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

BMT CTN PROTOCOL 1705

CSL BEHRING PROTOCOL CSL964_5001

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Amin Alousi I am approving this document.

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PROTOCOL SYNOPSIS

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

Co-Chairs: Amin Alousi, MD and John Magenau, MD

Study Design: This study is a phase III, multicenter, double-blinded, randomized, placebo-controlled trial designed to compare AAT and corticosteroids (CS) to placebo and CS as first line therapy for patients with high-risk acute GVHD.

Primary Objective: The primary objective of this trial is to compare the rate of complete response (CR) and partial response (PR) on Day 28 post-randomization between AAT and CS versus placebo to match (PTM) and CS in patients with high-risk acute GVHD.

Secondary Objectives: Secondary objectives are to assess the following:

1. Duration of response at 6 and 12 months post-randomization.
2. Cumulative incidence of non-relapse mortality (NRM) at 6 and 12 months post-randomization.
3. Overall survival (OS) and progression free survival (PFS) at 6 and 12 months post-randomization.
4. GVHD-free survival at Day 56 post-randomization.
5. Proportions of CR, very good partial response (VGPR), PR, and treatment failure (TF) at Days 7, 14, 21, 28, 56, and 86 post-randomization.
6. Proportion of patients with CR, PR (including subset with VGPR), and treatment failure (TF) at Days 7, 14, 21, 28, 56, and 86 post-randomization who receive ruxolitinib or other second line therapies approved by the protocol Chairs as next-line therapy and remain on AAT/PTM.
7. Incidence of systemic infections to assess safety.
8. Incidence of Adverse Events (AEs) at 30 days post last dose of drug to assess safety.
9. Incidence of chronic GVHD at 6 and 12 months post-randomization.
10. Incidence of disease relapse at 6 and 12 months post-randomization.

Exploratory Objectives: Exploratory objectives are as follows:

1. AAT levels in serum at Days 1, 8, 16, 24, 28, and 56 post-treatment initiation.
2. Stool concentrations of AAT at baseline and at Days 8 and 28 post-treatment initiation.
3. Blood ratios of T regulatory to T effector cells (Treg/Teff), Natural Killer (NK) cells and cellular immune subsets at baseline and at Days 14, 28, and 56 post-treatment initiation.
4. Serum levels of inflammatory cytokines and biomarkers at baseline and at Days 8, 28 and 56 post-treatment initiation.
5. Overall and organ-specific response rates comparison based on Minnesota (MN) risk groups (Revised Minnesota High vs Standard) and organ-specific response rates comparison based on biomarker-based risk groups.
6. Corticosteroid dose at baseline, Days 7, 14, 21, 28, 56, 86, 6 months and 12 months post-randomization.
7. CMV reactivation requiring therapy by Day 56 post-randomization.
8. Change in patient-reported outcomes from baseline to Day 28, Day 56 and 6 months post-randomization.

Inclusion Criteria: Patients meeting the eligibility criteria should be enrolled as soon as possible after the start of CS, but no more than 72 hours afterwards.

1. Patients experiencing their initial presentation of acute GVHD requiring systemic therapy after allogeneic transplant for any malignant or non-malignant indication.
2. The clinical diagnosis of acute GVHD requiring systemic therapy with CS. Patients can be enrolled with only a clinically established diagnosis. Biopsy of involved organs with acute GVHD is encouraged but is not required and should not delay study entry. Enrollment/randomization includes commitment to continue steroids with PTM or AAT as specified in the protocol, as well as the required follow-up observations. If, according to institutional practice, the intention to treat is dependent upon biopsy results, the patient should not complete enrollment on the BMT CTN 1705 study until the biopsy results are available.
3. Acute GVHD must meet one (either A or B) of following clinical features within 72 hours prior to enrollment:

    (A) 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) Either of the below:

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

4. Acute GVHD developing after allogeneic hematopoietic cell transplantation using any graft or donor source or conditioning intensity.
5. Patients should not have received systemic immune suppressive therapy for treatment of active GVHD except for a maximum of 72 hours of prior CS therapy prior to enrollment. Topical skin and GI CS (such as budesonide and oral beclomethasone diproprionate) are allowed.
6. Patients 12 years of age or older at time of enrollment.
7. Ability to provide written informed consent from patient, parent or legal guardian, and assent if applicable.

Exclusion Criteria

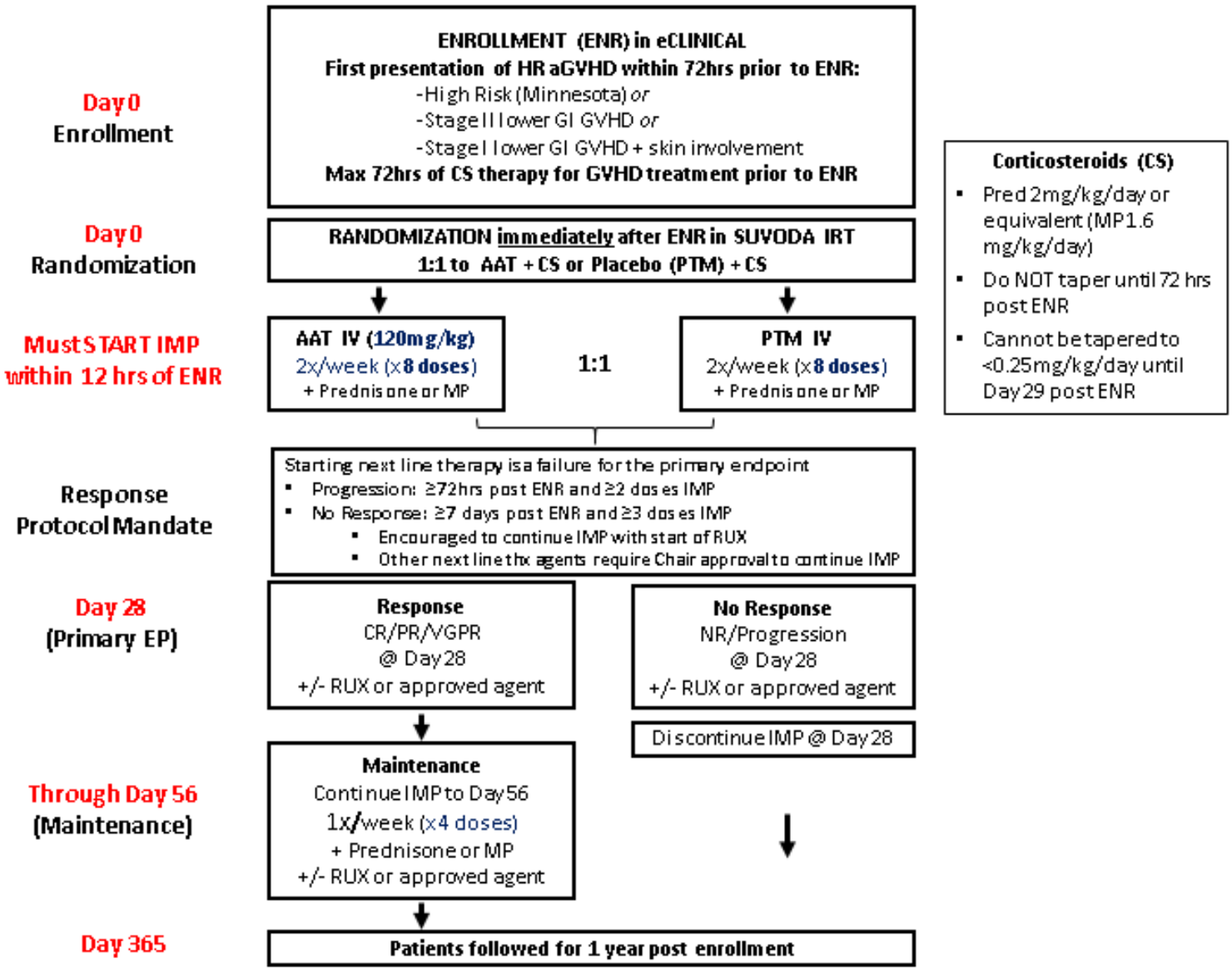
1. Patients with prior exogenous AAT exposure for GVHD prophylaxis.
2. Relapsed, progressing or persistent malignancy
3. Evidence of minimal residual disease (MRD) requiring withdrawal of systemic immune suppression.
4. Patients with acute GVHD developing after administration of a donor lymphocyte infusion (DLI) for relapse / progression of disease. Patients with acute GVHD after planned donor lymphocyte infusion or planned T cell or NK cell add back are eligible.
5. Patients with uncontrolled infections will be excluded. Infections are considered controlled if appropriate therapy has been instituted and, at the time of enrollment, no signs of progression are present. Progression of infection is defined as hemodynamic instability attributable to sepsis, new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.

6. A clinical presentation resembling de novo chronic GVHD or overlap syndrome (as defined in Appendix C) developing before or present at the time of enrollment.
7. Patients receiving other drugs for the treatment of GVHD. Note, GVHD prophylaxis agents (e.g., calcineurin inhibitors) may be continued at local Investigator's discretion.
8. Patients receiving systemic CS for any indication within 7 days before enrollment, except the following:
    a. CS administered as premedication for supportive care (such as before transfusion of blood products or before intravenous medications to prevent infusion reactions, fever, etc.).
    b. If steroid therapy has been administered for treatment of a non-GVHD related condition and tapered to < 0.6 mg/kg/day prednisone (0.5 mg/kg/day methylprednisolone) for 7 or more days prior to enrollment.
    c. Treatment of active GVHD with CS is allowed for up to 72 hours prior to enrollment.
9. Patients who are pregnant or breastfeeding.
10. Females of childbearing potential (FCBP) or males who can get a FCBP pregnant and have sexual contact with FCBP and are unwilling to use 2 effective forms of birth control or abstinence from the start of study drug treatment through 30 days after the last dose of study drug, Effective forms of birth control are listed in Appendix D.
11. Patients on renal replacement therapy.
12. Patients requiring continuous supplemental oxygen (O2 requirement > 2L/min to maintain peripheral O2 saturation [SpO2] > 90%).
13. Patients with active hepatic sinusoidal obstructive syndrome (SOS) and/or clinical evidence of impaired hepatic function (ascites or encephalopathy related to liver disease) who in the judgment of the treating physician are not expected to have normalized bilirubin by Day 56 after enrollment.
14. Patients with a history of hypersensitivity to AAT or any component of the investigational product or PTM (albumin), including congenitally IgA-deficient patients with antibodies to IgA or PTM.
15. Patients unlikely to be adherent to study specific assessments at the transplant center.

Treatment Description: All patients will receive prednisone 2 mg/kg/day PO (or methylprednisolone (MP) at 1.6 mg/kg/day IV) divided into 1-2 daily doses for at least 72 hours after enrollment. CS may be

	tapered as tolerated according to institutional practice. However, corticosteroid taper may not start sooner than 3 days after enrollment and the prednisone dose cannot be less than 0.25 mg/kg/day prednisone (MP 0.2 mg/kg/day) at Day 28 post-enrollment. Patients will be randomized 1:1 to receive AAT or PTM. Patients will receive AAT/PTM on Days 0 or 1, 4, 8, 12, 16, 20, 24, and 28. Responding patients will continue to receive AAT/PTM on Days 35, 42, 49, and 56.
Accrual Objective:	136 total patients will be enrolled and randomized 1:1 to AAT vs PTM.
Accrual Period:	The estimated accrual period is 3 years.
Study Duration:	Patients will be followed for 12 months following randomization.
Interim Analysis:	The study will consist of one interim analysis for futility after 76 patients are evaluable, at a time coincident with a regularly scheduled meeting of the National Heart, Lung, and Blood Institute (NHLBI)-appointed Data and Safety Monitoring Board (DSMB) review, then a final analysis after accrual and follow up for the primary endpoint is complete. There will be no interim analysis for efficacy. Policies and composition of the DSMB are described in the BMT CTN Manual of Procedures.
Stopping Guidelines:	The stopping guidelines serve as a trigger for consultation with the DSMB for additional review and are not formal "stopping rules" that would mandate automatic closure of study enrollment. Safety monitoring will be based on Day 56 NRM. Toxicity, adverse events, and other safety endpoints will be monitored regularly and reported to the DSMB at each meeting.

STUDY SCHEMA



IMP and CS dosing is the same for adolescent and adult patients.