Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment

Guidance for Industry

DRAFT GUIDANCE

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Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 drugs, biological products, therapeutic devices, and cell processing devices[2] for the prevention or treatment of acute graft-versus-host disease (aGVHD) or chronic graft-vs-host disease (cGVHD) after allogeneic hematopoietic stem cell transplantation (HSCT).[3] Specifically, this guidance addresses FDA's current thinking regarding the overall clinical development program and critical design elements for early and late phase trials for the intended populations.

This guidance is not intended to provide advice on the technical aspects of therapeutic or cell-processing devices. For feedback on the technical aspects of these devices, sponsors should request a presubmission meeting from the appropriate Center.[4]

This guidance focuses on clinical trial design, statistical analysis, or other issues specific to aGVHD or cGVHD, and it does not contain a discussion of the general principles regarding statistical analysis, clinical trial design, or drug development. Those general topics are addressed in other guidances for industry, including *E9 Statistical Principles for Clinical Trials* (September

[1] This guidance has been prepared by the Division of Hematological Malignancies 1 in the Center for Drug Evaluation and Research (CDER) in cooperation with the Oncology Center of Excellence (OCE), the Center for Biologics Research and Evaluation (CBER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drugs* include both human drug products and biological drug products regulated by CDER and CBER, unless otherwise specified.

[3] GVHD may also arise in other settings, such as after blood transfusions or after solid organ transplantation. GVHD in settings other than allogeneic HSCT are outside the scope of this guidance. For example, blood irradiators identified by product code MOT are outside the scope of this guidance.

[4] See the guidance for industry and FDA staff *Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program* (June 2023). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

1998)*, E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), and draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019), respectively.[5] Lastly, this guidance addresses only those clinical pharmacology issues that would require specific consideration for drugs intended to prevent or treat aGVHD or cGVHD.

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

Acute graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (cGVHD) are clinical syndromes that may arise after HSCT as a result of immunocompetent donor cells recognizing and reacting to disparity with major or minor histocompatibility antigens on recipient tissues. aGVHD has an acute onset and rapidly progressive course manifested as an inflammatory skin rash, elevated bilirubin, and enteritis with nausea and diarrhea; it generally occurs early after transplantation. cGVHD is marked by a more protracted course with chronic inflammation and/or fibrosis primarily affecting the skin, liver, lungs, and mucosal surfaces; it generally occurs months after transplantation.

The classical approach to prevention of GVHD involves pharmacological or physical methods to deplete alloreactive T cells in the immediate peritransplant setting with or without additional drugs to prevent activation of naive T cells. Should aGVHD or cGVHD occur despite these measures, treatment has depended largely on drugs that impair T cells. Major complications of such profound immunosuppression include serious infections and loss of immunological control of the underlying malignancy. Further basic science investigations have elucidated the molecular mechanisms behind the clinical manifestations of aGVHD and cGVHD, including cytokines, the innate immune system, and components of the adaptive immune system other than T cells. These scientific advances have provided opportunities for development of biomarkers to identify the specific immune dysfunction present in an individual patient and for development of drugs to modulate the immune system with precision rather than to just suppress the immune system broadly.

FDA has previously discussed the challenges with clinical trial design and endpoints for prevention of GVHD and for treatment of aGVHD in a public workshop[6] and has worked with

[5] When final, this guidance will represent the FDA's current thinking on this topic.

[6] "Workshop on Clinical Trial Endpoints for Acute Graft-vs-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation" held on May 19, 2009, in conjunction with the National Heart, Lung, and Blood Institute (NHLBI), National Cancer Institute (NCI), Center for International Blood and Marrow Transplant Research (CIBMTR), American Society for Blood and Marrow Transplantation (ASBMT), and National Institute of Allergy and Infectious Diseases (NIAID).

stakeholders regarding clinical trial design and endpoints for treatment of cGVHD.[7] Given the complexity of the clinical manifestation of aGVHD and cGVHD and the potential for a paradigm shift in the management of GVHD, FDA is providing this guidance with recommendations regarding the design and conduct of clinical trials and the types of supporting data that could facilitate efficient development of drugs and/or certain devices for the prevention or treatment of aGVHD or cGVHD.

III. DEVELOPMENT PROGRAMS

A. General Drug Development Considerations

1. Nonclinical Considerations

- As aGVHD and cGVHD are serious and life-threatening diseases, the recommendations for nonclinical programs described in the guidances for industry *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* (March 2010)*, S9 Nonclinical Evaluation for Anticancer Pharmaceuticals – Questions and Answers* (March 2010)*,* and *Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals* (March 2019) are generally applicable.

- For cellular or gene therapy products being developed for prevention or treatment of GVHD, also refer to 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. Biomarker and Diagnostic Device Considerations

- Sponsors intending to use a GVHD biomarker for regulatory purposes, including as an efficacy endpoint, may obtain feedback from FDA on the clinical validity and analytical validity of the proposed biomarker by requesting a Type C meeting.[8] Sponsor may also obtain feedback from FDA through the formal drug development tool (DDT) qualification process.[9]

[7] Martin, PJ, SJ Lee, D Przepiorka, MM Horowitz, J Koreth, GB Vogelsang, I Walker, PA Carpenter, LM Griffith, G Akpek, M Mohty, D Wolff, SZ Pavletic, and CS Cutler, 2015, National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: VI. The 2014 Clinical Trial Design Working Group Report, Biol Blood Marrow Transplant, 21(8):1343-1359.

[8] See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.

[9] For additional information on the DDT qualification process, see the DDT Qualification Programs web page at www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/default.htm and the guidance for industry and FDA staff *Qualification Process for Drug Development Tools* (November 2020).

- For drugs developed in a population selected on the basis of a biomarker of disease activity, 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 drug.[10] IVDs used in clinical trials of a drug will generally be considered investigational devices, subject to applicable regulations,[11] unless employed for an intended use for which the device is already cleared or approved. Drug sponsors of trials that utilize IVDs may request a study risk determination directly from Center for Devices and Radiological Health (CDRH) or the Center for Biologics Evaluation and Research (CBER) as appropriate, or in concert with the Investigational New Drug application (IND),[12,13] to determine whether an Investigational Device Exemption (IDE) is needed for the proposed trial to proceed under the IND. 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.[14]

3. Clinical Pharmacology Considerations

- Patients with GVHD are commonly prescribed concomitant medications, such as antifungal agents or other immunosuppressants, that are substrates, inducers, or inhibitors of cytochrome P450 (CYP) enzymes, other metabolizing enzymes, or transporters.

  – Sponsors should conduct in vitro metabolism studies to determine if a new GVHD drug is a substrate, inhibitor, or inducer of CYP3A or transporters (e.g., P-glycoprotein [P-gp], organic anion-transporting polypeptide [OATP]) prior to conducting the first clinical trial in patients with GVHD in order to better inform dose selection in the presence and absence of these agents.[15]

  – Sponsors should assess the in vitro ability of new GVHD drugs to act as a substrate or as a perpetrator of other metabolizing enzymes or transporters early in clinical development and to incorporate strategies for dose modifications in

[10] See the guidance for industry and FDA staff *In Vitro Companion Diagnostic Devices* (August 2014).

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

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

[13] See the guidance for industry *Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination* (October 2019).

[14] See the draft guidance for industry and FDA staff *Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product* (July 2016). When final, this guidance will represent the FDA's current thinking on this topic.

[15] See the guidance for industry *In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

clinical trials as warranted if interactions are expected. Additional clinical drug-drug interactions trials may be needed based on the in vitro results.

- Patients with GVHD may have organ impairment due to concurrent medications that affect renal or hepatic function (e.g., calcineurin inhibitors and high-dose chemotherapy, respectively) or due to liver involvement by GVHD. Sponsors should identify elimination pathways of the parent drug and its active metabolites early in drug development, and if renal or hepatic elimination pathways are identified, the sponsor should characterize the impact of organ impairment on the pharmacokinetics (PK) of the parent drug and active metabolites.[16] The impact of GVHD liver involvement on the PK of the parent drug or active metabolites should also be evaluated (e.g., population PK analysis).[17] Dose modifications for renal or hepatic impairment and for GVHD liver involvement should be included in late phase clinical trials.

- Although patients are presumed to be immunocompromised after HSCT, antibody responses may still occur. For biological products, the sponsor should characterize the development of anti-drug antibodies to the new GVHD drug.[18]

4. First-in-Human Trials

- The purpose of the first-in-human (FIH) trial is to identify the recommended phase 2 dose (RP2D) or the range of doses of a new investigational drug to be taken further into clinical development based on PK and pharmacodynamic (PD) data, clinical activity measures, clinical safety data, and tolerability. For additional information on FIH trials by GVHD indication, see Sections III.B.2, III.C.2, and III.D.2

- An accurate characterization of the new investigational drug may be limited when the study population has a high background rate of adverse events or when there are concurrent medications (e.g., preparative regimen, other immunosuppressive drugs, supportive care drugs, etc.) that may affect the PK, PD, or clinical activity. An FIH trial in healthy volunteers may be an alternative in select cases.

  – For the FIH trial, a single-ascending dose (SAD) study, and potentially a subsequent multiple-ascending dose (MAD) study, in healthy volunteers may be considered for drugs that are immunomodulatory, immunosuppressive, or that stimulate tissue repair, depending on the mechanism of action, expected

[16] See the draft guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling* (September 2020; when final, this guidance will represent FDA's current thinking on this topic) and the guidance for industry *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling* (May 2003).

[17] Ibid.

[18] See the guidances for industry *Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection* (February 2019) and *Immunogenicity Assessment for Therapeutic Protein Products* (August 2014).

biological effect, and anticipated exposure duration. FDA recommends that sponsors request feedback on the design of FIH trials of new GVHD drugs in healthy volunteers, including the limitations in exposure and other restrictions needed to protect the study participants.

- Note that due to differences in the constitution of the immune system in healthy volunteers, patients after allogeneic HSCT, and patients with aGVHD or with cGVHD, it is likely that an FIH trial in healthy volunteers will provide only a range of doses suitable for further study in patients with GVHD rather than a RP2D. Nonetheless, narrowing the dose range in this way may accelerate development in the intended population.

5. Early Phase Trials and Dose Optimization

- Sponsors should consider that lymphocyte homeostasis in patients after HSCT, especially those with active aGVHD or cGVHD, may differ from that in healthy volunteers or patients with other immunological disorders. As such, when selecting the starting dose for the clinical trial, the RP2D cannot be assumed to be the same in all populations.

- Since the treatment objective is to prevent GVHD or to ameliorate the signs and symptoms of active aGVHD or cGVHD, substantial toxicity from the study agent should be avoided and escalation to the maximal tolerated dose (MTD) may not be warranted if adequate pharmacological activity occurs at a lower dose. The criteria to be used for selecting the RP2D should be contemplated when designing the dose escalation rules. Ideally, dose escalation would be guided by a target drug level or biomarker rather than toxicity alone. Monitoring for dose-limiting toxicities (DLTs) is still needed in case the MTD is reached before the optimal biological dose (OBD) is found.

- In the absence of an in vitro correlate with efficacy for use as a pharmacodynamic biomarker in the dose escalation rules, the dose-escalation trial for prevention or treatment of GVHD may benefit from a control arm or may need larger cohorts than used in a typical dose-escalation design (e.g., 3+3 design) in order to generate sufficient data to select an OBD.

  - If choosing to expand or back-fill cohorts in the dose-escalation trial, include the criteria to be used to select the dose levels to be expanded.

  - Dose optimization may also be pursued using randomization between doses. For such studies, the cohorts should be large enough to generate sufficient data for exposure-response analyses and need not be designed for formal statistical comparisons of arms for efficacy.

  - Large single-arm expansion cohorts solely for exploratory purposes are discouraged. Any large single-arm trial should have a design based on clear

hypothesis testing, and the protocol should include justification of the sample size proposed.

- The dose and schedule of investigational new GVHD drugs should be optimized in the early phase trials before initiating the pivotal trials.

  - Clinical PK and PD data, clinical activity measures, clinical safety data, and nonclinical pharmacology data should be used to conduct integrated dose-response and exposure-response analyses for activity and safety for dose optimization.

  - Sponsors should evaluate clinical data over a range of dosages and in a sufficient number of patients with adequate duration of follow up to characterize the dose- and exposure-response relationships for efficacy, safety, and PD markers to support the optimal dosage(s) for further clinical development.

  - Dose-escalation trials with small cohorts may provide information to warrant further dose exploration in dose-expansion cohorts (e.g., exploration of a minimum of 2 dose levels with at least 20 participants per dose level) and/or in a randomized dosage-finding trial to generate the additional data needed for dose optimization. These trials need not be powered to demonstrate significant differences in efficacy by dose.

  - For drugs intended for administration for multiple cycles, and especially for drugs given long-term on an outpatient basis, tolerability should be taken into consideration when choosing the dose to be used in the pivotal trial. In general, for drugs intended for long-term administration or over multiple cycles, it is expected that dose modifications or discontinuations for adverse reactions are limited (e.g., at least 80% dose intensity is achieved over multiple cycles for at least 80% of the patients).

- If long-term treatment in the early phase trial is anticipated, the sponsor should provide early study stopping criteria to ensure that accrual does not continue when there is evidence of unacceptable late toxicity. The study protocol should specify the criteria for excess toxicity, the actual bounds for stopping, the basis for the assumptions used in the calculation, and the software/program used to calculate the bounds. The assumptions for the bounds should be based on a toxicity rate that is generally observed for the study population.

- In addition to dose, these early phase trials may also be used to assess other aspects of the treatment regimen, such as the optimal duration of therapy.

- If a therapeutic drug monitoring (TDM) device is needed for safe use of a drug, codevelopment of the TDM device should begin as early as possible in the clinical development timeline.

- For additional information on early phase trials by GVHD indication, see Sections III.B.2, III.C.2, and III.D.2.

6. Drug Combinations

- For testing a new drug as an add-on to an existing drug or standard drug combination for prevention or treatment of GVHD, the submission should include justification for the add-on strategy, including but not limited to a discussion of whether the drugs' mechanisms of action are complementary or potentially antagonistic, whether the patients in the trial were selected based on a specific immune dysfunction targeted by the new drug, whether the combination poses additional risks due to an increase in the degree of immunosuppression, and dosage optimization for the combination.

- Protocols for treatment of aGVHD or cGVHD should include instructions on whether GVHD prophylaxis should be continued when the new drug for treatment is started and whether prior drugs used for treatment of either aGVHD or cGVHD should be stopped or continued. In general, in the absence of a scientific rationale, drugs that failed as prior treatment of aGVHD or cGVHD should be discontinued, and the patients should be receiving the fewest number of immunosuppressive therapies concurrently.

7. Organ-Specific Systemic Therapies

- Organ-specific therapies have systemic exposure and mechanistically target the initiating event, effector mechanism, or tissue regeneration solely in a single organ (e.g., the small intestine) or in multiple related organs (e.g., the GI tract).

- Due to their limited functionality, organ-specific systemic therapies are likely to be developed in combinations with other drugs in order to assure success in aGVHD or cGVHD which affect multi-organs. See Section III.A.4 for caveats regarding combinations of drugs for prevention or treatment of GVHD.

- The clinical trial designs discussed in Sections III.B, III.C, and III.D apply to development of systemically-administered organ-specific therapies. Note, however, that even when an organ-specific claim is being sought, the assessment of any organ-specific benefit should be in addition to a GVHD-free survival (GFS), rather than in lieu of it. For example, in a clinical trial of a treatment to prevent lower GI aGVHD, GFS should be tested as an efficacy endpoint as well as lower GI aGVHD-free survival. Whether demonstration of an organ-specific effect in the absence of impact on the overall GVHD outcome would be sufficient to support a marketing application will be a review issue. Additional evidence of benefit, such as patient-reported outcomes, may be needed to conclude that the benefit-risk is favorable.

8. Organ-Specific Topical Therapies

- The objective of topical palliative therapies is to provide local symptomatic relief without systemic drug exposure. This guidance does not address clinical trial design for topical palliative treatments for aGVHD or cGVHD that are intended to purely provide symptomatic relief and are not disease-modifying. For advice on developing a topical palliative treatment specifically for aGVHD or cGVHD, sponsors should contact the relevant FDA review Division (e.g., Division of Ophthalmology for topical treatments of ocular GVHD).

B. Prevention of GVHD

1. Efficacy Endpoints

a. GVHD-Free Survival (GFS)

- GFS is the time from date of HSCT to date of onset of a GVHD event or death from any cause (see examples below). For this endpoint, GVHD should be diagnosed and graded or scored using valid criteria.[19] The GVHD event depends on the indication being sought. The following are examples:

  – Grades 2-4 aGVHD GFS: From date of HSCT to first occurrence of Grades 2-4 aGVHD with follow-up through 180 days post HSCT or death

  – Grades 3-4 aGVHD GFS: From date of HSCT to first occurrence of Grades 3-4 aGVHD with follow-up through 180 days post HSCT or death

  – Moderate-to-severe cGVHD GFS: From date of HSCT to first occurrence of moderate-to-severe cGVHD with follow-up through 24 months post HSCT or death

  – Acute and chronic GVHD GFS: From date of HSCT to first occurrence of Grades 2-4 aGVHD or moderate-to-severe cGVHD with follow-up through 24 months post HSCT or death

[19] For examples of diagnostic and staging or scoring criteria that FDA has accepted in marketing applications, see Harris, AC, R Young, S Devine, WJ Hogan, F Ayuk, U Bunworasate, C Chanswangphuwana, YA Efebera, E Holler, M Litzow, R Ordemann, M Qayed, AS Renteria, R Reshef, M Wölfl, YB Chen, S Goldstein, M Jagasia, F Locatelli, S Mielke, D Porter, T Schechter, Z Shekhovtsova, JL Ferrara, and JE Levine, 2016, International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium, Biol Blood Marrow Transplant, 22(1):4-10; and Lee, SJ, D Wolff, C Kitko, J Koreth, Y Inamoto, M Jagasia, J Pidala, A Olivieri, PJ Martin, D Przepiorka, I Pusic, F Dignan, SA Mitchell, A Lawitschka, D Jacobsohn, AM Hall, ME Flowers, KR Schultz, G Vogelsang, and S Pavletic, 2015, Measuring Therapeutic Response in Chronic Graft-versus-Host Disease. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. The 2014 Response Criteria Working Group Report, Biol Blood Marrow Transplant, 21(6):984-999.

- See Appendix 1 for an example estimand for Grades 2-4 aGVHD GFS. Supplementary analyses may include using the hypothetical strategy (censoring) at the time of graft rejection or relapse.

- The planned interval between assessments should be as short as possible in order to ensure that the metric is reliable. For example, monitoring for aGVHD may require assessments weekly through Day 100 and every 4 weeks through Day 180, and monitoring for cGVHD may require assessments at least every 4 weeks. The protocol should specify that the study visit activities should encompass events in the intervening period since the last visit. Optimally, an unscheduled visit should be used to collect data on events occurring between scheduled visits.

- To prevent bias in study conduct, the use of blinded treatments where feasible is recommended for randomized trials that assess GFS.

- The credibility of the GFS endpoint is highly dependent on the completeness of the data, and efforts should be made to minimize missing data. The statistical analysis plan (SAP) should include a plan for addressing missing data.

- For evaluation of GFS, the primary analysis set consists of all patients who received the allograft. With respect to the primary hypothesis testing method, FDA has accepted the log-rank test. Additional summary metrics that should be reported include the hazard ratio and 95% confidence interval.

b. Overall Survival (OS)

- OS is defined as the time from randomization to death from any cause. For evaluation of OS, the primary analysis set consists of all randomized subjects. With respect to the primary hypothesis testing method, FDA has accepted the log-rank test. Additional summary metrics that should be reported include the hazard ratio and 95% confidence interval.

- We recommend including a supplementary analysis of OS using OS defined as the time from the date of HSCT (instead of the date of randomization) to death from any cause.

2. Exploratory Trial Considerations

a. Initial Dose-Escalation Trials

- An FIH trial of a new investigational drug for prevention of GVHD is rarely acceptable. An example of an exception could be for a cell therapy unsuitable for study in a less complex population and where there is no scientific justification for study of the cell therapy outside of the HSCT setting. See additional information in Section III.A.4.

- See Section III.B.3 for caveats regarding patient-related and transplant-related factors to consider when designing an exploratory trial for GVHD prophylaxis. These factors may affect the observed adverse effects at any given dose level, so for single-arm dose-escalation trials in particular, substantial heterogeneity in these factors may preclude conclusions about dose-related toxicity.

- For the initial dose-escalation trial:

  – The patient population should be commensurate with the risk. In general, patients with a good prognosis using standard-of-care (SOC) transplantation procedures (e.g., acute leukemia in first remission or a lower-risk myelodysplastic syndrome with a human leukocyte antigen [HLA]-identical sibling donor) would not be appropriate for inclusion when preliminary evidence of efficacy has not yet been established or there is a known serious risk with the investigational drug.

  – The observation period for DLTs should be at least 28 days. For drugs with a known or expected delayed onset of adverse events or with a prolonged half-life, a longer observation period may be needed. For regimens that begin prior to transplantation and extend for several months, the DLT observation period should include the period of peak regimen-related toxicity (from start of therapy through Transplant Day 28) and at least an additional 28 days after that period (total 56 days).

  – As GVHD prophylaxis is supportive care, the target regimen should have little moderate toxicity and no severe toxicity. Anticipated adverse reactions may be informed by nonclinical studies, the FIH study in healthy volunteers, and trials in other diseases. However, given that the toxicities of the investigational drug may overlap with those of the preparative regimen, or that the investigational drug may exacerbate toxicities of the preparative regimen, attribution may not be possible. Therefore, the assessment of DLTs should reflect the need to not increase the risk of known toxicities in transplant recipients. The sponsor should identify the incidence of such toxicities with the background preparative regimen and plan the dose-escalation rule based on that incidence. For example, the 3+3 dose-escalation rule may still apply if the DLT criteria are defined as Common Terminology Criteria for Adverse Events (CTCAE) Grade 4-5 organ toxicities on Transplant Days 0-28.

b. Dose Optimization and Signal Verification

- For trials used for dose selection and efficacy signal verification:

  – Due to the impact of many concurrent factors on the occurrence of GVHD and on survival after transplantation (see Section III.B.3), and due to the uncertainty regarding the natural history of GVHD in populations expected to be included in pre-emption trials, historical control data may not be suitable to support design of a single-arm GVHD prevention trial, especially if small treatment effects are

being tested. Consequently, prevention trials beyond the initial dose-escalation phase should generally include a randomized control arm. Adaptive phase 2-3 studies may also be considered.[20] In certain circumstances, randomization among a wide range of doses would also be acceptable.

– See Section III.A.5 for additional considerations for dose optimization.

- As randomized exploratory trials are generally too small and too short in duration for comparative analyses of a time-to-event efficacy endpoint like GFS, one might instead use a short-term binary measure of activity, such as alive without prior Grades 2-4 acute GVHD on Transplant Day 100. The incidence of Grades 2-4 acute GVHD calculated by the cumulative incidence function is generally less credible due to inconsistent rates of competing risks. We consider that such endpoints are exploratory only and would not be suitable as the basis for efficacy in a marketing application.

- Early nonrelapse mortality (NRM) (e.g., prior to 100 days after HSCT) is used commonly in the study stopping rule for safety issues in clinical trials for GVHD, but this metric alone is not sufficient for safety monitoring when there is still uncertainty in the safety profile. Additional potential safety outcomes to monitor would include adverse reactions as defined in the DLT criteria, graft failure, and specific infections. Stopping bounds should be based on the known incidence of these events using the SOC or the same treatment plan without the investigational drug in the same patient population. It is also important to consider monitoring the need for dose reductions or withdrawals due to adverse reactions; for example, a rate of dose reduction or withdrawal greater than 20% may indicate that the dose is too toxic.

3. Pivotal Trial Considerations

a. Indications and Intended Populations

- GVHD prevention trials include studies of prophylaxis and studies of pre-emptive therapy.

– GVHD prophylaxis for HLA-identical related donor HSCT and for matched unrelated donor or other alternative donor HSCT are considered separate indications. Marketing applications seeking both indications should include a trial designed to generate data sufficient to test efficacy in each indication individually or separate trials for each indication.

– Pre-emptive therapy for a selected population with subclinical but no active GVHD and pre-emptive therapy to prevent worsening of GVHD from a lower severity to a higher severity are considered separate indications.

[20] See the guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics* (December 2019).

b. Establishing Clinical Benefit

- GFS is the clinical endpoint that represents clinical benefit for traditional approval for drugs or devices for prevention of GVHD. OS may be used as the primary endpoint, but as there are multiple potential root causes of death after HSCT, OS itself may not be sufficient to establish a treatment effect with regard to prevention of GVHD, so if OS is chosen as the primary endpoint in the pivotal trial to support a marketing application for prevention of GVHD, analysis of GFS should still be planned.

c. Pivotal Trial Design

- Pivotal trials to support a marketing application for prevention of GVHD should be randomized controlled trials. Although such trials generally seek to demonstrate superiority of the arm with the new investigational arm, noninferiority trials may be considered for populations where the expected GFS is high with SOC regimens, especially if the new investigational drug is expected to improve safety or compliance.

- The first pivotal trial for a new GVHD indication should be designed to isolate the treatment effect of the investigational drug.

  – Add-on designs and head-to-head comparisons are both appropriate for this setting (see Appendix 5 Glossary for trial design definitions).

  – For add-on designs, the protocol should use a specific base regimen rather than allowing investigator's choice. For example, because the effectiveness differs for different calcineurin inhibitors (CNI), a study of Drug A plus investigator's choice of CNI versus investigator's choice of CNI alone would not be adequate to isolate the treatment effect of Drug A. Instead, the specific CNI to be used should be identified in the protocol.

- Comparative effectiveness trial designs may be suitable for supplementary indications if the contribution of the drug to the treatment effect was established in a prior trial.

d. Patient and Transplant-Related Factors

- Critical patient-related factors that may impact the risk of GVHD or the survival component of the efficacy endpoint (GFS) should be taken into consideration when determining the eligibility criteria for the trial that will support a marketing application.

  – The eligible population should have sufficient expected survival to allow an adequate follow-up for assessment of GVHD. A good prognosis subgroup (e.g., acute leukemia in first remission) would have the least potential for refractory leukemia or early relapse confounding the assessment of GFS.

- Pediatric patients are known to have a lower risk of GVHD than adults. If a clinical trial includes both adult and pediatric patients, randomization should be stratified by age group.

- Critical transplant-related factors that may impact the risk of GVHD or the survival component of the efficacy endpoint (GFS) should be taken into consideration when determining the treatment plan for the trial that will support a marketing application.

  - The stem cell source may affect the risk of GFS. If the clinical trial allows use of either peripheral blood or marrow stem cells, this should be taken into account at randomization or at analysis.

  - The preparative regimen may affect the risk of relapse and the survival component of GFS. The use of long-acting biologics (such as antithymocyte globulin or anti-CD20 monoclonal antibodies) may affect the risk of GVHD. Ideally, the trial should include a single preparative regimen. If regimens of differing intensity are used, or if the preparative regimen includes a biologic that interacts with the infused stem cells, this should be justified, and there should be a plan to account for this at randomization or at analysis.

e. Treatment Plan

- The instructions for the complete GVHD prevention strategy should be detailed in the protocol.

  - See Sections III.A.4 and III.B.2 for information regarding optimization of the GVHD prevention strategy prior to conduct of the trial that will support a marketing application.

  - When using an SOC base regimen, the dose, administration schedule, and dose modifications for the drugs in the SOC regimen should be included in the protocol to reduce the chance that assessment of the treatment effect of the investigational drug is not confounded by clinical site-specific differences in use of the SOC regimen.

  - Differences in handling early treatment of aGVHD may affect subsequent occurrence of high grade aGVHD or onset of cGVHD. Include in the protocol the minimum recommended first-line treatment for aGVHD that may occur, so that differences in efficacy measures between treatment arms are not inadvertently impacted by differences in early aGVHD treatment.

  - Include in the protocol the recommended schedule of discontinuation or tapering for the investigational drug and for any SOC drugs in the regimen.

f. Marketing Applications

- See Section IV for special data collection considerations for the pivotal trial.

C. Treatment of Acute GVHD

1. Efficacy Endpoints

a. Response

- For documentation of response to treatment of aGVHD, FDA has accepted the definitions below with the response assessment conducted following 4 weeks of therapy (e.g., at the Day-29 visit) and using valid staging criteria for aGVHD.[21]

  – Complete Response (CR): Stage 0 in all organs (skin, liver, and GI tract) and no intervening additional therapy

  – Partial Response (PR): Improvement of at least 1 stage in 1 or more organs without progression in other organs, and no intervening additional therapy

  – Very Good Partial Response (VGPR): Improvement by at least one stage in one or more organs and

    - Skin: No rash or bullae, and residual erythema limited to <25% of the body surface, and

    - Liver: Total serum bilirubin concentration <2 mg/dL or <25 % of baseline at enrollment, and

    - Gut: Tolerating food or enteral feeding, predominantly formed stools, no overt gastrointestinal bleeding or abdominal cramping, no more than occasional nausea or vomiting, and

    - No intervening additional therapy

- See Appendix 2 for an example estimand for treatment of aGVHD.

- A minimum of 180 days of follow-up is required to establish durability of responses. The planned interval between assessments should be no less frequently than weekly for the first 8 weeks and at least monthly thereafter through Study Day 180. The protocol should specify that the study visit activities should encompass events in the intervening period since the last visit.

[21] See footnote 19.

- There are two measures of durability of the response as defined below. Both measures of durability of response are of interest for the evaluation of clinical benefit.

  – Duration of response (DOR) is defined as the time from the Day 28 response to the day of progression,[22] new systemic therapy for aGVHD,[23] or death from any cause, whichever occurs first. See Appendix 3 for an example estimand for duration of CR.

  – An additional measure of durability that considers the natural history of aGVHD, which may flare and resolve without additional systemic treatment, is defined as the time from the Day 28 response to the day of new systemic therapy for aGVHD or death from any cause, whichever occurs first.

- For the evaluation of response in randomized trials, the analysis set consists of all randomized patients. In single-arm trials, the analysis set is all patients who received any dose of study drug. The proportions of subjects achieving response and 95% confidence intervals should be reported. For a randomized trial, the primary analysis should use the difference in proportions to quantify the treatment effect.

- For the adjudication of response at Study Day 28, missing data is considered a failure. For the adjudication of DOR, the SAP should include a plan for addressing missing data.

b. Overall Survival (OS)

- See Section III.B.1.b. for the definition of OS.

2. Exploratory Trial Considerations

a. Initial Dose-Escalation Trials

- Conducting an FIH trial in patients with active aGVHD, a life-threatening disease, is discouraged; the doses used in the first cohorts may be subtherapeutic, and the assessment of toxicity may be confounded by adverse events due to the underlying GVHD or concomitant medications. If the product characteristics preclude study in an alternative population (see Section III.A.4), sponsors should consider a SAD window study in patients with aGVHD to identify a pharmacologically-active dose before commencing a MAD trial in this population.

- See Section III.C.3 for caveats regarding disease-related and treatment-related factors to consider when designing an exploratory trial for treatment of aGVHD.

[22] Progression is defined as worsening by one stage from nadir in any organ without improvement in other organs in comparison with the prior response.

[23] For the purposes of assessing DOR, new systemic therapy is defined as any new systemic treatment for aGVHD or an increase in the dose of corticosteroids to methylprednisolone equivalent (MPE) 2 mg/kg (±10%) or more.

- The patient population should be commensurate with the risk.

  – The benefit-risk assessment of a new drug that has a moderate degree of adverse events without preliminary evidence of activity for aGVHD may not be appropriate to study in patients with the least severe aGVHD who have a high response rate with topical therapy or first-line systemic corticosteroids alone.

  – Until the safety profile of the drug is better known, enrollment into early phase exploratory studies should be limited to patients who have achieved post-transplant neutrophil recovery.

- Dose escalation decision rules should take into consideration the need to minimize Grade 2 organ toxicities and avoiding any Grade 3 or higher toxicities.

- Trials to treat aGVHD would be expected to have a limited duration of treatment. Sponsors should specify the duration of treatment (e.g., to time of resolution of aGVHD) in the protocol. When treatment in the dose-escalation trial is planned to extend beyond Day 28, a rationale should be provided for the proposed duration of treatment. For patients who are taken off the investigational drug after achieving a CR, the protocol may also address retreatment in case of recurrence of aGVHD.

b. Dose Optimization and Signal Verification

- Response is the appropriate efficacy endpoint in exploratory trials of aGVHD treatments. For additional information, see Section III.C.3.

- The effects of the study drug in patients on steroids alone and in those on steroids plus a CNI or another systemic immunosuppressant medication should be tested.

- See Section III.A.5 for additional considerations for dose optimization.

3. Pivotal Trial Considerations

a. Indications and Intended Populations

- First-line therapy for aGVHD, therapy for steroid-refractory aGVHD (SR-aGVHD), and therapy for patients who have failed a prespecified number of lines of therapy represent three distinct indications. A separate trial for each indication is recommended, but prespecified analyses in separate cohorts in a single trial may also be used to support each indication independently. If sponsors intend to pursue multiple indications on the basis of one trial (e.g., treatment of SR-aGVHD and treatment of aGVHD failing two or more therapies), ensure that the protocol clearly describes the eligibility criteria for each cohort and that the trial design is adequate to provide evidence of effectiveness for each indication. Include the following in consideration of the intended population:

703 – For studies of first-line therapy for aGVHD, patients should not have been treated
704 with ≥1 mg/kg methylprednisolone equivalents (MPE) for more than 72 hours
705 prior to start of study drug.
706
707 – FDA considers the following criteria to be acceptable to define SR-aGVHD:
708
709 ▪ progressed after 3 days of treatment with MPE ≥2 mg/kg/day,
710
711 ▪ did not improve after 7 days of treatment with MPE ≥2 mg/kg/day,
712
713 ▪ progressed to a new organ after treatment with MPE ≥1 mg/kg/day for
714 isolated skin and/or upper GI GVHD, or
715
716 ▪ recurred during or after a steroid taper.
717
718 – At the present time, there are no standardized criteria for refractory to or failing a
719 prior therapy. Protocols for patients failing a prespecified number of lines of
720 therapy should include justification for how failure is defined.
721
722 b. Establishing Clinical Benefit
723
724 • Response endpoints have been used for traditional approval for treatments of
725 aGVHD.
726
727 – OR (defined as CR+PR) following 4 weeks of therapy is a clinical endpoint
728 accepted by FDA for traditional approval.
729
730 – For the purposes of demonstrating superiority, improvements in more
731 conservative endpoints may be considered. VGPR, a subset of PR with very
732 limited residual manifestation of disease, may be used in place of PR (e.g., the
733 endpoint would be CR + VGPR). Additionally, CR alone may be used as the
734 primary endpoint.
735
736 – As there are multiple potential root causes of death after HSCT, OS itself may not
737 be sufficient to establish a treatment effect with regard to treatment of aGVHD, so
738 if OS is chosen as the primary endpoint in the pivotal trial to support a marketing
739 application for aGVHD treatment, analysis of response should still be planned.
740
741 c. Pivotal Trial Design
742
743 • The first pivotal trial of a new indication for treatment of aGVHD should be designed
744 to isolate the treatment effect of the investigational drug.
745
746 • Pivotal trials to support a marketing application for first-line treatment of aGVHD
747 should be randomized controlled trials.
748

- Add-on designs and head-to-head comparisons are both appropriate (see Appendix 5 Glossary for definitions).

- Although such trials generally seek to demonstrate superiority of the arm with the new investigational drug, noninferiority trials may be considered for populations where the expected response is high with SOC regimens, especially if the new investigational drug is expected to improve safety or compliance.

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

- Enrollment on randomized trials should be stratified by factors associated with the likelihood of response, including a measure of aGVHD severity and patient age.

- For investigational drugs intended for use in second or later lines of therapy when a highly effective SOC therapy is available, the sponsor should conduct a randomized controlled trial to support a marketing application.

- In some cases, such as when the intended population has refractory disease and there are no available therapies, a marketing application might be supported by positive results from a single-arm trial. The sample size of the trial would need to be sufficient to show a meaningful clinical benefit and exclude an overall response rate (ORR) that is not meaningful for the intended population.

d. Patient-Related Factors

- Critical patient-related factors that may impact treatment response should be taken into consideration when determining the eligibility criteria, study design, and efficacy analyses.

  - Patients may have active disease at screening that may then improve due to changes in steroid dosing prior to start of study drug. Ensure that the protocol has an assessment of aGVHD on the day that the investigational drug is started. Include in the SAP how to handle patients who are responding to steroids or other pretreatment on the day that the investigational drug is started.

  - Pediatric patients may have response profiles that differ from adults. If a clinical trial includes both adult and pediatric patients, randomization should be stratified by age group. For conducting clinical investigations in pediatric populations, also refer to the draft guidance for industry, sponsors, and IRBs *Ethical Considerations for Clinical Investigations of Medical Products Involving Children* (September 2022)[24] and guidance for industry, *E11 (R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018).

[24] When final, this guidance will represent the FDA's current thinking on this topic.

- Baseline disease severity is a prognostic factor for aGVHD.
  - Provide objective criteria for categorizing aGVHD severity. Include the data or references to support the validity of the criteria.
  - If the eligible population is heterogeneous with regard to aGVHD severity, randomization should be stratified by a valid clinical or biomarker-based severity categorization.

- The wide array of drugs and methods used to prevent GVHD or treat aGVHD may results in a heterogeneity in specific aspects of immune dysfunction in patients presenting for treatment of aGVHD, especially for those with recurrent or refractory disease. The protocol should address how prior and concurrent GVHD drugs are taken into account when assessing efficacy outcomes.

e. Treatment Plan

- The treatment plan should be detailed in the protocol.
  - See Sections III.A.4 and III.B.2 for information regarding optimization of the regimen for treatment of aGVHD prior to conduct of a trial to support a marketing application.
  - In all cases, in order to ensure that the treatment effect of the investigational drug can be assessed in the trial, consider carefully what immunosuppressive drugs can be continued from the prestudy period to the on-study period. In general, drugs for long-term prophylaxis, such as CNIs, can be continued in the absence of a pharmacological contraindication (see Section III.A.5), but continued use of other treatments of aGVHD would need to be justified.
  - The protocol should include a plan for tapering immunosuppression, including steroids, any other drugs being continued for the treatment of aGVHD, and the drugs used for GVHD prophylaxis. The protocol should also specify the order in which drugs are to be tapered. The experience with these immunosuppression tapering instructions will provide the basis for standardized instructions in labeling.
  - We recommend that information be collected for the first aGVHD treatment administered after completion of study drug administration.
  - Consider providing for retreatment with the investigational drug in patients who respond initially and then have recurrence of aGVHD.

f. Marketing Applications

- See Section IV for special data collection considerations for the pivotal trial.

D. Treatment of Chronic GVHD

1. Efficacy Endpoints

a. Response

- For documentation of response to treatment of cGVHD, FDA has accepted the definitions below with the response assessments conducted serially through 6 months of therapy (e.g., up to and including the Week 25 visit) and using valid staging criteria for cGVHD.[25]

  – Complete Response (CR): Has no clinically active disease as defined by the organ-level complete response criteria in all organs,[26] and no intervening new therapy since start on study treatment.[27]

  – Partial Response (PR): Meets organ-level partial response criteria in one or more organs without progression[28] in any other organ in comparison to study baseline, and no intervening new therapy from study baseline.[29]

- See Appendix 4 for an example estimand for treatment of cGVHD.

- A minimum of 1 year of follow-up is required to establish durability of responses. The planned interval between assessments should be no less frequently than every 2-3 weeks for the first 6 months and at least every 3 months thereafter through completion of 1 year of follow-up. The protocol should specify that the study visit activities should encompass events in the intervening period since the last visit.

- There are two measures of durability of the response as defined below. Both measures of durability of response are of interest for the evaluation of clinical benefit.

[25] See footnote 19.

[26] Note that the overall response definition uses only the organ-level criteria and does not include the Global Score criteria. Additionally, for CR, the organ-level criteria should be met without regard to previous organ involvement (i.e., in order to exclude involvement of new organs, the response assessment requires data in all organs rather than just those involved at study baseline). PR can be excluded with partial data if there is progression from study baseline in any organ.

[27] For the purposes of assessing response and durability of response, new systemic therapy is defined as any new systemic treatment for cGVHD or an increase in the dose of corticosteroids to prednisolone equivalent (PE) 1 mg/kg (±10%) or more.

[28] See footnote 26.

[29] See footnote 27.

- Duration of response (DOR) is defined as the time from the date of first response to the date of progression,[30] new systemic therapy for cGVHD,[31] or death from any cause, whichever occurs first.

- An additional measure of durability that considers the natural history of cGVHD, which may flare and resolve without additional systemic treatment, is defined as the time from the date of first response to the date of new systemic therapy for cGVHD or death from any cause, whichever occurs first.

- For the evaluation of response in randomized trials, the analysis set consists of all randomized patients. In single-arm trials, the analysis set is all patients who received any dose of study drug. The proportions of subjects achieving response and 95% confidence intervals should be reported. For the primary analysis in a randomized trial, difference in proportions should be used to quantify the treatment effect.

- The credibility of the endpoints is dependent on the completeness of the data, and efforts should be made to minimize missing data. For adjudication of response and for adjudication of DOR, the SAP should include a plan for addressing missing data.

b. Overall Survival (OS)

- See Section III.B.1.b. for the definition of OS.

c. Patient-Reported Outcomes (PRO)

- PROs based on the symptoms of active cGVHD or residual effects of cGVHD may also be considered as the basis for an efficacy claim.

- The PRO tool should be validated for the context of use[32] and be age-appropriate. Examples of contexts of use include treatment of multisystem cGVHD agnostic of line of therapy, treatment of chronic ocular sicca due to irreversible lacrimal gland damage, etc.

- The PRO measure or concept of interest proposed to denote clinical benefit (e.g., change in symptom burden) should be well-defined and reliable. Given the heterogeneity in organ involvement by cGVHD, careful consideration should be given to whether the concept of interest is organ-specific or total score derived from multiple organs. Additionally, adequate follow-up is required to establish that the durability of the observed benefit is clinically meaningful. We recommend that

[30] For assessment of DOR, progression from nadir in an organ is defined as worsening according to the organ-level criteria from best prior organ status independent of changes in any other organ.

[31] See footnote 27.

[32] For additional information, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

sponsors submit the PRO development package and proposed statistical analysis plan to FDA for feedback prior to use of the PRO in a trial to support a marketing application.

d. Other Potential Measures of Efficacy

- FDA acknowledges that the ultimate goal for treatment of cGVHD is to promote restoration of tolerance, and as such, efficacy endpoints that reflect complete resolution of clinical disease that is durable in the absence of systemic therapy would be of interest. 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 feedback from FDA about the acceptability of the proposed novel endpoint prior to initiating the trial.

2. Exploratory Trial Considerations

a. Initial Dose-Escalation Trials

- Conducting an FIH trial in patients with active cGVHD may be challenging due to the confounding by adverse events due to the underlying GVHD or concomitant medications. Additionally, the benefit-risk may not be favorable for conduct of such a trial in patients with newly diagnosed cGVHD where there is an established SOC, and it would not be acceptable to conduct an FIH study as a combination with SOC. See Section III.A.4 for additional information.

- See Section III.D.3 for caveats regarding disease-related and treatment-related factors to consider when designing an exploratory trial for treatment of cGVHD.

- The patient population should be commensurate with the risk. The benefit-risk assessment of a new drug that has a moderate degree of adverse events without preliminary evidence of activity for cGVHD may not be appropriate to study in patients with mild cGVHD who have a high response rate with topical therapy or first-line systemic corticosteroids alone.

- Dose escalation decision rules should take into consideration the need to minimize Grade 2 organ toxicities and avoiding any Grade 3 or higher toxicities.

- Intra-patient dose escalation may be considered in select circumstances where risks can be minimized objectively. 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 dose to a higher level if that higher dose has been established as safe in subsequent cohorts. The protocol should specify the criteria for when intra-patient dose escalation is allowed, how the new dose is assigned, any changes in the monitoring plan needed to accommodate the change in dose, 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.

  - Long-term treatment may be considered in the dose-escalation trial, but when treatment is planned to extend beyond achievement of CR, a rationale should be provided for the proposed duration of treatment after response, and there should be objective criteria for when to discontinue treatment permanently.

  - For patients who are taken off the investigational drug after achieving a CR, the protocol may also address retreatment in case of recurrence of cGVHD.

- Early phase trials are also 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 pivotal trials designed to test for efficacy.

b. Dose Optimization and Signal Verification

- Response is the appropriate efficacy endpoint in exploratory trials of cGVHD treatments. For additional information, see Section III.D.3.

- The effects of study drug in patients on steroids alone and in those on steroids plus a CNI or another systemic immunosuppressant medication should be tested.

- See Section III.A.5 for additional considerations for dose optimization.

3. Pivotal Trial Considerations

a. Indications and Intended Populations

- First-line therapy for cGVHD, therapy for steroid-refractory cGVHD (SR-cGVHD), and therapy for patients who have failed a prespecified number of lines of therapy represent three distinct indications. A separate trial for each indication is recommended, but prespecified analyses of separate cohorts in a single trial may also be used to support each indication independently. If sponsors intend to pursue multiple indications on the basis of one trial (e.g., treatment of SR-GVHD and treatment of cGVHD failing two or more therapies), ensure that the protocol clearly describes the eligibility criteria for each cohort and that the trial design is adequate to provide evidence of effectiveness for each indication.

- Include the following in consideration of the intended population:

  - For studies of first-line therapy for cGVHD, patients should not have been treated with ≥1 mg/kg prednisone equivalents (PE) for more than 72 hours prior to start of study drug.

- FDA considers the following criteria to be acceptable to define cGVHD that failed steroids:
  - Manifestations progress despite the use of ≥1 mg/kg/day PE for at least 1 week,
  - Manifestations persist without improvement despite treatment with ≥0.5 mg/kg/day or 1 mg/kg every other day for at least 4 weeks,
  - Recurrence after a CR, or
  - Progression after a PR.
- At the present time, there are no standardized criteria for refractory to or failing a prior therapy with other drugs. Protocols for patients failing a prespecified number of lines of therapy should include justification for how failure is defined. If the intended population is one failing treatment with a specific drug, the submission should include data to support the criteria used to define "failure" for that drug.
- Patients with active cGVHD who are steroid-intolerant may not have the same response profile as those who are actually refractory to or recurrent after steroids or other treatments. Patients with steroid intolerance as the only treatment failure should be excluded in a study for treatment of steroid-refractory cGVHD.
- Patients with steroid-dependent cGVHD, i.e., those who recur during steroid taper and respond with an increase in steroid dose, would not be evaluable for response to a new treatment if the cGVHD resolved with the increased dose of steroids. Patients with steroid-dependent cGVHD should not be included in cGVHD treatment trials.

b. Establishing Clinical Benefit

- OR (defined as CR+PR) at any time within the first 6 months of treatment is a clinical endpoint accepted by FDA for traditional approval with supporting data on a clinically meaningful measure of durability.
- For the purposes of demonstrating superiority, improvements in more conservative endpoints, such as CR alone, may be considered.
- As there are multiple potential root causes of death after HSCT, OS itself may not be sufficient to establish a treatment effect with regard to treatment of cGVHD, so if OS is chosen as the primary endpoint in a trial to support a marketing application for cGVHD treatment, analysis of response should still be planned. A randomized trial is required to assess OS.

- As cGVHD is a chronic symptomatic disorder, a PRO endpoint may also be considered. When used as the basis of a claim for a systemic treatment of active cGVHD, the PRO endpoint should be supported by data showing that the treatment also has a direct effect on the clinical manifestations of cGVHD. A randomized trial is required to support indication for symptomatic improvement.

- There is currently no established endpoint to support a claim of "steroid-sparing" in the treatment of cGVHD. Sponsors who plan to pursue such a claim should seek input from FDA early in clinical development.

c. Pivotal Trial Design

- The first pivotal trial for a new indication for treatment of cGVHD should be designed to isolate the treatment effect of the investigational drug.

- Pivotal trials to support a marketing application for first-line treatment of cGVHD should be randomized controlled trials.

  - Add-on designs and head-to-head comparisons are both appropriate (see Appendix 5 Glossary for definitions).

  - Although such trials generally seek to demonstrate superiority of the arm with the new investigational arm, noninferiority trials may be considered for populations where the expected response is high with SOC regimens, especially if the new investigational drug improves safety or compliance.

  - To prevent bias in study conduct, the use of blinded treatments where feasible or blinded assessors is recommended for randomized trials. For studies with a PRO endpoint, the use of blinded treatments is essential for the credibility of the PRO results.

- In second or later lines of therapy when a highly effective SOC therapy is available, a randomized trial should be used to support the marketing application.

- In some cases, such as when the intended population has refractory disease and there are no available therapies, a marketing application might be supported by positive results from a single-arm trial. The sample size of the trial would need to be sufficient to show a meaningful clinical benefit and exclude an ORR that is not meaningful for the intended population.

d. Patient-Related Factors

- Critical patient-related factors that may impact treatment response, OS, or PROs should be taken into consideration when determining the eligibility criteria, study design, and efficacy analyses.

- Patients may have active disease at screening that may then improve due to changes in steroid dosing prior to start of study drug. Ensure that the protocol has an assessment of cGVHD on the day that the investigational drug is started. Include in the SAP how to handle patients who are responding to steroids or other pretreatment on the day that the investigational drug is started.

- Pediatric patients may have response profiles that differ from adults. If a clinical trial includes both adult and pediatric patients, randomization should be stratified by age group.

- Studies of new systemic cGVHD treatments generally include patients with moderate or severe disease.

  - Within the severe category, justification should be provided for the criteria used to exclude patients with fibrosing manifestations considered irreversible, such as advanced bronchiolitis obliterans, who would not be expected to respond to anti-inflammatory drugs.

  - If the eligible population is heterogeneous with regard to cGVHD severity, randomization should be stratified by a valid clinical or biomarker-based severity classification.

- Subcategories of cGVHD (e.g., classic, overlap, etc.) may be associated with prognosis. If eligibility criteria include all subcategories, the potential impact of these subcategories on efficacy outcomes should be addressed either at randomization or in the efficacy analysis.

- The wide array of drugs and methods used to prevent GVHD, treat aGVHD, and treat cGVHD may result in a heterogeneity in specific aspects of immune dysfunction in patients presenting for treatment of cGVHD, especially for those with recurrent or refractory disease. The protocol should address how prior and concurrent GVHD drugs are taken into account when assessing efficacy outcomes.

- It is acknowledged that cGVHD may occur after HSCT independent of the risk of relapse of the underlying malignancy, so clinical trials of new drugs for cGVHD should not exclude patients based on the risk of relapse. However, since relapse may occur during the expected 1-year follow-up for patients in cGVHD treatment trials, the statistical analysis plan should address the potential impact of fatal relapse on the OS endpoint in trials using OS as an endpoint.

- For trials that include a PRO endpoint, consideration should be given to the minimum burden of symptoms required for eligibility to allow detection of a response to treatment.

e. Treatment Plan

- The treatment plan should be detailed in the protocol.

  – See Sections III.A.4 for information regarding optimization of the dose and administration schedule for new cGVHD drugs prior to conduct of the trial that will support a marketing application.

  – To ensure that the treatment effect of the investigational drug can be assessed in the trial, which immunosuppressive drugs can be continued from the prestudy period to the on-study period must be considered carefully. In general, drugs for long-term prophylaxis, such as CNIs, can be continued in the absence of a pharmacological contraindication (see Section III.A.5), but continued use of other treatments of cGVHD would need to be justified. A rationale should be provided as to how the impact of the heterogeneity in background therapy will be controlled in the assessment of the efficacy endpoint.

  – The protocol should include a plan for tapering immunosuppression, including steroids, any other drugs being continued for the treatment of cGVHD, and the drugs used for GVHD prophylaxis. The protocol should also specify the order in which drugs are to be tapered. The experience with these immunosuppression tapering instructions will provide the basis for standardized instructions in labeling.

  – We recommend that information be collected for the first cGVHD treatment administered after completion of study drug administration.

  – Consider providing instructions for retreatment of patients who respond initially and then have recurrence of cGVHD.

f. Marketing Applications

- See Section IV for special data collection considerations for the pivotal trial.

IV. MARKETING APPLICATIONS

A. Assessment of Efficacy

- Assessments of efficacy in GVHD clinical trials are generally based on objective criteria. However, collection of only the investigator-determined GVHD stage or only the investigator-determined response is not sufficient to document efficacy. Case Report Forms (CRFs) should be designed to collect the raw data for efficacy assessments in order to allow independent adjudication. Ensure that the protocol stipulates an appropriate window for the primary efficacy assessment and that missing data are minimized.

- To assist with FDA's review of responses, the raw data supporting the study endpoints should be submitted in the marketing application.

  – For GVHD prevention trials, the raw data file should include all variables needed to assess for aGVHD and cGVHD (listed in the next two bullets) at each prespecified study visit and at unscheduled visits for new onset of aGVHD or cGVHD or for a change in grade or score, respectively.

  – For treatment of aGVHD trials, the raw data file should include all variables needed to apply the proposed staging system. For example, for standardized staging of aGVHD,[33] the following would be needed at each study visit: total bilirubin, diarrheal stool output episodes or volume, presence of grossly bloody stool, severe abdominal pain, skin rash percentage, presence of erythroderma with bullae or desquamation, presence of persistent nausea, vomiting or anorexia, and additional explanatory comments.

  – For treatment of cGVHD trials, the raw data file should include all variables needed to apply the proposed scoring system. For example, for use of the 2014 National Institutes of Health (NIH) Consensus Criteria[34] for cGVHD response, the following would be needed at each study visit: skin score (0-3), eye score (0-3), modified OMRS (0-12), esophagus score (0-3), UGI score (0-3), LGI score (0-3), lung score (0-3), FEV-1 (% predicted), joint score (0-3), P-ROM for each joint (4-7), total bilirubin, ALT, alkaline phosphatase, and additional explanatory comments for each.

- Sponsors are encouraged to develop an algorithmic approach using the raw data for independent assessment of efficacy. If such an algorithmic approach is used, the submission should include well-commented programs to replicate the output using only the submitted datasets and a detailed description of the algorithm, including a pseudocode.

- To allow FDA to confirm the analyses of the treatment effect, the submission should include an efficacy summary file with all enrolled patients for the pivotal study and for the integrated efficacy population.

[33] Harris, AC, R Young, S Devine, WJ Hogan, F Ayuk, U Bunworasate, C Chanswangphuwana, YA Efebera, E Holler, M Litzow, R Ordemann, M Qayed, AS Renteria, R Reshef, M Wölfl, YB Chen, S Goldstein, M Jagasia, F Locatelli, S Mielke, D Porter, T Schechter, Z Shekhovtsova, JL Ferrara, and JE Levine, 2016, International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium, Biol Blood Marrow Transplant, 22(1):4-10.

[34] Lee, SJ, D Wolff, C Kitko, J Koreth, Y Inamoto, M Jagasia, J Pidala, A Olivieri, PJ Martin, D Przepiorka, I Pusic, F Dignan, SA Mitchell, A Lawitschka, D Jacobsohn, AM Hall, ME Flowers, KR Schultz, G Vogelsang, and S Pavletic, 2015, Measuring Therapeutic Response in Chronic Graft-versus-Host Disease. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. The 2014 Response Criteria Working Group Report, Biol Blood Marrow Transplant, 21(6):984-999.

  - For GVHD prevention trials, the summary file should include variables such as: date of randomization (if applicable), treatment start date, transplantation date, date of onset of grades 2-4 aGVHD, date of onset of grades 3-4 aGVHD, date of onset of cGVHD, data of onset of moderate-to-severe cGVHD, date of first new systemic therapy for aGVHD or cGVHD, date of relapse, date of first new systemic therapy for treatment of relapse, date of death, date of last GVHD assessment.

  - For treatment of aGVHD trials, the summary file should include variables such as: date of randomization (if applicable), treatment start date, Day-28 date, Day-28 response, date of first new systemic therapy, date of first organ progression from nadir after Day 28, date of death, date of last aGVHD assessment.

  - For treatment of cGVHD trials, the summary file should include variables such as: date of randomization (if applicable), treatment start date, date of first response, first response, date of best response, best response, date of first new systemic therapy, date of first organ progression from nadir, date of death, date of last cGVHD assessment.

- Baseline demographic and disease characteristics are used to ensure consistency of the benefit-risk assessment in subgroup analyses. The following key information should be documented, collected on the CRFs, and submitted in the datasets supporting a marketing application:

  - Transplant information: Preparative regimen intensity, stem cell type, degree of patient-donor histocompatibility

  - GVHD prevention used: Prophylaxis regimen and/or graft manipulation to prevent GVHD.

  - GVHD treatments: All prior treatments of aGVHD and cGVHD. If collected as part of the Concomitant Medications data file, include a variable to identify the line of therapy.

- Regarding the on-study concomitant medications, include a variable for corticosteroid dose as MPE for aGVHD treatment trials and as PE for cGVHD treatment trials.

- Measurement of biomarkers and submission of the assay results are encouraged. See also Section III.A.2.

- Sponsors planning to use real world data[35] to support a GVHD drug marketing application should consult with FDA at the time of protocol development to ensure that the data sources will provide the data needed to assess the treatment effect. Important considerations include whether the sources capture the individual data elements needed to derive clinically accepted endpoints for demonstrating efficacy, and if so, the extent of misclassification, the timing and the frequency of assessment. Sponsors should plan for additional discussions regarding alternative measures if the data sources do not capture the key elements of the clinically accepted endpoints.

B. Assessment of Safety

- 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 the primary disease, an adverse drug reaction, or an unrelated intercurrent event (such as a car accident). Given the complexity of determining the root cause of death after allogeneic transplantation, we recommend that the analysis plan prespecify the details of a standardized approach[36] that will be applied to determining the root cause of death.

- As most drugs for treatment or prevention of GVHD have immunosuppressive properties, the submission should include a detailed analysis of infections.

- In addition to the adverse reactions due to class effects, the following transplant-related events should be considered in the analysis of adverse events of special interest: graft failure, relapse, post-transplantation lymphoproliferative disease, bleeding, nonrelapse mortality, overall survival.

- Plan to collect all-grade adverse events through at least 5 half-lives or 28 days (whichever is longer) from the last dose of study drug unless you have data that the biological effect extends beyond that period. For the longer-term follow-up, collection of related serious adverse events, relapse, and survival data are recommended.

[35] For additional information and guidances pertaining to real world data, see "*Real-World Evidence*" at https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence.

[36] See an example as published in Copelan, E, JT Casper, SL Carter, JA van Burik, D Hurd, AM Mendizabal, JE Wagner, S Yanovich, and NA Kernan, 2007, A Scheme for Defining Cause of Death and Its Application in the T Cell Depletion Trial, Biol Blood Marrow Transplant, 13:1469-1476.

APPENDICES

Appendix 1. Example Estimand for Prevention of Graft-versus-Host Disease (GVHD)

Clinical Question: Does the addition of the investigational drug product to a standard GVHD prophylaxis regimen improve acute GVHD (aGVHD) GVHD-free survival (GFS)?

Estimand Attribute	**Example**	
Population	• ≥12 years old • AML, MDS, or ALL in CR1 or CR2 • Planned for allogeneic HSCT with a matched unrelated donor	
Treatment	• Standard GVHD prophylaxis • Randomized study drug (investigational product or blinded placebo) through day + X post-HSCT	
Endpoint(s)	• Grades 2-4 aGVHD-free survival from HSCT through Day + 180 post-HSCT • Event 1: Death • Event 2: Grade 2-4 aGVHD Missing data plan is needed in the SAP	
Intercurrent Event	***Strategy***	***Description***
• Discontinuation of assigned treatment before Day 180	• Treatment Policy	• Discontinuation of assigned treatment before Day 180 visit is documented. Data on the main outcome are continued to be collected.
• Occurrence of graft failure	• Treatment Policy	• Occurrence of graft failure before Day 180 visit is documented. Data on the main outcome are continued to be collected.
• Use of a nonprotocol new systemic GVHD therapy before Day 180 without the occurrence of GVHD	• Treatment Policy	• Use of a new systemic therapy before Day180 visit is documented. Data on the main outcome are continued to be collected.
• Use of a nonprotocol new systemic GVHD therapy before Day 180 for treatment of cGVHD	• Treatment Policy	• Use of a new systemic therapy before Day180 visit is documented. Data on the main outcome are continued to be collected.
• Use of a nonprotocol new systemic GVHD therapy before Day 180 for treatment of aGVHD	• Composite	• Occurrence of aGVHD is considered an event.
• Death prior to onset of GVHD before Day 180	• Composite	• Death prior to Day 180 is considered an event.
• Relapse of primary malignancy	• Treatment Policy	• Relapse of primary malignancy is documented. Data on the main outcome are continued to be collected.
Population-level summary	Hazard ratio (95% CI) for the randomized population	

Abbreviations: ALL - acute lymphoblastic leukemia, AML - acute myeloid leukemia, CR1 - first complete response, CR2 - second complete response, HSCT - hematopoietic stem cell transplantation, MDS - myelodysplastic syndromes, SAP - statistical analysis plan, SOC - standard-of-care.

Appendix 2. Example Estimand for Treatment of Steroid-Refractory Acute GVHD (aGVHD)

Clinical Question: Does treatment with the investigational drug result in a Day-28 complete response (CR) + partial response (PR) rate that is at least x% without the need for additional treatments in patients with steroid-refractory aGVHD?

Estimand Attribute	**Example**	
Population	• ≥12 years old • Grade 2-4 aGVHD at baseline • Steroid-refractory: – Progressed after 3 days of treatment with 2 mg/kg MPE – No improvement after 7 days of treatment with 2 mg/kg MPE – Progressed to a new organ after treatment with 1 mg/kg MPE for skin or UGI aGVHD – Progressed from nadir during or after a steroid taper • No other prior aGVHD treatment	
Treatment	• Investigational drug through Week X • Continue steroid at current dose • Uniform steroid taper schedule • Continue GVHD prophylaxis	
Endpoint(s)	• Day-28 overall response • Success includes – CR or PR by prespecified criteria at Day 28 visit – Alive at Day 28 visit – No new systemic therapy before Day 28 visit Missing data at baseline or on Day 28 assessment is considered a non-response	
Intercurrent Event	***Strategy***	***Description***
• Discontinuation of assigned treatment before the Day 28 visit	• Treatment Policy	• Discontinuation of assigned treatment before Day 28 visit is documented. Data on the main outcome are continued to be collected.
• Use of a new systemic therapy before Day 28 (includes ≥2 mg/kg MPE)	• Composite	• Use of a new systemic therapy before Day 28 visit is considered a non-response.
• Death prior to the Day 28 visit	• Composite	• Death prior to Day 28 visit is considered a non-response.
• Relapsed of primary malignancy	• Treatment Policy	• Relapsed of primary malignancy is documented. Data on the main outcome are continued to be collected.
Population-level summary	Proportion (95% CI) of patients with CR or PR at the Day 28 visit among those who received at least one dose of the investigational drug	

Abbreviations: MPE - methylprednisolone equivalents, UGI - upper gastrointestinal.

Appendix 3. Example Estimand for Duration of Complete Response (CR)

Clinical Question: What is the duration of CR in patients with steroid-refractory acute GVHD (aGVHD) who achieve Day-28 CR without the need for additional therapies when treated with the investigational drug?

Estimand Attribute	**FDA Recommendation**	
Population	• Treated with Investigational Drug for steroid-refractory aGVHD • CR at the Day-28 visit	
Treatment	• Investigational drug through Week X • Uniform steroid taper schedule • Continue GVHD prophylaxis	
Endpoint(s)	• Duration of CR, defined as time from CR at Day-28 visit to whichever occurs first: − Recurrence of aGVHD in any organ − Initiation of new systemic therapy for aGVHD − Death from any cause Missing data plan needed in SAP	
Intercurrent Event	***Strategy***	***Description***
• Death from any cause after achieving CR on Day 28	• Composite	• Death is considered an event; document the date of death.
• Use of new systemic therapy for aGVHD after achieving CR on Day 28	• Composite	• Use of a new systemic therapy for aGVHD after achieving CR on Day 28 is considered an event; document date of new systemic therapy.
• Use of new systemic therapy for cGVHD after achieving CR on Day 28	• Treatment Policy	• Document relapse and continue to collect data on the main outcome.
• aGVHD recurrence	• Composite	• aGVHD recurrence is considered an event; document date of recurrence.
• Relapse of primary malignancy	• Treatment Policy	• Document relapse and continue to collect data on the main outcome.
• Use of topical therapy for aGVHD	• Treatment policy	• Document new therapy and continue to collect data on the main outcome.
Population-level summary	Median (95% CI) by Kaplan-Meier and range of duration of CR	

Abbreviation: SAP - statistical analysis plan.

Appendix 4. Example Estimand for the First-Line Treatment of Chronic GVHD (cGVHD)

Clinical Question: Does the investigational drug in combination with corticosteroids improve the complete response (CR) rate through the Week 25 visit in patients with new onset cGVHD of moderate to severe intensity without the need for additional new therapy prior to response (CR)?

Estimand Attribute	**FDA Recommendation**	
Population	• ≥12 years old • Moderate to severe new onset cGVHD • No more than x days on PE ≥1 mg/kg for treatment of cGVHD	
Treatment	• Placebo vs investigational drug x dose/schedule • Steroids uniform at PE 1 mg/kg/day • Uniform steroid taper schedule • May continue CNI or sirolimus prophylaxis • May continue topical therapies	
Endpoint	• CR achieved by Week 25 visit. • Success includes − CR by Week 25 visit − No new systemic therapy before CR − No death prior to Week 25 visit Missing data at baseline or by Week 25 assessment is a non-response	
Intercurrent Event	***Strategy***	***Description***
• Discontinuation of assigned treatment by Week 25 visit	• Treatment Policy	• Discontinuation of assigned treatment by Week 25 visit is documented. Data on the main outcome are continued to be collected.
• Use of a new systemic therapy prior to response by Week 25 visit	• Composite	• Use of a new systemic therapy by Week 25 visit is considered a non-response.
• Death prior to response by Week 25 visit	• Composite	• Death prior to Week 25 visit is considered a non-response.
• Relapse of primary malignancy	• Treatment Policy	• Relapse of primary malignancy is documented. Data on the main outcome are continued to be collected.
Population-level summary	Difference (95% CI) between two treatment groups in proportion of randomized patients meeting the endpoint by Week 25 visit	

Abbreviations: CNI - calcineurin inhibitor, PE - prednisone equivalents.

Appendix 5. Glossary of Terminology in This Guidance

A. Terms referring to the types of interventions for management of GVHD

Pre-emptive: Use of the drug for to prevent established subclinical GVHD from becoming clinically overt, or use of the drug to prevent worsening of GVHD from a lower severity to a higher severity.

Prophylaxis: Use of the drug for the prevention of GVHD from occurring.

Treatment: Use of the drug for amelioration of signs and symptoms of clinically-overt GVHD.

B. Terms referring to clinical trial designs

Add-on: An add-on study is a placebo-controlled trial of a new agent conducted in people also receiving standard treatment (e.g., new drug plus standard vs. placebo plus standard). The objective is to determine the treatment effect of the new drug relative to placebo when combined with a standard therapy.

Comparative effectiveness: A comparative effectiveness study compares two active interventions without necessarily isolating the treatment effect of an individual drug (e.g., combination chemotherapy vs. radiation, or combination regimen 1 vs. combination regimen 2). The objective is to determine which intervention provides the superior outcome.

Exploratory: Early phase trials designed to obtain data for the initial characterization of safety of a drug, preliminary evidence of efficacy, and/or dose optimization.

Head-to-head: A head-to-head study is a clinical trial of two therapies that are compared against each other either alone or in combination with a standard treatment (e.g., new drug vs. old drug, or new drug plus standard vs. old drug plus standard). The objective is to determine the treatment effect of the new drug relative to an old drug.

Pivotal: Adequate and well-controlled trial designed to provide data that establishes the safety and effectiveness of a drug as the basis of approval of a marketing application.

C. Additional terms used in the guidance

Line of therapy: A line of therapy is defined as the planned therapy consisting of one or more cycles of episodic treatment or a defined period of continuous treatment. This may consist of single-agent or combination therapy as well as a planned sequence of treatment phases. A line of therapy ends when the patient fails to achieve a response within a prespecified period (refractory), progresses after achieving a PR, or relapses after achieving CR.