STATUS PAGE
PROTOCOL **16-329**

Closed To New Accrual

Closure Effective Date: 10/05/2017
Reason: Study Accrual Goal Met

No new subjects may be enrolled in the study- as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

DANA-FARBER CANCER INSTITUTE
DANA-FARBER / HARVARD CANCER CENTER

Office for Human Research Studies

Protocol Front Sheet

DFCI Protocol No.: 16-329

1. PROTOCOL INFORMATION

Title: A Randomized Double-Blinded Phase 2 Study Evaluating a Proprietary Amino Acid Mixture (Enterade®) in Patients Receiving High-Dose Melphalan Conditioning Followed by Autologous Stem Cell Transplantation for Multiple Myeloma and Non-Hodgkin Lymphoma

Phase: Phase 2 **Sponsor Study Number:** N/A

2. DF/HCC STUDY CONTACT INFORMATION

Primary Study Contact: Kelly Masone **Email:** Kmasone@partners.org **Phone:** 617-632-4167

INVESTIGATORS: (List only those under DFCI IRB, *i.e.*, from institutions listed in Section 6 below)

Overall PI:	Brett Glotzbecker, MD	**Phone:**	617-632-5808	**Institution(s):**	DFCI	**Mgmt group:**	DFCI CTO
Site Responsible PI:	Zachariah Defelipp, MD	**Phone:**	617-632-2305	**Institution(s):**	MGH	**Mgmt group:**	MGH CTO

3. DRUG / DEVICE INFORMATION N/A:

☐ **Drug(s), Biologic(s)**:
Provided by:
IND Exempt: ☐ -or-
IND#: **Holder Type:** [pull down]
IND Holder Name:

☐ **Device(s) Name**:
Provided by:
IDE Exempt: ☐ -or-
IDE #: **Holder Type:** [pull down]
IDE Holder Name:

4. PROTOCOL COORDINATION, FUNDING, MODE

Regulatory Sponsor:
DF/HCC Investigator Brett Glozabecker, MD

CTEP Study: No

Funding/Support (check all that apply):
☒ Industry: Entrinsic Health
☐ Federal Organization:
Grant #:
☐ Internal Funding:
☐ Non-Federal:
☐ Other:

Primary Disease Group: Multiple Myeloma

Protocol Involves (check all that apply as listed in the protocol document, even if not part of the research but is mandated by the protocol document):

☒ Chemotherapy
☐ Immunotherapy
☐ Surgery
☒ Bone Marrow/Stem Cell Transplant
☐ Cell Based Therapy
☐ Gene Transfer (use of recombinant DNA or synthetic nucleic acid molecules)
☐ Radiation Therapy
☐ Hormone Therapy
☐ Vaccine
☐ Engineered Cell Therapy (ECT)
☐ Data Repository
☐ Exercise/Physical Therapy
☐ Genetic Studies
☒ Human Material Banking
☒ Human Material Collection
☒ Medical Record Review
☒ Questionnaires/Surveys/Interviews
☐ Radiological Exams
☐ Required Biopsy Study
☐ Human Embryonic Stem Cell
☒ Quality of Life
☐ Other: Supportive Care

5. SUBJECT POPULATION (also applies to medical record review and specimen collection studies)

Total Study-Wide Enrollment Goal: 114 **Greater than 25% of the overall study accrual will be at DF/HCC:** ☒ Yes ☐ No

Total DF/HCC Estimated Enrollment Goal: 114 **Adult Age Range:** 18+ **Pediatric Age Range:** N/A

Will all subjects be recruited from pediatric clinics? ☐ Yes ☒ No

If enrolling both adults and pediatric subjects, anticipated percent of pediatric subjects: N/A

Retrospective Medical Record Reviews only (Please provide date range): from to

6. DF/HCC PARTICIPANTS UNDER DFCI IRB (check all that apply)

☐ Beth Israel Deaconess Medical Center (BIDMC)
☐ Boston Children's Hospital (BCH)
☒ Brigham and Women's Hospital (BWH)
☒ Dana-Farber Cancer Institute (DFCI)
☒ Massachusetts General Hospital (MGH)
☐ Beth Israel Deaconess Medical Center – Needham (BIDMC-Needham)
☐ Dana-Farber/New Hampshire Oncology-Hematology (DFCI @ NHOH)
☐ Dana-Farber at Steward St. Elizabeth's Medical Center (DFCI @ SEMC)
☐ Dana-Farber at Milford Regional Cancer Center (DFCI @ MRCC)
☐ Mass General/North Shore Cancer Center (MGH @ NSCC)
☐ Mass General at Emerson Hospital – Bethke (MGH @ EH)
☐ DF/BWCC in Clinical Affiliation with South Shore Hospital (DFCI @ SSH)

7. NON-DF/HCC PARTICIPANTS UNDER DFCI IRB (check all that apply)

☐ Cape Cod Healthcare (CCH)
☐ Lowell General Hospital (LGH)
☐ New Hampshire Oncology-Hematology-P.A. (NHOH)
☐ Newton-Wellesley Hospital (NWH)
☐ Faulkner Hospital (FH)
☐ New England Cancer Specialists (NECS)
☐ Broad Institute

8. DF/HCC INITIATED STUDIES ONLY - INSTITUTIONAL PARTICIPANTS UNDER OTHER IRB (N/A:)

DF/HCC Multi-Center Protocols: (list institution/location)

DF/PCC Network Affiliates: (list institution/location)

Protocol Number: 16-329

Approval Date: 08/30/2016 (IRB meeting date when protocol/consent approved or conditionally approved)

Activation Date: 10/05/2016 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

Date Posted	Revised Sections	Approved Date	Version Date (OnCore)
11/09/16	Protocol and Eligibility Checklist replaced due to Amendment #1	10/25/16	N/A
01/11/17	Temporary closure due to possible contamination of study agent: dark substance in bottle. Sending to infection control for further information; **All study treatment must stop;** Amendment #3 (Effective 01/09/17)	01/11/17	N/A
04/24/17	Re-open to enrollment due to Amendment #5	04/20/2017	n/a
05/01/17	MGH site added: Protocol, Consent Form and Front Sheet replaced due to Amendment #2	12/16/16	04/27/17
05/24/17	Protocol and Consent Form replaced due to Amendment #6	04/26/17	05/02/17
08/11/17	Administrative Update #1: Nursing PES update	N/a	N/a
08/22/17	Study renewal/ Consent form footer replaced due to Continuing Review #1	08/03/17	08/21/17
10/05/17	Study closure – accrual goal met	10/04/17	N/A
07/02/2018	Study renewal/Consent Form footer replaced per Continuing Review #2	06/28/2018	07/02/2018
05/07/2019	Study renewal due to Continuing Review #3 (Note Consent Form removed due to Data Analysis)	05/06/2019	N/A

DF/HCC Protocol #: 16-329

TITLE: A Randomized Double-Blinded Phase 2 Study Evaluating a Proprietary Amino Acid Mixture (Enterade®) in Patients Receiving High-Dose Melphalan Conditioning Followed by Autologous Stem Cell Transplantation for Multiple Myeloma and Non-Hodgkin Lymphoma

Coordinating Center: Dana-Farber/Harvard Cancer Center

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NCI-Supplied Agent(s): N/A

Other Agent(s): Enterade® (Entrinsic Health)

Study Exempt from IND Requirements per 21 CFR 312.2(b).

Amendment 3/ / January 3, 2017

SCHEMA

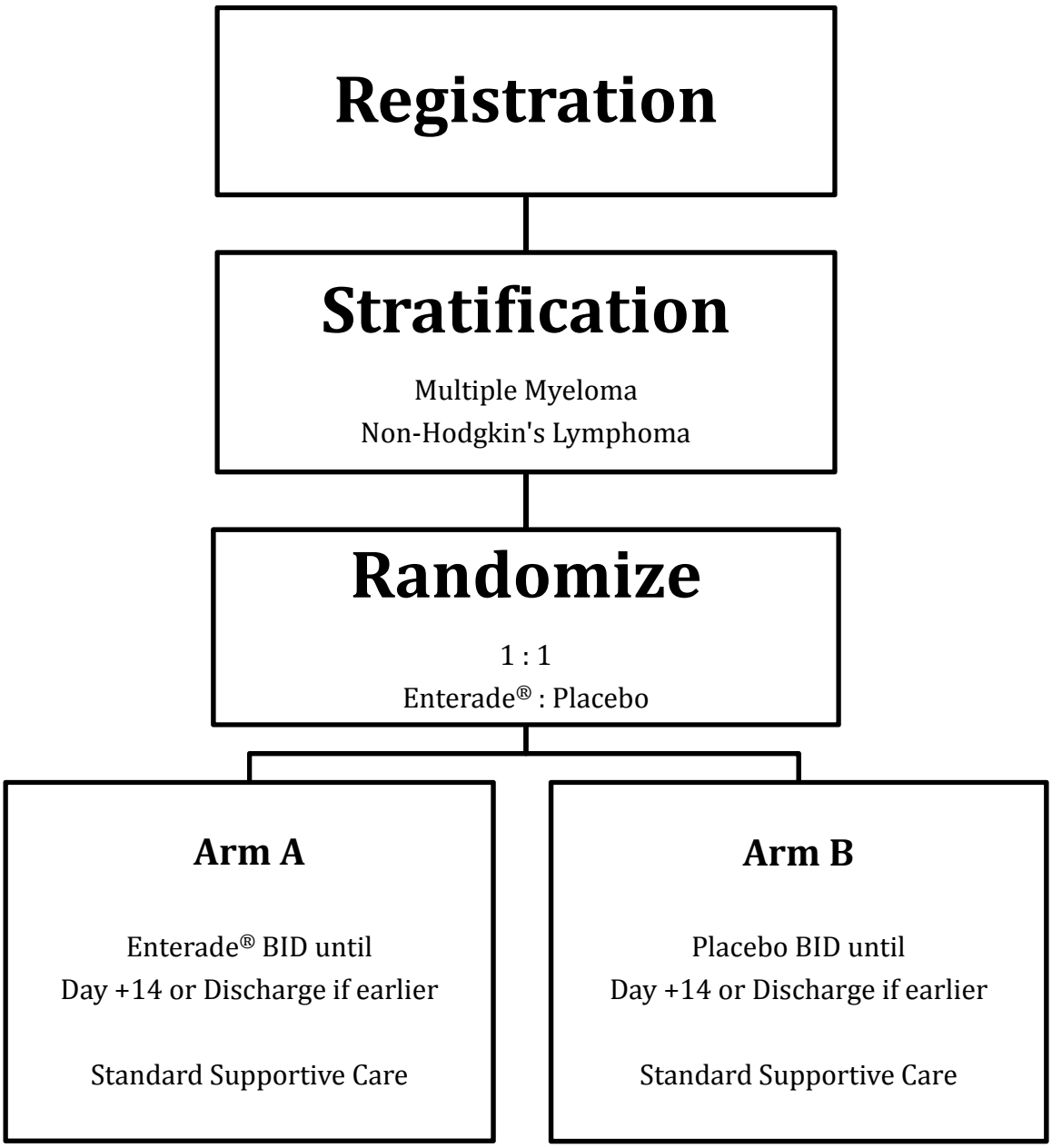

Registration
Stratification
Multiple Myeloma
Non-Hodgkin's Lymphoma
Randomize
1 : 1
Enterade® : Placebo
Arm A
Enterade® BID until
Day +14 or Discharge if earlier
Standard Supportive Care
Arm B
Placebo BID until
Day +14 or Discharge if earlier
Standard Supportive Care

TABLE OF CONTENTS

1. OBJECTIVES

This study involves a prospective, 2-arm randomized, double blinded Phase 2 investigation of the effectiveness of an amino acid mixture, Enterade® versus placebo in reducing diarrhea associated with melphalan conditioning in patients undergoing autologous stem-cell transplantation for Multiple Myeloma or Non-Hodgkin Lymphoma. The hypothesis is that Enterade® when combined with standard supportive care will help maintain the small bowel's ability to absorb fluids and lead to a reduction in diarrhea volume, as well as patient reported gastrointestinal symptoms and improved quality of life following autologous hematopoietic stem cell transplantation (HSCT) with Melphalan conditioning as compared to standard supportive care alone.

1.1 Study Design

This study will be a single-center, double blinded, 2-arm randomized Phase 2 trial, designed to compare the efficacy of Enterade® versus placebo in decreasing gastrointestinal toxicity in patients undergoing autologous HSCT with high-dose Melphalan conditioning. This study will enroll 114 patients with Multiple Myeloma or Non-Hodgkin Lymphoma admitted for autologous HSCT. The trial will randomize patients over an approximately 12 month period. Randomization will be stratified by diagnosis (Multiple Myeloma vs. Non-Hodgkin Lymphoma). Arm A will receive Enterade® (one 8-oz bottle) twice daily from admission and/or the day of conditioning to day +14 (or discharge if occurs prior to day +14) following transplantation in conjunction with institutional standard of supportive care. Arm B will receive a placebo twice daily from admission and/or the day of conditioning to day +14 (or discharge if occurs prior to day +14) in addition standard of care per institutional guidelines.

1.2 Primary Objectives

The primary objective of the study will be to compare the incidence of NCI-CTCAE 4.03, grade 3 or higher gastrointestinal toxicity in the fourteen days following autologous HSCT between the medical food product, Enterade®, with standard of care versus placebo with standard of care, following Melphalan conditioning.

1.3 Secondary Objectives

- To compare average total daily stool volume between patients receiving Enterade® and placebo
- To compare average daily stool frequency between the Enterade® and placebo groups
- To compare duration of hospitalization (days) from admission to discharge
- To compare change in weight, as a percent of initial weight, between patients receiving Enterade® and placebo from admission and/or the first day of conditioning to day +14
- To compare daily calorie counts from the day of admission, day +7 and day +14 following HSCT between patients receiving Enterade® or placebo
- To compare total use of anti-diarrheal medications (number of medications, mean number of daily doses) from randomization to discharge from the inpatient setting
- To compare use of antibiotic medications from randomization until discharge from the inpatient setting

- To compare the incidence of fever and neutropenia between the Enterade® and placebo groups.
- To compare duration (days) of neutropenia between the Enterade® and placebo groups.
- To characterize the tolerability of Enterade® as measured by the number of total 8-oz Enterade® bottles consumed throughout the trial, and average drinks per day.
- To assess patient reported health-related quality of life in patients receiving melphalan conditioning and the intervention Enterade® or placebo using the EPIC Bowel Domain, and the FAACT and FACIT-D symptom inventory at day +14 following HSCT.
- To assess stool inflammation with fecal lactoferrin on admission, and day +7 following HSCT
- To assess markers of systemic inflammation and nutrition, including CRP and pre-albumin on admission, and day +7 and day +14 following HSCT
- To assess plasma endotoxin and cytokine levels of IL-1β, TNF-α, in all patients receiving Melphalan with serum samples collected at day +7 after transplantation.

2. BACKGROUND

2.1 Study Disease(s)

The alkylating agent, Melphalan, remains the mainstay of conditioning for autologous HSCT in multiple myeloma and non-Hodgkin lymphoma patients.[1,2] Gastrointestinal symptoms represent the most significant non-hematologic toxicity following high-dose Melphalan conditioning. [2,3] These symptoms include mucositis, diarrhea, nausea, vomiting and decreased appetite. High dose chemotherapy also induces protein catabolism, disruption of the gastrointestinal mucosa, and oxidative stress.[4-7] Increased intestinal permeability facilitates translocation of microorganisms and endotoxins into the bloodstream; which can lead to neutropenic fevers and even sepsis. [8-10]

As such, Melphalan functions as a radiomimetic agent in its impact on the integrity of the gastrointestinal tract. The mucosal sequelae of Melphalan and the subsequent enteritis are similar to those induced by total body irradiation, with approximately 40% of patients experiencing CTCAE grade 2 or higher diarrhea following conditioning regimens containing Melphalan.[11]

For the purposes of this study, participants could have received the original formulation of Melphalan or the newer formula called Evomela depending on the availability in the pharmacy.

2.2 IND Agent(s)

2.2.1 IND Agent #1: N/A

2.3 Other Agent(s)

Enterade® is a proprietary blend of electrolytes and amino acids in concentrations within the daily dose range recommended by the World Health Organization (WHO). All components are GRAS (Generally Recognized as Safe), approved and without toxicity. Enterade® is a bottled drink that is administered orally in 8 oz. commercially available bottles. Patients will be instructed to drink two bottles of Enterade® or placebo each day, at least thirty minutes before meals or one hour after

meals but do not need to finish an entire bottle during a single ingestion. No other restrictions on diet or dose time will be required.

Please see Section 8.1 for a detailed description of Enterade® and its ingredients.

The placebo will consist of water with natural flavoring agents and stevia, in the same composition as used in Enterade®.

2.4 Rationale

To date, the efficacy of enteral nutrition therapy to support HSCT patients, particularly for those experiencing enteritis from radiation or melphalan conditioning, has been unclear. Despite the high prevalence of severe diarrhea in this population, there is limited evidence base for its treatment. Standard of care represents exclusion of acute infection with *Clostridium difficile* followed by the use of anti-diarrheal agents, and in particular, anti-motility agents to prevent fluid loss, as well as opioids to relieve abdominal discomfort and reduce motility.

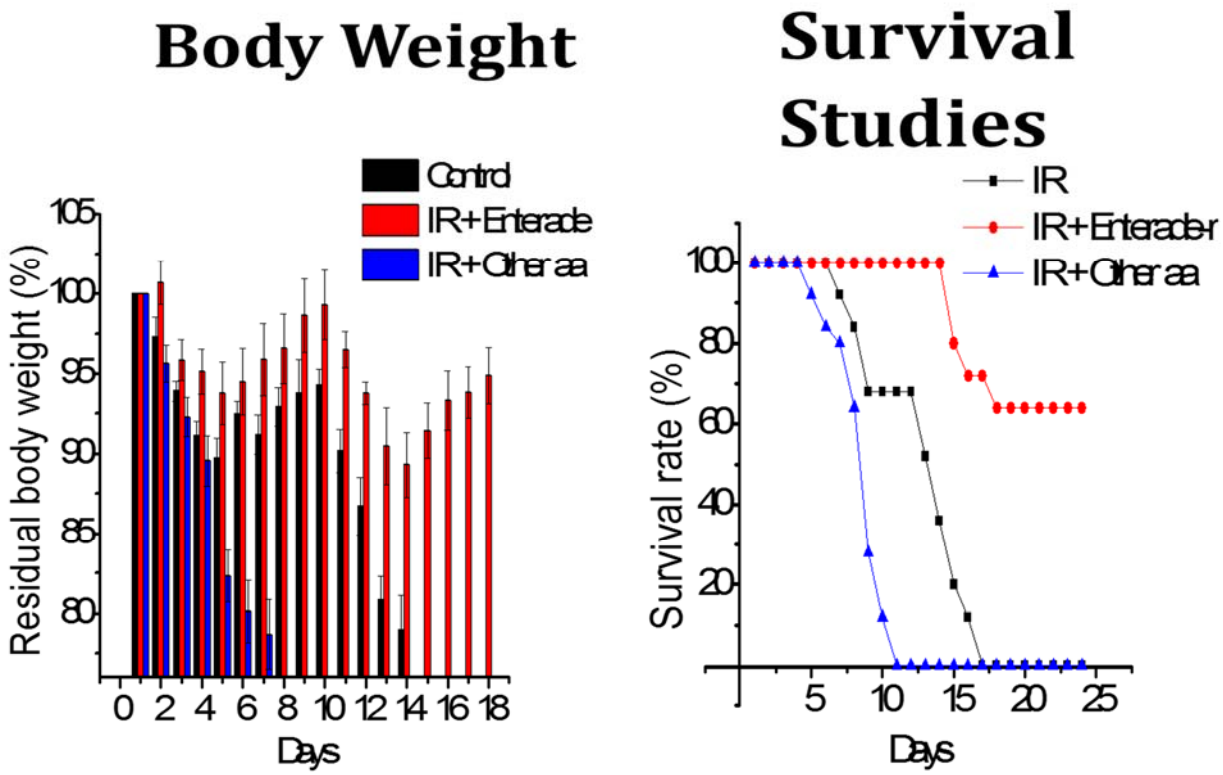
Enteral nutrition can play a role in the treatment of acute enteritis. While intestinal damage from radiation and chemotherapy results in impaired absorption and enzyme production, there may be benefit in the use of elemental diets.[12,13] The amino acid most studied in HSCT is glutamine. Glutamine is a classic nonessential amino acid used as a major fuel by intestinal mucosal cells and by lymphocytes and other immune cells. In prospective, randomized, double blind trials, intake of oral glutamine was not associated with significant differences between study groups in hospital length of stay, days on parenteral nutrition, neutrophil recovery, incidence of positive blood cultures and sepsis, diarrhea severity or incidence, or severity of mucositis.[14,15]

Enterade® is a medical food composed of an amino acid mixture delivered as a beverage. Enterade® contains only nutrients, flavoring and sweeteners, listed as GRAS (generally recognized as safe). It is created by using 7 of the 20 amino acids that make up the body. All other ingredients are natural. It consists of a combination of water, amino acids (Valine, Aspartic Acid, Serine, Isoleucine, Threonine, Lysine, Glycine, Tyrosine), sodium chloride, natural flavor, sodium citrate, potassium chloride, gum acacia, calcium chloride, magnesium chloride, and stevia.

These specific nutrients can facilitate retention of the absorbing capacity of the small intestine. It does not contain nutrients that are poorly absorbed, thus eliminating the presence of unabsorbed nutrients and electrolytes in the gut lumen, which reduces the risk of osmotic diarrhea. In a study of irradiated mice, Enterade® improved survival and improved body weight following irradiation. On electron microscopy of the ileum, there was loss of cell-to-cell contact after irradiation, which was restored after the introduction of Enterade®. This study also suggested that the irradiated mice who received Enterade® had lower levels of plasma endotoxin and IL-1β suggesting less bacterial translocation and inflammation as compared to the control population.

Figure 1: Mitigation using Enterade® improved mouse survival and improved body weight

following irradiation.



(A) Residual weight of irradiated mice that received saline (control), Enterade®, or a mixture of amino acids that had reduced absorption and no beneficial effect on the mucosal barrier following irradiation (other AA). Mice treated with other aa showed > 20% weight loss in less than 10 days, whereas control animals reached > 20% weight loss by the 15th day. Mice treated with the correct amino acid mixture showed steady weight gain beyond 18 days. (B) Mice treated with the correct amino acid mixture showed >66% survival beyond 25 days. Mice receiving the poorly absorbed AA died earlier than the saline controls. N=25 animals/group. Error bar represents SEM.

This prospective, double-blinded, phase 2 randomized study is to assess the effectiveness of Enterade® in reducing diarrhea associated with high dose Melphalan chemotherapy. The hypothesis is that Enterade® when combined with standard supportive care will help maintain the small bowel's ability to retain fluids leading to a reduction in diarrhea volume, patient reported gastrointestinal symptoms and improved quality of life after autologous HSCT with Melphalan conditioning when compared to standard supportive care alone.

2.5 Correlative Studies Background

One of the secondary endpoints in this study will involve evaluation of plasma endotoxin and circulating cytokine levels in peripheral blood samples. Radiation and chemotherapy associated enteritis results in loss of mucosal integrity and increased paracellular permeability across the intestinal mucosa. This leads to increased bacterial translocation as well as increased systemic inflammation.

To assess systemic inflammation, blood samples for cytokine analysis will be collected at day +7

following autologous HSCT in a 5 mL EDTA tube and stored in the clinical facility until they are ready to be tested. Commercially available ELISA assays will be used to assess pro-inflammatory cytokines such as IL-1β, and TNFα. Gut inflammation will be assessed through the analysis of fecal lactoferrin, with stool specimens collected on admission, and day +7 following autologous transplantation.

Additionally, stool samples will also be collected from participants on or before admission, and on a weekly basis for gut microbiome analysis until day +14 or discharge if it occurs prior to day +14. Chemotherapy and radiation result in a decrease in the number and diversity of intestinal microbiota and result in enteritis from disruption of the mucosal epithelium. However, it is unclear what role commensal flora may play in minimizing gut inflammation, and maintaining gut barrier function.[16]

These correlative studies will characterize the response of the gut microbiome to chemotherapeutic conditioning for autologous transplantation and may also help identify characteristic microbial signatures that minimize inflammation and gut barrier function in some patients, as well as whether elemental supplementation with amino acids influences the type and diversity of gut microbes that reconstitute the intestinal mucosa following engraftment.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologically or cytologically confirmed Multiple Myeloma, or Non-Hodgkin Lymphoma and must be undergoing Melphalan conditioning for autologous HSCT.

3.1.2 Age equal or greater than 18 years old.

3.1.3 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

3.1.4 Participants must have adequate organ and marrow function to proceed to transplant.

3.1.5 Ability to tolerate thin liquids by mouth at the time of admission.

3.1.6 The effects of Enterade® on the developing human fetus are unknown. For this reason and other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) at the time of study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of the trial.

3.1.7 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Participants who have had radiotherapy within 4 weeks prior to entering the study or those who have not recovered from GI adverse events due to induction therapy.

3.2.2 Participants who are receiving any other investigational agents. Participants who are receiving standard of care induction therapy on a clinical trial may be eligible after discussion with the overall principal investigator.

3.2.3 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 Known allergy to Stevia.

3.2.5 Participants receiving any medications or antibiotics to treat *Clostridium difficile* infection prior to the initiation of the study will be ineligible for this study.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active *Clostridium difficile* infection or history of *Clostridium difficile* infection.

3.2.7 Participants with evidence of diarrhea as defined by three or more loose or liquid stools per day or loose watery stool (greater volume of stool), that occurs more frequently than usual and lasting for more than three days prior to admission, history of inflammatory bowel disease, irritable bowel syndrome, colectomy or bariatric surgery, Celiac disease.

3.2.8 Participants with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Pregnant and nursing women are excluded from this study because of teratogenicity and toxicity risks associated with the conditioning regimen for patients undergoing autologous HSCT.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not

registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 Guidelines for Other Investigative Sites

Not Applicable

4.4 Registration Process for Other Investigative Sites

Not Applicable

5. TREATMENT AND/OR IMAGING PLAN

5.1 Treatment Regimen

Patients found to be eligible for the study will be enrolled and randomized into either the Enterade® treatment arm (Arm A) or placebo (Arm B). During the course of their admission, those patients randomized to Arm A will be given two 8 oz. bottles daily of Enterade® from admission and/or the day of conditioning until day +14 or until discharge if discharged prior to day +14 following autologous HSCT, to augment their daily diet. Those randomized to Arm B will be given two 8 oz. bottles of placebo from admission and/or the day of conditioning until day +14 or until discharge if discharged prior to day +14 following autologous HSCT, to augment their daily diet. The average length of inpatient stay for the 159 patients undergoing transplantation for Multiple myeloma was 17 days with a range of 14-26 days in the year 2014. Amongst the 81 patients undergoing transplantation for NHL, the average length of stay in 2014 was 22 days with a range of 17 to 58 days.

Enterade® and placebo administration will begin on the day prior or the day of initiation of conditioning. Enterade® or placebo will be administered on an inpatient basis only. Their daily consumption of Enterade® or placebo will be recorded as a fraction of each bottle consumed. Timing of Enterade® or placebo administration will be at least thirty minutes prior to meals or at least one hour after meals but patients need not consume each bottle in one sitting and can continue to consume the drink in sips throughout the day.

Randomization will be completed by the Office of Data Quality.

Table 1: Arm A Enterade® and Standard Supportive Care				
Agent	**Pre-medications/ Precautions**	**Dose**	**Route**	**Schedule**
Enterade®	None	8 oz.	Oral	BID
Standard Supportive Care Regimen	At Investigator's Discretion	At Investigator's Discretion	At Investigator's Discretion	At Investigator's Discretion

Table 2: Arm B Placebo and Standard Supportive Care				
Agent	**Pre-medications/ Precautions**	**Dose**	**Route**	**Schedule**
Placebo	None	8 oz.	Oral	BID
Standard Supportive Care Regimen	At Investigator's Discretion	At Investigator's Discretion	At Investigator's Discretion	At Investigator's Discretion

Reported adverse events and potential risks are outlined in Section 7. Appropriate dose modifications are described in Section 6. No other investigational agents will be used to treat the participant's diarrhea during this trial. Institutional standard of care for the treatment of diarrhea, including loperamide, lomotil or other similar agents will be allowed in both arms of the study.

5.1.2 **Blinding**

The only difference between Enterade® and the placebo will be the color of the cap. Participants, physicians and nursing staff will not be made aware of which bottle cap represents either Enterade® or placebo. The only people with access to which arm each participant is on will be ODQ and the research pharmacy staff. To maintain the blindness for the study team, pharmacy will put the Enterade or placebo into a secondary container. Blindness will be kept to both participants and the study team until all data have been recorded.

5.2 Pre-Treatment Criteria

There are no specific pre-treatment criteria prior to initiation of trial therapy.

5.3 Agent Administration

5.3.1 Enterade®

Two 8 oz. bottles of Enterade® or placebo will be provided to participants for oral consumption on a daily basis for from admission and/or the day of conditioning until day +14, or until discharge if discharged prior to day +14, following autologous HSCT. Enterade® is a bottled drink and is packaged in 8 oz. bottles that are commercially available. The placebo will consist of water, stevia and natural flavors and will be packaged in the same way as Enterade®.

Participants will be instructed to drink two bottles of Enterade® or placebo per day. The recommended timing of Enterade® or placebo administration will be at least 30 minutes before meals or at least one hour after meals. Patients can continue to consume small amounts of Enterade® or placebo throughout the day and do not need to consume an entire bottle in one sitting. Other types of carbohydrate-based beverages such as Gatorade should be avoided.

Caregivers do not need to apply any particular precautions in the handling of Enterade® or placebo.

For further information regarding dosing, and handling please refer to Section 8.1.

5.3.2 Other Modality(ies) or Procedures

Not Applicable

5.4 General Concomitant Medication and Supportive Care Guidelines

Concomitant supportive care can include institutional standard of care for the management of diarrhea and enteritis, including anti-diarrheal agents such as loperamide, lomotil, diluted tincture of opium, intravenous fluids, and other similar agents. There is no anticipated or known potential for interaction of Enterade® with concomitantly administered drugs of the cytochrome P450 system.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of Enterade® administration will be from admission and/or the day of conditioning until day+14 following HSCT or the day of discharge if it occurs prior to day +14. In the absence of treatment delays due to adverse event(s), treatment may continue until day +14 following HSCT or until one of the following criteria applies:

- Unacceptable adverse event(s)
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- The patient is discharged from the hospital

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the Research Project Manager.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Dr. Brett Glotzbecker at 617-632-5808. Pager #43273.

5.6 Duration of Follow Up

Participants will be followed until discharge or until day +14, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the Research Project Manager.

5.8 Unblinding

There are no plans for unblinding during this study. Should an event occur where unblinding is believed to be necessary for the care of the patient, the case will be discussed with the study PI.

6. DOSING DELAYS/DOSE MODIFICATIONS

There will be no dose modifications of enterade. The amount tolerated will be recorded. If the patient is unable to drink thin liquids as a result of a transplant related complication, the Enterade® will be stopped and the reason for stopping will be recorded. They will restart the Enterade® when able to tolerate thin liquids again. Enterade® can be restarted at any point and will go back to the twice daily schedule as tolerated.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events List(s)

7.1.1.1 Adverse Event List(s) for Enterade®

The formulation of Enterade® consists of generally recognized as safe constituents including electrolytes, stevia, and amino acids, within WHO recommended required daily doses. We do not anticipate any toxicity or potential risks. Patients may experience mild discomfort associated with the drink, including off-putting taste, smell, nausea, abdominal discomfort, or constipation.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site:

  http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- **For expedited reporting purposes only:**
  - AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Table 3: DF/HCC Reportable AEs

Attribution	Gr. 2 & 3 AE Expected	Gr. 2 & 3 AE Unexpected	Gr. 4 AE Expected*	Gr. 4 AE Unexpected*	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	Not required	Not required	10 Business Days	10 Business Days	10 Business Days
Possible Probable Definite	Not required	10 Business Days	10 Business Days	10 Business Days	10 Business Days

* If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.

7.3.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the DFCI IRB. However, they still must be reported through the routine reporting mechanism (i.e. case report form).

Grade 4 expected events related to stem cell transplantation, including neutropenia, neutropenic fever, thrombocytopenia, minor bleeding (epistaxis), bruising, electrolyte abnormalities, rashes, and infections (pneumonia, line sepsis, cellulitis), nausea, diarrhea, mucositis, vomiting, and veno-occlusive disease, will not require reporting as SAEs, as these are expected events in the course of transplantation.

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

Not Applicable

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

8.1.1 **Description**

Enterade® consists of a combination of amino acids and electrolytes, flavorings and stabilizers:

Amino Acids	Electrolytes and Other Ingredients
Valine	Sodium Chloride
Aspartic	Natural Flavor
Serine	Sodium Citrate
Isoleucine	Potassium Chloride
Threonine	Gum Acacia
Lysine	Calcium Chloride
Glycine	Magnesium Chloride
Tyrosine	Stevia

The placebo was formulated to match the flavor and consistency of Enterade®. It is composed of water with natural flavoring agents and stevia.

8.1.2 **Form**

Enterade®, which is delivered as a beverage, was formulated with specific nutrients that can retain the absorbing capacity of the small intestine after irradiation. The placebo will consist of water with natural flavoring agents and stevia, in the same composition as used in Enterade®.
Enterade® and placebo will be supplied in the same packaging, as prepared by Entrinsic Health, with the exception of the bottle cap, which will be different colors based on whether it is the medical food or the placebo.

8.1.3 **Storage and Stability**

Enterade® or placebo is stable at room temperature and can also be refrigerated.

8.1.4 **Compatibility**

Enterade® or placebo should not be reconstituted or mixed with other agents.

8.1.5 **Handling**

Enterade® or placebo can be handled without any precautions or special equipment.

8.1.6 **Availability**

Enterade® and placebo will be supplied through Entrinsic Health with distribution done through Seaboard International (Tampa, FL). For the trial, Entrinsic Health will stock 12-24 bottle cases at the BWH and MGH Pharmacy. Patients will be supplied with two 8 oz. bottles daily free of charge from admission until day +14 following HSCT, or until discharge, if discharged prior to day +14. Two 8 oz. bottles of Enterade® or placebo will

be given to the patient by his/her clinical nurse twice a day. It can be refrigerated if not completely ingested at one time. It can also be stored at room temperature if this is preferred by the patient.

8.1.7 **Preparation**

Participants will receive two 8 oz. bottles of Enterade® or placebo daily. No further dilution or preparation will be necessary.

8.1.8 **Administration**

Patients will be instructed to drink two 8 oz. bottles of Enterade® or placebo per day. The timing of Enterade® or placebo administration will be at least 30 min before meals or at least one hour after meals. Patients do not need to finish a bottle during a single ingestion. For example, sipping during the day is allowed. No other restrictions on diet or dose timing will be required. Enterade® or placebo administration will begin on the day of admission and will be administered until day +14 following transplantation. There is no need to drink another bottle of Enterade or placebo if the liquid is vomited. It can be mixed with water if desired.

8.1.9 **Ordering**

Enterade® or placebo stock will be replenished by Entrinsic Health. They will stock full 12-24 bottle cases distributed through Seaboard International.

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 **Destruction and Return**

Unused or expired supplies of Enterade® or placebo will be returned to the supplier, Entrinsic Health throughout the duration of the study or be disposed of as non-toxic waste per institutional standard operating procedure.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

9.1.1

For the cytokine assays, the CRC will drop off tubes and labels to the inpatient floor by day +6. Peripheral blood samples will be collected by the RN from the patient's central venous catheter in six 10 mL EDTA vials on day +7 following HSCT. The samples will be picked up by the CRC and brought to the Pasquarello Tissue Laboratory at DFCI. Samples will be refrigerated, processed, and evaluated at DFCI, using commercially available ELISA based assays to measure IL-1β, and TNFα.

The CBC with differential, pre-albumin, and CRP will be drawn by the RN from the patient's central venous catheter as per current standard of care in the post-HSCT setting. Labs are sent to and processed at the BWH or MGH clinical laboratory.

9.2 Special Studies

9.2.1 Evaluation of the gut microbiome in the autologous HSCT population receiving Enterade® or placebo

- **Outcome Measure** Stool bacterial composition and diversity
- **Method of Assessment** Stool samples will be banked for 16S ribosomal RNA gene sequencing to profile stool bacterial composition. This will allow for evaluation of stool diversity and variability of bacterial species.
- **Timing of Assessment** Stool samples will be collected on admission, and on a weekly basis during the course of inpatient admission.

Stool samples will be collected while patients are inpatient in sterile specimen containers. The samples will be picked up by the CRC and will be transported in biohazard bags to the BWH clinical laboratory. Once collected, stool specimens will be placed immediately at 4C. Within 24 hours of collection, the stool samples will be picked up by the CRC and transported to the Crimson Core Specimen Bank at Brigham and Women's Hospital where they will be frozen in a -80C freezer for storage.

10. STUDY CALENDAR

Baseline evaluations are to be conducted in accordance with FACT guidelines for HSCT and may be within 45 days of starting therapy. Baseline assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

Arm A: Enterade® and Standard Supportive Care					
	Screening	Admission*	D0 of HSCT	D+7 of HSCT	D+14 of HSCT
Informed Consent	X				
Demographics	X				
Performance Status	X				
Medical History	X				
Concurrent Meds	X	X	X	X	X
Stool Frequency		X	X	X	X
Stool Volume		X	X	X	X
Stool Collection		X[3]	X	X	X
Physical exam		X	X	X	X
Vital Signs	X	X	X	X	X
Height	X				
Weight		X		X	X
Calorie Counts		X		X	X
Adverse Event Evaluation		X	X	X	X
Medication and Diet History		X	X	X	X
Quality of Life					X
CTCAE		X	X	X	X
EPIC					X
Fecal Lactoferrin		X		X	
Cytokine blood draw				X	
Pre-albumin		X		X	X
CRP		X		X	X
CBC w/ diff[1]		X	X	X	X
Chemistry Panel[2]		X	X	X	X
Enterade®		X	X	X	X
Amount of Enterade® Consumed		X	X	X	X
* For NHL patients t≈0 is D-7 of HSCT, For MM patients t≈0 is D-3 of HSCT					

1. CBC w/diff includes White Blood Cell count (WBC), Hematocrit (HCT), Platelet count, and Absolute Neutrophil Count (ANC).
2. Chemistry Panel includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, AST/SGOT, ALT/SGPT, alkaline phosphatase, total bilirubin, magnesium, phosphorous
3. The admission stool sample may be collected at any point between screening and admission.

Arm B: Placebo and Standard Supportive Care					
	Screening	Admission*	D0 of HSCT	D+7 of HSCT	D+14 of HSCT
Informed Consent	X				
Demographics	X				
Performance Status	X				
Medical History	X				
Concurrent Meds	X	X	X	X	X
Stool Diary		X	X	X	X
Stool Frequency		X	X	X	X
Stool Volume		X	X	X	X
Stool Collection		X[3]	X	X	X
Physical exam		X	X	X	X
Vital Signs	X	X	X	X	X
Height	X				
Weight		X		X	X
Calorie Counts		X		X	X
Adverse Event Evaluation		X	X	X	X
Medication and Diet History		X	X	X	X
Quality of Life					X
CTCAE		X	X	X	X
EPIC			X		X
Fecal Lactoferrin		X		X	
Cytokine blood draw				X	
Pre-albumin		X		X	X
CRP		X		X	X
CBC w/ diff[1]		X	X	X	X
Chemistry[2]		X	X	X	X
Placebo		X	X	X	X
Amount of Placebo Consumed		X	X	X	X
* For NHL patients t≈0 is D-7 of HSCT, For MM patients t≈0 is D-3 of HSCT					

1. CBC w/diff includes White Blood Cell count (WBC), Hematocrit (HCT), Platelet count, and Absolute Neutrophil Count (ANC).
2. Chemistry Panel includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, AST/SGOT, ALT/SGPT, alkaline phosphatase, total bilirubin, magnesium, phosphorous
3. The admission stool sample may be collected at any point between screening and admission.

11. MEASUREMENT OF EFFECT

11.1 Other Response Parameters

Not applicable

12. DATA REPORTING / REGULATORY REQUIREMENTS

12.1 Data Reporting

12.1.1 Method

The DF/HCC Office of Data Quality will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) according to the schedule set by the ODQ. Data should be entered within 14 business days of the corresponding visit.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Collaborative Agreements Language

Not Applicable

13. STATISTICAL CONSIDERATIONS

This is a randomized, double-blinded phase 2 trial of comparing the efficacy of the investigational drug, Enterade® versus placebo in conjunction with standard-of-care (SOC) in decreasing diarrhea-related gastrointestinal (GI) toxicity in patients undergoing autologous hematopoietic stem cell transplantation (HSCT) with melphalan conditioning for Multiple Myeloma or non-Hodgkin Lymphoma.

13.1 Study Design/Endpoints

The study is a one stage phase II trial with two arms. The primary endpoint is the incidence of NCI-CTCAE 4.0 grade 3 or higher diarrhea GI toxicity in the 14 days following autologous HSCT. The primary endpoint will be evaluated at day 14 after autologous HSCT. A total of 114 patients

(57 patients per arm) will be randomly assigned in 1:1 ratio to either the investigational drug (Arm A) or placebo (Arm B) prior to autologous HSCT.

Based on the preliminary data with SOC alone, we hypothesize that the grade 3 or higher diarrhea GI toxicity will be 30% in the placebo arm. With the investigational drug, we project that the grade 3 or diarrhea higher GI toxicity will be 10% . With the sample size 57 per arm, there will be 80% power to detect a 20% difference in grade 3 or higher diarrhea GI toxicity between two arms. This power calculation is based on Fisher's exact test at one-sided type I error rate of 0.05.

13.2 Accrual Rate and Study Duration

Based on the current practice, we conservatively anticipate that the accrual rate will be approximately 12 patients per month and thus the accrual will complete within one year. The projected accrual targets presented below is based on patients at DFCI who underwent autologous HSCT for Multiple Myeloma or Non-Hodgkin Lymphoma between 2013 and 2014. In the year 2013, 274 patients underwent autologous transplantation for Multiple Myeloma (182 patients) or Non-Hodgkin's Lymphoma (92 patients). The following year, 159 patients underwent autologous transplantation for Multiple Myeloma and 81 for Non-Hodgkin's Lymphoma, accounting for a total of 240 patients. We anticipate recruitment of approximately sixty percent of eligible patients.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	4	=	6
Not Hispanic or Latino	50	+	58	=	108
Ethnic Category: Total of all subjects	(52)	+	(62)	=	(114)
Racial Category					
American Indian or Alaskan Native		+	1	=	1
Asian	1	+	1	=	2
Black or African American	2	+	3	=	5
Native Hawaiian or other Pacific Islander		+	1	=	1
White	49	+	56	=	105
Racial Category: Total of all subjects	(52)	+	(62)	=	(114)

13.3 Randomization/Stratification Factors

After enrollment, patients will be randomized in 1:1 ratio between two arms using

permuted block algorithm within strata. Randomization will be stratified based on diagnosis of Non-Hodgkin Lymphoma or Multiple Myeloma prior to transplantation. No additional interim monitoring will be performed that is unique to each stratum. Efficacy determination will be the same for each stratum as noted in the primary and secondary endpoints outlined in section 1.2 and 1.3.

13.4 Interim Monitoring Plan

All adverse events will be monitored closely. Monitoring of key safety endpoints (GI toxicity, fever, neutropenia) will be conducted in accordance with the DF/HCC DSMB meeting (see Section 12.2). The investigational drug is a medical food composed of an amino acid mixture and generally recognized as safe constituents. We thus do not anticipate any toxicity or potential risks. However, taking the advantage of a randomized trial with a standard treatment arm, we will compare all grade 2 or higher treatment related toxicity in accordance with the DSMB meeting.
If, at any of these looks, this difference is significant at the two-sided level of 0.05, this would trigger a consultation with the DF/HCC DSMB for additional review. However, this will not be formal stopping rules that would mandate automatic closure of study enrollment. In addition, we will assess the feasibility of the trial at the first look. With the anticipated accrual rate, we project 2-3 looks before the completion of the accrual.

13.5 Analysis of Primary and Secondary Endpoints

The primary analysis will be the modified intention-to-treat (ITT) analysis for the primary endpoint of grade 3 or higher diarrhea GI toxicity occurred within 14 days of autologous HSCT. Although it is unlikely to occur, patients who are randomized but do not receive autologous HSCT or do not receive any study drug will be replaced and not be included in the primary or secondary analysis. The proportion of grade 3 or higher GI toxicity in the 14 days following autologous HSCT will be compared using Fisher's exact test.

Secondary endpoints as listed in Section 1.3 include frequency and duration of fever and neutropenia, average total daily stool volume, average daily stool frequency, change in weight, calorie consumption, stool microbiome, total use of anti-diarrheal medications, use of antibiotic medications, tolerability, patient reported quality of life (QOL), and the length of hospital stay. Correlative studies include assessment of cytokine levels, fecal lactoferrin, and markers of nutrition and inflammation. For group comparison, Fisher's exact test or a Chi-square test, as appropriate, will be used for categorical variables and Wilcoxon-Rank-Sum or t-test, as appropriate, will be used for continuous variables. In addition, correlation analysis between the primary and secondary endpoints will be performed and multivariable linear regression and logistic regression analysis will be explored to identify factors that are associated with the primary outcome and to identify a subset patients who develop grade 3 or higher GI toxicity. For the analysis of pre-to-post treatment change, graphical assessments, McNamer's test or Wilcoxon-Signed rank test as appropriate, and regression analysis will be utilized.

As to the assessment of patient reported QOL, we project that 70% of all randomized patients will agree to participate in the QOL assessment. This projection is based previous QOL assessment in the HSCT setting. In particular, we are interested in the overall Epic bowl

domain score whether this score is higher in the Enterade arm compared with the placebo arm (the higher score the better). For example, if the effect size of epic bowel domain score (i.e., mean difference between two groups divided by its standard deviation) is 0.7, there will be 86% power to detect this difference. If the effect size is 0.8, then there will be 94% power to detect this difference. This power calculation is based on asymptotic power of the Wilcoxon-Rank-Sum test at the two sided significance level of 0.05 without adjustment for multiple comparisons and assuming the sample size 40 in each arm. As to the missing items in each QOL assessment, we will take a standard approach to handling individual missing items that are received. That is, if an item is missing, the subscale score will be prorated by multiplying the sum of the subscale by the number of items in the subscale and then dividing by the number of items actually answered.

Although we hypothesize that Enterade in combination with SOC will help stabilize small bowel environment, since there have been no rigorous comparative studies performed, all secondary endpoints will be evaluated in an exploratory analysis to characterize the GI response to chemotherapeutic conditioning for autologous HSCT and thus will serve hypothesis-generating purpose for future clinical/scientific research. For this reason, provision of power statement is limited for secondary endpoints.

13.6 Reporting and Exclusions

13.6.1 Evaluation of Toxicity

All participants who receive any amount of study drug will be evaluable for toxicity from the time of their first treatment.

13.6.2 Evaluation of the Primary Efficacy Endpoint

Analyses will be modified intent-to-treat per Section 13.5. All eligible participants who receive the study treatment in the study will be assessed for response/outcome to therapy, even if there are major protocol therapy deviations.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: FACIT-D

FACIT-D (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACIT-D (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACIT-D (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C5	I have control of my bowels	0	1	2	3	4
ITF1	I move my bowels more frequently than usual	0	1	2	3	4
ITU2	I am afraid to be far from a toilet	0	1	2	3	4
D1	I have to limit my social activity because of diarrhea (diarrhoea)	0	1	2	3	4
D2	I have to limit my physical activity because of diarrhea (diarrhoea)	0	1	2	3	4
D3	I have to limit my sexual activity because of diarrhea (diarrhoea)	0	1	2	3	4
D4	I am embarrassed by having diarrhea (diarrhoea)	0	1	2	3	4
D5	I have abdominal cramps or discomfort due to my diarrhea (diarrhoea)	0	1	2	3	4
D6	My problem with diarrhea (diarrhoea) keeps/wakes me up at night	0	1	2	3	4
ITF3	I must move my bowels frequently to avoid accidents	0	1	2	3	4
ITF5	I wear pads or protection to prevent soiling my underwear	0	1	2	3	4

APPENDIX C: FAACT

FAACT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C6	I have a good appetite	0	1	2	3	4
ACT1	The amount I eat is sufficient to meet my needs	0	1	2	3	4
ACT2	I am worried about my weight	0	1	2	3	4
ACT3	Most food tastes unpleasant to me	0	1	2	3	4
ACT4	I am concerned about how thin I look	0	1	2	3	4
ACT6	My interest in food drops as soon as I try to eat	0	1	2	3	4
ACT7	I have difficulty eating rich or "heavy" foods	0	1	2	3	4
ACT9	My family or friends are pressuring me to eat	0	1	2	3	4
O2	I have been vomiting	0	1	2	3	4
ACT10	When I eat, I seem to get full quickly	0	1	2	3	4
ACT11	I have pain in my stomach area	0	1	2	3	4
ACT13	My general health is improving	0	1	2	3	4

APPENDIX D: EPIC BOWEL DOMAIN

Page 1

Do Not Mark in This Space

BOWEL HABITS

The next section is about your bowel habits and abdominal pain.
Please consider **ONLY THE LAST 4 WEEKS**.

1. How often have you had rectal urgency (felt like I had to pass stool, but did not) **during the last 4 weeks**?

More than once a day	1		
About once a day	2		
More than once a week	3	(Circle one number)	42/
About once a week	4		
Rarely or never	5		

2. How often have you had uncontrolled leakage of stool or feces?

More than once a day	1		
About once a day	2		
More than once a week	3	(Circle one number)	43/
About once a week	4		
Rarely or never	5		

3. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) **during the last 4 weeks**?

Never	1		
Rarely	2		
About half the time	3	(Circle one number)	44/
Usually	4		
Always	5		

4. How often have you had bloody stools **during the last 4 weeks**?

Never	1		
Rarely	2		
About half the time	3	(Circle one number)	45/
Usually	4		
Always	5		

5. How often have your bowel movements been painful **during the last 4 weeks**?

Never..... 1
Rarely..... 2
About half the time..... 3 (Circle one number)
Usually..... 4
Always.....5

6. How many bowel movements have you had on a typical day **during the last 4 weeks**?

Two or less..... 1
Three to four.....2 (Circle one number)
Five or more.....3

7. How often have you had crampy pain in your abdomen, pelvis or rectum **during the last 4 weeks**?

More than once a day..... 1
About once a day..... 2
More than once a week..... 3 (Circle one number)
About once a week.....4
Rarely or never..... 5

8. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem
a. Urgency to have a bowel movement	0	1	2	3	4
b. Increased frequency of bowel movements.....	0	1	2	3	4
c. Watery bowel movements.....	0	1	2	3	4
d. Losing control of your stools.....	0	1	2	3	4
e. Bloody stools	0	1	2	3	4
f. Abdominal/ Pelvic/Rectal pain...	0	1	2	3	4

9. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem..... 1
Very small problem..... 2
Small problem.....3 (Circle one number)
Moderate problem..... 4
Big problem..... 5

APPENDIX E: MEDICATION AND DIET HISTORY FORM FOR STOOL COLLECTION

Participant Name:
Participant MRN:
Stool sample collection date:
Day of transplant:

Antimicrobials: Please list all oral and IV antibiotics, antifungals, or anti-viral therapies given to the participant at the time of the stool sample collection.

1.
2.
3.
4.
5.
6.
7.
8.

Gastrointestinal (GI) prophylaxis: Please list the names of all GI prophylaxis medications (eg. Omeprazole, TUMS, Maalox, Carafate), being given to the participant at the time of the stool sample collection.

1.
2.
3.
4.
5.
6.

Diet: please note the type of nutrition that the participant is receiving at the time of the stool sample collection.

[ ] Regular diet
[ ] Formula via nasogastric or gastric tube
[ ] Total parenteral nutrition
[ ] Other diet _____

APPENDIX F: CTCAE CRITERIA

This study will utilize the NCI-CTCAE v4.03 for toxicity and Serious Adverse Event (SAE) reporting. A copy of the CTCAE v4.03 can be downloaded from the website:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

All appropriate treatment areas should have access to a copy of the CTCAE v4.03.

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity.					
Duodenal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the duodenum and another organ or anatomic site.					

DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	**16329**
Protocol Name:	A Randomized Double-Blinded Phase 2 Study Evaluating a Proprietary Amino Acid Mixture (Enterade®) in Patients Receiving High-Dose Melphalan Conditioning Followed by Autologous Stem Cell Transplantation for Multiple Myeloma and Non-Hodgkin Lymphoma
DFCI Site PI:	Brett Glotzbecker, MD
DFCI Research Nurse:	Kristen Cummings and Heidi DiPietro/ Kathleen McDermott
DFCI/BWH CRC:	Lauren Johnston #40515

Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.
Please also refer to ONC 15: Oncology Nursing Protocol Education Policy
***** Remember to check the ALERT PAGE*****

SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL

Study Design	• Description of the study agent (Enterade) : Section 2.3; 8.1 • The Study Design is in Section: 1.1 • The Study Rationale is in Section. 2.4 • Definition of cycle : N/A
Dose Calc.	N/A
Study Drug Administration	Agent *Administration* Guidelines : Section 5.1; 5.3; 8.1.6; 8.1.8 • Randomized Enterade treatment (Arm A) or Placebo (Arm B) • Two 8 oz bottles daily (Enterade or Placebo) from admission to Day +14 or until discharge • Dosing ordered for twice a day at 7:30 and 16:30: Timing at least 30 minutes prior to meal or 1 hour after but patients need not consume in one sitting may consume in sips throughout the day. Dosing ordered for twice a day at 7:30 and 16:30 • Admission day – Supplement is ordered x 1. Can be given at any point – no requirements about timing premeals. • If supplement not completed at time of next dose then discard rest of dose (see charting tips)
Dose Mods & Toxicity	*Dose Modifications/Dosing Delay*: • No dose modifications see: Section 6.0 • NCI CTCAE criteria, version 4.03 (section 7.2
Con Meds	*Concomitant Therapy Guidelines/Recommendations* are in Section 6.4 **Supportive measures:** ❖ Calorie Counts: Around admission, day +7 and day +14 (or day of discharge if prior to Day +14) by Nutrition staff ❖ FACT QOL and Epic Domain questionnaires by medical team
Required Data	*Study Calendar and Assessment Required data* are outlined: Section 10 • Daily labs: CRP/prealbumin : Admission, Day 7, Day 14 (or day of discharge if prior to Day +14). • Special Studies Stool Samples: Section 9.1 • Admission, Day 0, Day +7, Day +14 (or day of discharge if prior to Day +14) • • Biomarkers: The time points are in Section 9.1 • Cytokines Day +7 (Blood tubes provided and after drawn place in dedicated bin on unit for CRC to collect)
Charting Tips	**Intake: All study agents require documentation of administration time as well as the amount tolerated** • Amount drank should be documented in the Intake-> Other section of the Intake/Output Flowsheet. • At time of discarding the bottle, document how much was drank in mL in the flow sheet. • Flow sheet documentation can occur at any point after supplement given but before or at the time of next supplement. **Output:** ✓ Strict I/Os should be kept daily. ✓ Stool output needs to be documented daily in the Output -> Stool assessment section of the Intake/Output Flowsheet. ✓ Incontinence, Stool Appearance and Stool amount should be documented. If the stool is formed then a x1 as currently documented is fine. If there is mixed urine/stool – this should be documented in a separate row with the volume of the output. **Weights:** o Weights should be documented in EPIC on Admission, Day +7 and Day +14 (or day of discharge if prior to Day +14).