LCCC 2037: Addition of olanzapine to standard CINV prophylaxis in hematopoietic stem cell transplant

Short Title: Olanzapine for nausea/vomiting prophylaxis in recipients of hematopoietic stem cell transplants

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Signature Page

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Jonathan Ptachcinski

PI Signature:

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LIST OF ABBREVIATIONS

AE	Adverse event
BID	*Bis in die* (twice daily)
CINV	Chemotherapy Induced Nausea and Vomiting
CPO	Clinical Protocol Office
CRF	Case Report Form
CR	Complete response
DOC	Department of Corrections
DSMC	Data safety monitoring committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
HCT	Hematopoietic Stem Cell Transplant
IDS	Investigational drug service
LCCC	Lineberger Comprehensive Cancer Center
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
PI	Principal investigator
PRO-CTCAE	Patient Reported Outcomes-Common Terminology Criteria for Adverse Events
PRC	Protocol review committee
SAE	Serious adverse event
UNC	University of North Carolina

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This is a single institution prospective, randomized, double blind, placebo-controlled trial evaluating olanzapine's role as a prophylaxis for chemotherapy induced nausea and vomiting (CINV) in hematopoietic stem cell transplant (HCT) recipients. The study subjects will be randomized into two arms, placebo and study drug arms. Within each arm, there will be 2 cohorts consisting of autologous recipients and allogeneic recipients. All subjects will receive standard CINV prophylaxis in accordance with NCCN guideline-based therapy and per institutional standard. Subjects randomized to the study drug arm will receive standard prophylaxis plus olanzapine starting with the first dose of highly or moderately emetogenic conditioning chemotherapy (see Appendix D) and continuing for 3 days after the last dose of highly or moderately emetogenic conditioning chemotherapy. Subjects randomized to the placebo arm will follow the same schedule as those receiving study drug however will receive a matched placebo instead of olanzapine. Subjects will be monitored (see section 8.1) prior to the start of study drug or placebo, on each day they receive study drug or placebo, and for two additional days beyond the last dose of study drug or placebo (for a total of 5 days of monitoring after the last dose of highly or moderately emetogenic chemotherapy). Conditioning regimens are patient specific and can range from 1-7 days, therefore subjects will take olanzapine or placebo for a maximum of 10 days. The efficacy of olanzapine will be evaluated by comparing the rates of complete response as defined in section 3.1.

1.2 Background

Chemotherapy induced nausea and vomiting (CINV) occurs in up to 80% of patients on active therapy and remains a significant barrier to quality of life[1]. CINV can alter electrolytes and enteral nutrition which can have a detrimental effect on patient adherence and health outcomes[2]. HCT patients are at increased risk for CINV because many of the conditioning regimens require multiple days of high-dose chemotherapy that are, in many cases, associated with highly-emetogenic potential. Thus, most conditioning regimens require a 3-drug regimen for optimal CINV prophylaxis.

1.3 Current Standard of Care

Current guidelines support the use of olanzapine in addition to a 3 drug CINV regimen for highly emetogenic chemotherapy, however some controversy remains as to olanzapine's place in therapy with moderately emetogenic chemotherapy. In HCT, current practice at UNC utilizes an neurokinin-1 receptor antagonist (NK1 RA), serotonin receptor antagonists (5-HT3 RA) and corticosteroid for CINV prophylaxis in conditioning regimens including moderate and highly emetogenic chemotherapy in accordance with ASCO and NCCN recommendations [3, 4].

1.4 Study Treatment

Olanzapine, an atypical antipsychotic, antagonizes dopamine, serotonin, catecholamines, acetylcholine, and histamine receptors which helps prevent acute, breakthrough and delayed nausea [5]. Olanzapine has shown benefit when used as prophylaxis in solid tumor patients receiving single-day highly emetogenic chemotherapy [2]. The addition of olanzapine to 5HT-3 antagonist, NK-1 antagonist, and dexamethasone resulted in significantly more complete responses (CR) and more patients without CINV when compared to placebo in the acute, delayed and overall time periods. Data with olanzapine as CINV prophylaxis is not clear in HCT patients, but one retrospective study by Trifilio *et. al*. illustrates possible benefit in HCT [6]. They compared an aprepitant-based regimen (aprepitant, ondansetron, and steroid) to an olanzapine-based regimen (olanzapine, ondansetron, and steroid) and found that patients in the olanzapine group had significantly less acute and delayed nausea. In addition, the olanzapine-based regimen required significantly less PRN rescue medication compared to the aprepitant based regimen. These results ultimately provided the foundation for the FOND-O study, a prospective trial that added olanzapine as part of CINV prophylaxis in both hematologic malignancies and HCT patients.

The FOND-O study compared fosaprepitant, ondansetron, and dexamethasone (FOND) to fosaprepitant, ondansetron, dexamethasone and olanzapine (FOND-O). The inclusion of olanzapine resulted in significantly less delayed and overall nausea but did not affect the acute phase. While the FOND-O study was the first to look at utilizing olanzapine as part of 4 drug CINV prophylaxis in HCT, there were only 68 HCT patients included in the study. Only 24 allogeneic transplants and 44 autologous transplants were enrolled, and only 34 of these patients actually received olanzapine. In addition, the FOND-O study utilized an olanzapine dose of 10 mg on each day of chemotherapy continued through chemotherapy day 3 [7].

1.5 Rationale for Clinical Study

The purpose of our proposed study is to build upon the FOND-O results by doing a prospective, randomized, placebo-controlled study, focused entirely on HCT recipients, and powered to detect olanzapine's potential role in CINV prophylaxis in recipients of HCT. Based upon the available literature in both solid and hematologic malignancies the benefit outweighs the risk of adding olanzapine to standard CINV prophylaxis. The primary endpoint is complete response- defined as no emesis and no more than minimal nausea (see section 3.1) starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing 5 days beyond the last dose of highly or moderately emetogenic conditioning chemotherapy. Secondary endpoints are defined explicitly in section 3.2. Patient reported frequency and severity of nausea are secondary endpoints that will be collected with a validated PRO-CTCAE questionnaire [8].

Dose Rationale: Current guidelines recommend an olanzapine dose of 5 or 10 mg for CINV prophylaxis, but more evidence suggests that the 5 mg dose is as effective as the 10 mg dose in both delayed and overall nausea [9].

2.0 STUDY OBJECTIVES

All analyses will be done separately for the patients receiving allogenic and autologous transplants.

2.1 Primary Objectives

2.1.1 To compare the overall rate of complete response (CR) [section 3.1] between patients on study treatment [experimental arm], defined as receiving olanzapine plus standard three drug CINV prophylaxis regimen, and patients receiving usual care [standard of care arm], defined as receiving placebo plus standard three drug CINV prophylaxis **during the study assessment period (see section 3.1 for study assessment period).**

2.2 Secondary Objectives

2.2.1 To compare the total number of rescue medications needed for breakthrough CINV between the experimental and standard of care arms for the same assessment period

2.2.2 To compare the number of patients achieving minimal nausea between the experimental and standard of care arms for the same assessment period for the same assessment period

2.2.3 To compare the patient reported frequency of nausea between patients on the experimental and standard of care arms for the same assessment period for the same assessment period

2.2.4 To compare the patient reported severity of nausea between patients the experimental and standard of care arms for the same assessment period for the same assessment period

2.2.5 To compare number of episodes of emesis between patients the experimental and standard of care arms for the same assessment period for the same assessment period

3.0 Criteria for Evaluation / Study Endpoints

3.1 Primary Endpoint:

3.1.1 Complete response- **Must satisfy all three of the following criteria for the entire duration of the study assessment period. The study assessment period is defined as starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for 5 days after the last dose of highly or moderately emetogenic conditioning chemotherapy. The study treatment starts with the first dose of highly or moderately emetogenic chemotherapy and continues for 3 days after the last dose of highly or moderately emetogenic conditioning chemotherapy.**

- No emesis
- A score no higher than "rarely" to the PRO-CTCAE question "In the last 24 hours, how often did you have nausea?"
- A score no higher than "mild" to the PRO-CTCAE question "In the last 24 hours, what was the severity of your nausea at its worst?"

3.2 Secondary Endpoints

3.2.1 Number of rescue medications administered during the following time period: starting with the first dose of highly or moderately emetogenic chemotherapy and continuing for 5 days after last dose of highly or moderately emetogenic conditioning chemotherapy administration. A rescue medication is defined as documented administration of an anti-emetic agent other than those that are scheduled for CINV prophylaxis.

- Will be reported separately based on the following time periods
  - Acute: Starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for one day after the last dose of highly or moderately emetogenic conditioning chemotherapy.
  - Delayed: Starting with the second day after completion of highly or moderately emetogenic conditioning chemotherapy and continuing through the fifth day after completion of highly or moderately emetogenic chemotherapy.

3.2.2 Percent achieving minimal nausea- Must satisfy both of the criteria below starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for 5 days after the last dose of highly or moderately emetogenic conditioning chemotherapy.

- **Pro-CTCAE nausea frequency score of rarely or less to the PRO-CTCAE question "In the last 24 hours, how often did you have nausea?"**
- **Pro-CTCAE nausea severity score of mild or less to the PRO-CTCAE question "In the last 24 hours, what was the severity of your nausea at its worst?"**

3.2.3 Patient reported frequency of nausea (PRO-CTCAE Scale: Never, Rarely, Occasionally, Frequently, Almost constantly) to the PRO-CTCAE question "In the last 24 hours, how often did you have nausea?"

- Will be reported separately based on the following time periods:
  - Acute: Starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for one day after the last dose of highly or moderately emetogenic conditioning chemotherapy.
  - Delayed: Starting with the second day after completion of highly or moderately emetogenic conditioning chemotherapy and continuing through the fifth day after completion of highly or moderately emetogenic chemotherapy

3.2.4 Patient reported severity of nausea (PRO-CTCAE Scale: None, Mild, Moderate, Severe, Very severe) to the PRO-CTCAE question "In the last 24 hours, what as the severity of your nausea at its worst?"

- Will be reported separately based on the following time periods:
  - Acute: Starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for one day after the last dose of highly or moderately emetogenic conditioning chemotherapy.
  - Delayed: Starting with the second day after completion of highly or moderately emetogenic conditioning chemotherapy and continuing through the fifth day after completion of highly or moderately emetogenic chemotherapy

3.2.5 Documented episodes of emesis during the study assessment period

- Will be reported separately based on the following time periods:
  - Acute: Starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for one day after the last dose of highly or moderately emetogenic conditioning chemotherapy.
  - Delayed: Starting with the second day after completion of highly or moderately emetogenic conditioning chemotherapy and continuing through the fifth day after completion of highly or moderately emetogenic chemotherapy.

3.2.6 Documented somnolence according to CTCAE v5

- Will be documented daily starting with the first dose of olanzapine and continuing through 2 days after the last dose of olanzapine

3.2.7 QTc Prolongation according to CTCAE v5

- Will be documented according to the Time and Events table in Section 8 and will use the pre-transplant/screening EKG as a baseline
- Fredericia calculation will be used (see Appendix C)

4.0 SUBJECT ELIGIBILITY

In order to participate in this study a subject must meet ALL of the eligibility criteria outlined below.

4.1 Inclusion Criteria

4.1.1 Written informed consent obtained to participate in the study and HIPAA authorization for release of personal health information.

4.1.2 Recipients receiving autologous or allogeneic HCT for any disease

4.1.3 Any conditioning chemotherapy regimen considered a standard BMT conditioning regimen (Appendix D)

4.1.4 Age >18 years old

4.1.5 ECOG Performance Status of 0-2

4.1.6 Subject is willing and able to comply with study procedures based on the judgement of the investigator or protocol designee.

4.2 Exclusion Criteria

4.2.1 Patients must not have started conditioning chemotherapy prior to consent. Note: test dose Busulfan is not part of conditioning chemotherapy

4.2.2 Known allergy to olanzapine

4.2.3 Baseline QTc >500 msec as calculated by Fredericia formula (see Appendix C for calculation)

4.2.4 Patients receiving post-transplant cyclophosphamide as planned GVHD prophylaxis

4.2.5 Pregnant or breastfeeding (NOTE: patients pregnant or breast-feeding are not eligible to proceed to transplant).

4.2.6 Has a known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ

cervical or bladder cancer, or other cancer for which the subject has been disease-free for at least five years.

4.2.7 Treatment with any investigational drug within 7 days prior to registration.

4.2.8 Subject is receiving prohibited medications (ciprofloxacin or fluvoxamine) as listed in Section 5.6 of the protocol that cannot be discontinued/replaced by an alternative therapy.

5.0 STUDY DESIGN

5.1 General Design

This study is a single institution, randomized, double blind, placebo-controlled trial evaluating olanzapine's role when added to standard three-drug anti-emetic therapy as a prophylaxis agent for chemotherapy induced nausea and vomiting (CINV) in HCT patients. Subjects are randomized 1:1 to either placebo or olanzapine. A randomization list will be generated by the statistician and sent directly to IDS for implementation. Randomization will be done separately for the allogenic and autologous transplant patients, and use blocks of size 6. Within the allogeneic recipients, randomization will be stratified by those receiving myeloablative conditioning (MAC) vs. reduced intensity conditioning (RIC). The study population will consist of subjects treated at UNCMC on the Bone Marrow Transplant service (Med T). Research personnel will contact subjects regarding study participation during the preadmission counseling visit.

All subjects will complete conditioning chemotherapy as determined by their UNC BMT physician's discretion. Conditioning regimens are patient specific and can range from 1-7 days [Appendix D]. A baseline assessment of nausea symptoms will occur prior to receipt of any highly or moderately emetogenic chemotherapy and then will occur every morning of highly or moderately emetogenic conditioning chemotherapy and continue for 5 days after the last dose of highly or moderately emetogenic conditioning chemotherapy. Study procedures will include administration of the study drug (placebo or olanzapine) and administration of a targeted NCI Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE**).** Active participation in the study is expected to last 5 days after the last dose of highly or moderately emetogenic conditioning chemotherapy regimen (the total number of treatment days will be dependent on the duration of the conditioning chemotherapy regimen). An end of study visit will then take place at transplant day +10 (+/- 2 days)

5.2 Schema

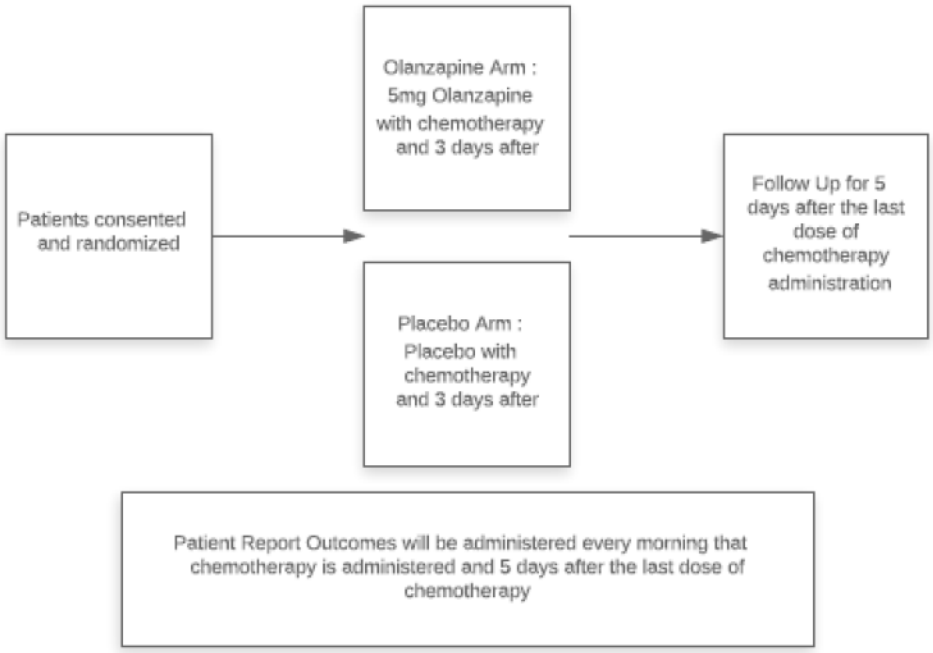

Figure 1. Schematic of Study Design needs to have each day of conditioning chemo

Participants will be administered study drug (placebo or olanzapine) starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for 3 days after the last dose of highly or moderately emetogenic conditioning chemotherapy.

5.3 Treatment Dosage and Administration

REGIMEN DESCRIPTION					
Agent	**Pre-medications; Precautions**	**Dose**	**Route**	**Schedule**	**Status**
Olanzapine (or placebo)	None	5 mg	By Mouth	Prior to chemotherapy for first administration, then nightly for the remainder of days of administration	Study Drug
Ondansetron*	None	16-24 mg	By Mouth or IV	Daily, prior to each dose of conditioning chemotherapy	Standard of care

Dexamethasone	None	8-20 mg	By Mouth or IV	Daily, prior to each dose of conditioning chemotherapy	Standard of care
Aprepitant*	None	130 mg	IV	Prior to first dose of chemotherapy. A second dose may be given in instances where conditioning chemotherapy duration exceeds 5 days, per institutional standard	Standard of care

*A similar agent of the same class may be substituted at an equivalent dose (see NCCN Antiemesis guidelines for specific dose recommendations) based on product/formulary availability

5.4 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives at least 1 dose of study treatment on this protocol will be evaluable for toxicity. Each subject will be assessed for the development of any toxicity according to the Time and Events table (Section 8.0). Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), **version 5.0**. Dose adjustments should be made according to the system showing the greatest degree of toxicity. Olanzapine is well tolerated with somnolence and QTC prolongation being the most common adverse effects [10]. Study drug (olanzapine or placebo) may be dose reduced or held at the discretion of the attending physician. Patients in whom 2 or more doses of study drug are held will be excluded from the efficacy analysis however still followed for the safety analysis.

Example of non-hematological Toxicity Dose Reductions	
Event	**Action**
Somnolence	
Grade 1	None
Grade 2-3	Reduce study drug to 2.5 mg nightly
Grade 4	Hold next dose. If toxicity resolves to grade 1-2 within 24 hours, resume study drug at a dose of 2.5 mg nightly. If not resolved to ≤ grade 2, permanently discontinue study drug
Prolonged QTC (calculated by Fredericia)	
Grade 1-2	Reduce study drug to 2.5 mg nightly
Grade 3	Permanently discontinue study drug

5.4.1 Missed Doses

If a dose is not able to be given within the specified timeframe, or if a patient vomits soon after taking a dose, then that dose will be skipped, and the patient will resume as scheduled the following day.

5.5 Concomitant Medications/Treatments/Supportive Care Allowed

Subjects will receive all needed supportive care during the study to manage other side effects related to administration of chemotherapy. Examples of supportive agents include anti-diarrheal agents, anti-constipation agents, and other supportive medications at the discretion of the treating physician.

5.6 Prohibited Medications

Prohibited Concurrent Medications/Treatments include **fluvoxamine** and **ciprofloxacin**. Other known inhibitors/inducers of CYP2D6 and CYP1A2 are listed below; however, no action is required for patients taking these medications.

Inhibitors	**Inducers**
Fluvoxamine (prohibited)	carbamazepine
ciprofloxacin (prohibited)	insulin
cimetidine	methylcholanthrene
amiodarone	modafinil
efavirenz	nafcillin
fluoroquinolones	beta-naphthoflavone
furafylline	omeprazole
interferon	rifampin
methoxsalen	Rucaparib
mibefradil	Teriflunomide
ticlopidine	
Crisaborole	
Rucaparib	
Citalopram	
Ribociclib	

5.7 Duration of Therapy

Treatment with olanzapine or placebo starts with the first dose of highly or moderately emetogenic conditioning chemotherapy and continues for 3 days after the last dose of highly or moderately emetogenic conditioning chemotherapy for a maximum of 10 days, unless subjects decide to withdraw from the study.

5.8 Duration of Follow Up

All subjects will be followed in the hospital starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for 5 days after

the last dose of highly or moderately emetogenic conditioning chemotherapy, or until death, whichever occurs first after removal or completion of study treatment for determination of study endpoints. Subjects removed from study treatment for unacceptable AEs will be followed for resolution or stabilization of the adverse event(s).

5.9 Study Withdrawal

If a subject decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The subject should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the objectives outlined in the protocol.
- A complete final evaluation at the time of the subject's study withdrawal should be obtained with an explanation of why the subject is withdrawing from the study.
- If the subject is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.
- If the reason for removal of a subject from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive subject withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided.

6.0 DRUG INFORMATION

6.1 Olanzapine

For additional information on olanzapine refer to the package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020592s062021086s040021253s048lbl.pdf

6.1.1 How Supplied

Ondansetron, aprepitant and dexamethasone is a commonly used regimen for chemotherapy induced nausea and vomiting. Olanzapine will be stored in and dispensed from UNC Investigational Drug Service (IDS). IDS is blinding the study treatment by placing olanzapine or placebo inside of a masked oral capsule. Olanzapine is available as a tablet in 2.5, 5, 7.5, 10, 15, and 20 mg strengths. Scheduling and dosing of standard of care CINV prophylaxis drugs (ondansetron, aprepitant, and dexamethasone) are administered according to the conditioning regimen (Appendix D)

6.1.2 Storage and Handling

Olanzapine should be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [10]. Olanzapine will be stored and handled by the IDS at UNCMC.

6.1.3 Route of Administration

Olanzapine tablet will be taken by mouth as a masked oral capsule.

6.1.4 Method of Administration

Olanzapine can be taken with or without food. The first dose will be given prior to start of chemotherapy (+/- 1 hour) and subsequent doses will be given nightly at 2100 (+/-2 hours).

6.1.5 Drug Ordering and Accountability

The investigator or designee is responsible for keeping accurate records of the clinical supplies. Drug supply will be maintained by UNC IDS and dispensed to the patient floor for administration to the patient by a registered nurse

6.1.6 Return and Retention of Study Drug

Upon completion or termination of the study, all unused and/or partially used product will be destroyed at the site per institutional policy (e.g., UNC IDS drug destruction policy).

6.1.7 Adverse Events

The most common adverse effects of olanzapine of particular interest in this study are QTC prolongation and somnolence

6.2 Placebo

6.2.1 How Supplied

Placebo will be stored in and dispensed from UNC Investigational Drug Service (IDS). IDS is blinding the study treatment by placing olanzapine or placebo inside of a masked oral capsule. Scheduling and dosing of standard of care CINV prophylaxis drugs (ondansetron, aprepitant, and dexamethasone) are administered according to the conditioning regimen (Appendix D)

6.2.2 Storage and Handling

Placebo should be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [10]. Placebo will be stored and handled by the IDS at UNCMC.

6.2.3 Route of Administration

Placebo tablet will be taken by mouth as a masked oral capsule.

6.2.4 Method of Administration

Placebo can be taken with or without food. The first does will be given prior to start of chemotherapy (+/- 1 hour) and subsequent doses will be given nightly at 2100 (+/-2 hours).

6.2.5 Drug Ordering and Accountability

The investigator or designee is responsible for keeping accurate records of the clinical supplies. Drug supply will be maintained by UNC IDS and dispensed to the patient floor for administration to the patient by a registered nurse

6.2.6 Return and Retention of Placebo

Upon completion or termination of the study, all unused and/or partially used product will be destroyed at the site per institutional policy (e.g., UNC IDS drug destruction policy).

7.0 CLINICAL ASSESSMENTS

Clinical assessments will be performed as outlined in the Time and Events Table in Section 8.1

7.1 Assessment Descriptions

7.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Baseline/Screening and throughout the study as summarized in the Time and Events Table in Section 8.0. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

7.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

7.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases will be recorded at Screening and a focused assessment on symptoms/toxicity will be performed thereafter.

7.1.4 Physical Examination

A complete physical examination including height (at screening only), weight, Performance status ECOG and **vital signs (i.e.,** temperature and blood pressure) will be performed by a co-investigator who is a physician or advanced practice provider at Screening and the first Study Visit #1.

Qualified staff (MD, NP, RN, and PA) may complete the abbreviated physical exam at all other visits.

New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

7.1.5 Adverse Events

Events should be assessed per NCI-CTCAE criteria v5.0. Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study drug will be recorded in the case report form (CRF).

7.2 Patient Reported Outcomes (Quality of life assessment)

PRO-CTCAE tools to assess frequency and severity of nausea included in Appendix A.

8.0 EVALUATIONS AND ASSESSMENTS

The NCI Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE) will be administered every morning starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for 5 days after the last dose of highly or moderately emetogenic conditioning chemotherapy (see section 8.1).

8.1 Time and Events Table

SAMPLE	Screening Pre-study[1]	Each Day of Chemo	Post-chemo Day 1	Post-chemo Day 2	Post-chemo Day 3	Post-Study Treatment Follow-up		
						Post-chemo Day 4	Post-chemo Day 5	End of study period[2]
Informed Consent	X							
Demographics	X							
Medical History	X							
Concomitant Medications	X							
Physical Exam	X							
Frequency of nausea PRO-CTCAE		X[3]	X	X	X	X	X	
Severity of nausea PRO-CTCAE		X[3]	X	X	X	X	X	
PRN Rescue Medications during study period								X
EKG	X (within 2 weeks prior to admission)		X					X
Olanzapine or Placebo Administration[4]		X	X	X	X			
Review notes for sedation		X	X	X	X	X	X	
Review notes for emesis		X	X	X	X	X	X	

Assessment for AE[5]		X	X	X	X			X

Footnotes to Time and Events Table

1. Medical history and physical exam may be performed within 2 weeks prior to day 1 of study drug treatment. Other evaluations except for pregnancy test must be performed within 2 weeks priors to Day 1 (D1) of study treatment. Serum B-HCG must be performed within 30 days prior to admission and may be repeated at the pre-admission visit for women of child-bearing potential per UNC HCT Recipient eligibility and Evaluation Policy [Policy Stat ID: 6994125].

2. The end of treatment visit should only occur when subjects permanently stop study treatment and should be performed on transplant day +10 (+/- 2 days). Subjects who have an ongoing ≥grade 2 or serious AE (SAE) at this visit will continue to be followed until the event is resolved or deemed irreversible by the investigator.

3. Baseline assessment of nausea symptoms using the targeted PRO-CTCAE instrument will be performed prior to administration of chemotherapy on the first day of conditioning therapy. Subsequent assessments will occur every morning until 5 days after conditioning therapy.

4. The first administration of Olanzapine or placebo will be prior to start of chemotherapy (+/- 1 hour). Subsequent doses will be given nightly at 2100 (+/-2 hours).

5. Toxicity will be assessed using CTCAE v5.0

8.2 Assessment of Safety

Any subject who receives at least one dose of study therapy on this protocol will be evaluable for toxicity. Each subject will be assessed daily per the time and events table outlined in section 8.1 for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI CTCAEv5.0.

8.3 Assessment of Efficacy

Frequency of nausea	Never	Rarely	Occasionally	Frequently	Almost Constantly
Severity of nausea	None	Mild	Moderate	Severe	Very Severe

All subjects will be included in an intention to treat analysis for efficacy and CINV prevention. PRO-CTCAE scales will be administered starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for 5 days after the last dose of highly or moderately emetogenic conditioning chemotherapy. Please see time and events table in section 8.1 for specific information

9.0 ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug or study treatment) in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Conditioning chemotherapy for transplantation results in ≥ grade 3 anemia, thrombocytopenia, leukopenia (including neutropenia, lymphopenia). These are expected complications of transplant experienced by all patients and are not known side effects of olanzapine. Thus, these will not be considered adverse events in this study. Additionally, hypokalemia and hypomagnesemia are common due to conditioning chemotherapy. Therefore, only ≥ grade 3 for hypokalemia and hypomagnesemia will be considered adverse events. Mucositis and infusion reactions can occur as a result of conditioning chemotherapy and should not be attributed to olanzapine as these are not known side effects, even at higher doses. The most common adverse effects of olanzapine of particular interest in this study are QTC prolongation and somnolence [10].

9.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the study treatment is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a study treatment

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study treatment exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with study treatment exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with study treatment exposure, but otherwise uncommon in the population (e.g.,

tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the study treatment caused the event.

- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the study treatment group than in a concurrent or historical control group

9.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved study treatment or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

9.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization; *
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse study treatment-related experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

9.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for 5 days after the last dose of highly or moderately emetogenic

conditioning chemotherapy. Collected information should be recorded in the Case Report Forms (CRF) for that subject. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

9.3 SAEs or Serious SARs

9.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin starting with the first dose of highly or moderately emetogenic conditioning chemotherapy and continuing for 5 days after the last dose of highly or moderately emetogenic conditioning chemotherapy.

9.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within OnCore® for that subject within 24 hours of learning of its occurrence. Additionally, the project manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

9.4 Adverse Event Reporting

9.4.1 IRB Reporting Requirements:

UNC:

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem.

9.5 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies

charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight of Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of subjects treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, the UNC IRB and DSMB.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design

This is a single center, randomized, double blind, placebo controlled study evaluating olanzapine's role in CINV prophylaxis in HCT patients. Each patient will receive olanzapine or placebo starting with the first dose of highly or moderately emetogenic conditioning chemotherapy (typically lasting 1-7 days) and continuing 3 days beyond the last dose of highly or moderately emetogenic conditioning chemotherapy. Primary and secondary objectives are listed in sections 3.1 and 3.2.

10.2 Sample Size, Accrual and Duration of Accrual

The following design will be used: Assuming the rate of complete response in the placebo arm is 24% and that the rate in the olanzapine arm will be higher (55%), we will need 68 total patients in each arm (34 in each cohort of autologous recipients and allogeneic recipients) for a total of 136 [7]. With this number of patients, we will have 80% power to detect a difference, using a chi-squared test with two-sided alpha of 0.05, if the rate in the olanzapine arm is 80%. To account for dropout, we plan to enroll 150. Since olanzapine is an FDA approved drug commonly used for CINV, we anticipate a high accrual rate of approximately 50%. We anticipate screening about 300 patients to reach our target accrual of 150 total patients. Since we do about 165 adult transplants per year we estimate that enrollment will last about 1.5-2 years.

10.3 Data Analysis Plans

All analyses will be reported separately for those receiving allogenic and autologous transplants.

- Primary endpoint: Complete response- no emesis and no more than minimal nausea as defined by a score of 'Rarely' or less on the PRO-CTCAE within the first 5 days of chemotherapy (see section 3.1). A chi-squared test will be used to compare the rates of complete response between olanzapine and placebo arms.
- Secondary endpoints:
    - Number of rescue medications through first 5 days after last chemo administration. A Wilcoxon Rank Sum test will be used to compare the difference in number of rescue medications between the olanzapine and placebo arms.

Percentages will be reported and Chi-squared tests (or Fisher's exact tests if cell sizes are small) will be used to compare percentages between arms.

- Percent achieving minimal nausea (score of 'Rarely' or less on the PRO-CTCAE).
- Maximum patient reported frequency of nausea (PRO-CTCAE Scale: Never, Rarely, Occasionally, Frequently, Almost constantly) during the acute and delayed phases
- Maximum patient reported severity of nausea (PRO-CTCAE Scale: None, Mild, Moderate, Severe, Very severe) during the acute and delayed phases
- Number of episodes of emesis during the acute and delayed phases

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federalwide Assurance (FWA) number
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.

- The Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.3 Registration Procedures

All patients must be registered by the BMT study coordinator at UNC before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the BMT study coordinator.

11.4 Data Management and Monitoring/Auditing

The BMT clinical research group of the UNC LCCC will serve as the coordinating center for this trial. Accrual will be tracked in OnCore®. All data will be collected and entered through a web based clinical research platform, Redcap®.

11.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

11.5.2 Single Subject Exceptions

For Institutions Relying on UNC's IRB:
Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

11.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs, please follow the guidelines below:

Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the subject, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

11.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor correspondence to Investigators, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug/investigational product seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents

should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, auditing and monitoring of trials will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

12.0 REFERENCES

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5. Navari, R.M. and M. Aapro, *Antiemetic Prophylaxis for Chemotherapy-Induced Nausea and Vomiting.* N Engl J Med, 2016. **374**(14): p. 1356-67.
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9. Yang, T., et al., *Efficacy of olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting: a meta-analysis.* Br J Clin Pharmacol, 2017. **83**(7): p. 1369-1379.
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13.0 APPENDICES

13.1.1 Appendix A. PRO-CTCAE

Frequency of nausea: "In the last 24 hours, how often did you have nausea?"

Severity of nausea: "In the last 24 hours, what was the severity of your nausea at its worst?"

Frequency of nausea scores:	Never	Rarely	Occasionally	Frequently	Almost Constantly
Severity of nausea scores:	None	Mild	Moderate	Severe	Very Severe

13.1.2 Appendix B. Prohibited Medications or Those to be used with Caution

One of the medications you are receiving during this clinical trial is **Olanzapine. Olanzapine** interacts with some drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the counter remedy), or anything that you buy from the health food store or grocery store (herbal supplement). Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you**.

- **Olanzapine** is processed by a certain enzyme in the liver called CYP2D6. Drugs that increase the activity of this enzyme are called "inducers", and drugs that decrease the activity of this enzyme are called "inhibitors". **Olanzapine** must be used very carefully with other medicines that are **inducers** or **inhibitors** of CYP2D6.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category
- Before you start the study, your study doctor will work with your regular prescriber to switch the following medications if you are taking them: **Fluvoxamine and/or ciprofloxacin**
- Your regular prescribers should look at this web site: http://medicine.iupui.edu/clinpharm/ddis/table.asp to see if any medicine they want to prescribe is on a list of drugs to avoid. Your study doctor may also have a list of medications for you to show your regular prescribers instead of, or in addition to, this website.
- Other medicines can be a problem with your study drugs.
    - You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
    - Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at _____.

13.1.3 Appendix C. Fredericia's Formula

QTc = QT/(RR^0.33)

QTC= Corrected QTc
QT= QT interval
RR= 60/heart rate

13.1.4 Appendix D. Conditioning Regimens

The list below encompasses the majority of planned conditioning regimens for patients undergoing HCT. For any not included below, patients will receive olanzapine on any days of highly or moderately emetogenic chemotherapy plus an additional three days after. Daily monitoring for safety and efficacy in accordance with the time and events table in section 8.1 will occur for an additional 2 days following the last dose of olanzapine.

Study drug plan for chemotherapy regimen BEAM (autologous)

Transplant day	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4
Chemotherapy agent	BCNU	VP16 + Cyrarabine	VP16 + Cyrarabine	VP16 + Cyrarabine	VP16 + Cyrarabine	Melphalan					
Study drug Given	X	X	X	X	X	X	X	X	X		
Monitoring	X	X	X	X	X	X	X	X	X	X	X

Study drug plan for chemotherapy regimen melphalan (autologous)

Transplant day	-1	0	+1	+2	+3	+4
Chemotherapy agent	Melphalan					
Study drug Given	X	X	X	X		
Monitoring	X	X	X	X	X	X

Study drug plan for chemotherapy regimen Benda-EAM (autologous)

Transplant day	-7	-6	-5	-4	-3	-2	-1	0	+1	+2	+3	+4
Chemotherapy agent	Bendamustine	Bendamustine	VP16 + Cyrarabine	VP16 + Cyrarabine	VP16 + Cyrarabine	VP16 + Cyrarabine	Melphalan					
Study drug Given	X	X	X	X	X	X	X	X	X	X		
Monitoring	X	X	X	X	X	X	X	X	X	X	X	X

Study drug plan for chemotherapy regimen carmustine + thiotepa (autologous)

Transplant day	-6	-5	-4	-3	-2	-1	0	+1
Chemotherapy agent	Carmustine	Thiotepa	Thiotepa					
Study drug Given	X	X	X	X	X	X		
Monitoring	X	X	X	X	X	X	X	X

Study drug plan for chemotherapy regimen CE (autologous)

Transplant day	-4	-3	-2	-1	0	+1	+2	+3
Chemotherapy agent	Carboplatin + Etoposide	Carboplatin + Etoposide	Carboplatin + Etoposide					
Study drug Given	X	X	X	X	X	X		
Monitoring	X	X	X	X	X	X	X	X

Study drug plan for chemotherapy regimen RIC fludarabine/melphalan (allogeneic)

Transplant day	-5	-4	-3	-2	-1	0	+1	+2	+3	+4
Chemotherapy agent	Fludarabine*	Fludarabine*	Fludarabine*	Fludarabine*	Melphalan					
Study drug Given					X	X	X	X		
Monitoring					X	X	X	X	X	X

Study drug plan for chemotherapy regimen RIC fludarabine/busulfan (allogeneic)

Transplant day	-6	-5	-4	-3	-2	-1	0	+1
Chemotherapy agent	Fludarabine*	Fludarabine + busulfan	Fludarabine + busulfan	Fludarabine*	Fludarabine*			
Study drug Given		X	X	X	X	X		
Monitoring		X	X	X	X	X	X	X

Study drug plan for chemotherapy regimen NMA fludarabine/cyclophosphamide/TBI (allogeneic)

Transplant day	-6	-5	-4	-3	-2	-1
Chemotherapy agent	Fludarabine + Cyclophosphamide	Fludarabine*	Fludarabine*	Fludarabine*	Fludarabine*	TBI
Study drug Given	X	X	X	X		
Monitoring	X	X	X	X	X	X

Study drug plan for chemotherapy regimen NMA fludarabine/cyclophosphamide (allogeneic)

Transplant day	-5	-4	-3	-2	-1	0	+1
Chemotherapy agent	Fludarabine + Cyclophosphamide	Fludarabine + Cyclophosphamide	Fludarabine*	Fludarabine*	Fludarabine*		
Study drug Given	X	X	X	X	X		
Monitoring	X	X	X	X	X	X	X

Study drug plan for chemotherapy regimen MAC fludarabine/busulfan (allogeneic)

Transplant day	-5	-4	-3	-2	-1	0	+1	+2	+3
Chemotherapy agent	Fludarabine + busulfan	Fludarabine + busulfan	Fludarabine + busulfan	Fludarabine + busulfan					
Study drug Given	X	X	X	X	X	X	X		
Monitoring	X	X	X	X	X	X	X	X	X

Study drug plan for chemotherapy regimen MAC busulfan/cyclophosphamide (allogeneic)

Transplant day	-7	-6	-5	-4	-3	-2	-1	0	+1	+2	+3
Chemotherapy agent	Busulfan	Busulfan	Busulfan	Busulfan	Cyclophosphamide	Cyclophosphamide					
Study drug Given	X	X	X	X	X	X	X	X	X		
Monitoring	X	X	X	X	X	X	X	X	X	X	X

Study drug plan for chemotherapy regimen MAC cyclophosphamide/Total Body Irradiation (TBI)

Transplant day	-6	-5	-4	-3	-2	-1	0	+1	+2	+3
Chemotherapy agent	TBI	TBI	TBI	Cyclophosphamide	Cyclophosphamide					
Study drug Given				X	X	X	X	X		
Monitoring				X	X	X	X	X	X	X

* - Fludarabine is minimally emetogenic and does not warrant routine prophylaxis when given as a single agent.