FAQs for BMT CTN PROTOCOL 1705 v2.0

A Randomized, Double-Blind, Placebo-Controlled Multicenter Phase III Trial of Alpha 1-Antitrypsin (AAT) Combined with Corticosteroids vs. Corticosteroids Alone for the Treatment of High Risk Acute Graft-versus-Host Disease (GVHD) Following Allogeneic Hematopoietic Stem Cell Transplant.

1. Why run a GVHD phase III treatment trial?

Graft-versus-Host-Disease (GVHD) is an important cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT) and remains one of the main barriers to successful allogeneic transplants. BMT CTN 1705 is a phase III, multicenter, double-blind, randomized, placebo-controlled trial designed to compare Alpha 1-Antitrypsin (AAT) and corticosteroids to placebo and corticosteroids as first-line therapy for patients with high-risk acute GVHD. This registration trial has the potential to change clinical practice if it demonstrates the superiority of AAT plus corticosteroids in patients with high-risk acute GVHD, compared to treatment with steroids alone.

2. Why is BMT CTN 1705 a phase III trial?

This study includes a randomized comparison to a control group, while rigorously controlling the type I error rate at a 2.5% one-sided significance level, meeting the typical requirements for a phase III trial. Note that this study has a smaller sample size than is commonly seen in phase III, due to the large effect size being targeted. If the efficacy requirement is met with the proposed sample size, the sponsors intend to submit an Investigational New Drug application to the Food and Drug Administration. Even if the efficacy requirement is not met, the study still yields an estimate of the effect size of the treatment from a randomized comparison, providing useful information for future research on this treatment.

3. Why was AAT (Zemaira®) chosen as the experimental arm of BMT CTN 1705?

A growing body of evidence has demonstrated AAT to not only possess the ability to inhibit serine proteases, but also exert anti-inflammatory and tissue protective effects independent of protease inhibition. Multiple experimental models of allogeneic HCT have shown that administration of AAT both reduces the development of as well as provides effective therapy for established GVHD. These models implicate a reduction of inflammatory cytokines and an induction of anti-inflammatory cytokines as being integral to AAT's efficacy[2-4]. Proof-of-concept clinical trials confirmed activity of AAT in the challenging subset of patients with steroid refractory acute GVHD (with overall response rates of ~65%)[5,6], supporting further investigation of this agent in a randomized clinical trial.

4. How is high-risk acute GVHD defined in this trial?

High risk acute GVHD in BMT CTN 1705 is defined as:

a. High-risk acute GVHD according to Refined Minnesota (MN) criteria shown below[1]. Using Refined MN score approximately 15% of patients are classified as high-risk acute GVHD. With standard corticosteroid therapies the Day 28 CR/PR rate of MN high-risk acute GVHD patients is 43% with 6-month non-relapse mortality rate of NRM 44%.

High-risk by Refined Minnesota Criteria (any one below):

Single organ involvement

a. Stage 4 skin

b. Stage 3-4 lower GI

c. Stage 1-4 liver

Multiple organ involvement

a. Stage 1-2 lower GI plus any liver

b. Stage 2 lower GI plus any skin

c. Stage 3-4 lower GI plus any liver or skin

d. Any three-organ involvement

OR

b. Isolated stage 2 involvement of the lower GI tract
OR
c. Stage 1 lower GI tract disease with skin involvement

5. What is the rational of including acute GVHD patients not meeting Refined MN high-risk definition?

The inclusion of patients with either (a) isolated stage 2 lower GI tract acute GVHD or (b) stage 1 lower GI tract disease with skin involvement was discussed by protocol team at length. The team agreed that while these patients do not meet the Refined MN definition for high-risk GVHD, their response rates to standard GVHD therapies and expected NRM rates closely mimic those of high-risk Refined MN patients. Further, the group recognized the contribution that steroid-refractory lower GI GVHD plays in transplant-related mortality and that a reduction in its occurrence remains an unmet need. Recently, a database of 309 consecutive patients (between the years of 2009-2012) with GI GVHD was analyzed from The University of Texas, MD Anderson Cancer Center. From this analysis, patients with isolated lower GI stage 2 GVHD appear to have a Day 28 response rate of about 50%, while Day 28 response rates for patients with stage 1 lower GI tract disease with skin involvement were 53%. These observations were validated for similar patients enrolled onto two consecutive acute GVHD trials within the BMT CTN (BMT CTN 0302[8] and BMT CTN 0802[9] trials) (for detailed analysis please see Table 1 of study protocol). Importantly, combining these subsets of GI GVHD with the Refined MN high-risk groups, to expand the definition of high risk GVHD would significantly increase study eligible patients from roughly 15% to 25-30% of all new acute GVHD cases.

6. Will assigning MN high-risk acute GVHD designation to newly diagnosed GVHD patients be difficult for the participating centers?

The Refined MN Criteria is simple to use, intuitive and based on routinely available clinical information used to grade acute GVHD. In addition the participating centers will have access to an easy-to-use, free, public webpage (http://z.umn.edu/MNAcuteGVHDRiskScore) which makes the process of assigning risk-category to an individual patient simple and error-free. The website is compatible with all hand-held devices and smart phones, and the process requires <60 seconds. Of note, these criteria were previously used in the BMT CTN 1501[10] protocol with excellent participating center compliance.

7. Why is 120mg/kg twice weekly dose of AAT is being used in BMT CTN 1705?

The target level of AAT, based on both in vitro and clinical data suggest that targeting a level of ≥ 3.5 mg/mL may provide the optimal regulation of T cells and cytokines to ameliorate GVHD symptoms.

This target level of AAT is likely to provide sustained AAT levels, thereby enhancing Tregs and reducing the pro-inflammatory cytokines. A PK model of 1000 subjects has been used to simulate a variety of AAT doses and dose regimens, with the intent to identify those which result in mean AAT peak level estimates around or above the upper limit of normal, i.e., ≥ 2.5 mg/mL (unpublished data). Based on this simulation, the dose of 120 mg/kg twice weekly for 4 weeks achieved median trough levels ≥ 3.5 mg/mL. In addition, this dosing regimen shows that > 50% of the simulated GVHD subjects at this dose regimen achieve serum AAT levels above normal physiologic levels (≥ 2.5 mg/mL) during the period of up to 28 Days after acute GVHD diagnosis. The cumulative weekly dose (240 mg/kg/week) is similar to the dose regimen of 270 mg/kg/week shown to be safe in Marcondes et al trial[6].

8. Why is the study utilizing 2mg/kg prednisone (or equivalent) as the minimum starting dose in all patients with high-risk acute GVHD?

- The starting dose of prednisone at 2mg/kg (or equivalent) BMT CTN 1705 study was selected to ensure consistency after careful consideration of prior GVHD treatment trials. Relatively limited prospective data is available for use of dosages less than 2mg/kg of prednisone.
- The study is limited to high-risk acute GVHD patients according to either Refined MN criteria or patients identified from MD Anderson Cancer Center database. Both data sources consisted of patients receiving frontline therapy with 2mg/kg of prednisone (or equivalent).
- 2mg/kg prednisone was the starting steroid dose used in BMT CTN 0302 and 0802 studies that included ~35% of patients with high-risk acute GVHD as defined in current protocol. Additionally, 2mg/kg prednisone was the starting dose for the control-arm of BMT CTN 1501.
- The use of slightly higher starting dosages is permitted per protocol, such as methylprednisolone 2mg/kg (2.5mg/kg prednisone), if consistent with usual care at the treating center.
- Providers are allowed to taper after 72 hours.

9. What is the primary endpoint and why?

The primary endpoint of the study is rate of acute GVHD CR/PR on Day 28 post-randomization, without the need of further therapy in both arms. The study has adopted the Day 28 responses for primary endpoint, as acute GVHD response rates at this time point have previously been validated to predict rates of later transplant-related mortality (TRM). For example, in University of Minnesota analysis, Day 28 responses were similar to Day 56 responses and better than Day 14 responses in TRM. In multiple regression analysis, patients with no response at Day 28 were 2.78 times more likely to experience TRM before 2 years than patients with a response[7].

10. Why include pediatric cases after enrollment of 40 adult patients?

The inclusion of pediatric cases was considered carefully by the BMT CTN 1705 protocol team. There is data available in adolescents and children with other plasma-derived AAT products (e.g., in Type 1 Diabetes patients); however, unfortunately no safety or pharmacokinetic data are available for pediatric acute GVHD patients. Additionally, the type and dose of AAT agent (Zemaira®) employed in the current protocol has not been studied in pediatric patients. For these reasons, the protocol will exclude patients below 18 years until safety data are available for the first 40 patients enrolled. At that point, the protocol will be amended to allow patients between the ages of 12-18 years.

11. Why is an interim futility analysis needed? What does a non-binding futility analysis entails?

Interim analyses for futility are often recommended to allow for early stopping of the trial when the results partway through the study do not look sufficiently promising to continue. This is done to save time and money on the trial and allow valuable resources to be diverted to other studies and patients. Futility stopping rules are often explicitly written in the protocol; however, a non-binding futility rule gives the Data Safety Monitoring Committee additional leeway to continue the trial even when the stopping boundary for futility is crossed. This may be done for example when they feel it is important to collect more information on important secondary endpoints.

12. Will patients with treatment failure unblinded?

No, patients who meet 'treatment failure' as defined in the protocol will not be unblinded. All subsequent therapies will be the discretion of treating physicians. Only in emergency situations involving the safety of the subject, the Investigator may break the blind. The possibility of a crossover design was carefully considered during protocol discussion. Although this would enable non-responders to access AAT, the protocol team had concerns that un-blinding procedures would reduce the interpretability of key secondary endpoints that required longer follow-up.

13. Is there a need for a multi-center network to meet the objectives?

Yes. Although GVHD is a common post-transplant complication, no single center treats a sufficient number of high-risk patients to complete this study in a reasonable timeframe.

14. Is the accrual goal feasible?

Yes. We carefully analyzed BMT CTN data from the past acute GVHD studies (BMT CTN 0802 & 0302) from both Core and Affiliate centers and supplemented this with a separate survey of Core & Affiliate Centers to determine willingness to participate.

15. What are the proposed plans for data acquisition, transfer, management and analysis?

A web-based data entry platform will be used to collect study data. Data are transmitted via an encrypted link between the web server and browser using secure socket layer (SSL) technology. SSL is the standard used by banks in their electronic transactions. This platform includes online missing forms reports as well as other reports as deemed useful by the transplant centers. A User's Guide and Data Management Handbook will be developed for reference.

Analysis files will be prepared prior to each Data and Safety Monitoring Board (DSMB) meeting. Most analyses will be conducted using SAS and following the statistical analysis plans outlined in the protocol.

16. **Are there any specific study training plans necessary to accomplish the research goals (e.g. workshops, study certification)?**

Site staff will need to participate in a Site Initiation Visit at their transplant center. Study coordinators will need to be trained on data entry for the study.

17. Accrual Estimates: *please see separate document*

References

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10. BMT CTN 1501: A Randomized, Phase II, Multicenter, Open Label, Study Evaluating Sirolimus and Prednisone in Patients with Refined Minnesota Standard Risk, Ann Arbor 1/2 Confirmed Acute Graft-Versus-Host Disease