Myelodysplastic Syndromes: Developing Drug and Biological Products for Treatment

Guidance for Industry

DRAFT GUIDANCE

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Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drug and biological products[2] for the treatment of the myelodysplastic syndromes (MDS). Specifically, this guidance addresses FDA's current thinking regarding the overall development program and clinical trial designs for the development of drugs to support an indication for the treatment of MDS.[3] This guidance is specific to the development of drugs that are considered disease-modifying, and not drugs that are considered as supportive therapy (e.g., erythropoiesis-stimulating agents). Furthermore, the guidance will not address drug development for MDS/myeloproliferative neoplasm overlap syndromes, such as chronic myelomonocytic leukemia, which are considered a separate class of myeloid neoplasms.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

MDS are a heterogenous group of clonal hematologic disorders characterized by ineffective hematopoiesis, myeloid dysplasia, cytopenias, and potential transformation into acute myeloid

[1] This guidance has been prepared by the Oncology Center of Excellence, the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research in consultation with the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drug* or *drugs* include drug products approved under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

[3] In addition to consulting guidances, sponsors should contact the appropriate review division to discuss specific issues that arise during the development of drugs for the treatment of MDS.

leukemia (AML). The International Agency for Research on Cancer classifies MDS and related neoplasms on the basis of morphological, clinical, and genomic parameters, including specific genetic abnormalities.[4] The incidence of MDS increases with age, ranging from 0.1 per 100,000 people in ages less than 15 years to 37.5 per 100,000 people in ages 75 and older.[5]

Prognostic scoring systems are commonly used to assess prognosis for patients with MDS, for example, the International Prognostic Scoring System (IPSS) and IPSS-Revised (IPSS-R), which consider percentage of blasts in the bone marrow, cytogenetics, and degree of cytopenia to determine risk.[6,7] While these systems are used to stratify patients into lower-risk and higher-risk groups, prognostic criteria are not predictive of response to treatment.

The general categories of treatment available to patients with MDS include supportive care, disease-modifying drugs, and allogeneic hematopoietic stem cell transplantation (HSCT). Supportive care includes transfusion therapy, erythropoiesis-stimulating agents, and antibiotics. Disease-modifying drugs approved for the treatment of MDS, such as hypomethylating agents, are used for disease control, alone or in preparation for HSCT. HSCT is the only curative option and is reserved for eligible patients with higher-risk disease.

New classes of drugs that target specific pathogenetic mutations are potential alternatives to conventional myelosuppressive drugs for the treatment of MDS. While achievement of remission and improvement in survival remain standard endpoints in measuring the effectiveness of drugs for MDS, the palliation of symptoms or reduction in treatment burden may be considered meaningful in certain circumstances (see discussion in III.B below).

The differences in treatment of a heterogeneous patient population and development of a wide range of new drug classes contribute to the complexity of clinical development programs for new drugs for MDS. This guidance addresses these considerations and provides recommendations regarding the design and conduct of clinical trials and the types of supporting data that may facilitate efficient development of drugs for the treatment of MDS.

III. DEVELOPMENT PROGRAM

A. General Drug Development Considerations

1. Nonclinical

[4] For examples, see Swerdlow SH, Campo E, Harris NL, et al (eds), WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, 2017. Consult www.iarc.fr for resources with the latest diagnostic criteria for MDS classification (accessed May 13, 2021).

[5] National Cancer Institute SEER*Explorer: Myelodysplastic syndromes (MDS). Available from: https://seer.cancer.gov/explorer/application.html (accessed May 14, 2021).

[6] Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079–2088.

[7] Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454-2465. doi:10.1182/blood-2012-03-420489

- The Agency's recommendations for the nonclinical programs for treatments of malignancies are summarized in the guidances for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010), *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers* (June 2018) and *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations* (May 2019). These guidances apply to drugs for MDS.

- For development programs for lower-risk MDS with expected long-term survival, additional studies should be considered that typically would not be needed for higher-risk MDS with expected short-term survival (e.g., carcinogenicity, a complete program on reproductive and developmental toxicity), as appropriate. See ICH S9 Questions and Answers and the FDA guidance *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations.*

- For cellular or gene therapy drugs being developed for the treatment of MDS, sponsors should also consult the guidances for industry *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (November 2013) and *Long Term Follow-Up after Administration of Human Gene Therapy Products* (January 2020).

2. Devices

- For drugs with a specific therapeutic target, an in vitro companion diagnostic device (referred to as a "companion diagnostic" herein) may be needed. A companion diagnostic is an in vitro diagnostic device (IVD) that provides information that is essential for the safe and effective use of the corresponding therapeutic product. Sponsors developing a targeted drug for MDS should take into consideration the need for a companion diagnostic early in the drug development timeline.[8] Sponsors may also consult CDRH or CBER as appropriate through a presubmission to obtain advice on codevelopment of a companion diagnostic with a therapeutic product.[9]

- IVDs used in clinical trials of a drug will generally be considered investigational devices, subject to applicable regulations,[10] unless employed for an intended use for which the device is already cleared or approved. See also Section IV.A.

3. Clinical Pharmacology Considerations

- Patients with MDS, especially those with higher-risk MDS, may be prescribed concomitant medication that are substrates, inducers, or inhibitors of cytochrome P450 (CYP) enzymes. In particular, triazole antifungals are moderate to strong CYP3A inhibitors that may be prescribed to reduce the risk of invasive fungal infections in

[8] For guidance pertaining to companion diagnostics, see the CDRH internet page on companion diagnostics (https://www.fda.gov/medical-devices/in-vitro-diagnostics/companion-diagnostics).

[9] See the guidance for industry *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (June 2023).

[10] See 21 CFR 812, 21 CFR 50, and 21 CFR 56 for applicable regulations.

patients with MDS. Such drugs may increase the systemic exposure and, thus, decrease the tolerability of MDS drugs that are metabolized by CYP3A. Additional studies should be used to address this potential risk.

- Sponsors should conduct in vitro metabolism studies to determine if the new MDS drug is a substrate, inhibitor, or inducer of CYP3A prior to conducting the first-in-human (FIH) trial.

- If the new MDS drug is a CYP3A substrate, sponsors should proactively incorporate strategies for dosage modification with concomitant use of moderate and strong CYP3A inhibitors early in their clinical development programs. If available, sponsors may leverage pharmacokinetic data (e.g., exposure-response relationships for safety and effectiveness, clinical drug interaction studies) from patients with other malignancies who have received the new drug to estimate the potential effect of the concomitant use of the new drug with CYP3A inhibitors and determine an appropriate dosing regimen of the new drug with moderate or strong CYP3A inhibitors in patients with MDS. The development of physiologically based pharmacokinetic models may aid in assessing the effect of some CYP3A modulators on the MDS drug and should be considered.

- If the new MDS drug is a substrate of, inhibits, or induces any major CYP enzyme or other metabolic enzymes in vitro, sponsors should conduct clinical drug interaction studies to determine appropriate mitigation strategies. FDA's recommendations regarding such studies are described in the guidance for industry *Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*.[11]

- Supportive care drugs for patients with MDS, which may include antimicrobial prophylaxis (e.g., fluoroquinolones) and antiemetics (e.g., 5-HT3 receptor antagonists), may prolong the QT interval. Sponsors should conduct an adequate assessment early in clinical development to assess the QT prolongation potential of the MDS drug as described in FDA's guidance.[12] If the MDS drug has the potential to prolong the QT interval, the protocol should include appropriate strategies for mitigation of QT prolongation, including a list of prohibited concomitant medications associated with QT prolongation and/or more frequent monitoring of ECG and electrolytes, particularly in patients with nausea, vomiting, or diarrhea.

- Patients with MDS, especially older adults, may have impaired hepatic or renal function. Prior to enrolling patients with organ impairment on trials of drugs for MDS, the sponsor should identify elimination pathways of the parent drug and its active metabolites. If renal or hepatic elimination pathways are identified, the sponsor should characterize the impact of organ impairment on the pharmacokinetics of the parent drug or active

[10] See the Guidance for Industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

[12] See FDA Guidance for Industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005).

metabolites early in clinical development as described in FDA guidances.[13] This information provides the basis of dosage modifications for patients with organ impairment in late phase clinical studies.

- Food can impact the systemic exposure of MDS drugs that are administered orally. In addition, dosage regimens that require multiple oral dosage administrations daily may necessitate giving the drug around mealtimes. An evaluation of food effect on drug absorption should therefore be conducted early in the drug development process and in accordance with the recommendations described in FDA's guidances on food effect.[14,15]

4. Specific Populations

- Representative Populations
  To allow for a meaningful evaluation of the assessment of the MDS drug the sponsor should design clinical studies to include adequate numbers of patients that are representative of the US patient population and collect sufficient data (pharmacokinetics, pharmacodynamics, efficacy, safety) from each clinically relevant group. The data should be sufficient for assessing the effects of the MDS drug in patients from different ethnic and racial backgrounds in the population pharmacokinetics and exposure-response analyses to inform product safety and effectiveness for labeling.

- Pediatric Patients
  a) FDA encourages sponsors to address the pediatric population early in their clinical development plan for drugs for the treatment of MDS. For example, adolescent patients should be considered for enrollment along with adults in trials for the treatment of MDS.[16]

  b) When it is not clear that dosing for pediatric patients can be derived with certainty from adult data, or for FIH studies in younger pediatric patients, studies in the pediatric population should begin with a phase 1 trial of the new drug as monotherapy. The phase 1 monotherapy trial population need not be limited to patients with MDS, but the acceptability of the recommended phase 2 dosage (RP2D) should be confirmed in a small cohort of pediatric patients with MDS before conducting larger trials for MDS in the pediatric population.

[13] See the guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling* (March 2024) and the guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003).

[14] See the guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations* (February 2019).

[15] See the guidance for industry *Food-Effect Bioavailability and Fed Bioequivalence Studies* (December 2002).

[16] See the guidance for industry *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials* (March 2019) and the guidance for industry and IRBs *Cancer Clinical Trial Eligibility Criteria: Minimum Age Considerations for Inclusion of Pediatric Patients* (July 2020).

c) Section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires that marketing applications for certain oncology drugs that are directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer contain reports of molecularly targeted pediatric cancer investigations, unless a deferral or waiver is granted. The requirement for pediatric investigations applies even if the drug is for an indication for which orphan designation is granted.[17] Sponsors of molecularly-targeted MDS drugs should discuss the applicability of these requirements as early as end-of-phase 1 to allow sufficient time to develop a pediatric study plan, if needed.[18]

- Older Adult Patients
  a) For clinical trials of MDS drugs, sponsors should enroll a population that is representative of the older age range of patients with the disease. FDA encourages for trials of drugs for MDS.

  b) FDA recommends an assessment of older adults (e.g., age 65 years or older) for physiologic function at study baseline to assist in identifying subgroups that may be at risk for an adverse outcome when treated for MDS. Sponsors may consider using an available geriatric assessment tool or propose a new tool for use in the clinical trials. A simple assessment tool evaluating single or multiple aspects of function with limited burden to the patient is preferred. Sponsors should meet with FDA as early as possible to discuss the incorporation of an existing or a new assessment tool for older adult patients in MDS clinical trials.

- Patients with Organ Impairment
  a) For late phase clinical trials of MDS drugs, sponsors should enroll a population that is representative of patients diagnosed with MDS, including those with impaired renal and hepatic function. Appropriate renal and hepatic impairment studies should have been conducted or the impact of renal and hepatic impairment on the exposure of the parent drug and its active metabolites assessed adequately to provide appropriate dosage modifications as stated in section III.A.3.

- Pregnant Patients

  a) The MDS population includes young adult patients. Pregnant patients may be diagnosed with MDS during their pregnancy. The standard of care in this circumstance is not well-defined. As such, pregnant patients with MDS in certain circumstances may be considered for inclusion in clinical trials for new MDS drugs based on a thorough benefit-risk evaluation and when the trial offers the possibility of treatment benefit to the patients and/or fetus.

[17] For additional information, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* (May 2021).
[18] For additional information see the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

b) Data from relevant nonclinical studies to support safety in pregnant patients should be available prior to enrolling pregnant patients in clinical trials for MDS drugs. In addition, safety data for the drug from previous human exposure, even for indications other than MDS, should be included in the assessment of risks.

c) When a pregnancy has been identified during clinical trials for MDS drugs, the benefits and risks of continuing participation versus stopping use of the investigational drug should be reviewed with the pregnant patient. A second informed consent process reflecting additional benefit-risk considerations is advisable for patients who choose to continue participation in the clinical trial for MDS drugs during pregnancy.

d) Sponsors should consider meeting with FDA early in development to discuss when and how to include pregnant patients in the clinical trials. For general guidance on when pregnant patients may be included in clinical trials, see the draft guidance for industry, *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials* (April 2018).[19]

5. Safety Reporting Considerations

- Patients with MDS may have adverse events due to the underlying disease. Additionally, many MDS drugs are designed to be myelosuppressive and are expected to result in complications from cytopenias. Preclinical studies and the analysis of class effects may also reveal expected toxicities for the investigational drug. Sponsors should inform FDA of the anticipated serious adverse events that the Sponsor does not plan to report individually in an expedited manner. An IND safety report must be submitted to FDA if an aggregate analysis indicates that the events are occurring more frequently in the investigational drug treatment group.[20] Additional information can be found in the guidance for industry and investigators Safety Reporting Requirements for INDs and BA/BE Studies.[21]

- Although investigators are required[22] to report all serious adverse events to the sponsor immediately, this requirement may be burdensome and not useful when several serious adverse events are expected at a high rate, such as might occur with the cytopenic complications of treatment of MDS. Under such circumstances, sponsors may propose an alternative reporting arrangement for Investigators in the protocol or in a specific waiver request to FDA, and FDA will provide comment on whether the alternative reporting arrangement is acceptable. For early phase trials, the alternative reporting arrangement

[19] When final, this guidance will represent the FDA's current thinking on this topic.
[20] See generally, 21 CFR 312.32
[21] See *Safety Reporting Requirements for INDs (Investigational New Drug Applications) and BA/BE (Bioavailability/Bioequivalence) Studies* (December 2012), and the draft guidance for industry *Sponsor Responsibilities – Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021). When final, this guidance will represent the FDA's current thinking on this topic.
[22] See 21 CFR 312.64. See also the draft guidance for industry *Investigators Responsibilities – Safety Reporting for Investigational Drugs and Devices* (September 2021). When final, this guidance will represent the FDA's current thinking on this topic.

may be limited to an alternative timeframe for the Investigator to report a serious adverse event to the Sponsor.

- Patients with MDS may experience relapse while participating in a clinical trial. MDS-related events, such as relapse or death from relapse, should not be submitted by the Sponsor as an IND safety report unless there is evidence suggesting a causal relationship between the investigational drug and the event, such as an aggregate analysis showing that relapse occurred more frequently in the investigational drug group.

B. Efficacy Endpoints

1. Time-to-Event Endpoints for MDS

Overall Survival (OS)

- OS is defined as the time from randomization to the date of death from any cause.
- For patients who are alive at the data cut-off, the observations for time-to-event are censored at the last date of documented survival.

Event-Free Survival (EFS)

- EFS is not an established clinical benefit endpoint for new drugs for MDS. For EFS to be considered for regulatory decision making, supportive information should include an assessment of its association with established clinical benefit endpoints in MDS, such as response rate and OS.

a) Statistical Considerations for Time-to-Event Endpoints

i. The general principles for the design and analysis of clinical trials as outlined in ICH *E9* apply to trials for MDS drugs.[23] The bullets below are additional considerations specific to MDS trials and can also be thought of as discussing specific attributes of the estimand concept, which is further discussed in the ICH guidance for industry *E9 (R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.*[24]

ii. For time-to-event endpoints in a randomized trial for MDS, the primary analysis set consists of all randomized subjects. With respect to the primary analysis method, FDA has accepted the log-rank test. Although FDA is open to discussion about other methods, the sponsor should submit a justification to FDA for the proposed method. Additional summary metrics that should be reported include the estimated medians (where meaningful), hazard ratios, and 95% confidence intervals.

[23] See the ICH guidance for industry *E9 Statistical Principles for Clinical Trials* (September 1998).
[24] May 2021.

iii. Trials that use a time-to-event endpoint other than OS as the primary endpoint should specify a statistical analysis plan for OS. This plan should include the assumed power, analysis method, analysis population, and interim stopping boundaries. Such a plan should be specified regardless of whether OS will be formally tested in the statistical analysis plan.

iv. Some patients who enroll in MDS trials may undergo allogeneic HSCT after randomization, which may impact OS. Additionally, as more effective drugs for MDS are approved, subsequent therapies may impact OS. As these treatments are integral to the practice of medicine, the primary analysis of time-to-event endpoints in MDS should be conducted without censoring for such treatment.[25] Refer to Appendix 2 of the draft guidance for industry *Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment* for a general discussion about interpretation of the treatment effect when HSCT occurs as a post-randomization event.

v. Secondary and sensitivity analyses of time-to-event endpoints should follow a prespecified statistical analysis plan. These analyses may include the use of alternatively-defined endpoints, alternatively-defined populations, or using alternative analysis methods.

2. Binary Endpoints Used Commonly for MDS

Complete Remission (CR)

- For documentation of CR, FDA has used the following definition:

  1) Marrow blasts: < 5% by morphologic examination,
  2) Hemoglobin: > 11 g/dL,
  3) Platelet count: > 100 x Gi/L,
  4) Absolute neutrophil count (ANC): > 1 Gi/L,
  5) Absence of leukemic blasts in the peripheral blood by morphological examination, and
  6) Responses must last at least 4 weeks.

- Alternative definitions for CR rate should be accompanied with appropriate justification.

- The protocol should provide for maximum windows of time between marrow sampling and peripheral blood tests used to establish CR. Windows of up to 14 days may be justifiable. The CR date is assigned as the date of marrow sampling or peripheral count recovery, whichever is later. Missing data are considered failure to achieve CR. Additional considerations may be needed depending on the extent of the missing data, differences in missing data between the arms when the MDS study is

[25] See the draft treatment policy discussion in the draft ICH *E9(R1)*. When final, this guidance will represent the FDA's current thinking on this topic.

randomized, and whether the study is open-label. See section III.D.4 for a discussion of trial procedures critical to the assessment of CR and section IV.B.1 for the discussion of the adjudication of CR for the purpose of labeling.

- See Appendix 3 for an example estimand for treatment of MDS.

- For CR, the duration of complete remission (DOCR) is defined as the time from CR to relapse or death from any cause, whichever comes first. Adequate follow-up is required in order to establish that the durability of CR is meaningful. As responses can occur well after treatment initiation, the planned follow-up for DOCR should be based on time from response to data cut-off rather than time from randomization to data cut-off. See Appendix 4 for an example estimand for duration of CR.

- Hematological relapse from CR is defined as increase in bone marrow blasts by morphology, persistent reappearance of blasts in the peripheral blood by morphology, or persistent worsening of cytopenias. Specific parameters should be specified in the protocol.

- In general, once CR is established by marrow examination, further follow-up for relapse may be limited initially to physical examination and peripheral blood tests. The known time to relapse for the regimen in the control arm or from other historical data should be used when planning the frequency and duration of testing for relapse. In order to determine DOCR as accurately as possible, the assessments should be performed more frequently than in standard practice. When relapse is suspected on the basis of the follow-up physical examination or peripheral blood counts, additional testing may be performed to confirm the finding, but the date of relapse is set to the date of the first assessment that suggested relapse.

b) Partial Remission (PR)

- For documentation of PR, FDA has used the following definition:

1) Bone marrow blasts decreased by ≥ 50% over pretreatment but still ≥ 5%
2) Hemoglobin > 11 g/dL,
3) Platelet count > 100 x Gi/L,
4) Absolute neutrophil count (ANC) > 1 Gi/L, and
5) Absence of leukemic blasts in the peripheral blood my morphological examination
6) Responses must last at least 4 weeks

- Because the potential utility of CR as an endpoint is similar to that of PR, the endpoint used should be CR+PR. PR responses alone would not be sufficient to establish benefit.

- For CR+PR, the duration of response (DOR) is defined as time from first response of CR or PR to hematological relapse or death from any cause, whichever occurs first.

Adequate follow-up is needed in order to establish that the durability of CR+PR is meaningful.

- Hematological relapse from PR is defined as increase in bone marrow blasts by morphology, persistent reappearance of blasts in the peripheral blood by morphology, or persistent worsening of cytopenias. As with hematological relapse from CR, specific parameters should be specified in the protocol.

- Once PR is established by marrow examination, further follow-up for relapse (or increase in response status to CR) should be specified per protocol. As with CR responses, when relapse is suspected on the basis of the follow-up physical examination or peripheral blood counts, additional testing may be performed to confirm the finding, but the date of relapse is set to the date of the first test that suggests relapse.

- See Appendix 3 for an example estimand for CR + PR.

c) Transfusion Independence (TI) and Red Blood Cell Transfusion Independence (RBC-TI)

- Durable TI is an endpoint that is applicable to drugs for the treatment of patients with MDS.

- RBC-TI is an endpoint that is applicable to drugs for the treatment of patients with LR-MDS with isolated RBC transfusion dependence.

- When durable TI or RBC-TI are used, these endpoints should be supported by evidence showing an effect of the treatment on an endpoint reflecting anti-MDS activity.

- TI is defined as the absence of red blood cell and platelet transfusions for a prespecified period of time during continued treatment. RBC-TI is defined as the absence of RBC transfusions for a prespecified period of time during continued treatment. The credibility of the data is dependent on the protocol specifying the minimal parameters for use of transfusions and documentation that the instructions were followed. Hence, an important supporting analysis would include an assessment of serial measurements of blood counts to ensure that the observed TI or RBC-TI was an actual treatment effect and not a bias in the administration of transfusions by the investigator.

- TI should be assessed as a response achieved in the subgroup of patients who were transfusion dependent (TD) at baseline (conversion from TD to TI with treatment) separately from the subgroup of patients who were TI at baseline (maintenance of TI with treatment). For patients with active MDS, TD at baseline has been based on receipt of two or more red blood cell units or platelet transfusions within at least 56 days prior to the start of study treatment. However, alternative definitions of TD at

baseline may be proposed if there is adequate justification. Analyses of platelet TI and RBC-TI separately should be used to establish consistency of the components of the TI endpoint.

d) Statistical Considerations for Binary Endpoints

- For single-arm MDS trials:

1) The analysis set consists of all patients treated with investigational drug.[26] If the proposed indication focuses on the target of the drug, the analysis set should include only those patients confirmed positive for the target using the proposed candidate IVD companion diagnostic or clinical trial assay(s) bridged to the companion diagnostic.
2) For binary endpoints, proportions and their 95% confidence interval should be reported.
3) Reports of interim and final analyses should include the duration of follow-up. Interim analyses are typically based on testing a null rate; showing superiority to such a null rate may not be sufficient for establishing efficacy.

- For randomized MDS trials:

1) The analysis set consists of all randomized patients.
2) For binary endpoints, the primary analysis may be based on Fisher's Exact test; the Cochran-Mantel-Haenszel test may apply when stratification factors were used at randomization. Proportions and their 95% confidence intervals should be reported. Any additional metrics to quantify the treatment effect, such as the difference in proportions, ratio of proportions or odds ratio, should be prespecified.
3) For targeted drugs, a secondary analysis should be performed where the analysis set is restricted to patients confirmed positive for the target.
4) Interim analyses should report the requisite time for duration of follow-up. Treatment effect should be both significant and clinically meaningful. Interim analyses should provide a reasonably mature assessment of OS.
5) When response rate is the primary endpoint, special considerations arise for designs that use interim analyses of efficacy. In such designs, the response rate at each interim analysis is estimated using partial sums. As a result, it is critical that response be defined in such a way that a patient's response data does not change once they have been included in an analysis. A common approach is to restrict responses to those which occur within a prespecified time interval and prior to progression or subsequent therapy, whichever occurs earlier.

- DOR for CR±PR may be calculated using the Kaplan-Meier method using relapse or any-cause death as events. Estimated median and range should be reported. When the

[26] In cases of personalized products with the potential for a high rate of manufacturing failure, additional efficacy analyses based on enrolled patients may be needed even in a single-arm trial in order to assess the impact of manufacturing failure on the efficacy endpoint.

number of study subjects is small, or when follow-up is short, the Kaplan-Meier estimate may not be stable. In this circumstance, the observed median and range of observed DOR may be reported. Sensitivity analyses may include calculation of DOR using non-protocol-specified MDS drugs in the absence of documented relapse as an additional event, or calculation of DOR with censoring at HSCT.

- A key issue in the assessment of trials with response rate as the primary endpoint is the magnitude of response. Results from such a trial should be both statistically persuasive and clinically meaningful. Raw estimates from trials with interim analyses are often biased. Where possible, supplemental analyses should be performed to provide an unbiased estimate of the effect.

3. Other Potential Measures of Efficacy for MDS

- Minimal Residual Disease (MRD) is not an established endpoint in clinical trials for MDS drugs at this time. However, as technologies improve and new clinical findings emerge, MRD may be considered as supporting evidence of efficacy for new drugs that have demonstrated durable CR in patients with MDS. For additional information on the use of MRD as an efficacy endpoint, see the guidance for industry *Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment* and Section III.B.3 of the guidance for industry *Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment.*[27]

- Key efficacy endpoints may also include well-defined and reliable patient-reported outcome measures. When sponsors propose to use such measures as the basis of a claim for MDS drugs, such endpoints should be supported by data showing that the treatment also has a direct effect on the MDS. Furthermore, adequate enrollment of patients from the United States should be included for reliable interpretation of patient-reported outcome data. For additional information, refer to the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims* and the draft guidance for industry *Core Patient-Reported Outcomes in Cancer Clinical Trials*.[28]

- FDA acknowledges that as technology progresses and clinical trial data accumulate, alternative biomarkers or measures of efficacy may be proposed for use as endpoints in clinical trials for MDS drugs. When considering the use of efficacy endpoints other than those listed above, especially in a trial to be used to support a marketing application, sponsors should obtain advice from FDA about the acceptability of the proposed novel endpoint prior to initiating the trial.

[27] January 2020 and August 2020, respectively. When the latter is final, the guidance will represent the FDA's current thinking on this topic.

[28] December 2009 and June 2021, respectively. When the latter is final, the guidance will represent the FDA's current thinking on this topic.

- Sponsors planning to use real-world data or generate real-world evidence to support a marketing application for an MDS drug should obtain advice from FDA prior to protocol development to ensure that the proposed data sources may be fit for use to assess the treatment effect.[29] Important considerations include, among others, whether relevant data elements (e.g., marrow results, peripheral blood differentials, etc.) needed to derive clinically accepted endpoints for demonstrating efficacy are sufficiently captured, including timing of assessments and frequency of assessments, and the potential degree of outcome misclassification. Sponsors should plan for additional discussions regarding alternative outcome measures if the data sources do not adequately capture the key elements necessary to evaluate clinically accepted endpoints.

C. Exploratory Trial Considerations

1. First-in-Human (FIH) Trials

- Many drugs developed for the treatment of higher-risk MDS may be myelosuppressive and/or genotoxic, including epigenetic modifiers. For patients with lower-risk MDS, supportive care has been the mainstay of treatment, typically with the goal of achieving transfusion independence. For this reason, FIH trials in patients with lower-risk MDS should generally be avoided as these patients have a longer life expectancy.
- For certain new MDS drugs that are nonmyelosuppressive, nongenotoxic, and not epigenetic modifying, it may be possible to conduct the FIH trial in healthy volunteers or patients with lower-risk MDS. The advantage to this approach is that the safety profile may be simpler to determine in the absence of confounding adverse events due to underlying higher-risk MDS. FDA recommends that sponsors request feedback on the design of FIH trials of new MDS drugs specifically in healthy volunteers, including the limitations in exposure and other restrictions needed to protect healthy volunteers participating in such studies.
- Combination regimens may be effective for the treatment of MDS. Nonetheless, the FIH trial should be limited to assessment of one drug at a time, and study of the combination should not commence until there is adequate information about safety and tolerability of the individual drugs. Rare exceptions to this principle are described in the guidance for industry *Codevelopment of Two or More New Investigational Drugs for Use in Combination* (June 2013).
- For MDS drugs that are CYP3A substrates, sponsors should consider enrolling patients on azole antifungals or other CYP3A inhibitors in FIH trials to generate data needed to select a safe dosage with these concomitant drugs (see section III.A.3).
- Sponsors developing cellular or gene therapy products for the treatment of MDS

[29] For further information regarding the use of real-world data and real-world evidence in regulatory decision-making, refer to FDA's suite of guidance documents on this topic available at https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence.

should also consult the guidances for industry *Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products* (June 2015), *Long Term Follow-Up after Administration of Human Gene Therapy Products* (January 2020) and *Considerations for the Development of Chimeric Antigen Receptor T cell Products* (January 2024),.

2. Exploratory Trial Population

- For dose-escalation trials being conducted to determine the RP2D, the eligible population is usually limited to patients whose disease has not responded to approved drugs. Patients with higher-risk MDS, who typically respond poorly to approved drugs, might also be considered for such trials even without prior treatment, but if doing so, the consent form should clearly state the implications of foregoing approved drugs to participate in the clinical trial.

- Multiple genetic mutations and molecular pathways have been identified as contributing to the pathogenesis and persistence of MDS. For new drugs proposed to target these mutations or pathways, the clinical development program should have an early phase trial that includes patients with and without the putative target to assess the need in later phase trials to select patients based on the presence of the target. Including marker-negative patients might not be necessary for drugs that target a cell surface receptor, especially when preclinical data suggest no potential for a treatment effect in the absence of the cell surface receptor.

3. Dose-Escalation Trials

- For dose-escalation trials, the general principles for selection of the safe starting dosage as described elsewhere[30] also apply to drugs being developed for the treatment of MDS. The safe starting dosage for a study in patients with MDS may differ from the starting dosage for a study in healthy volunteers. Nonclinical data should also be used to determine the slope of the dosage-toxicity curve, the anticipated therapeutic dosage range, and the maximal exposure to plan the increments in dosage between cohorts in the escalation portion of the trial. For drugs that are CYP3A substrates, the selection of a safe starting dosage should also consider the concomitant use of drugs that are CYP3A4 inhibitors such as azole antifungals (see section III.A.3).

- The protocol should describe the specific rule-based or model-based criteria used to guide the decision on whether to proceed with escalating the dosage in subsequent cohorts. For dose-escalation trials of episodic outpatient chemotherapy for patients with MDS, escalation to higher dosages is generally limited by the rate of severe, life-threatening, or fatal events (grades 3-5) termed dose-limiting toxicities (DLTs), and the MTD as identified by the 3+3 rule has no more that 17% DLTs. This paradigm, however, is not applicable to all types of drugs for MDS. For example, such a rule could allow greater toxicity than acceptable for continuous treatment or

[30] See ICH *S9* and ICH *S9 Questions and Answers*.

maintenance that extends for years, including palliative therapies with TI as an endpoint. On the other hand, the rule could result in premature closure of a trial of a preparative regimen for HSCT, where grade 3 toxicities are common. Hence, the criteria proposed to guide dose-escalation decisions should consider the types, severities, and rates of toxicities accepted with standard regimens of similar intensity in the intended population (see Appendix 1 for examples). The protocol should describe the data that support the assumptions used to develop the criteria for guiding dose-escalation.

- For many cytotoxic drugs used for the treatment of cancer, there is a strong dosage-response effect, and to achieve the highest response rate, the cited goal of the dose-escalation trial is to identify the MTD. This is not necessarily true for targeted drugs for the treatment of MDS, for which the pharmacodynamic effect may plateau at doses lower than maximally-tolerated. Hence, the goal of the dose-escalation trial should be to determine the RP2D. The protocol should include a definition of the RP2D, and the determination of the RP2D should take into consideration the safety, tolerability, pharmacokinetic, pharmacodynamic, and efficacy data (see also section III.D.2).

- Based on the design of the dose-escalation trial, participants in the initial cohorts of the trial may not receive optimal treatment, which may be a disadvantage for patients with MDS who need effective treatment. Despite the desire to ensure that patients with MDS are treated with pharmacologically-active dosages of a drug, intra-patient dose-escalation based on lack of very early response may not be scientifically valid; a complete characterization of safety, tolerability, and efficacy at any dosage level usually requires treatment for multiple cycles. Intra-patient dose-escalation may be considered in select circumstances where risks can be minimized objectively. For example, if there is an established pharmacodynamic biomarker for safety, intra-patient dose escalation may be feasible with frequent monitoring of the biomarker. Additionally, for patients who have received multiple cycles of treatment without evidence of cumulative toxicity or therapeutic activity, it may be beneficial to escalate the individual patient's dosage to a higher level if that higher dosage has been established as safe in subsequent cohorts. The protocol should specify the criteria for when intra-patient dosage escalation is allowed, how the new dosage is assigned, any changes in the monitoring plan needed to accommodate the change in dosage, and how the safety and efficacy data will be evaluated for such patients.

- The planned duration of treatment should be described clearly in the protocol. Continuous treatment beyond achievement of a response may be considered in the dose-escalation trial but there should be objective criteria for when to discontinue treatment permanently, including high-grade toxicities.

- Early phase trials are the place to determine the expected time to response, allowing study treatment to continue in the absence of toxicity unless prespecified

levels of disease response have not occurred within a maximum number of cycles. Such information will provide support for the treatment plan proposed for confirmatory trials designed to test for efficacy.

- Certain toxicities, such as anemia or neutropenia, are expected with many MDS drugs. Treatment of such usual toxicities is considered standard practice, and detailed instructions need not be included in the protocol unless a specific treatment is critical for the safe use of the investigational drug. Based on established class toxicities, mechanism of action and/or nonclinical studies, there may also be unusual drug-specific toxicities. Until treatment is standardized in practice, instructions for management of patients with such unusual drug toxicities should be included in the protocol.

4. Exploratory Expansion Cohorts

- A small cohort of patients treated at the presumptive RP2D can be useful to further evaluate safety prior to start of additional trials. In the absence of data from a safety expansion cohort, the confirmatory trial should include a very early interim safety analysis to corroborate the safety of the RP2D.

- Dose-escalation trials are typically limited in sample size and frequently do not identify an optimal dosage. Different dosages of the drug should be evaluated early in clinical development, including beyond the initial dose-escalation phase.

- Evaluation of more than one dosage is recommended to allow robust information to help facilitate adequate efficacy and safety assessment of the drug and ensure adequate justification of the selected dosage prior to embarking on a confirmatory trial. Dose- and exposure-response analyses for safety, efficacy, and pharmacodynamic biomarkers are useful approaches to support the recommended dosage.

- Responses as defined in section III.B.2 are generally acceptable measures of activity that should be included in exploratory early phase clinical trials in MDS. Non-CR or PR responses (e.g., marrow complete response, hematologic improvement (HI), shorter term transfusion-independence, etc.) may reflect the activity of the drug, but these responses should guide development of alternative strategies to improve response (i.e., different schedules or use in combinations) rather than being viewed as a success.

- A small cohort of patients treated at the presumptive RP2D can also be used to provide a preliminary assessment of efficacy to support design of additional trials.[31] Such a cohort generally includes no more than 20 patients. Large single-arm expansion cohorts solely for exploratory purposes are not recommended. Any large single-arm trial should have a design based on clear hypothesis testing, and

[31] See guidance for industry *Expansion Cohorts: Use in First in Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics* (March 2022).

the protocol should justify the sample size proposed.

- Time-to-event endpoints are difficult to interpret in single-arm trials and, therefore, are generally not useful in assessing efficacy in exploratory early phase trials. Data for such endpoints, however, should still be collected since such data could be useful in designing the confirmatory trials if other objective measures of efficacy support further development of the drug.

- To ensure the safety of study participants, the expansion cohort plan should include stopping rules for excessive toxicity that would require pausing enrollment to evaluate whether the treatment plan should be modified.

  a. The acceptable rate and type of toxicities will depend on the treatment setting as discussed for development of DLT criteria in section III.C.3.

  b. For patients with higher-risk MDS, toxic events for stopping rules might include treatment-related deaths, prolonged neutropenia or thrombocytopenia lasting past cycle day 28 in the absence of disease, and high-grade nonhematological adverse reactions.

  c. The protocol should describe the exact bounds for the stopping criteria, the statistical method used to calculate the bounds, and the basis for the clinical assumptions used in the calculation. FDA recommends that the bounds be calculated to assure a high probability (> 60-70%) of pausing the trial at the lowest unacceptable toxicity rate while minimizing the probability of pausing (< 30%) when the toxicity rate is acceptable. Nonstringent design parameters may be used to achieve these operating characteristics.

D. Confirmatory Trial Considerations

1. *Confirmatory Trial Population*

- The protocol should use the current diagnostic criteria for MDS or for a specific MDS type to describe the eligible population. Sponsors should seek advice from FDA rather than using potentially outdated criteria to match a population used in support of a prior approval.

- For clinical trials being designed to support a marketing application, the eligibility criteria should reflect the characteristics of the general population with MDS. Exclusion criteria should be limited to disease- or patient-related factors associated with a lack of benefit or an unacceptable risk of toxicity from the investigational drug based on data in early phase trials.

- Since the natural history of MDS varies considerably among patients, clinical trials designed to support a marketing application should enroll patients of similar risk (higher-risk versus lower-risk). However, if the treatment is targeted, enrollment of the targeted population across risk groups may be justified based on results in the

703 early phase trial.

704 • If transfusion dependence (TD) is used to select the confirmatory trial population,
705 the eligibility criteria should clearly define TD at baseline (see Section III.B.2.c).

706 • For clinical trials of a biomarker-selected MDS population, the eligibility criteria
707 should state clearly what assay is to be used to select patients with the cognate
708 target, the tissue (blood, marrow, etc.) used for the assay, and the level of the target
709 needed to meet eligibility.

710
711 2. *Dose Selection and Treatment Plan*
712 • The dosage of the MDS drug in the treatment regimen should be optimized before
713 initiating the confirmatory trials.[32] Conduct integrated dose-response and exposure-
714 response analyses by pooling available pharmacokinetic, pharmacodynamic,
715 efficacy, and safety data to support dosage optimization. The results of such
716 analyses should be included in the protocol to justify the dosage, including when
717 the dosing regimen is different in patients with lower-risk vs. higher-risk MDS.

718 • For drugs planned to be administered for multiple cycles, and especially for drugs
719 given long-term, beyond achievement of a response, on an outpatient basis,
720 tolerability should be taken into consideration when choosing the dosage to be used
721 in the confirmatory trial. In general, for drugs planned to be given long-term or
722 over multiple cycles, it is expected that dosage modifications or discontinuations
723 for adverse reactions are limited to less than 20% of the patients, and that at least
724 80% dose intensity is achieved over multiple cycles for at least 80% of the patients.
725 When significant toxicities occur and/or dosage reductions are implemented,
726 sponsors should take PK samples to assess the resulting drug concentrations to aid
727 in establishing exposure-response relationships for safety.

728 • The protocol should include dosage modification strategies for patients taking
729 certain concomitant drugs (e.g., strong CYP3A inhibitors) or those that experience
730 adverse events during the study as well as dosage strategies in patients with renal
731 or hepatic impairment (e.g., a lower dosage in patients with renal impairment
732 compared to those with normal renal function). The experience with these
733 instructions during study conduct provides the basis for dosage modification
734 instructions in labeling.

[32] See draft guidance for industry *Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases* (January 2023). When final, this guidance will represent the FDA's current thinking on this topic.

3. *Confirmatory Trial Design*
   a. General Considerations for Confirmatory Trial Designs
      i. The principles of designing trials to demonstrate efficacy for the purposes of supporting a marketing application are described in general guidance,[33] and these general principles are applicable to trials for MDS drugs. Below are additional recommendations specific for trials of MDS drugs.

      ii. To prevent bias in study conduct or in selection of poststudy treatments, the use of blinded treatments where feasible is recommended for randomized trials.

      iii. The use of specific genetic targets and other prognostic factors used for eligibility or risk stratification should be described in detail. For patients with relapsed or refractory MDS, the protocol should state clearly whether these prognostic factors are measured at the time of diagnosis or at the time of relapse.

         - A detailed statistical analysis plan stating the trial hypotheses, sample size, analysis timing, and analysis methods should be submitted before trial initiation. The sample size calculation should be based on the expected efficacy in the control arm and the anticipated treatment effect of the investigational drug with respect to the primary endpoint in the planned patient population. Estimating the outcome for the control arm in a molecular subgroup may be challenging for MDS drugs with new molecular targets that were not studied previously with standard care regimens. When there is little extant data to support the assumptions for the anticipated treatment effect, sponsors may consider an adaptive design or other novel approach.[34] In such a case, the sponsor should request feedback from FDA on the proposed design prior to initiating the trial.

      iv. Single-arm MDS trials designed to determine a response rate compared to historical data are challenging. Key criteria that define the endpoint and population have changed over time, including response criteria and risk criteria. For this reason, randomized trials are generally recommended to establish efficacy.

      v. When the design includes an active comparator, the control arm should be the standard of care for the study population (e.g., investigational drug vs. standard of care). Placebo comparators may be considered in add-on trials

[33] See guidance for industry ICH *E8(R1) General Considerations for Clinical Studies* (April 2022), *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021). *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001) and the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) (when final, this guidance will represent the FDA's current thinking on this topic).

[34] For example, see the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (November 2019).

(e.g., investigational drug+standard of care vs. placebo+standard of care) if they are the appropriate treatment for the control arm.

vi. It is common for multiple efficacy endpoints (i.e., OS, CR) to be assessed in a clinical trial for MDS drugs. The statistical analysis plan should prespecify a multiple testing strategy for important secondary endpoints that adjusts for multiplicity conditioned on demonstrating a positive outcome for the primary endpoint[35]. Note that effects on secondary endpoints are generally not sufficient to support a marketing application in the absence of demonstration of an effect on the prespecified primary endpoint. Additionally, even if an effect on a secondary endpoint is demonstrated, it may not be acceptable for labeling if it is not an established efficacy endpoint; for example, the composite of CR+PR+HI may not be suitable for labeling due to the inclusion of HI.

vii. In large, randomized trials, an interim analysis for futility is strongly recommended to ensure that the benefit-risk profile for enrolled patients continues to be favorable. FDA has accepted group sequential/early stopping designs for interim analyses. For interim analyses for efficacy, sufficient follow-up time may be needed to assess important endpoints, such as duration of response, OS, and safety, that would be needed to determine the overall benefit-risk. FDA is willing to discuss the potential pitfalls in a timely fashion when the sponsor is considering early study termination based on interim efficacy analysis results.

viii. The timing of analysis of continued response (e.g., DOR) should be prespecified to mitigate bias in study result interpretation.

ix. FDA has accepted OS and durable CR+PR as clinical endpoints that represent clinical benefit for approval for MDS drugs.

x. Trials intended to support a marketing application for the treatment of MDS may be randomized or single-arm in design, depending on the endpoint, patient population, and available therapy. FDA recommends that sponsors request advice from FDA on proposed study designs for this indication.

b. Treatment of MDS with transfusion dependence

i. Durable TI may represent a direct clinical benefit resulting from the relief from the burdens of insufficient hematopoiesis due to MDS. FDA has accepted TI as an endpoint that represents clinical benefit for approval for MDS drugs.

ii. Trials intended to support a marketing application for this indication may be randomized or single-arm in design depending on the patient population and available therapy. Best supportive care may be acceptable as a comparator in a randomized trial only for a patient population without

[35] See the guidance for industry *Multiple Endpoints in Clinical Trials Guidance for Industry* (October 2022).

available therapies. In certain clinical settings, a single-arm trial may be appropriate for approval if there are adequate historical data to support the null hypothesis.

4. *Confirmatory Trial Procedures*

- Baseline demographic and disease characteristics are used to ensure consistency of the benefit-risk profile by subgroup analyses. The following key MDS-specific information should be documented and collected on the case report forms:

  i. Disease (e.g., WHO-based diagnosis[36]),

  ii. Disease status at enrollment (e.g., newly-diagnosed, relapse, etc.),

  iii. Genetic profile and/or risk group at diagnosis and at enrollment (use of the most contemporary accepted risk stratification is recommended),

  iv. Baseline blood counts (i.e., hemoglobin, absolute neutrophil count, platelets)

  v. Baseline bone marrow blasts

  vi. Cytogenetic risk category

  vii. All prior treatments for MDS

  viii. Baseline functional assessments (where applicable, geriatric assessment is recommended).

- Patients with MDS receiving intensive chemotherapy or high-dose chemotherapy for transplantation are expected to have a high rate of low-grade adverse reactions. For studies of drugs with well-established safety profiles, consideration should be given to collection of a limited amount of safety data.[37] For new drugs with unclear safety profiles, all adverse events should be collected regardless of grade or attribution.

- To ensure that data will be available for the assessment of potential interactions between new drugs and other drugs used commonly for patients with MDS, the dates and dosages of concomitant medications, especially antifungal medications, should be accurate.

- To assess confounding in efficacy analyses due to subsequent post-study treatments, the following post-study information should be documented and collected on the case report forms:

[36] See footnote 4.

[37] See the guidance for industry *Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Investigations* (February 2016).

i. At least the first post-study treatment and the reasons for the treatment choice and

ii. HSCT date for patients proceeding to transplantation with an on-study response or as a post-study salvage treatment.

IV. REGULATORY SUBMISSIONS

A. Investigational New Drug Applications

- General requirements for INDs apply to development programs for MDS drugs. See sections III.A and III.C for recommendations on submission of FIH trials in MDS as the IND-initiating study. Sponsors may request advice from FDA through the pre-IND program.

- FDA supports the use of innovative trial designs[38], such as master protocols, for efficient drug development in MDS. For IND submissions that contain innovative trial designs, FDA recommends consultation through the pre-IND program. For additional recommendations on master protocols, see guidance for industry *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics* (March 2022).

- An investigational device used in a trial, including for patient selection in IND protocols for targeted drugs for use in MDS, is subject to the FDA's investigational device exemption (IDE) regulations[39] as well as 21 CFR parts 50 and 56. Whether a sponsor needs to submit an IDE application is dependent on whether the device used in the trial is considered significant risk (SR), non-significant risk (NSR), or exempt. Sponsors may request a study risk determination directly from CDRH (through a Study Risk Determination pre-submission)[40] or in concert with the IND (see the guidance for industry *Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination)*[41] to determine whether an IDE is needed for the proposed trial to proceed under the IND. See also section III.A.2.

B. Marketing Applications

1. Assessment of Efficacy

[38] See, for instance, FDA's Complex Innovative Trial Design Meeting Program: https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-meeting-program
[39] See 21 CFR 812.
[40] See the guidance for industry *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (June 2023).
[41] October 2019.

- Assessments of efficacy in MDS clinical trials are generally based on objective criteria, such as neutrophil counts and marrow blast percentage. To allow FDA to confirm the analyses of the treatment effect, the raw data supporting the study endpoints should be submitted in the marketing application.
    a) If bone marrow pathology results exceed the character limit for a variable in an xpt file, a pdf of the report may be acceptable.

    b) To assist with the adjudication of responses, the submission should include a summary response file (see Appendix 2) for the confirmatory study and for the integrated efficacy population.

    c) For studies with an endpoint of TI (see section III.B.2.c), the submission should include a summary transfusion analysis data file (see Appendix 2) for at least the confirmatory study.

    d) To assist with the assessment of response and TI, the submission should include a file with the dates of RBC and platelet transfusions and the number of units transfused.

2. Assessment of Safety

- Patients with MDS may experience greater adverse events due to their disease. Assessment of toxicities of the new MDS drug in different disease settings (e.g., solid tumor patients) and in healthy volunteers is helpful in ascertaining causality of adverse events.

- To assist with the adjudication of causality of fatal adverse events, the submission should include a data file with the date of death, study day of death, proximate cause of death (usually as reported by the investigator), and the root cause of death as determined by the sponsor. The root cause is generally categorized as a direct effect of active MDS, an adverse reaction, or an unrelated intercurrent event (such as car accident). When the sponsor is considering additional categories for root cause, feedback on the proposed categories should be sought at the presubmission meeting.

- For myelosuppressive MDS drugs, an analysis should be performed to determine the incidence of prolonged thrombocytopenia (platelets < 50 Gi/L) or neutropenia (ANC < 0.5 Gi/L) past cycle day 28 in the absence of active MDS.

3. Clinical Pharmacology

- If the MDS drug is a substrate of CYP3A or other CYP enzymes, the submission should include analyses of the effect of concomitant drugs, including moderate and strong inhibitors and inducers of CYP3A or other CYP enzymes on the systemic exposure of parent drug and its active metabolites, on safety and efficacy, and whether the available safety and efficacy data support the proposed dosage modifications for concomitant treatment with moderate and strong inhibitors and inducers of CYP3A or other CYP enzymes (see section III.A.3).

- If the MDS drug or its major metabolite(s) is an inhibitor or inducer of metabolism enzymes or transporters, the submission should include analyses of the effect of the parent drug and major metabolites on the systemic exposure of concomitant drugs that are substrates of metabolism pathway or transporter and have a likelihood of coadministration (e.g., commonly used antimicrobials, iron chelators, or other drugs used for supportive care, or other MDS drugs in the combination regimen).

- The submission should include the results of studies on the effects of renal and hepatic impairment on the systemic exposure of the parent drug and its active metabolites (see section III.A.3).

- Include population pharmacokinetic and exposure-response analyses for efficacy, safety, and pharmacodynamic biomarkers to support the proposed recommended dosing regimen and any needed dosage adjustments based on patient factors (e.g., MDS risk level, renal impairment, hepatic impairment, body weight, age, sex, race, pregnancy, concomitant drug use).

GLOSSARY

Terms referring to the types of MDS treatment regimens are defined as follows when used in this guidance

Episodic treatment: A treatment plan of multiple cycles of short-term administrations of intensive or reduced intensity treatment. A typical course of episodic first-line treatment for MDS consists of repeated cycles of reduced intensity therapy with or without HSCT.

Continuous treatment: Repeated cycles of treatment, usually without a drug-free period. A typical course of continuous treatment of MDS consists of daily dosing.

Terms referring to intensities of MDS treatment regimens are defined as follows when used in this guidance

Intensive therapies: Regimens expected to cause high-grade organ toxicity (including neurologic, pulmonary, cardiac, gastrointestinal, genitourinary, renal, hepatic, or cutaneous toxicities) or where the expected duration of neutropenia may approach 42 days from the start of the treatment cycle. Intensive regimens for higher-risk MDS include induction chemotherapy often followed by HSCT.

Reduced intensity therapies: Lower dosages of cytotoxic chemotherapy or targeted drugs with limited or no expected organ toxicities.

APPENDICES

Appendix 1: Example DLT Criteria for MDS Drugs

Setting	Hematological SAR Criteria[a]	Nonhematological SAR Criteria
Healthy Volunteer	Any grade ≥ 2	Any grade ≥ 2
Continuous Long-Term Treatment (e.g., maintenance)	Any grade ≥ 3 ANC or PLTS lasting more than 7 days	Any grade 3 lasting > 72 hours Any grade ≥ 4 Hy's law cases Any AR that leads to dosage reduction or withdrawal
Episodic Reduced Intensity Therapy for lower-risk MDS	Any grade ≥ 4 ANC or PLTS lasting more than 7 days	Any grade 3 (with exceptions)[b] Any grade ≥ 4 Hy's law cases Any AR that leads to dosage reduction or withdrawal
Episodic Reduced Intensity Therapy for higher-risk MDS (e.g., azacitidine)	Any grade ≥ 4 ANC or PLTS lasting past cycle day 28	Any grade 3 (with exceptions)[b] Any grade ≥ 4 Hy's law cases Any AR that leads to dosage reduction or withdrawal
Episodic Intensive Chemotherapy for HR-MDS (e.g., 7+3)	Any grade ≥ 4 ANC or PLTS lasting past cycle day 42	Grade ≥ 4 organ toxicity[c] Hy's law cases
CAR T Cells	Any grade ≥ 4 ANC or PLTS lasting past day 42, or marrow cellularity < 5% at day 42	Grade ≥ 3[d] CRS (with exceptions)[b] Grade ≥ 3 neurotoxicity[e] Other Grade ≥ 3 toxicity [c] (with exceptions for some Grade 3 toxicities)[b,] Grade ≥ 3 acute GVHD or Grade 2 steroid refractory aGVHD[f]
Myeloablative Preparative Regimen (e.g., high-dosage busulfan)	No ANC recovery to > 0.5 Gi/L by day 21 (PBSC), 28 (marrow), or 42 (UCBT)	Grade ≥ 4 organ toxicity[c]

Abbreviations: ANC - absolute neutrophil count, AR – adverse reaction, CAR - chimeric antigen receptor, CRS - cytokine release syndrome, PBSC - peripheral blood stem cells, PLTS - platelet count, SAR - suspected adverse reaction, and UCBT - umbilical cord blood transplantation.

[a] Not applicable in the presence of active MDS. Patients with active MDS are not evaluable for a hematological DLT.

[b] May exclude grade 3 toxicities that resolve within a prespecified time frame (e.g., 72 hours).

[c] Adverse reactions involving neurologic, pulmonary, cardiac, gastrointestinal, genitourinary, renal, hepatic, or cutaneous systems.

[d] Refers to Lee Criteria, 2014 or ASTCT CRS Consensus Grading, 2019.

[e] Refers to ASTCT immune effector cell-associated neurotoxicity syndrome (ICANS) Consensus Grading, 2019 or NCI- CTCAE criteria. In the remainder of the table, grade number refers to NCI-CTCAE criteria.

[f] Refers to MAGIC criteria for grading and applicable to patients who receive allogeneic CART cells or post transplant donor derived CAR T cells.

Appendix 2: Additional Data Files for Marketing Applications for MDS Drugs

The following variables are recommended for custom data files to assist with endpoint adjudication.

Variables That Assist Morphologic Response Assessment

- Study identification number
- Site identification number
- Unique subject number
- Treatment arm
- Date of start of study drug
- Date of last study drug
- Study day of last study drug
- Date of last platelet transfusion prior to CR*
- Study day of last platelet transfusion prior to CR*
- Date of last RBC transfusion prior to CR*
- Study day of last RBC transfusion prior to CR*
- Date of last hematopoietic growth factor use prior to CR*
- Study day of last hematopoietic growth factor use prior to CR*
- Date of CR*
- Study day of CR*
- Date of ANC used for CR response*
- Study day of ANC used for CR response*
- ANC used for CR response*
- Date of ANC used to confirm CR response (≥ 4 weeks following initial CR)*
- Study day of ANC used to confirm CR response (≥4 weeks following initial CR)*
- ANC used to confirm CR response (≥4 weeks following initial CR)*
- Date of hemoglobin used for CR response*
- Study day of hemoglobin used for CR response*
- Hemoglobin used for CR response*
- Date of hemoglobin used to confirm CR response (≥ 4 weeks following initial CR)*
- Study day of hemoglobin used to confirm CR response (≥ 4 weeks following initial CR)*
- Hemoglobin used to confirm CR response (≥ 4 weeks following initial CR)*
- Date of platelet count used for CR response*
- Study day of platelet count used for CR response*
- Platelet count used for CR response*
- Date of platelet count used to confirm CR response (≥ 4 weeks following initial CR)*
- Study day of platelet count used to confirm CR response (≥ 4 weeks following initial CR)*
- Platelet count used to confirm CR response (≥ 4 weeks following initial CR)*
- Date of peripheral blast percentage used for CR response*
- Study day of peripheral blast percentage used for CR response*
- Peripheral blast percentage used for CR response*
- Date of peripheral blast percentage used to confirm CR response (≥ 4 weeks following initial CR)*
- Study day of peripheral blast percentage used to confirm CR response (≥ 4 weeks following initial CR)*
- Peripheral blast percentage used to confirm CR response (≥ 4 weeks following initial CR)*
- Date of marrow used for CR response*

- Study day of marrow used for CR response*
- Marrow blasts percentage used for CR response*
- Presence of persistent dysplasia (yes/no) in marrow at CR response
- Date of relapse from CR*
- Study day of relapse
- Date of transplantation
- Study day of transplantation

* If PR is an endpoint in the study, these measures should also be provided for PR.

Variables That Assist the Transfusion Independence Assessment

- Study identification number
- Site identification number
- Unique subject number
- Treatment arm
- Date of start of study drug
- Date of last study drug
- Study day of last study drug
- RBC transfusion dependence at baseline (yes/no)
- Number of RBC units during baseline period
- Platelet transfusion dependence at baseline (yes/no)
- Number of platelet units during baseline period
- Transfusion dependence for either RBC or platelets at baseline (yes/no)
- Date of last RBC transfusion prior to start of study treatment
- Hemoglobin prior to last RBC transfusion during baseline period
- Date of last platelet transfusion prior to start of study treatment
- Platelet count prior to last platelet transfusion during baseline period
- RBC transfusion independence (TI) criteria met post baseline (yes/no)
- Platelet TI criteria met post baseline (yes/no)
- TI criteria met for both RBC and platelet transfusions post baseline (yes/no)
- Date of start of RBC TI
- Study day of start of RBC TI
- Date of end of RBC TI
- Duration of RBC TI post baseline
- Date of start of platelet TI
- Study day of start of platelet TI
- Date of end of platelet TI
- Duration of platelet TI post baseline
- Date of start of RBC and platelet TI
- Study day of start of RBC and platelet TI
- Date of end of RBC and platelet TI
- Duration of RBC and platelet TI post baseline

- Date of last study follow-up
- Study day of last study follow-up
- Status at last study follow-up (alive and TI, alive and transfusion-dependent, dead, or lost)

Appendix 3: Example Estimand for Treatment of MDS

Clinical Question*:* Does treatment with the investigational drug result in a complete response (CR) + partial response (PR) rate by Month X that is at least x% without the need for additional treatments in patients with MDS eligible for disease modifying therapy?

Estimand Attribute	**Example**	
Population	• ≥ 18 years old • MDS eligible for disease modifying therapy[1] • ≥ 5% blasts in marrow at baseline or present with cytopenias in ≥1 of 3 lineages, as defined in protocol	
Treatment	• Investigational drug	
Endpoint(s)	• CR or PR achieved by Month X. • Success includes: - CR or PR by prespecified criteria by Month X - All testing +/- 14 days from marrow sampling - No new systemic therapy or HSCT before CR or PR - No death prior to CR or PR response Missing baseline or response assessment data is considered a non-response	
Intercurrent Event	***Strategy***	***Description***
• Use of an additional or alternative disease-modifying therapy prior to response.	• Composite	• Use of an additional or alternative disease modifying therapy or HSCT prior to response is considered a nonresponse.
• Death prior to response assessment.	• Composite	• Death prior to response assessment is considered a non-response.
• Discontinued treatment prior to response assessment	• Treatment Policy	• Discontinuation of assigned treatment before response assessment is documented. Data on the main outcome continue to be collected.
• Received hematopoietic growth factor (HGF) and/or transfusions within a prespecified time period prior to response	• Composite	• Use of HGF and transfusions within a prespecified time period prior to response assessment is considered a non-response.
Population-level summary	• Single-arm trial: Proportion (95% CI) of patients with CR or PR by Month X among those who received at least one dose of the investigational drug	

	• Randomized trial: Proportion (95% CI) of patients with CR or PR by Month X who were randomized

[1] Reasons for eligibility for disease modifying therapy may include IPSS-R >3.5 (or higher-risk per contemporary classification system) or relapsed or refractory MDS.

Appendix 4: Example Estimand for Duration of Complete Response (CR)

Clinical Question: What is the duration of CR in patients with MDS eligible for disease-modifying therapy who achieve CR by month X when treated with the investigational drug?

Estimand Attribute	**FDA Recommendation**	
Population	• Treated with Investigational Drug for MDS • CR by Month X	
Treatment	• Investigational drug	
Endpoint(s)	• Duration of CR, defined as time from CR, by Month X, to whichever occurs first: - Hematological relapse per prespecified criteria - Death from any cause Missing data plan needed in SAP	
Intercurrent Event	***Strategy***	***Description***
Death from any cause after achieving CR by Month X	• Composite	• Death is considered an event; document the date of death
MDS relapse per prespecified criteria	• Composite	• MDS relapse is considered an event; document date of recurrence.
Underwent HSCT after achieving CR	• Treatment policy	• Document HSCT and continue to collect data on the main outcome.
Use of an additional or alternative non-protocol therapy for MDS after achieving CR by Month X	• Hypothetical	• Censor at date of last assessment prior to alternative therapy
Population-level summary	Median (95% CI) by Kaplan-Meier and range of duration of CR	