 1.159 [if African American]
10. Patients must use highly effective contraception (for reference, see Appendix 0). Female patients must be surgically sterile or be postmenopausal or must agree to the use of highly effective contraception during the period of therapy and in the following 208 days after discontinuation of study treatment. Since NMS-03592088 has potential induction of CYP3A4 WOCBP must be advised that hormonal contraceptives might lose efficacy and must use alternate form of highly effective contraception. Male patients must be surgically sterile or must agree to use highly effective contraception during the period of therapy and in the following 118 days after discontinuation of study treatment.
11. Capability to swallow capsules intact (without chewing, crushing, or opening)
12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study indications or procedures
13. Signed and dated IEC or IRB-approved informed consent form indicating that the patient is aware of the neoplastic nature of his/her disease and has been informed of the procedures to be followed, the investigational nature of the therapy, potential benefits, side effects, discomforts, risks and alternative treatments.

6.2. Patient Exclusion Criteria

The presence of any of the following will exclude a patient from study enrollment:

1. Current enrollment in another interventional clinical study unless currently only participating in the survival follow up part.
2. Diagnosis of acute promyelocytic leukemia or BCR-ABL-positive leukaemia
3. Currently active second malignancy, except for adequately treated basal or squamous cell skin cancer and/or cone biopsied in situ carcinoma of the cervix uteri and/or superficial bladder cancer.

4. Patients with known leukemia involvement of CNS
5. Hematopoietic stem cell transplantation (HSCT) within 3 months of treatment start and/or persistent non-hematologic toxicities of Grade ≥2 related to the transplant
6. Active acute or chronic graft versus host disease (GVHD) requiring immunosuppressive treatment
7. Patients with QTcF interval ≥ 480 milliseconds or with risk factors for torsade de pointes (e.g., uncontrolled heart failure, uncontrolled hypokalemia, history of prolonged QTc interval or family history of long QT syndrome). For patients receiving treatment with concomitant medications known to prolong the QTc interval, replacement with another treatment needs to be considered. If replacement or discontinuation is not clinically feasible, a careful risk/benefit evaluation should be performed prior to enrollment.
8. Pregnancy. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) within the screening period prior to start of study drug.
9. Breast-feeding or planning to breast feed during the study or within 3 months after study treatment.
10. Known hypersensitivity to any of the components of the NMS-03592088 drug product.
11. Any of the following in the previous 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis
12. Known active, life threatening or clinically significant uncontrolled systemic infection.
13. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness
14. Active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) C infection.
15. Known active gastrointestinal disease (e.g., Crohn's disease, ulcerative colitis, or short gut syndrome) or other malabsorption syndromes that would impact on drug absorption.
16. Known active gastrointestinal ulcer
17. Other severe or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study or could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.
18. Known diagnosis of myasthenia gravis or any known history of MG autoantibodies at screening window
19. Concomitant anticoagulant use that is not already stabilized therapeutically.

20. Subjects under legal protection or unable to express their consent; subjects deprived of liberty; subjects who are not members or not beneficiaries of a social security scheme
21. Signs or symptoms of myasthenia gravis or stroke during screening
22. Concomitant medications with the potential to cause de novo myasthenia gravis, worsening of myasthenia gravis or cause myasthenia gravis-like symptoms as in https://myasthenia-gravis.com/clinical/drugs-vaccines-to-avoid (also see 9.2.7.2.1 for a corresponding list)
23. Uncontrolled hypertension, atrial fibrillation or flutter, ventricular arrhythmia or receiving treatment for cardiac rhythm disorder or diabetes that is not adequately controlled.

7. SCHEDULE OF EVENTS

CCI [redacted]

8. ENROLLMENT PROCEDURES

Patients considered suitable for study will be informed about study, both verbally and by written information. The patients will be given ample time for reading the information provided and to ask others' opinion. The patients who will participate into the study will sign and date the informed consent form (ICF) before starting any trial related procedures; the Investigator will also sign and date the form.

After the signature of the ICF, a screening number will be centrally assigned to the patient, allowing the screening process for eligibility to begin. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
Upon completion of the screening evaluation, patients meeting all the eligibility criteria will be enrolled and, for the Phase I portion of the study, the Sponsor will assign the dose level and schedule. The enrollment number will be centrally assigned and maintained throughout all the study duration. Patients who do not meet all the eligibility criteria will be declared screening failure. Screening and enrollment numbers will be centrally managed by the Sponsor or designee (details reported in the Study Manual).

In order to obtain the screening number and the patient number for each patient, the Investigator will enter the information required in an online application made available to the centers by the Sponsor (details reported in the Study Manual).

Eligibility confirmation is automatically notified to the Sponsor/or delegate by e-mail. The assignment of the screening and enrollment numbers will be provided within one working day and will be automatically notified to the site by e-mail.

In case of the web site is not available because of any reason, the Investigator will fill in a registration/enrollment form and fax it to Sponsor or designee. Specific details concerning the enrollment procedure are reported in the Study Manual. Eligibility of a patient is a responsibility of the Investigator. Verification of the confirmed eligibility will be performed by the Sponsor or authorized personnel delegated by the Sponsor during the course of the study.

No study drug will be dispensed to a patient until the entire registration process is completed. It is recommended to start the treatment within 1-4 days from patient enrollment.

For the Phase I portion of the study, the Sponsor or designee will notify all the participant sites of the inclusion of a new patient and will inform them of the next possible enrollment date. Clinical safety from all cycles as well as the PK data available will be reviewed prior to escalating to the next dose level of both schedules. Dose escalations will be decided jointly between the Investigators and the Sponsor after data review.

For the starting dose and dose escalation rules, see Sections 5.1 and 5.2.

For the backfill cohorts and the Phase II portion of the study, following the ICF signature, in order to get the patient’s screening number, the Investigator will provide the basic information required in the clinical data management system made available by the Sponsor. The assigned screening number will be sequential within the site where the patient has been recruited.

Upon completion of the screening evaluation, the Investigator will enter relevant information in the clinical data management system, confirming or not patient’s eligibility. Patients meeting all the eligibility criteria will be enrolled. The assigned enrollment number will be sequential regardless of the center where the patient has been recruited. Enrollment will be competitive among the participating sites.

At any time, enrollment may be restricted to patients with specific prior lines/therapies and/or mutations, based on Sponsor decision.

The Sponsor will control the patient assignment to cohorts and may stop or pause cohorts in any phase or part of the study based on safety, efficacy or strategic reasons.

Further details on the above procedures, including the notifications from Investigator to Sponsor and vice versa, are reported in the general module of the Study Manual.

9. TREATMENT

Only qualified personnel familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

9.1. Study Products Description

CCI

[redacted]

9.1.1. Drug Preparation and Dispensing

NMS-03592088 will be administered as home-based treatment. Site personnel must ensure that patients clearly understand the directions for self-medication. The Investigator (or delegate) will dispense to the patient the doses of NMS-03592088 covering no more than one cycle at a time. The daily doses will be made out of a number of capsules according to the dose level (in mg/day) at which the patient has been assigned for a given cycle, without adjustment for body size (flat dose).

In Schedule A, at each cycle, patients will take the assigned daily dose for 21 consecutive days (from Day 1 to Day 21). No drug should be given for the subsequent 7 days (i.e. Days 22-28), to ensure a 7-day resting period.

In Schedule B, at each cycle, patients will take the assigned daily dose for 28 consecutive days (i.e., from Day 1 to Day 28), with no resting period.

The dose and schedule in Phase II or backfill cohorts may be adapted to a loading/ maintenance regimen. Initially, NMS-03592088 will be administered, on Cycle 1, at 360 mg/day (loading dose) for 5 consecutive days, followed by 150 mg/day (maintenance dose) for 23 consecutive days. The same maintenance dose (150 mg/day) will be administered from Cycle 2 onwards, unless dose modifications are needed based on the toxicities observed. Additional dosing may be explored in the Phase II or backfill as long as dosing or expected exposures are no higher than escalation-cleared exposure equivalents that that haves been studied for safety and tolerability adequately during escalation.

The study medication has to be stored under refrigerated conditions (between 2°C and 8 °C or 36°-46°F), out of the reach and sight of children. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other containers.

9.1.2. Patient Education & Information

All patients will receive their doses of NMS-03592088 together with a patient's diary, which includes also the instructions relevant to drug administration. The site personnel handling the study medication must ensure that patients fully understand that the treatment period (cycle) comprises 28 days (4 weeks), consisting in 21 consecutive days of daily administration followed by a 7-day resting period (Schedule A) or 28 consecutive days of daily drug administration (Schedule B).

Additionally, the patients should be informed:

- to take NMS-03592088 every day as prescribed by their doctor.
- to take NMS-03592088 at the same time each day ,generally 1 hour before breakfast, with a glass of plain water; water is allowed during fasting period. For the food effect sub-study the sponsor will define the standard meal in the study manual.
- In the rare event that the patient forgets to take NMS-03592088 at the usual time, to take it as soon as possible within 2 hours from the usual time, in fasting condition or otherwise to skip the dose and in any case record the events on the patient's diary.
- if the patient misses one day, to take the usual planned daily dose the next day, if scheduled. The prescribed daily dose of NMS-03592088 should not be doubled and the number of capsules missed and the reason should be tracked in the patient's diary.
- if vomiting occurs during or after having taken the daily dose, not to take extra capsules that day and to take the usual planned daily dose the next day, if scheduled. The daily prescribed dose of NMS-03592088 should not be doubled and the events should be recorded in the patient's diary.
- to adhere to the principles of safe handling and storage of the study medication. Breaking/crushing or opening the capsules must be avoided. In such cases, record of the broken capsules should be kept in the patient's diary. In case of opening of the capsules, avoid contact or inhalation. In case of skin contact, the patient should be instructed to

wash the affected area with plenty of water or soap and water. In case of eye-contact, the patient should be instructed to rinse thoroughly with plenty of water and seek medical advice as soon as possible.

- to return all packaging (bottles **and** single cartons) as well as not-taken capsules (if any) and the patient diary to the site personnel.

These instructions should be given to the patient at the pre-treatment visit and restated on subsequent visits, in particular when a new drug supply is provided.

9.1.3. Procedure for Handling Drug Spills

Precautions for drug handling of cytotoxic agents should be followed for NMS-03592088. In case of opening of the capsules, avoid contact or inhalation. In case of skin contact, the affected area should be washed with plenty of water or soap and water. Any contaminated clothing should be removed. In case of eye-contact, rinse thoroughly with plenty of water. Seek medical advice as soon as possible.

9.1.4. Storage and Stability

CCI [redacted]

[redacted]

9.1.5. Source of Drug

CCI [redacted]

9.1.6. Drug Accountability

NMS-03592088 must not be used outside the context of this protocol. Under no circumstances should the Investigator or site personnel supply study product to other Investigators or clinics, or allow the supplies to be used other than as directed by this protocol.
In this protocol the study drug may be administered to patient, according to the selected schedule, until the criteria for withdrawal as detailed in Section 10 are met. Drug accountability should continue to be performed until the patient's last dose of NMS-03592088.

Adequate records on receipt, use, return, loss, or other disposition of medication must be maintained and electronically captured in the dedicated eCRF page. If needed, specific drug accountability forms supplied by the Sponsor or designee or computer records used by the pharmacy at the investigational site, and agreed with the Sponsor or designee, can be also used to provide drug accountability information. In either case, information describing study drug supplies and their disposition, patient by patient, must be provided, signed by the Investigator (or the pharmacist or other person who dispensed the drug) and collected by the study monitor. Requisite data includes relevant dates, quantities, batches or code numbers, and patient identification for patients who received study drug. At the end of the study, after verification by the study monitor and upon authorization of the Sponsor, the unused study drug may be destroyed at the site as dictated by the appropriate standard procedures of the participating institution. Destruction must be documented. Alternatively, all unused product will be returned to the Sponsor or Manufacturer on behalf of the Sponsor. If disposed locally, all used bottles and containers of study product should be discarded according to the standard institutional policy.

9.2. Treatment Administration

9.2.1. Treatment Dose and Schedule

CCI

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.2.2. Duration of Treatment

Patients may continue on study treatment until disease progression, unacceptable toxicity, investigator decision, withdrawal of consent by the patient or other discontinuation criteria detailed in Section 10 are met. Note: If patient is clinically stable and has observation of blasts reduction or suspected disease stabilization in the judgment of the investigator the investigator may continue dosing after an adverse event taking into account dose modification in section 9.2.3.

A participant patient is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure as shown in the Schedule of Events in Section 1.

9.2.3. Dose Modifications

Adverse events that are intolerable or severe will be managed by treatment interruption and/or dose reduction depending on the circumstance. Dose reductions and delay will be based on adverse events at least possibly related to the study drug.

Dose modifications may occur during a cycle or at the start of a new cycle. All dose modifications for the start of a new cycle should be based on the most severe toxicity observed in the previous cycle. In the event of multiple toxicities, the dose modification should be based on the worst toxicity observed (according to the NCI CTCAE v 5.0).

Any modifications to the NMS-03592088 dose should be documented in the eCRF.

9.2.3.1. Re-treatment Criteria and Cycle Delay

For a patient with non- hematological toxicities, a new cycle of treatment may begin when toxicities (except for alopecia) are ≤ Grade 1or have recovered to pre-treatment status. If these conditions are not met, treatment should be delayed for 1 week and up to a maximum of 2 weeks, to allow for recovery. If, after this period, toxicities do not recover to the pre-defined level, patient will be withdrawn from the study unless the patient is demonstrating clinical benefit as agreed by the Investigator and Sponsor.

9.2.3.2. Dose Reductions and Interruptions

If a patient experiences a DLT during Cycle 1, the patient should be discontinued from the study, unless the patient is demonstrating clinical benefit and can continue the treatment at a reduced dose, as agreed by the Investigator and Sponsor. If a patient experiences a non-hematological adverse event meeting DLT criteria after Cycle 1, administration of NMS-03592088 should be held until the drug related toxicity has resolved to Grade ≤1 or baseline grade. Upon resolution of the toxicity, the patient should restart study drug at the next lower dose level depending on the severity and type of toxicity observed and after discussion with Sponsor or designee. If the patient experiences persistent Grade 4 myelosuppression in the absence of disease progression, dose reduction can be considered starting from Cycle 3.

CCI [redacted]

France specific: In case of G4 non hematological toxicity reoccurrence, NMS-03592088 must be permanently discontinued.

Suggested dose reduction and interruption or discontinuation criteria are described in Table 1 and are provided as guidance to the Investigators.

Table 1. Recommended Dose Modification Criteria* for Treatment-Related Toxicity Observed During or Prior a Treatment Cycle

CCI

[redacted]

CCI [redacted]

CCI [redacted]

9.2.4. Extension Treatment

Not applicable.

9.2.5. Overdose and Medication Error Instructions

There are no known antidotes for NMS-03592088 overdose. In the case of an overdose clinical care must monitor for both acute and long-term effects. The Sponsor Pharmacovigilance should be notified immediately (i.e. within 24 hours) according to procedures described in part 11.5.1.7. Study monitor should be also contacted to discuss the details of any overdose.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the product,
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, the medication error and, if applicable, any associated adverse event(s) must be captured on an adverse event (AE) eCRF page (refer to Safety Assessments, Section 11.5, for further details).

9.2.6. Unblinding

Not applicable.

9.2.7. Assessment and Management of Potential Neurologic Toxicity

9.2.7.1. Background

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 2. Drug-induced Tremors and Corresponding Neurologic Signs

CCI [redacted]

9.2.7.2. Patient management

CCI [redacted]

[redacted].

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI

Table 3. Drugs to avoid

CCI

9.2.7.3. Dose Modifications

Criteria for dose adjustments and interruptions are reported in Table 1.

9.2.8. Tumor Lysis Syndrome

CCI

[redacted]

9.2.9. Differentiation Syndrome

Differentiation syndrome (DS) is a potentially fatal complication of effective leukemia treatments, initially reported in patients with acute promyelocytic leukemia undergoing induction therapy with all-trans retinoic acid (ATRA) or arsenic trioxide [64].

DS has been described in patients with AML receiving novel targeted therapeutics including IDH inhibitors and FLT3 tyrosine kinase inhibitors. While frequency of the event has been reported to be 14%-19% for IDH inhibitors [65;66], the event is much less frequent with FLT3 inhibitors (1% for gilterinib (Xopata®) [67]. Terminal myeloid differentiation of bone marrow blasts in association with a clinical DS has also been reported in patients treated with quizartinib [68]. [redacted]

Symptoms of DS are non-specific and may include fever, weight gain, edema, hypotension, rash, renal dysfunction, malaise, dyspnea and pleural and/or pericardial effusions, in addition to marked neutrophil-predominant leukocytosis. DS was reported to occur as early as 1 day and up to 5 months after initiation of treatment with IDH inhibitors. Prompt identification of early signs and symptoms and intervention are essential to avoid serious complications. Therapeutic intervention may include oral hydroxyurea to mitigate leukocytosis and steroid therapy, as appropriate.

9.2.10. Concomitant Medications and Other Therapy

All concomitant medications and other therapies must be recorded in the eCRF. Directives for supportive care are outlined below.

9.2.10.1. Antiemetics Support

In Phase I (dose escalation), emesis prophylaxis is not allowed in Cycle 1, until nausea and/or vomiting have been clearly identified as study-medication expected adverse events. In the subsequent cycles, if needed, prophylactic therapy is allowed using institutional guidelines for treatment and/or published guidelines [69,70].

9.2.10.2. Antidiarrheal Support

Treatment with antidiarrheal drugs is recommended once the onset of the earliest signs of diarrhea is present. Loperamide or other antidiarrheal agents used by the Institution might be started at the occurrence of Grade 1 diarrhea (increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline). Recommendation for Loperamide use should be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours. This therapy should continue for 12 hours after the last liquid stool. Patients may take loperamide 4 mg every 4 hours during the night. In no instance should loperamide be

administered for more than 48 consecutive hours because of the risk of paralytic ileus. Patients should be instructed to refer to the center in case of diarrhea lasting > 24 hours despite optimal supportive care or diarrhea with fever.

The patients should contact the Investigator or the study nurse if they experience diarrhea for the first time during the treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; an inability to take liquids by mouth due to nausea and vomiting; or an inability to get diarrhea under control with loperamide within 24 h. In addition to loperamide, the patients should be provided with an antibiotic therapy as per institutional guidelines. Patients should be instructed to refer immediately to the center in case of occurrence of these symptoms. Patients with colitis/ileus, neutropenic fever or infection should also be hospitalized promptly for IV antibiotic therapy.

9.2.10.3. Hematopoietic Support

In Phase I prophylactic use of G-CSF or initiation of erythropoietin in Cycle 1 is not recommended, but may be instituted in Cycle ≥2 in patients who are having difficulty with severe neutropenia or anemia.
Patients who have been treated for ≥ 4 weeks with erythropoietin prior to the first cycle may continue on the existing treatment.
Patients with neutropenic fever or infection should be hospitalized promptly for IV antibiotic therapy and may receive therapeutic CSFs as appropriate.
Red blood cell and platelet transfusions should be administered as warranted.

9.2.10.4. Antiacids

Patients using H2-receptor antagonists must take them between at least 12 hours before and 2 hours after a dose of NMS-03592088, antiacids between at least 4 hours before and 2 hours after a dose, to avoid any potential effect on NMS-03592088 absorption.

Proton pump inhibitors (PPI) are allowed if administered between at least 10 hours before and 1 hour after the dose. Sponsor might opt to restrict further PPI use.

9.2.10.5. Other Permitted Concomitant Medications

CCI [redacted]

[redacted]

9.2.10.6. Other Anticancer or Experimental Therapy

CCI [redacted]

9.2.10.7. Phototoxicity Prevention

CCI [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

9.2.10.8. Potential interactions with other medicinal products

[redacted]

[redacted]

[redacted]

[redacted]

CCI

[redacted]

[redacted]

[redacted]

[redacted]

10. PATIENT WITHDRAWAL FROM STUDY PARTICIPATION

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons.

If a patient does not return for a scheduled visit, every effort should be made to contact him/her. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the reason for withdrawal, requests the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

Patients may continue with therapy with the study medication unless any of the following occurs:

- Disease progression or relapse at any time;
  Note: If patient is clinically stable and has observation of blasts reduction or suspected disease stabilization in the judgment of the investigator the patient may continue with dosing after an adverse event taking into account dose modification in section 9.2.3;
  Note: Patient must *discontinue treatment for failure to achieve at least partial response after 9 cycles*
- Global deterioration of health status requiring discontinuation;
- First-cycle DLT, unless the patient is demonstrating clinical benefit and can continue the treatment at a reduced dose, as agreed by the Investigator and Sponsor;
- CCI [redacted] with systemic and/or bulbar impairment
- Unacceptable study drug-related toxicities incompatible with continuation of treatment with NMS-03592088 according to the judgment of the Investigator, even at a reduced dose;
- Change in the patient's medical status (including pregnancy) such that the Investigator believes that patient safety may be compromised or that it would be in the best patient's interest to stop treatment;
- Treatment delay for >14 days due to treatment related non-hematologic toxicity unless the patient is demonstrating clinical benefit as agreed by the Investigator and Sponsor;
- The patient becomes eligible for hemopoietic stem cell transplantation (HSCT)
- Substantial deviation from specified inclusion or exclusion criteria or non-compliance by the patient with protocol requirements;

- Investigator's decision;
- Patient’s refusal to continue study treatment;
- Patient lost to follow up;
- Death;
- Study terminated by Sponsor.

Patient will be withdrawn from the study in case of:

- Withdrawal of consent;
- Patient lost to follow up;
- Death;
- Study terminated by Sponsor.

Data to be collected for the end of study treatment/withdrawal are described in the Schedule of Events, reported in Section 1.

Patients will be followed for at least 28 days after the last dose of study drug for adverse events and for 18 months from patient’s first study drug dose for survival status.

11. ASSESSMENTS

11.1. Timing of Assessments

Schedule of Events, reported in Section 1, summarizes information on the timing of assessments to be performed during Phase I and Phase II portions of the study. Protocol waivers or exemptions are not allowed.

Procedures conducted as part of the participant's routine clinical management (e.g., bone marrow aspirate or biopsy) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Events.

11.2. Disease Assessments

Peripheral blood and/or bone marrow aspirate/biopsy will be collected for cytogenetic molecular and phenotypic characterization of the disease at the study entrance, during treatment, as applicable, and at the end of treatment.

11.2.1. Immunophenotyping, Cytogenetic and Molecular Characterization

CCI [redacted] For further details regarding antigens to be assessed by FACS, please refer to Study Manuals.

11.2.2. Detection of FLT3-ITD or D835/I836 mutations

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

11.3. Efficacy Assessments

Efficacy assessments will be based on analysis of full blood count, bone marrow aspirate or biopsy and, for patients with extramedullary disease, on clinical examination and/or imaging, as appropriate.

11.3.1. Laboratory Assessments: Hematology

Hematology should include hemoglobin, RBC, PLT, WBC with differential counts (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) and blast cells. It should be done at screening and at the same day when bone marrow samples are obtained for the disease assessment (see Section 1, Schedule of Events).

11.3.2. Disease Assessments: Bone Marrow Aspirate/Biopsy

A bone marrow aspirate/biopsy obtained from hipbone or from another appropriate site, will be performed:

- During Phase I, at screening and at the end of treatment, regardless of when the patient discontinues the study. During treatment at Day 1 on Cycle 2, 3 and then at every even subsequent cycle. If a bone marrow aspirate or biopsy has been collected within 7-days of the nominal date (excluding the screening sample) it need not to be repeated.
- During Phase II, at screening and at the end of treatment, regardless of when the patient discontinues the study. During treatment at Day 1 on Cycles 2, 3, 4, 6, 8 and then every three subsequent cycles. For AML patients who achieve a CR, CRh or CRi collection of bone marrow aspirate or biopsy sample will be repeated 1 month after achievement of the first remission, to confirm response. If a bone marrow aspirate or biopsy has been collected within 7-days of the nominal date (excluding the screening sample) it need not be repeated.

- At Investigator's discretion

Throughout the clinical study, bone marrow and/or blood samples collected at screening and at the end of treatment will be used also for centralized NGS analysis and biomarkers expression evaluation. For further details on these evaluations see Section 11.6.2 and the Study Manuals.

11.3.3. Clinical evaluation of Extramedullary Disease

For all patients, clinical evidence of extramedullary disease (EMD) will be collected, in the eCRF, in terms of presence/absence of the disease. The site of involvement will also be reported in the eCRF.During the study, the EMD status will be clinically evaluated at screening, during the physical examinations performed on treatment, at the same times of disease evaluation, at the end of treatment and at Investigator's discretion .

In the presence of EMD, lesions must be followed by imaging and/or other clinical evaluations, and the choice of methods is at the Investigator's discretion. For CMML patients, splenomegaly should always be assessed using CT or MRI scan (3-D ultrasound will be acceptable if other aforementioned scans are not available within the allotted timeframes of the intra-study evaluation).

11.3.4. Definition of the response

The response to treatment will be evaluated:

- For AML patients, following criteria as defined by the ELN recommendations [6, 7]. For reference, see Appendix 2;
- For CMML patients, following the International Working Group criteria [56]. For reference see Appendix 3, Appendix 4 and Appendix 5.

11.4. Outcomes Research Assessments

Not applicable.

11.5. Safety Assessments

Safety assessments include collection of AEs, SAEs, triplicate 12-lead ECGs, vital sign measurements, physical examinations and safety laboratory tests. These will be performed periodically at baseline, during treatment and at End of Treatment (and/or at Investigators' discretion).

Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 5.0), timing, seriousness, and relatedness.

Baseline signs and symptoms will be recorded at baseline and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

11.5.1. Adverse Event Assessment

11.5.1.1. Definition of Adverse Events

11.5.1.1.1. Adverse Event

According to ICH definition and EU directive (2001/20/EC), an AE is defined as any untoward medical occurrence in a patient or a clinical trial patient administered a medicinal product and which does not necessarily have to have a causal relationship with the use of the product. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or diagnosis temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any untoward medical occurrence, which occurs outside the period of patient follow-up defined in the protocol, is not considered an AE. Symptoms or medically significant laboratory or instrumental (e.g., by electrocardiography) abnormalities of a pre-existing condition should not be considered an AE. However, occurrence of new symptoms, laboratory or instrumental abnormalities, as well as worsening of pre-existing ones, is considered AEs.

11.5.1.1.2. Serious Adverse Events

A serious adverse event (SAE) is an adverse event that falls into one or more of the following categories:

- Results in death;
- Is life-threatening, i.e., an event which, in the view of the Investigator, placed the patient at risk of death at the time of event (it does not include an event which hypothetically might have caused death if it were more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity, where disability is defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per clinical judgment;
- Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child);
- Is any other important medical event, i.e., may not result in death, be life-threatening, or require hospitalization, but based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the points above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

A non-serious adverse event is any adverse event that does not meet the criteria listed above or the outcome cannot be determined with the information provided.

Each adverse event has to be classified by the Investigator as serious or non-serious.

In this study the following do not have to be classified as SAEs:

- Admission to hospital required by the protocol;
- Hospitalization for routine treatment or monitoring of the studied indication not associated with any deterioration in patient's clinical condition;
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE;
- A procedure requiring hospitalization planned prior to starting the study treatment; must be documented in the Source Documents and the e-Case Report Form (e-CRF). Prolonged hospitalization for a complication remains a reportable SAE;
- Hospitalization for an elective treatment of a pre-existing condition unrelated to the studied indication;
- Events definitely related to disease progression.

However, all Adverse Events with outcome deaths occurring during the reporting period have to be reported as SAEs, even if due to disease progression.

11.5.1.1.3. Adverse Events of Special Interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

During the dose escalation part of the study neurological adverse events involving the neuromuscular transmission CCI [redacted]) have been reported with NMS-035920088 (See section 9.2.7.1). External ocular movements deficit with ptosis and diplopia were the typical pattern.

The occurrence of any sign and/or symptom suggestive of a CCI [redacted], such as:

a) ptosis, diplopia, weakness, muscular weakness (after exertion), dysphagia, dysphonia, dyspnea

b) fatigue, asthenia, hyposthenia, hypoactivity, if associated with any of the above

should prompt the evaluation by a neurologist and, if the diagnosis of CCI [redacted] is confirmed, the event should be reported as AESI.

All AESIs [diagnosis and specific sign(s)/symptom(s)] have to be reported within 24 hours according to the procedures described for serious adverse event in section 11.5.1.7.

11.5.1.2. Unexpected Adverse Event

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information that, for the present CT, is the Investigator Brochure (IB) [55].

11.5.1.3. Eliciting Adverse Event Information

The Investigator has to report all directly observed AEs and all AEs spontaneously reported by the trial patient using concise medical terminology. In addition, each trial patient will be questioned about adverse events at each clinic visit following signature of the Informed Consent Form. The question asked will be “Since your last clinical visit have you had any health problems?”

11.5.1.4. Adverse Event Reporting Period

The adverse event reporting period for this trial begins upon signing of informed consent and ends 28 days after the last study treatment administration.

However, if a patient begins a new anticancer therapy earlier than 28 days after the last dose of study treatment administration, the adverse event reporting period will end at the time the new anticancer therapy starts.

All the adverse events that occur in trial patients during the adverse event reporting period must be reported to the Sponsor, whether or not the event is considered related to the study treatment.

11.5.1.5. Adverse Event Follow Up after the End of the Reporting Period

The following events should be followed after the end of the reporting period (i.e., 28 days after the last study treatment administration):

1. SAEs with outcome ‘not recovered’ or ‘unknown’ at the end of the reporting period.
2. Non-serious events classified as related to the investigational study treatment with outcome ‘not recovered’ or ‘unknown’ at the end of the reporting period.

These events should be followed until they resolve or until the Investigator determines, whenever possible, that they have become “chronic” or “stable”. Resolution of such events is to be documented on the SAE Form and/or on eCRF.

In addition, if after the end of the reporting period, suspected serious adverse reactions or deaths are reported to the Investigator and he/she believes that they are related to the IMP, it is the Investigator’s responsibility to report these suspected serious adverse reactions to the Sponsor. Such suspected serious adverse reactions will be reported using a Serious Adverse Event Report or by any other way chosen by the Investigator.

11.5.1.6. Relationship to the Investigational Medicinal Product

The relationship of the adverse event will be assessed by means of the question "Is there a reasonable possibility that the event may have been caused by the study drug?" The Investigator should respond to this question with either 'Yes' or 'No'.

'No' equals to Unrelated/Unlikely, i.e. there is no reasonable possibility that the study drug caused the event; Yes equals to = Related, i.e. there is a reasonable possibility that the study drug caused the event.

11.5.1.7. Reporting Requirements

Each adverse event has to be classified by the Investigator as SERIOUS or NON-SERIOUS (as per paragraph 11.5.1.1.2). This classification of the event determines the reporting procedures to be followed. If a serious adverse event occurs, reporting will follow local and international regulations, as appropriate.

If a serious adverse event occurs the Sponsor Pharmacovigilance has to be notified within 24 hours of awareness of the event by the Investigator, by e-mail (here below Pharmacovigilance address/contacts). Further detailed reporting procedures are described in the Study Manual.

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The initial report should be followed by submission of more detailed adverse event information as soon as it is available. Additional follow-up should be provided up to the resolution of the SAE, the Investigator determines it has become chronic or stable (not recovered) or a new anticancer therapy is initiated.

Reporting requirements for adverse events are summarized in the following table.

REPORTING REQUIREMENTS FOR ADVERSE EVENTS

Seriousness	Reporting Time	Type of Report
SERIOUS	Within 24 hours	Initial report on designated SAE form
	As soon as available	Follow-up/Final report on designated SAE form
NON-SERIOUS	As per eCRF procedure	Appropriate section of eCRF

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported by Sponsor or designee to all competent Regulatory Authorities, to the Ethics Committees and to all the Investigators involved, according to local regulations and requirements stated in ICH Good Clinical Practice.

In the rare event that the Investigator does not become aware of the occurrence of a serious adverse event immediately (for example, if an outpatient trial patient initially seeks treatment elsewhere), the Investigator has to report the event within 24 hours after learning of it and document his/her first awareness of the adverse event.

Serious adverse events should also be consistently recorded in the appropriate section of eCRF.

Non-serious adverse events have to be reported in the appropriate section of eCRFs only excluding Adverse Events of Special Interest (see section 11.5.1.1.3).

11.5.1.8. Recording Adverse Events in the Case Report Forms

Information on AEs must be evaluated by a physician and recorded in source documents such as the hospital file. AEs have to be reported in the eCRF as aforementioned. The Investigator will also be asked to assess the relationship between the AE and the investigational medication.

- Preexisting Conditions

In this study, a preexisting condition (ie, a disorder present before the AE reporting period started and recorded in the medical history) should not be reported as AE unless the condition worsens or episodes increase in frequency during the AE reporting period.

All relevant symptoms, occurring after the ICF signature and before the first drug intake, should be reported (with CTC grade) in the baseline AE page, including disease-related symptoms (e.g. fatigue, bone pain, etc). Abnormal lab values do not need to be reported as AE if related to the disease (e.g. anemia, thrombocytopenia), or a medical condition already reported in Medical History (e.g. hyperglycemia for a patient with diabetes).

- Procedures

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AE. However, the medical condition for which the procedure was performed should be reported if it meets the definition of AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as AE and the resulting appendectomy should be recorded in the source documents.

- Symptoms of the Disease

All relevant symptoms present before the AE reporting period started, have to be recorded in medical history. During treatment. the specific symptoms of the disease have to be reported as adverse events if they match with new occurrence or worsening in severity or in frequency versus the baseline visit. Note: the general wording “Progression of the disease” should not be reported as adverse event.

- Abnormal Laboratory Findings

Abnormal laboratory findings occurring during the AE reporting period have to be recorded as adverse events when they cause treatment change (dose omission/reduction/delay/discontinuation) or when require clinical intervention (e.g., hospitalization for further investigation or management of the laboratory abnormality). Disease-related anemia and/or thrombocytopenia requiring transfusion support should not be reported as AE if management of the event(s), e.g. transfusion need, has not changed since ICF signature, but they should be reported as AE if the event(s) results in dose omission/delay/discontinuation/reduction, or in case the event worsens requiring hospitalization (not previously needed) or more frequent transfusions.
Note: uncomplicated and asymptomatic abnormal laboratory findings have not to be reported as adverse events. The corresponding values have to be reported only in the relevant eCRF sections (e.g., hematology, biochemistry).

- Abnormal Findings in vital signs, physical exams and/or ECG

Abnormal findings in vital signs, physical exam and/or ECG, have to be reported as adverse events if they are clinically significant new events or events worsening as compared to baseline. Clinical significance is defined as any variation, which has medical relevance based on at least one of the following criteria:

- Induces relevant clinical signs or symptoms;
- Requires active intervention;
- Requires change of study medication (dose omission / reduction / delay / discontinuation);
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

11.5.1.9. Grading of Adverse Event Severity

In this study the severity/intensity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0) of the US National Cancer Institute (see website:https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf)

For each event, each change in severity grade should be reported. If an event swings repeatedly back and forth from a grade to another, it is possible to record it as <intermittent AE>.

For adverse events not reported in the CTCAE Version 5.0, the Investigator will use the Grade or adjectives reported in Table 4.

Table 4. Grading of Adverse Event Severity for Events not reported in the CTCAE Version 5.0

Grade	Adjective	Description
Grade 1	Mild	Does not interfere with patient's usual function
Grade 2	Moderate	Interferes to some extent with patient's usual function
Grade 3	Severe	Interferes significantly with patient's usual function
Grade 4	Life-threatening	Results in threatening to life or in an incapacitating disability
Grade 5	Death	Death related to AE

Note the distinction between the term "serious" and "severe", which are not synonymous. The term "severe" is used to describe the intensity of a specific event (i.e., severe headache) while the term "serious" is based on patient/event outcome or action criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. For example, vomiting Grade 1 for which a hospitalization occurred is a serious event even if the event is not severe.

11.5.1.10. Exposure In Utero

If a female patient becomes or is found to be pregnant while receiving the study drug or within 208 days from its discontinuation, the Investigator should transmit this information using the Part I of Exposure in Utero (EIU) Form to Sponsor Pharmacovigilance. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. However, if the patient begins a new anticancer therapy before 208 days after the last dose of study treatment administration, the exposure "in utero" reporting period will end at the time the new treatment is started.

The Investigator will follow the patient until completion of the pregnancy or until pregnancy termination (i.e., induced abortion) and then notify the Sponsor Pharmacovigilance of the outcome within 5 days or as specified below. The Investigator will provide this information completing Part II of EIU form. The reason(s) for an induced abortion must be specified.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator should follow the procedures for reporting serious adverse events, i.e., report the event to the Sponsor (as described in Section 11.5.1.7)

In the case of a live birth, the "normality" of the newborn must be assessed at the time of birth and for a minimum follow-up of at least three months.

The "normality" of an aborted fetus can be assessed by gross visual inspection unless pre-abortion laboratory findings are suggestive of a congenital anomaly.

Other pregnancy outcomes that are classified as SAEs:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality. In addition, any infant death after 1 month that the Investigator assesses as possibly related to the "in utero" exposure to the study drug should also be reported.

If a female partner of a male patient taking the IMP becomes pregnant while the male patient is still on IMP or within 118 days after last dose of IMP, the male patient taking IMP should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately. If a pregnancy related event is reported in a female partner of a male patient, the Investigator should ask if the female partner is willing to share information with the Sponsor Pharmacovigilance and allow the pregnancy related event to be followed up to completion.
The Investigator has to submit the information of pregnancy or suspect pregnancy of a female partner of a male patient to the Sponsor Pharmacovigilance, by e-mail, using the EIU Form, within 24 hours from his/her awareness of the event.

11.5.2. Laboratory Safety Assessments

Laboratory safety assessments will include repeated evaluation of hematology, biochemistry and coagulation parameters, urinalyses and pregnancy test, according to timing reported in Section 1, Schedule of Events (Table and related footnotes). Investigators may order additional blood tests for planning treatment administration, dose modification, or further evaluation of adverse events.

The following laboratory parameters will be used to monitor safety:

CCI

[redacted]

CCI [redacted]

[redacted]

- [redacted]

- [redacted]

[redacted]

[redacted]

- [redacted]

CCI

[redacted]

11.5.3. Other Safety Assessments

The following safety assessments will also be performed, according to timing reported in Section 1, Schedule of Events:

CCI [redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI

[redacted]

CCI [redacted]

11.6. Other Assessments

11.6.1. Pharmacokinetic Assessments

11.6.1.1. Blood Sampling in Phase I

CCI [redacted]

[redacted]

Table 5. PK Blood Sample Collection for Schedule A (Phase I: Dose Escalation)

CCI

[redacted]

Table 6. PK Blood Sample Collection for Schedule A (Phase I: Dose Expansion)

CCI

[redacted]

Table 7. PK Blood Sample Collection for Schedule B (Phase I: Dose Escalation)

CCI

[redacted]

Table 8. PK Blood Sample Collection in the backfill cohorts (Phase I)

CCI

[redacted]

Table 9. PK Blood Sample Collection in the backfill cohort for food effect investigation

CCI

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.6.1.2. Blood Sampling in Phase II

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 10. PK Blood Sample Collection Schema (Phase II -all patients)

CCI [redacted]

Details on PK samples collection, processing, storage and shipping instructions are provided in the Study Manual. Timing of sampling may be modified based upon emerging PK data from the dose escalation part of the study. Analysis will be performed at the central facility delegated by the Sponsor.

11.6.1.3. Urine Sampling

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.6.1.4. Bioanalytical method in plasma and urine

CCI [redacted]

11.6.2. Translational Research

11.6.2.1. DNA extraction for genomic analysis

CCI [redacted]

11.6.2.2. NGS Analysis of FLT3 and other selected genes

CCI [redacted]

11.6.3. Biomarker assessment

CCI [redacted]

11.6.3.1. PIA analysis for FLT3 pathway

CCI [redacted]

[redacted]

11.6.3.2. Circulating CSF1 analysis

CCI [redacted]

12. STATISTICAL METHODS

12.1. Sample Size Calculation

CCI

[redacted]

[redacted]

[redacted]

Table 11. Estimated 95% Confidence Intervals for Assumed CRc Rates at Interim Analysis for Futility

CCI

[redacted]

12.2. Definition of Analyzed Study Populations

For the purpose of the analysis, the following patient populations are defined and the endpoints, to be analyzed in these populations, are specified:

- *Enrolled Patients*: This population will include all patients who are enrolled in the clinical study, regardless of whether patients receive treatment or not. This population will be evaluated in the analysis of patients' disposition.
- *Treated Patients*: The treated patient population consists of all enrolled patients who actually receive at least one treatment administration. This population will be evaluated in the analysis of patient disposition, baseline characteristics, treatment exposure, efficacy and safety.
- *Patients evaluable for determination of DLT (by dose schedule and dose level)*: for each schedule and dose level tested, this population includes all patients enrolled in dose escalation part who receive at least 70% of drug in the first cycle, unless the reason for non compliance is drug-related toxicity, and for whom a DLT assessment is available within the DLT window. In case the patient does not fulfill one or more of the aforementioned criteria, he/she will be replaced.
- *Patients evaluable for efficacy analysis (efficacy dataset):* This is the patient population which consists of all enrolled patients in the Phase II part who are treated at the RP2D, have ≥1 on-treatment hematologic assessment(s) (i.e. they must have adequate bone marrow response evaluation). Patients who experience early death or withdrew prior to response assessment, or had technically suboptimal bone marrow sample precluding assessment, are non-evaluable for response and are excluded from the efficacy dataset. For cohort 1 and 2, only the subset of patients with FLT3-ITD mutation and no D835 and I836 mutations based on the central test will be included in this population.
- *Patients evaluable for PK analysis:* treated patients will be considered evaluable if they have sufficient baseline and on-study sampled material to provide interpretable results.

12.3. Analyses

12.3.1. Study Conduct and Patient Disposition

Patients' disposition and reasons for ending the treatment and the study will be presented in frequency distribution tables and individual data listings. The patients not meeting the eligibility criteria, and who are considered protocol violators as well as the ones failing to receive a complete first cycle will be identified and described by individual data listing. Reasons for stopping treatment will be summarized as frequency distribution in the treated patient population and, if clinically interesting, in other patient subsets. Untreated patients will be identified and described separately. For patients involved in the Phase II portion of the trial, all below mentioned analyses and data listings will be presented by cohort.

12.3.2. Baseline Characteristics

Descriptive statistics of the baseline characteristics will be generated across all treated patients. Frequency distributions will be presented for the categorical/categorized variables. Summary statistics including mean, standard deviation, median, minimum, maximum and the number of assessed patients will be calculated, as appropriate, for the quantitative variables. Individual data will be presented in listings.

12.3.3. Treatment Administration/Compliance

The treatment exposure and the compliance with study treatment will be descriptively analyzed in the treated patient population and, if clinically interesting, in other patient subsets. Descriptive statistics (e.g. min, max, mean, standard deviation, and median value) will be calculated on a per-patient basis for the following variables: the number of cycles administered, the overall duration of treatment, the actual and total doses administered, and the absolute and relative dose intensity. Frequency distributions of patients and/or cycles will be used to describe dose modifications, delays and omissions, as well as the reasons for deviation from the planned therapy. These data will be presented as reported in the relevant CRF sections.

12.3.4. Efficacy Analyses

CCI

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

12.3.5. Outcomes Research Analyses

Not applicable.

12.3.6. Safety Analyses

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

12.3.7. Analyses of Other Endpoints

12.3.7.1. Molecular Features in Biological Samples

Exploratory analyses on the relationship between molecular features and treatment efficacy variables in AML and CMML patients treated with NMS-03592088 will be performed if sufficient data are collected.

12.3.7.2. Pharmacokinetics

The PK concentration population is defined as all enrolled patients treated who have at least one concentration. The PK parameter analysis population is defined as all enrolled patients treated who have at least 1 of the PK parameters of interest.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.3.7.3. Relationship of corrected QT changes to treatment exposure

CCI [redacted]

12.3.7.4. Translational Research

CCI [redacted]

12.4. Interim Analysis Plan

12.4.1. Futility Analysis

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

12.4.2. Safety Analysis

CCI

[redacted]

CCI

[redacted]

[redacted]

[redacted]

CCI [redacted]

Table 12. Safety Boundaries for Toxicity Monitoring

CCI [redacted]

Empirical stopping rules for drug-related toxicities and drug-related deaths, will be applied to first 24, 27, 30 and 36 patients. The enrollment will be stopped if the numbers of patients who experience toxicity occur as follows: 8 out of first 24, 9 out of the first 27, 12 of the first 36.

Note: These rules are based on a per patient count, not the absolute number of events experienced by an individual patient. No single patient can count more than once toward these safety rules.

12.5. Data Monitoring Committee

An Official Independent Data Monitoring Committee is not foreseen. Regular teleconferences will be organized between the Investigators and the Sponsor to strictly review all relevant safety issue (e.g., grade 3-4 clinical and laboratory events, drug-related Serious Adverse Events and Deaths) and take decision on the dose escalation, where applicable (as also mentioned in Section 5.2 Dose Escalation).

13. END OF THE TRIAL

For the purpose of this study, the end of the trial is defined as the date of the last visit of the last patient, including follow up.

14. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The Investigator must permit study-related monitoring, audits performed by the Sponsor or designee, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

It is important that the Investigator and his/her relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

The sponsor or designee is responsible for the data management of the study including quality checking of the data. That means that following data entry or electronic receipt of data, data validation will take place and Forms/Reports for data clarifications will be addressed to the Investigator. Data management activities will address the coding and review of terms by scientific and clinically qualified staff.

15. DATA HANDLING AND RECORD KEEPING

15.1. Electronic Case Report Forms (eCRFs)

An eCRF must be completed by the Investigator or authorized delegate for each patient enrolled in Phase I and for each patient screened (enrolled/screening failure) in Phase II.

It is the Investigator's or authorized delegate's responsibility to ensure completion and to review and authorize release of the eCRF for each enrolled Clinical Trial Patient. The signature on the eCRF serves to attest that the information contained in the eCRF is true, accurate and reliable. At all times, the Investigator has full responsibility for the accuracy, legibility, completeness, and timeliness of all data (e.g., clinical data, laboratory results) reported in the eCRF and in the related data clarification tools (e.g., Data Clarification, Discrepancy Notes, Queries).

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigational Site. Source documents would include, but are not limited to, hospital/clinic records, physicians' and nurses' notes, appointment books, original laboratory result reports, ECG, x-rays, signed informed consent forms (ICF).

15.2. Record Retention

Any study records and documents, including signed ICFs, pertaining to the conduct of the study, must be retained by the Investigator for the period of time specified in the Clinical Trial Agreement, unless local regulations or institutional policies require a longer retention period.

Data Controller (Sponsor) may store patient's data up to the expiration of the term required for undertaking and maintaining any IP claims (which is not less than 25 years). Biological samples may be stored for up to 15 years after the end of the research study and then will be destroyed.

No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

15.3. Confidentiality of Clinical Trial or Study Documents

All documents and information given to the Investigator by the Sponsor with respect to NMS-03592088 and study MKIA-088-001 are strictly confidential.

The Investigator agrees that he/she and the members of his/her team will use the information only in the framework of this Clinical Trial, for carrying out the Clinical Trial Protocol. This agreement is binding as long as the confidential information has not been disclosed to the public by the Sponsor.

The Investigator must not disclose any information of Clinical Trial Protocol as well as any information extracted from it to other parties without the prior written authorization of the Sponsor. The only exception is upon request of the representatives of the Competent Authorities; in the latter case, the Investigator commits himself to informing the Sponsor prior to disclosure of information to these authorities.

16. ETHICS

16.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Clinical Study Protocol, Protocol Amendments, Informed Consent Forms, Investigator Brochure and other relevant documents (e.g., advertisements) must be submitted to IRB(s)/IEC(s) by the Investigator(s) and/or Sponsor/Delegate Party in accordance with local regulations reviewed and approved by the IRB(s)/IEC(s) before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. In that case, the Investigator must notify the IRB/IEC, the Sponsor or Delegated Party and Regulatory Authority, as applicable, as soon as possible after the implementation.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

16.2. Ethical Conduct of the Trial

This study will be conducted in accordance with and with the following:

- The Clinical Trial Protocol.
- Ethical principles derived from international guidelines including the Declaration of Helsinki [80] and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Current and applicable laws and regulations.

The Investigator will be responsible for:

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR [78], ICH E6 R2 guidelines [77], the IRB/IEC, European regulation 536/2014 for clinical studies [79], as applicable, and all other applicable local regulations.

16.2.1. Serious Breaches

The EU Regulation No 536/2014 and the EMA Guideline for the notification of serious breaches contain a requirement for the notification of serious breaches. A serious breach is

defined as "A breach of GCP or the trial protocol which is likely to affect to a significant degree

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial".

In the event that a serious breach is suspected, the Sponsor must be contacted. The serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor or entity/person legally authorised by the Sponsor will report it to the relevant Competent Authorities within 7 days.

16.3. Informed Consent Process

It is the responsibility of the Investigator (or a person designated by the Investigator when accepted by local regulations) to give each individual full and adequate explanation regarding the nature of the study (e.g., objectives, aims, methods and procedures of the study, anticipated benefits, possible risks and potential hazards involved). The Investigator or his/her delegate will answer all questions regarding the study.

Participants must be informed that their participation is voluntary and that they have the right to withdraw from the study at any time.

Participants will be required to sign before any trial-related procedure is undertaken, a statement of informed consent (ICF) that meets the requirements of ICH guidelines, 21 CFR 50 and Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, local regulations, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the signed ICF(s) must be provided to the participant.

16.4. Personal Data Protection

Participants will be assigned a unique identifier by the Sponsor or designee. Any participant records or datasets that are transferred to the Sponsor or designee will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor or designee in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor or designee, by appropriate IRB/IEC members, and by inspectors from Regulatory Authorities.

17. SPONSOR DISCONTINUATION CRITERIA

Nerviano Medical Sciences reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigator must contact all participating patients. As directed by Nerviano Medical Sciences or the Delegated Party, all study materials must be collected and all case report forms completed to the greatest extent possible.

18. DISSEMINATION AND PUBLICATION OF RESULTS

Results of the study may be presented or published. The conditions regulating dissemination of the information derived from this clinical study are described in the Clinical Trial Agreement.

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APPENDICES

Appendix 1. ECOG Performance Status

Grade	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

(From Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655).

Appendix 2. Response Criteria in AML

Appendix 2.1.: Reporting Criteria in AML according to ELN 2022

Appendix 2.2.: Reporting Criteria in AML according to ELN 2017

Appendix 2.1. Response Criteria in AML according to ELN 2022

Response Criteria in AML (2022)	
Category	**Definition**
Response	
Complete Remission (CR) *,†,‡	BM blasts <5%; absence of circulating blasts; NO EMD; ANC ≥1.0 × 10^9/L (1000/µL); platelet count ≥100 × 10^9/L (100 000/µL)
CR with partial hematologic recovery (RCh) *,†,‡	ANC ≥0.5 × 10^9/L (500/µL) and platelet count ≥50 × 10^9/L (50 000/µL) otherwise all other CR criteria met Comment: If CRh used, CRi should only include patients not meeting the definition of CRh
CR with incomplete hematologic recovery (CR_i) *,†,‡	All CR criteria except for residual neutropenia <1.0 × 10^9/L (1000/µL) or thrombocytopenia <100 × 10^9/L (100 000/µL)
Morphologic leukemia-free state (MLFS)	BM blasts <5%; absence of circulating blasts; NO EMD; NO hematologic recovery required ⁑
Partial remission (PR)	Decrease of BM blast percentage to 5 to 25%; and decrease of pretreatment BM blast by at least 50%; All hematologic criteria of CR;
No response	Patient evaluable for response but not meeting the criteria for CR, CRh,CRi, MLFS or PR
Non-evaluable for response	Non-evaluable for response will include patients lacking an adequate bone marrow response evaluation. This category will include patients with early death, withdrawal prior to response assessment, or a technically suboptimal bone marrow sample precluding assessment
Progressive Disease	
Relapse	
Relapsed disease (after CR, CRh or CRi)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least one week apart; or development of extramedullary disease

BM, bone marrow; PB, peripheral blood; ANC, absolute neutrophil count; EMD, extramedullary disease; WBC, white blood cell.

*To recognize the potential for continuing improvements in blood counts after myelosuppressive therapy, response definitions for patients with marrow blast clearance (< 5%) may be adjusted to reflect the best hematologic response achieved prior to commencement of the next treatment cycle. Aspirate reports that include MLFS, CRh, or CRi should note the potential for post-marrow blood counts to alter the final response designation. Patients should not have received G-CSF, nor platelet transfusions within 7 days prior to hematologic response determination.

†For patients with CR, CRh, or CRi, the presence of a low percentage of circulating blasts in the blood may represent a regenerating marrow and should not be interpreted as persistent disease. In such cases the blasts generally disappear within a week.

‡A response landmark for CR, CRh, or CRi should be stated, eg, after 2 cycles of intensive therapy; this landmark may be longer for nonintensive based treatment options, eg, 180 days.

⁑Marrow should not merely be "aplastic"; bone marrow spicules should be present; at least 200 cells should be enumerated in the aspirate or cellularity should be at least 10% in the biopsy

(Adapted from Döhner H et al., Blood. 2022 Sep 22;140(12):1345-1377)

Appendix 2.2. Response Criteria in AML according to ELN 2017

Response Criteria in AML (2017)

Category	Definition
Response	
Complete Remission (CR)	BM blasts <5%; NO circulating blasts and blasts with Auer rods; NO EMD; ANC ≥1.0 × 10^9/L (1000/µL); platelet count ≥100 × 10^9/L (100 000/µL)
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0 × 10^9/L [1000/µL]) or thrombocytopenia (<100 × 10^9/L [100 000/µL])
Morphologic leukemia-free state (MLFS)	BM blasts <5%; NO blasts with Auer rods; NO EMD; NO hematologic recovery required *
Partial remission (PR)	Decrease of BM blast to 5-25%; and decrease of pretreatment BM blast by at least 50%; All hematologic criteria of CR;
Stable Disease	Absence of CR, CR_i, MLFS, PR; and criteria for PD not met #
Progressive Disease	
Progressive disease (PD)	Evidence for an increase in BM blast percentage and/or increase of absolute blast counts in the blood §: • >50% increase in BM blasts over baseline (a minimum 15% increase in cases with <30% blasts at baseline; or persistent BM blast >70% over at least 3 months; without at least a 100% improvement in ANC (>0.5 × 10^9/L [500/µL], and/or platelet >50 × 10^9/L [50 000/µL] nontransfused); OR • >50% increase in PB blasts (WBC × % blasts) to >25 × 10^9/L (>25 000/µL) (in the absence of differentiation syndrome); OR • New EMD
Relapse	
Hematologic Relapse (after CR, CR_i)	BM blasts ≥5%; or reappearance of blasts in the blood; or development of EMD

BM, bone marrow; PB, peripheral blood; ANC, absolute neutrophil count; EMD, extramedullary disease; WBC, white blood cell.

* BM should not be merely 'aplastic': at least 200 cells should be enumerated or cellularity should be at least 10%

Period of stable disease should last at least 3 months;

§ In general, at least 2 cycles of a novel agent should be administered; the protocol requires blast increase in 2 consecutive marrow assessments at least 4 wk apart; the date of progression should then be defined as of the first observation date

(From Döhner H et al., Blood. 2017 Jan 26;129(4):424-447)

Appendix 3. Response criteria in CMML
(not applicable for Phase II)

Proposed Criteria for measurement of treatment response in adult CMML patients

Complete Response (CR): presence of ALL of the following improvements *
BM: ≤5% myeloblasts (including monocytic blast equivalent in case of CMML) with normal maturation of all cell lines and return to normal cellularity *
Osteomyelofibrosis absent or equal to "mild reticulin fibrosis" (≤grade 1 fibrosis) #
Peripheral blood: WBC ≤10 × 10^9 cells/L Hgb ≥11 g/dL Platelets ≥100 × 10^9/L; ≤450 × 10^9/L Neutrophils ≥1.0 × 10^9/L Blasts 0% Neutrophil precursors reduced to ≤ 2% Monocytes ≤1 × 10^9/L Extramedullary disease: Complete resolution of extramedullary disease present before therapy (eg, cutaneous disease, disease-related serous effusions), including palpable hepatosplenomegaly
Complete Cytogenic remission
Resolution of previously present chromosomal abnormality (known to be associated with myelodysplastic, syndrome myeloproliferative neoplasms, or MDS/MPN), as seen on classic karyotyping with minimal of 20 metaphases or FISH ^
Partial Remission
Normalization of peripheral counts and hepatosplenomegaly with bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity **except** in cases of MDS/MPN with ≤5% bone marrow blasts at baseline
Marrow Response
Optimal marrow response: Presence of all marrow criteria necessary for CR without normalization of peripheral blood indices as presented above.
Partial marrow response: Bone marrow blasts (and blast equivalents) reduced by 50%, but remaining >5% of cellularity, **or** reduction in grading of reticulin fibrosis from baseline on at least 2 bone marrow evaluations spaced at least 2 mo apart

Proposed Criteria for measurement of treatment response in adult CMML patients

Clinical Benefit
Requires **one** of the following in the absence of progression or CR/partial response and independent of marrow response (clinical benefit response must be verified at ≥8 wk) to be considered a clinical benefit *Erythroid response*: Hgb increase by ≥2.0 g/dL Transfusional independence (TI) for ≥ 8 wk for patients requiring at least 4 packed red blood cell transfusions in the previous 8 wk Only red blood cell transfusions given based on physician's judgment for a pretreatment Hgb of ≤8.5 g/dL will count in the red blood cell TI response evaluation § *Platelet response:* Transfusion independence when previously requiring platelet transfusions of at least a rate of 4 platelet transfusions in the previous 8 wk Pretreatment ≤20 × 10^9/L: increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100% Pretreatment >20 × 10^9/L but ≤ 100 × 10^9/L: absolute increase of ≥30 × 10^9/L § *Neutrophil response* Pretreatment ≤0.5 × 10^9/L at least 100% increase and an absolute increase ≥0.5 × 10^9/L Pretreatment >0.5 × 10^9/L and ≤1.0 × 10^9/L At least 50% increase and an absolute increase ≥0.5 × 10^9/L § *Spleen response* Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable

Hgb, Hemoglobin.

* *Presence of dysplastic changes, which may be interpreted within the scope of normal range of dysplastic changes, may still exist in the presence of CR as allowed in MDS IWG. Marrow should exhibit age-adjusted normocellularity in CR. Persistent low-level dysplasia is permitted given patientivity of assignment of dysplasia.*

\# *If there is no significant fibrosis present on the initial bone marrow biopsy, a second biopsy is not required to prove resolution of fibrosis. Grading of fibrosis in measurement of treatment response should be according to the European Consensus System (Thiele J et al., Haematologica 2005, see* Appendix 4 *of this protocol).*

§ *Resolution of abnormal peripheral blood counts must persist for at least 2 separate analyses over at least 8 wk. In the case of proliferative MDS/MPN, CR will include resolution of thrombocytosis to a normal platelet count (150-450 × 109/L) and resolution of leukocytosis to WBC ≤10 × 109 cells/L but ≥1.5 × 109/L. Hgb should be maintained >11 g/dL and platelets ≥100 × 109/L without the support of transfusions. Clinical benefit may occur when these changes occur in absence of other changes required for CR or marrow response. Platelet and packed red blood cell transfusion independence (TI) would be considered for clinical benefit, and duration of TI should be monitored. Reduction in myeloid precursors (promyelocytes, myelocytes, metamyelocytes) and nucleated red blood cells to less than appreciable levels (≤2-3%) and/or 1 × 109/L monocytosis in the absence of infection, cytokine treatment, or other reactive causes.*

^ *Loss of cytogenetic burden of disease by (via FISH or classic karyotyping) known to adversely affect prognosis is required to reach complete cytogenetic remission. Decrease in the cytogenetic burden of disease must be by ≥50% (via FISH or classic karyotyping) to be indicative of a partial cytogenetic response. Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on the perforhumance characteristics of the specific probes used.*

(Modified from Savona MR et al., Blood 2015, Mar 19; 125(12):1857-1865)

Appendix 4. European Consensus on Grading Bone Marrow Fibrosis

Consensus on the grading of myelofibrosis

Grading	Description *
MF - 0	Scattered linear reticulin with no intersections (cross-overs) corresponding to normal bone marrow
MF - 1	Loose network of reticulin with humany intersections, especially in perivascular areas
MF - 2	Diffuse and dense increase in reticulin with extensive intersection, occasionally with only focal bundles of collagen and/or focal osteosclerosis
MF - 3	Diffuse and dense increase in reticulin with extensive intersection with coarse bundles of collagen, often associated with significant osteosclerosis

**Fiber density should be assessed in hematopoietic (cellular) areas.*

(From Thiele J et al., Haematologica. 2005 Aug)

Appendix 5. Proposed criteria for measurement of disease progression in adult CMML

Proposed criteria for measurement of disease progression in adult CMML patients

Combination of 2 major criteria, 1 major and 2 minor criteria, or 3 minor criteria from list
Major Criteria
Increase in blast count* Less than 5% blasts: ≥ 50% increase and to > 5% blasts 5%-10% blasts: ≥ 50% increase and to > 10% blasts 10%-20% blasts: ≥ 50% increase and to > 20% blasts 20%-30% blasts: ≥ 50% increase and to > 30% blasts**
Evidence of cytogenetic evolution *** Appearance of a previously present or new cytogenetic abnormality in complete cytogenetic remission via FISH or classic karyotyping; Increase in cytogenetic burden of disease by ≥ 50% in partial cytogenetic remission via FISH or classic karyotyping
New Extramedullary disease - Worsening splenomegaly Progressive splenomegaly that is defined by IWG-MRT: the appearance of a previously absent splenomegaly that is palpable at >5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of >10 cm - Extramedullary disease outside of the spleen To include new/worsening hepatomegaly, granulocytic sarcoma, skin lesions, etc.
Minor Criteria
Transfusion dependence §
Significant loss of maximal response on cytopenias ≥ 50% decrement from maximum remission/response in granulocytes or platelets
Reduction in Hgb by ≥ 1.5 g/dL from best response or from baseline as noted on complete blood count
Evidence of clonal evolution (molecular)#

Hgb, Hemoglobin.
** Blasts as measured from the bone marrow.*
*** Patients with development of AML from MDS/MPN; 20-30% blasts may be allowed on some clinical trials for patients with MDS/MPN.*
**** Increase in cytogenetic burden of disease by ≥n50% (via FISH or classic karyotyping). Given variability of fluorescent probes used in FISH, cytogenetic normalization via FISH will depend on specific probes used.*
§ Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the past month for a hemoglobin level of less than 8.5 g/dL that was not associated with clinically overt bleeding. Cytopenias due to therapy should not be considered in assessment of progression.
 # The identification of new abnormalities using single nucleotide polymorphisms arrays (SNP-A) or sequencing, or a clearly significant increase in mutational burden of a previously detected abnormality. Precise criteria for defining new abnormalities and what exactly constitutes a significant increase in mutational burden are open to interpretation and we suggest that this criterion should be used conservatively based on current evidence.

(Modified from Savona MR et al., Blood 2015, Mar 19; 125(12):1857-1865)

Appendix 6. Drugs That May Prolong QT

A list of drugs known to prolong QT interval is reported below. This list should not be considered exhaustive. Consult individual drug labels for specific information on whether a compound is known to prolong QT.

Drugs That May Prolong QT

Drug Class	**Generic Drug Name**
Class 1A antiarrhytmics	Quinidine Procainamide Disopyramide
Class IC antiarrhythmics	Flecainide Propafenone Moricizine
Class III antiarrhythmics	Amiodarone Sotalol Bretylium Ibutilide Dofetilide
Antipsychotics	Thioridazine Mesoridazine Chlorpromazine Prochlorperazine Trifluoperazine Fluphenazine Perphenazine Pimozide Risperidone Ziprasadone Lithium Haloperidol
Tricyclic/tetracyclic antidepressants	Amitriptyline Desipramine Doxepin Dosulepin hydrochloride Imipramine Maprotiline
Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) antidepressants	Venlafaxine

Drugs That May Prolong QT

Drug Class	**Generic Drug Name**
Macrolide antibiotics	Azithromycin Erythromycin Clarithromycin Dirithromycin Roxithromycin Tulathromycin
Fluoroquinolone antibiotics	Moxifloxacin Gatifloxacin
Azole antifungals	Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole
Antimalarials	Amodiaquine Atovaquone Chloroquine Doxycycline Halofantrine Mefloquine Proguanil Primaquine Pyrimethamine Quinine Sulphadoxine
Antiprotozoals	Pentamidine
Antiemetics	Droperidol Dolasetron Granisetron Ondansetron
Antiestrogens	Tamoxifen
Immunosuppressants	Tacrolimus

Appendix 7. Inhibitors and inducers for CYP-mediated metabolism.

Table 13 provides examples of clinical inhibitors for CYP-mediated metabolism This table is not intended to be an exhaustive list .

Also refer also to CYTOCHROME P450 DRUG INTERACTION TABLE - Drug Interactions (iu.edu); Flockhart DA, Thacker, D., McDonald, C., Desta, Z. The Flockhart Cytochrome P450 Drug-Drug Interaction Table. Division of Clinical Pharmacology, Indiana University School of Medicine (Updated 2021). https://drug-interactions.medicine.iu.edu/. Accessed [March 2017] and Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers | FDA

Table 13. Examples of clinical inhibitors for CYP-mediated metabolism

	Strong inhibitors	Moderate inhibitors
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine	methoxsalen, mexiletine, oral contraceptives, vemurafenib
CYP2C8	gemfibrozil	clopidogrel, deferasirox, teriflunomide
CYP2C19	fluconazole, fluoxetine, fluvoxamine, ticlopidine	cenobamate, felbamate, voriconazole
CYP3A4	The inhibitors below cause a ≥10-fold increase in AUC of sensitive substrate(s): cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and ombitasvir (and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole. The inhibitors below cause a 5- to 10-fold increase in the AUC of sensitive substrate(s): ceritinib, clarithromycin, idelalisib, nefazodone, nelfinavir	aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit juice, imatinib, isavuconazole, tofisopam, verapamil

Note: Strong and moderate inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥5-fold, and ≥2 to <5-fold, respectively. Drug- drug interaction data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].

Abbreviations:
AUC: area under the concentration-time curve; CYP: cytochrome P450

The Table 14 provides examples of clinical inducers for CYP-mediated metabolism This table is not intended to be an exhaustive list.

Table 14. Examples of clinical inducers for CYP-mediated metabolism

	Strong inducers	Moderate inducers
CYP1A2	-	phenytoin, rifampin, smoking, teriflunomide
CYP2C8	-	Rifampin
CYP2C19	rifampin	apalutamide, efavirenz, enzalutamide, phenytoin
CYP3A	apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenytoin, rifampin, St. John's wort	bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, sotorasib

Note: Strong and moderate inducers are drugs that decreases the AUC of sensitive index substrates of a given metabolic pathway by ≥80% and ≥50% to <80%, respectively. Drug-drug interaction data were collected based on a search of the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61].

Abbreviations:
AUC: area under the concentration-time curve; CYP: cytochrome P450.

Appendix 8. Recommended Birth Control Methods

Genotoxicity cannot be excluded as per ICH guidelines, therefore patients must be adviced on highly effective contraceptives.

For the purpose of this protocol, methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods and therefore recommended.

Since NMS-03592088 has potential induction of CYP3A4 WOCBP must be advised that hormonal contraceptives might lose efficacy and must use alternate form of highly effective contraception.

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

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