RUSH UNIVERSITY MEDICAL CENTER IRB PROTOCOL

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Aprepitant- and olanzapine- containing regimens for prevention of acute and delayed nausea and vomiting associated with high dose melphalan and BEAM in autologous stem cell transplant patients

PROTOCOL FACE PAGE

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program

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Abbreviations

5-HT_3	Serotonin
ADAMHA	Alcohol, Drug Abuse, and Mental Health Administration
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
ASCT	Autologous Stem Cell Transplant
BEAM	Carmustine (**B**iCNU); **E**toposide; Cyarabine (**A**ra-C);**M**elphalan
CINV	Chemotherapy Inducted Nausea and Vomiting
CNS	Central nervous system
CR	Complete response
EKG	Electrocardiogram
ESMO	European Society of Medical Oncology (ESMO)
FLIE	Functional Living Index-Emesis
HIV	Human immunodeficiency virus
IRB	Institutional Review Board
MASCC	Multinational Association of Supportive Care in Cancer
NCCN	National Comprehensive Cancer Network
NIH	National Institutes of Health
QTc	Corrected QT interval
RUMC	Rush University Medical Center
SAE	Serious Adverse Events
SCT	Stem Cell Transplant
VAS	Visual Analog Scale

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1. PROTOCOL SUMMARY

This is a multi-center, randomized, non-inferiority phase 3 study conducted to determine an appropriate anti-emetic regimen for patients receiving melphalan for an autologous stem cell transplant (SCT). Candidates for this trial will include patients aged 18-80 years with hematologic malignancies receiving high dose melphalan as part of a conditioning regimen for an autologous stem cell transplant. Patients will be enrolled in 3 arms. Patients in Arm A will receive an aprepitant containing anti-emetic regimen. Patients in Arm B will receive an olanzapine containing anti-emetic regimen. Patients in Arm C will receive an aprepitant plus olanzapine containing anti-emetic regimen. Patients must be able to tolerate oral medications.

Patients will be carefully monitored for rates of emesis, nausea, and mucositis. Any adverse events will be recorded. Impact on quality of life will also be assessed. A total of 184 patients will be accrued to each arm. It is anticipated that the accrual period will last approximately 2-3 years. The primary endpoint of this study is a complete response, defined as no emesis and no rescue therapy within 120 hours of melphalan administration.

2. OBJECTIVES

The **primary aim** of this study is to obtain an overall complete response (CR), defined as no emesis and no rescue therapy within 120 hours of melphalan administration. The time interval of 120 hours was chosen because it can be assumed that additional cofactors (e.g., mucositis and antibiotic use) influence rates of nausea and vomiting after this point in time.

Secondary objectives include:

- Acute CR, defined as no emesis or rescue therapy in 0 to 24 hours
- Delayed CR, defined as no emesis or rescue therapy in 25 to 120 hours
- Very delayed CR, defined as no emesis in 121 to 168 hours
- Rates of emesis
- Nausea (Any)
- Significant nausea
- Mucositis (Any)
- Significant mucositis
- Impact on quality of life
- Time to neutrophil and/or platelet engraftment (days)

At study completion an estimate of the efficacy of aprepitant or olanzapine containing anti-emetic regimens in preventing nausea and vomiting after high dose melphalan in stem cell transplant patients will be possible.

3. BACKGROUND AND RATIONALE

High dose melphalan, by itself or in combination with other chemotherapy, is a very common alkylating agent used in conditioning regimens for autologous stem cell transplant. Acute toxicities of high dose melphalan include myelosuppression, mucositis, hepatotoxicity, and nausea and vomiting. Chemotherapy inducted nausea and vomiting (CINV) has been patient reported as one of the most feared adverse effects of patients receiving chemotherapy (Bloechl-Daum, et al 2006). Without appropriate supportive care, patients could experience significant acute and delayed CINV with melphalan.

When first introduced serotonin (5-HT_3) antagonists, alone or combined with dexamethasone, improved rates of nausea and emesis in stem cell transplant patients (Ballen *et al*, 2001; Einhorn *et al*, 2011). The addition of aprepitant, a neurokinin-1 antagonist, to 5HT_3 antagonists and dexamethasone in SCT patients receiving high dose melphalan has been shown to be beneficial in preventing CINV (Jordan *et al*, 2011; Pieliechowski *et al*, 2011; Stiff *et al,* 2013; Schmitt *et al,* 2014; Bechtel *et al*, 2014).

Most commonly used guidelines for anti-emetic therapy for CINV include ASCO, MASCC/ESMO, and NCCN.[1-3] ASCO guidelines recommend to consider aprepitant in combination with a 5-HT_3 antagonist and dexamethasone for high dose chemotherapy with stem cell or bone marrow transplant.[1] MASCC/ESMO guidelines recommend aprepitant in combination with 5-HT3 antagonist and dexamethasone for patients who are at high or moderate risk for delayed CINV.[2] NCCN classifies melphalan as a moderate emetic risk agent, resulting in 30-90% of patients experiencing CINV without supportive anti-emetics.[3] Historically, a 5-HT_3 antagonist and dexamethasone ± aprepitant was the only recommended option for moderate emetic risk chemotherapy.[3] Recently, the NCCN added an olanzapine regimen to the anti-emetic guidelines for moderate-high emetic risk regimens and an olanzapine + aprepitant regimen for high emetic risk regimens (Table 1).[3] Differences in guideline recommendations are due to lack of evidence for appropriate anti-emetic regimen in the SCT patient population.

Table 1: Summary of recommendations for anti-emetic therapy in patients receiving melphalan

	ASCO	MASCC/ESMO	NCCN	NCCN
Updated	2011	2013	2014	2018
Criteria	High dose chemotherapy with stem cell rescue	High to moderate risk delayed CINV	Moderate risk agents (Melphalan)	Moderate risk agents (Melphalan) High risk (Carmustine)
Recommendation	Aprepitant + 5-HT_3 antagonist + dexamethasone	Aprepitant + 5-HT_3 antagonist + dexamethasone	5-HT_3 antagonist + Dexamethasone ± Aprepitant **OR** Olanzapine + 5-HT_3 antagonist + Dexamethasone	Olanzapine + Aprepitant + 5-HT_3 antagonist + Dexamethasone

Olanzapine is an atypical antipsychotic that blocks multiple neurotransmitters in the central nervous system (Navari *et al*, 2014). The exact mechanism of olanzapine reducing CINV is unknown; however, it blocks dopamine and serotonin neurotransmitters, possibly contributing to its anti-emetic effect (Navari *et al*, 2014).

Olanzapine has been studied in phase I-III trials for the prevention of CINV in patients receiving highly emetogenic chemotherapy for solid tumors (Navari *et al*, 2014). In a phase III trial by Navari *et al*, chemotherapy naïve patients who received cisplatin or cyclophosphamide and doxorubicin for solid tumors were randomized to either olanzapine or aprepitant in combination with palonosetron and dexamethasone (Table 2). Olanzapine, palonosetron, and dexamethasone were comparable to aprepitant, palonosetron, and dexamethasone in the control of chemotherapy induced emesis (Table 2). Nausea was significantly better controlled with the olanzapine containing regimen (Table 2). This study led to the addition of olanzapine in the NCCN anti-emesis guidelines for the prevention of CINV in patients receiving highly or moderately emetogenic regimens.

Table 2: Results of olanzapine or aprepitant in combination with palonosetron and dexamethasone in patients receiving highly emetic chemotherapy. (Navari *et al*, 2011).

	Olanzapine Arm N = 121	Aprepitant Arm N = 120
Treatment	• Day 1: Olanzapine 10 mg, palonosetron 0.25 mg, dexamethasone 20 mg • Day 2-4: Olanzapine 10 mg QD	• Day 1: Aprepitant 125 mg, palonosetron 0.25 mg, and dexamethasone 12 mg • Day 2-3: Aprepitant 80 mg QD and dexamethasone 4 mg BID
Acute CR (24 hours)	97%	87%
Delayed CR (2-5 days)	77%	73%
Overall CR (0-120 hours)	77%	73%
Without acute nausea	87%	87%
Without delayed nausea	69%	38%
Without overall nausea	69%	38%

*CR was no emesis or no rescue medications

Olanzapine is now an acceptable option for patients receiving highly or moderately emetogenic chemotherapy (NCCN). Olanzapine is not a cytochrome P450 inhibitor and would have minimal drug interactions (Bymaster *et al*, 1996). In addition, olanzapine may reduce opioid requirements in cancer patients with uncontrolled pain, cognitive impairment, or anxiety (Khojainova *et al*, 2002; Navari *et al,* 2014). Side effects of olanzapine are listed in Section 10.4. Aprepitant, due to high cost, is often not covered under patient insurance plans, and with autologous SCTs moving to the outpatient setting, olanzapine would be an attractive option. In conclusion, olanzapine may be a potential alternative for use in the SCT patient population. To our knowledge, this is the first study comparing aprepitant to olanzapine in patients receiving high dose melphalan or BEAM in preparation for an autologous SCT.

4. THERAPEUTIC AGENTS

4.1 Melphalan

Supplied as: 50 mg vial
Reconstitution directions: The sterile diluents contains sodium citrate 0.2 g, propylene glycol 6 ml, ethanol (96%) 0.52 ml, and water for injection for a total of 10 ml
Storage and stability:

- Store vials at room temperature
- Protect from light
- Do not refrigerate the reconstituted product
- Reconstituted solutions must be further diluted immediately, discard unused portion
- Drug administration must be completed within 60 minutes of initial reconstitution.

Preparation: Reconstitute by rapidly injecting 10 ml of the supplied diluents into the vial to yield a final concentration of 5 mg/ml. Shake vigorously until the solution is clear. Immediately dilute the dose to be administered in 0.9% Sodium Chloride, USP, to a concentration no greater than 0.45 mg/ml. Refrigerated storage of the reconstituted product results in precipitation
Clinical considerations: Hydration pre and post melphalan per RUMC guidelines
Toxicities: See Section 10.0

4.2 Aprepitant

Supplied as: 40 mg, 80 mg, and 125 mg capsules
Storage and stability: Store at room temperature

Clinical considerations: May be taken with or without food. Aprepitant is a substrate of CYP3A4 and coadministration with drugs that inhibit or induce CYP3A4 may result in increased or reduced plasma concentrations of aprepitant. Aprepitant is an inducer of CYP2C9 and coadministration with drugs that are metabolized by CYP2C9 may result in lower plasma concentrations of these drugs.
Toxicities: See Section 10.0

4.3 Olanzapine
Supplied as: 2.5, 5, 7.5, 10, 15, and 20 mg tablets; 5, 10, 15, 20 mg orally disintegrating tablets
Storage and stability: Store at room temperature. Protect tablets from light and moisture.
Clinical considerations: May schedule in the evening with or without food
Toxicities: See Section 10.0

4.4 Ondansetron
Supplied as: 4, 8 mg tablets; 4, 8 mg orally disintegrating tablets (ODT); 40 mg/ml oral solution; 2 mg/ml injection; 20 mL multidose vials
Storage and stability: Store at room temperature. Protect oral solution from light.
Clinical considerations: May take with or without food. Ondansetron ODT place on top of tongue where it will dissolve in seconds, than swallow saliva. Administration with liquid is not necessary.
Toxicities: See Section 10.0

4.5 Dexamethasone
Supplied as: 0.5, 0.75, 1, 1.5, 2, 4, 6 mg tablets; 0.5 mg/5mL and 1 mg/mL solutions for oral administration; 4mg/mL and 10 mg/mL injection for intravenous or intramuscular use
Storage and stability: Store tablets and solution at room temperature. Protect from moisture and dispense in a well closed light resistant container. Discard oral opened bottle after 90 days. Intravenous injection should be stored at room temperature and protected from light.
Clinical considerations: May take with or without food. Recommend with food to prevent upset stomach.
Toxicities: See Section 10.0

5. CRITERIA FOR SUBJECT ELIGIBILITY

5.1 Subject Inclusion Criteria:

- Age
  - 18-80 years
- Autologous transplantation containing high dose melphalan as part of the conditioning regimen
  - Single or two day melphalan
  - BEAM (carmustine, etoposide, cytarabine, melphalan)
- Able to tolerate oral medications

5.2 Subject Exclusion Criteria:

- Nausea and vomiting within 12 hours before planned high dose conditioning chemotherapy
- Any antiemetic treatment within 24 hours before planned high dose conditioning chemotherapy
- Pregnancy
- Baseline QTc > 500ms
- History of seizures

- History of central nervous system (CNS) disease
- Human immunodeficiency virus (HIV)

6. RECRUITMENT PLAN

Patients will be considered for this protocol and recruited as appropriate according to their selected conditioning regimen for their autologous SCT. Patients who fulfill the eligibility criteria as listed in Section 5 will be recruited by a SCT attending prior to admission. Informed consent will be obtained by one of the participating investigators authorized to obtain consent.

After consent is obtained, confirmation of patient eligibility will be done by the oncology research pharmacist or SCT pharmacist. Confirmation of patient eligibility will be performed the day of admission followed by randomization.

This protocol will take due notice of NIH/ADAMHA policies concerning inclusion of women and minorities in clinical research populations. We expect that the study population will be fully representative of the range of patients referred for transplant without exclusion as to age, gender, or ethnic background within the limits of transplant eligibility. Pregnant women are excluded from participation in this study.

Rush University Medical Center will serve as the primary site for Phase 1 of this study. After a sufficient number of patients are successfully enrolled or 6 months passes and no research plan amendments are to be considered, then other sites will be enrolled to continue the same study for Phase 2.

7. PRETREATMENT EVALUATION

The following tests must be performed prior to starting pre-transplant conditioning regimen:

- EKG

8. TREATMENT/INTERVENTION PLAN

The selection of conditioning regimen most appropriate for the patient based on their disease status, age, extent of prior therapy, organ function and presence of significant co-morbidities is done by the treating SCT physician. All patients to be included in this study will be treated with high dose melphalan or BEAM. All patients will be admitted to the SCT Unit. The treating SCT physician will select the conditioning regimen most appropriate for the patient based on their disease status, age, extent of prior therapy, organ function and presence of significant co-morbidities. All patients will be treated with high dose melphalan or BEAM.

Patients will be randomized to the following treatment arms:

- Arm A: Aprepitant containing anti-emetic therapy
- Arm B: Olanzapine containing anti-emetic therapy
- Arm C: Aprepitant plus olanzapine containing anti-emetic therapy

Schedule of anti-emetic therapy is based on conditioning chemotherapy regimen and outlined in Section 8.1.

Post treatment anti-emetic therapy is outlined in Section 8.3.

8.1 Treatment Schedule

- **Conditioning regimen: One day melphalan**

ARM A: Patients receiving one day melphalan and randomized to **aprepitant** will receive:

Day	-1	0 ASCT	+1	+2
Melphalan	X			
Aprepitant	125 mg	80 mg	80 mg	
Ondansetron	16 mg	16 mg	16 mg	16 mg
Dexamethasone	12 mg	8 mg	8 mg	8 mg

- Melphalan: 140-200 mg/m^2/day IV given on Day -1
- ASCT: stem cell rescue on Day 0
- Aprepitant: 125 mg orally one hour prior to chemotherapy on Day -1 and 80 mg orally on Days 0 and +1
- Ondansetron: 16 mg orally daily on Days -1,0,+1 and +2
- Dexamethasone: 12 mg orally 30 minutes prior to chemotherapy on day -1 and 8 mg orally on days 0, +1 and +2. Dose may be given as 4 mg orally twice daily on days 0 to +2. The dose of dexamethasone was reduced when co-administered with aprepitant according to recommended highly emetogenic regimen in the Emend® package insert.

ARM B: Patients receiving one day melphalan and randomized to **olanzapine** will receive:

Day	-1	0 ASCT	+1	+2
Melphalan	X			
Olanzapine	10 mg	10 mg	10 mg	10 mg
Ondansetron	16 mg	16 mg	16 mg	16 mg
Dexamethasone	20 mg	8 mg	8 mg	8 mg

- Melphalan: 140-200 mg/m^2/day IV given on Day -1
- ASCT: stem cell rescue on Day 0
- Olanzapine: 10 mg orally daily on Days -1,0,+1 and +2
- Ondansetron: 16 mg orally daily on Days -1,0,+1 and +2
- Dexamethasone: 20 mg orally 30 minutes prior to chemotherapy on Day -1 and 8 mg orally on days 0 to +2. Dose may be given as 4 mg orally twice daily on Days 0 to +2.

Arm C: Patients receiving one day melphalan and randomized to **aprepitant + olanzapine** will receive:

Day	-1	0 ASCT	+1	+2
Melphalan	X			
Aprepitant	125 mg	80 mg	80 mg	
Olanzapine	10 mg	10 mg	10 mg	10 mg

Ondansetron	16 mg	16 mg	16 mg	16 mg
Dexamethasone	12 mg	8 mg	8 mg	8 mg

- Melphalan: 140-200 mg/m^2/day IV given on Day -1
- ASCT: stem cell rescue on Day 0
- Aprepitant: 125 mg orally one hour prior to chemotherapy on Day -1 and 80 mg orally on Days 0 and +1
- Olanzapine: 10 mg orally daily on Days -1,0,+1 and +2
- Ondansetron: 16 mg orally daily on Days -1,0,+1 and +2
- Dexamethasone: 12 mg orally 30 minutes prior to chemotherapy on Day -1 and 8 mg orally on days 0 to +2. Dose may be given as 4 mg orally twice daily on Days 0 to +2.

- **Conditioning regimen: Two day melphalan**

ARM A: Patients receiving two day melphalan and randomized to **aprepitant** will receive:

Day	**-2**	**-1**	**0 ASCT**	**+1**	**+2**
Melphalan	X	X			
Aprepitant	125 mg	80 mg	80 mg	80 mg	
Ondansetron	16 mg	16 mg	16 mg	16 mg	16 mg
Dexamethasone	12 mg	8 mg	8 mg	8 mg	8 mg

- Melphalan: 100 mg/m^2/day IV given on Days -2 and -1
- ASCT: Stem cell rescue on Day 0
- Aprepitant: 125 mg orally one hour prior to chemotherapy on Day -2 and 80 mg orally on Days -1, 0, and +1
- Ondansetron: 16 mg orally daily on Days -2, -1, 0, +1, and +2
- Dexamethasone: 12 mg orally 30 minutes prior to chemotherapy on day -2 and 8 mg orally on Days -1, 0, +1 and +2. Dose may be given as 4 mg orally twice daily on Days -1, 0, +1 and +2. The dose of dexamethasone was reduced when coadministered with aprepitant according to recommended highly emetogenic regimen in the Emend® package insert.

ARM B: Patients receiving two day melphalan and randomized to **olanzapine** will receive:

Day	**-2**	**-1**	**0 ASCT**	**+1**	**+2**
Melphalan	X	X			
Olanzapine	10 mg	10 mg	10 mg	10 mg	10 mg
Ondansetron	16 mg	16 mg	16 mg	16 mg	16 mg
Dexamethasone	20 mg	8 mg	8 mg	8 mg	8 mg

- Melphalan: 100 mg/m^2/day IV given on Days -2 and -1
- ASCT: Stem cell rescue on Day 0
- Olanzapine: 10 mg orally daily on Days -2, -1, 0, +1, and +2
- Ondansetron: 16 mg orally on daily on Days -2, -1, 0, +1, and +2

- Dexamethasone: 20 mg orally 30 minutes prior to chemotherapy on day -2 and 8 mg orally on Days -1, 0, +1 and +2. Dose may be given as 4 mg orally twice daily on Days -1, 0, +1 and +2.

Arm C: Patients receiving two day melphalan and randomized to **aprepitant + olanzapine** will receive:

Day	-2	-1	0 ASCT	+1	+2
Melphalan	X	X			
Aprepitant	125 mg	80 mg	80 mg	80 mg	
Olanzapine	10 mg	10 mg	10 mg	10 mg	10 mg
Ondansetron	16 mg	16 mg	16 mg	16 mg	16 mg
Dexamethasone	12 mg	8 mg	8 mg	8 mg	8 mg

- Melphalan: 100 mg/m^2/day IV given on Days -2 and -1
- ASCT: Stem cell rescue on Day 0
- Aprepitant: 125 mg orally one hour prior to chemotherapy on Day -2 and 80 mg orally on Days -1, 0, and +1
- Olanzapine: 10 mg orally daily on Days -2, -1, 0, +1, and +2
- Ondansetron: 16 mg orally on daily on Days -2, -1, 0, +1, and +2
- Dexamethasone: 12 mg orally 30 minutes prior to chemotherapy on day -2 and 8 mg orally on Days -1, 0, +1 and +2. Dose may be given as 4 mg orally twice daily on Days -1, 0, +1 and +2.

- **Conditioning regimen: BEAM**

ARM A: Patients receiving BEAM and randomized to **aprepitant** will receive:

Day	-6	-5 to -2	-1	0 ASCT	+1	+2
Carmustine	X					
Etoposide		X				
Cytarabine		X				
Melphalan			X			
Aprepitant	125 mg	80 mg	80 mg	80 mg	80 mg	
Ondansetron	16 mg	16 mg	16 mg	16 mg	16 mg	16 mg
Dexamethasone	12 mg	8 mg	8 mg	8 mg	8 mg	8 mg

- Carmustine: 300 mg/m^2/day IV given on Day -6
- Etoposide: 200 mg/m^2 IV twice daily on Days -5 to -2
- Cytarabine: 200 mg/m^2 IV twice daily on Days -5 to -2 (Give after etoposide)
- Melphalan: 140 mg/m^2/day IV given on Day -1
- ASCT: Stem cell rescue on Day 0
- Aprepitant: 125 mg orally one hour prior to chemotherapy on Day -6 and 80 mg orally on Days -5, - 4, -3, -2, -1, 0, and +1
- Ondansetron: 16 mg orally daily on Days -6, -5, - 4, -3, -2, -1, 0, +1, and +2

- Dexamethasone: 12 mg orally 30 minutes prior to chemotherapy on Day -6 and 8 mg orally daily on Days -5, - 4, -3, -2, -1, 0, +1, and +2. Dose may be given as 4 mg orally twice daily on Days -5, - 4, -3, -2, -1, 0, +1, and +2. The dose of dexamethasone was reduced when co-administered with aprepitant according to recommended highly emetogenic regimen in the Emend® package insert.

ARM B: Patients receiving BEAM and randomized to the **olanzapine** will receive:

Day	-6	-5 to -2	-1	0 ASCT	+1	+2
Carmustine	X					
Etoposide		X				
Cytarabine		X				
Melphalan			X			
Olanzapine	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Ondansetron	16 mg	16 mg	16 mg	16 mg	16 mg	16 mg
Dexamethasone	20 mg	8 mg	8 mg	8 mg	8 mg	8 mg

- Carmustine: 300 mg/m^2/day IV given on Day -6
- Etoposide: 200 mg/m^2 IV twice daily on Days -5 to -2
- Cytarabine: 200 mg/m^2 IV twice daily on Days -5 to -2 (Give after etoposide)
- Melphalan: 140 mg/m^2/day IV given on Day -1
- ASCT: Stem cell rescue on Day 0
- Olanzapine: 10 mg orally daily on Days -6, -5, - 4, -3, -2, -1, 0, +1, and +2
- Ondansetron: 16 mg orally daily on Days -6, -5, - 4, -3, -2, -1, 0, +1, and +2
- Dexamethasone: 20 mg orally 30 minutes prior to chemotherapy on Day -6 and 8 mg orally daily on Days -5, - 4, -3, -2, -1, 0, +1, and +2. Dose may be given as 4 mg orally twice daily on Days -5, - 4, -3, -2, -1, 0, +1, and +2.

ARM C: Patients receiving BEAM and randomized to the **aprepitant + olanzapine** will receive:

Day	-6	-5 to -2	-1	0 ASCT	+1	+2
Carmustine	X					
Etoposide		X				
Cytarabine		X				
Melphalan			X			
Aprepitant	125 mg	80 mg	80 mg	80 mg	80 mg	
Olanzapine	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Ondansetron	16 mg	16 mg	16 mg	16 mg	16 mg	16 mg
Dexamethasone	12 mg	8 mg	8 mg	8 mg	8 mg	8 mg

- Carmustine: 300 mg/m^2/day IV given on Day -6
- Etoposide: 200 mg/m^2 IV twice daily on Days -5 to -2
- Cytarabine: 200 mg/m^2 IV twice daily on Days -5 to -2 (Give after etoposide)
- Melphalan: 140 mg/m^2/day IV given on Day -1
- ASCT: Stem cell rescue on Day 0
- Aprepitant: 125 mg orally one hour prior to chemotherapy on Day -6 and 80 mg orally on Days -5, - 4, -3, -2, -1, 0, and +1

- Olanzapine: 10 mg orally daily on Days -6, -5, - 4, -3, -2, -1, 0, +1, and +2
- Ondansetron: 16 mg orally daily on Days -6, -5, - 4, -3, -2, -1, 0, +1, and +2
- Dexamethasone: 12 mg orally 30 minutes prior to chemotherapy on Day -6 and 8 mg orally daily on Days -5, - 4, -3, -2, -1, 0, +1, and +2. Dose may be given as 4 mg orally twice daily on Days -5, - 4, -3, -2, -1, 0, +1, and +2.

8.2 Rescue Anti-emetics

Rescue medication for breakthrough CINV is left up to the discretion of the treating physician. For additional information on rescue therapy for CINV see Section 11.3.

8.3 Anti-emetic Therapy Post Treatment/Intervention

Anti-emetic medication will be administered post treatment/intervention plan according to institutional protocols.

9. EVALUATION DURING TREATMENT/INTERVENTION

In the pre-study period, all pertinent demographics (age and gender) and medical data (site, underlying malignancy, ECOG rating, and conditioning chemotherapy) will be recorded.

Subjects will be provided the standard of care according to each institution's guidelines. Subjects will be evaluated for primary and secondary outcomes using a diary that includes the following tools:

- Record episodes of vomiting and/or retching and rescue therapy completed daily for 7 days
- Visual analog scale (VAS) on a 10 mm scale to record nausea/mucositis and its severity (See Appendix 19.1) completed daily for 7 days
  - VAS < 1 no nausea/mucositis
  - VAS 1-3 mild nausea/mucositis
  - VAS 4-7 moderate nausea/mucositis
  - VAS 8-10 severe nausea/mucositis
- Functional Living Index-Emesis (FLIE) questionnaire assessed quality of life (See Appendix 19.2). Baseline was obtained on Day -1 and repeated on the morning of Day +5.

Subjects will be asked to record a daily dairy for episodes of vomiting/retching (number and time) and rescue therapy. Daily episodes of nausea/mucositis using a visual analogue scale from 0 to 10, with 0 indicating no nausea/mucositis and 10 indicating maximal nausea/mucositis. Each subject will receive 7 forms to complete as the diary will be recorded over a period of 7 days. Time 0 is end of melphalan infusion. An attending, advanced practice professional, pharmacist or pharmacy student contacted each subject every 24 hours to remind the subject to complete the forms. If a pharmacist or pharmacy student is unavailable (e.g. weekend coverage), the attending physician or advanced practice professional.

- Form 1: 0-24 hours
- Form 2: 25-48 hours
- Form 3: 49-72 hours
- Form 4: 73-96 hours
- Form 5: 97-120 hours
- Form 6: 121-144 hours
- Form 7: 145-168 hours

In addition, attending physician will document in daily progress notes complaints of nausea and or emesis.

10. TOXICITIES/SIDE EFFECTS

10.1 Toxicity Grading

Toxicities will be graded on a sale of 0 to 4 as described by the NCI-Common Terminology for Adverse Events (CTCAE), version 4.0. Adverse events were recorded and graded by the principal investigator as mild (temporary event well tolerated by the patient), moderate (event resulting in discomfort for patient and impairing normal daily activity), or severe (event resulting in substantial impairment of normal daily activity).

10.2 Melphalan

The major toxicity of melphalan toxicity is myelosuppression and is treated by donor stem cell infusion and supportive care. Most patients will develop moderate to severe mucositis of the oral and GI tracts which is prevented with cryotherapy and managed with supportive care. Acute and delayed nausea and vomiting will be experienced after high dose melphalan and can be significantly diminished with anti-emetics. Most patients develop diarrhea and this is treated symptomatically. High doses of melphalan may contribute to damage of vital organs such as the liver, kidney, or lung. Late effects include sterility and secondary malignancies.

10.3 Aprepitant

Side effects experienced in conjunction with highly and moderately emetogenic chemotherapy included alopecia, anorexia, asthenia, fatigue, constipation, diarrhea, hiccups, and nausea. Rare but serious side effects include Stevens-Johnson syndrome/toxic epidermal necrolysis and hypersensitivity reactions.

10.4 Olanzapine

Side effects include dizziness, postural hypotension, constipation, somnolence, and tremor. Other likely side effects include hyperglycemia, hyperlipidemia, weight gain, and increased appetite. Rare but serious side effects include seizures, tardive dyskinesia neuroleptic malignant syndrome, and neutropenia. Boxed warnings for increased risk of death and suicide are reported for patients who are elderly with dementia-related psychosis who are prescribed olanzapine as an anti-psychotic.

10.5 Ondansetron

Side effects include headache, malaise, fatigue, constipation, diarrhea, and dizziness. Rare but serious side effects reported include hypersensitivity reactions, and QT interval prolongation.

10.6 Dexamethasone

Side effects include fluid and electrolyte disturbances, hyperglycemia, cardiac abnormalities, abdominal distention, elevation in serum liver enzyme levels, hepatomegaly, and increased appetite. Dermatologic side effects include acne, allergic dermatitis, dry scaly skin, ecchymosis and petechiae, erythema, impaired wound healing, increased sweating, rash, striae, thin fragile skin, thinning scalp hair, and urticaria. Long term use can lead to musculoskeletal side effects

including loss of muscle mass, osteoporosis, pathologic fracture of long bones, steroid myopathy, and tendon rupture. Neurologic side effects reported include convulsions, depression, emotional instability, euphoria, headache, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, and vertigo. Rare ophthalmic side effects include exophthalmos, glaucoma, increased intraocular pressures, and posterior subcapsular cataracts. Other likely side effects reported include abnormal fat deposits, decreased resistance to infection, hiccups, malaise, and mood face.

The definitions and reporting of serious adverse events (SAEs) is defined in Section 16.2.

11. CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Clinical endpoints: The primary aim of this study is to obtain an overall complete response (CR), defined as no emesis and no rescue therapy within 120 hours of melphalan administration. Acute CR, delayed CR, rates of emesis, nausea, significant nausea, rates of mucositis, adverse events, and impact on quality of life will be monitored as secondary endpoints.

11.1 Complete response, acute and delayed complete response

Patients will be monitored by the SCT team including attending physicians, advanced practice professionals, pharmacists, and/or nurses.

An **overall complete response** is defined as no emesis and no rescue therapy within 120 hours of melphalan administration. The time interval of 120 hours was chosen because it can be assumed that additional cofactors (e.g., mucositis and antibiotic use) influence rates of nausea and vomiting after this point in time.

Acute complete response is defined as no emesis or rescue therapy in 0 to 24 hours**. Delayed complete response** is defined as no emesis or rescue therapy in 25 to 120 hours. **Very delayed complete response** is defined as no emesis in 121 to 168 hours.

Rates of emesis and use of rescue therapy will be collected as described in Sections 11.2 and 11.3.

11.2 Rates of emesis, nausea, significant nausea, and rates of mucositis

Rates of emesis, nausea, and mucositis will be documented and collected daily using the subject diary (See Appendix 19.1).

A Visual analog scale (VAS) on a 10 mm scale will be used to record nausea/mucositis and its severity (See Appendix 19.1). This will be assessed and completed daily for 7 days using the following severity scale:

- VAS < 1 no nausea/mucositis
- VAS 1-3 mild nausea/mucositis
- VAS 4-7 moderate nausea/mucositis
- VAS 8-10 severe nausea/mucositis

11.3 Rescue therapy

Rescue therapy will be documented daily in the subject diary. In addition, rescue therapy will be collected by viewing the Medication Administration Record in the electronic patient chart. Rescue medications for CINV include the following:

- Any **additional** doses for CINV including:
  - Aprepitant
  - Dexamethasone
  - Olanzapine
  - Ondansetron
- **Any** doses for CINV including:
  - Any other $5HT_3$ antagonist
  - Dronabinol
  - Haloperidol
  - Metoclopramide
  - Nabilone
  - Prochlorperazine
  - Promethazine
  - Scopolamine

The use of proton pump inhibitors and hydrogen receptor blockers are allowed and may be used at the discretion of the treating physician. In addition, benzodiazepines were allowed in this patient population as they are used for various indications, including anxiety and insomnia.

11.4 Quality of life

Quality of life will be assessed by the FLIE Questionnaire (See Appendix 19.2). This will be assessed and completed by subjects at baseline, on Day -1 (if baseline is different than day -1) and repeated the morning of Day +5.

The FLIE is a validated nausea and vomiting specific patient-reported outcome instrument comprising of two domains (Nausea and Vomiting) with nine identical items in each domain. The first item in each domain asks the patient to rate how much nausea (vomiting) he/she has experiences over the past five days. The remaining eight items assess the impact of nausea (vomiting) on the following aspects of patient's daily life: ability to enjoy meals/liquids, ability to prepare meals/do household tasks, ability to perform daily functions, ability to perform usual recreation/leisure activities, willingness to spend time with family and friends, extent to which the side effect has caused personal hardship and hardship on others.

Each item is answered using a 100-mm (1 to 7 points) VAS with anchors corresponding to "none/not at all" and "a great deal" and tick marks dividing the scale into six equal categories. The endpoint, no impact on quality of daily life is operationally defined as an average item score of >6 on seven point scale.

11.5 Time to Engraftment

Time to neutrophil engraftment would be defined as an absolute neutrophil count (ANC) recovery to ≥ 500 cells/mm^3 sustained for 48 hours of ANC ≥ 1000 cells/mm^3 sustained for 24 hours. Day one of neutropenia would be the first day post conditioning chemotherapy where the ANC < 1000 cells/mm^3.

Time to platelet engraftment would be defined as a platelet count recovery ≥ 100,000/μL sustained for 48 hours. Day one of thrombocytopenia would be the first day post conditioning chemotherapy where the ANC < 100,000/μL.

12. CRITERIA FOR REMOVAL FROM STUDY

Patients may be removed from the study at any point deemed appropriate by the Principal Investigators, Co-Investigators, or if requested by the patient. However, once the pre-transplant conditioning regimen is given, patients will continue on study until after administration of anti-emetic regimen and will receive supportive care as appropriate. Failure to use preventative anti-emetic medications after conditioning chemotherapy would most likely result in significant nausea and vomiting.

13. BIOSTATISTICS

The population under study is adult patients with high risk or advanced malignancies requiring an autologous stem cell transplantation with melphalan as part of the conditioning regimen. Based on the literature, a 60% CR in the control group was calculated by the weighted average of three aprepitant studies and 70% CR in the treatment groups with a non-inferiority margin of 4%. An estimated sample size of is 429 patients (143 in each arm) was calculated based on the percent overall CR in both treatment groups in the Navari et al trial with 80% power. (Navari 2016). A pre-planned interim analysis will be performed after the inclusion of 210 patients. The accrual period will be approximately 2-3 years.

The non-inferiority margin for this trial was estimated with the fixed margin method. Three placebo-controlled trials were included in a meta-analysis to estimate the placebo effect size. We calculated the pooled risk difference with 95% CIs using a random-effects model. We considered the upper bound of the pooled CI to be M1 = -8%. We calculated M2 with 50% preserved-effect for RD and found our non-inferiority margin to be approximately 4%. A sequential testing procedure will be used to test for both non-inferiority and superiority controlled at the 2.5% level.

Each patient will be followed until discharge.

14. RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

14.1 Research Participant Registration

All patients will be provided written informed consent. Obtain informed consent by following procedures defined in section entitled Informed Consent Procedures. See Appendix 19.3 for Informed Consent.

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility (See Section 5). During the registration process registering subjects will be required to complete a protocol specific Eligibility Checklist (See Appendix 19.4). The Eligibility Checklist will be completed by the primary investigators or co-investigators prior to admission and emailed to the Principal Investigators (heme_oncinpatientpharmacist@rush.edu). Once emailed, this will reserve the subject a spot in the study until confirmation of additional exclusion criteria on day of admission.

Confirmation of subject eligibility will be done by the oncology research pharmacist or SCT pharmacist on the day of admission. This is to account for documentation for the additional exclusion criteria that cannot be assessed prior to admission (Nausea and vomiting within 12 hours before planned high dose chemotherapy or any anti-emetic treatment within the last 24 hours; baseline

QTc). SCT pharmacists will confirm subject eligibility and document confirmation in a Research Admission Note in the subject's chart (See Appendix 19.5). On the day of admission, if the subject does not meet the additional criteria as assessed by the pharmacist, the pharmacist is to contact the Principal Investigators to remove subjects from the study.

14.2 Randomization

Subjects who meet eligibility criteria on the day of admission will be included in randomization. A stratified randomization method will be used to control and balance age, gender, and conditioning chemotherapy regimens. A separate randomization block will be generated to account for age, gender and conditioning chemotherapy regimen. Subjects will be assigned to the appropriate blocks. The following blocks will be used for stratified randomization:

- Block 1: One Day Melphalan; Age 18-65; Female
- Block 2: One Day Melphalan; Age 18-65; Male
- Block 3: One Day Melphalan; Age 66-80; Female
- Block 4: One Day Melphalan; Age 66-80; Male
- Block 5: Two Day Melphalan; Age 18-65; Female
- Block 6: Two Day Melphalan; Age 18-65; Male
- Block 7: Two Day Melphalan Age 66-80; Female
- Block 8: Two Day Melphalan Age 66-80; Male
- Block 9: BEAM Age 18-65; Female
- Block 10: BEAM Age 18-65; Male
- Block 11: BEAM Age 66-80; Female
- Block 12: BEAM Age 66-80; Male

Randomization will be managed in an excel spreadsheet by the Principal Investigators. Randomization will occur once the Eligibility Checklist (Appendix 19.4) is completed and emailed by the primary investigators or co-investigators. Randomization results will be emailed to the recruiting attending physician and pharmacists.

15. DATA MANAGEMENT ISSUES

The responsibilities of the investigators include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized subject record.

15.1 Quality Assurance

Monthly registration reports will be generated to monitor subject accruals and completeness of registration data by the principal investigators. Routine data quality reports will be generated to assess missing data and inconsistencies by the principal investigators. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

15.2 Data and Safety Monitoring

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance and departmental procedures for quality control. During the protocol development and review process, each protocol will be

assessed for its level of risk and degree of monitoring required. Every type of protocol will be addressed, and the monitoring procedures will be established at the time of protocol activation.

16. PROTECTION OF HUMAN SUBJECTS

16.1 Privacy

RUMC may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization for. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB.

16.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The report should contain the following information:

- Subject's name
- Medical record number
- Disease/histology
- Protocol number and title
- Date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following:
    - An explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

16.3 Costs

The subject will be responsible for the costs of standard medical care, including the anti-emetic treatment, all hospitalizations, and any transplant related complications.

17. INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the IRB of this Center. The consent form will include the following:

- The nature and objectives, potential risks and benefits of the intended study
- The length of study and the likely follow up required
- Alternatives to the proposed study (This will include available standard and investigational therapies. In addition subjects will be offered an option of supportive care of therapeutic studies.)

- The name of the investigator(s) responsible for the protocol
- The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol specific procedures can be carried out, the consenting professional will fully explain the aspects of subject privacy concerning research specific information. In addition to signing the IRB Informed Consent, all subjects must agree to the Research Authorization component of the informed consent form. Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18. REFERENCES

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19. APPENDIX

19.1 Subject Diary

The following is to be completed on Day 0 to Day + 6 every morning. This is an example of Day 0.

Patient Diary Day 0 (0-24 hours)	
Patient Name:	Date:
Patient signature:	Witness initials:

I. Vomiting Assessment

1. Have you experienced any vomiting in the past 24 hours? Y☐$_1$ N☐$_0$
   a. If YES, how many episodes? _____
2. Have you experienced any retching or dry heaving in the past 24 hours? Y☐$_1$ N☐$_0$
3. Have you used any rescue medication to treat your nausea or vomiting In the past 24 hours? Y☐$_1$ N☐$_0$

II. Nausea Assessment

4. In the past 24 hours, how has your nausea been? Please circle number below.

No nausea — 0 1 2 3 4 5 6 7 8 9 10 — Nausea as bad as it could be

III. Mucositis Assessment

5. In the past 24 hours, how has your mouth pain been? Please circle number below.

No mouth pain — 0 1 2 3 4 5 6 7 8 9 10 — Mouth pain as bad as it could be

V. Notes

19.2 FLIE Questionnaire

The following is to be completed at baseline, on Day -1 (if Day -1 is different than baseline) and repeated the morning of Day +5.

Patient FLIE Questionnaire Day + 5	
Patient Name:	Date:
Patient signature:	Witness initials:

I.	**Nausea**	
1. How much nausea have you experienced in the past 5 days?		
A great deal	1 2 3 4 5 6 7	Not at all
2. Has nausea affected your ability to maintain usual recreation or leisure activities during the past 5 days?		
A great deal	1 2 3 4 5 6 7	Not at all
3. Has nausea affected your ability to make meals or do tasks during the past 5 days?		
A great deal	1 2 3 4 5 6 7	Not at all
4. Has nausea affected your ability to enjoy meals during the past 5 days?		
A great deal	1 2 3 4 5 6 7	Not at all
5. Has nausea affected your ability to enjoy fluids during the past 5 days?		
A great deal	1 2 3 4 5 6 7	Not at all
6. Has nausea affected your ability to see family/friends during the past 5 days?		
A great deal	1 2 3 4 5 6 7	Not at all
7. Has nausea affected your daily functioning during the past 5 days?		
A great deal		Not at all

	1	2	3	4	5	6	7

8. Has nausea affected your personal hardship during the past 5 days?

A great deal	1	2	3	4	5	6	7	Not at all

9. Has nausea affected your hardship on others during the past 5 days?

A great deal	1	2	3	4	5	6	7	Not at all

II. Vomiting

1. How much vomiting have you experienced in the past 5 days?

A great deal	1	2	3	4	5	6	7	Not at all

2. Has vomiting affected your ability to maintain usual recreation or leisure activities during the past 5 days?

A great deal	1	2	3	4	5	6	7	Not at all

3. Has vomiting affected your ability to make meals or do tasks during the past 5 days?

A great deal	1	2	3	4	5	6	7	Not at all

4. Has vomiting affected your ability to enjoy meals during the past 5 days?

A great deal	1	2	3	4	5	6	7	Not at all

5. Has vomiting affected your ability to enjoy fluids during the past 5 days?

A great deal	1	2	3	4	5	6	7	Not at all

6. Has vomiting affected your ability to see family/friends during the past 5 days?

A great deal	1	2	3	4	5	6	7	Not at all

7. Has vomiting affected your daily functioning during the past 5 days?

A great deal 1 2 3 4 5 6 7 Not at all

8. Has vomiting affected your personal hardship during the past 5 days?

A great deal 1 2 3 4 5 6 7 Not at all

9. Has vomiting affected your hardship on others during the past 5 days?

A great deal 1 2 3 4 5 6 7 Not at all

19.3 Informed Consent

Subject Information and Consent Form

See separate document

RUSH UNIVERSITY MEDICAL CENTER
IRB PROTOCOL

IRB#: 14102001

19.4 Eligibility Checklist

To be filled out by the primary investigators or co-investigators prior to admission and emailed to the Principal Investigators. All pertinent demographics (age and gender) and medical data (site, underlying malignancy, ECOG rating, and conditioning chemotherapy) will be recorded. Once emailed, this will reserve the subject a spot in the study until confirmation of additional exclusion criteria on day of admission.

I. Patient Demographics	
Name:	
Age (years):	
Gender: Choose an item.	
II. Medical Data	
Practice Site: Choose an item.	
Underlying Malignancy: Choose an item.	
ECOG: Choose an item.	
Conditioning Chemotherapy: Choose an item.	
III. Eligibility Assessment	
Inclusion 1. The patient is between 18-80 years of age 2. The patient is receiving an auto SCT with melphalan or BEAM 3. The patient can tolerate oral medications Exclusion 4. The patient does **not** have a history of seizures 5. The patient is **not** pregnant 6. The patient does not have HIV 7. The patient does not have previous history of CNS disease	
I attest that the patient meets the above criteria. Recruiting attending physician: Choose an item.	Date: Click here to enter a date.

19.5 Research Admission Note

The Research Admission Note is to be completed by a SCT or research pharmacist the day the subject is admitted. This is to account for additional exclusion criteria that cannot be assessed prior to admission (Nausea and vomiting within 12 hours before planned high dose chemotherapy or any anti-emetic treatment within the last 24 hours; QTc) and to provide a calendar for treatment schedule. SCT pharmacists will confirm subject eligibility and document confirmation using this Research Admission Note. On the day of admission, if the subject does not meet the additional criteria as assessed by the pharmacist, the pharmacist is to contact the Principal Investigators to remove subjects from the study.

Research Admission Note

This is a research note for IRB#14102001. The purpose of this note is to confirm patient eligibility and to document treatment randomization.

I have confirmed patient has not experienced any nausea or vomiting within 12 hours or any anti-emetic treatment within 24 hours before planned high dose chemotherapy. I have also confirmed that patient baseline QTc < 500 ms by checking the results of the required pre-admission EKG.

Patient has been randomized to ARM (A/B/C).

Calendar of patient diary and questionnaires:

Day	Date	Patient form to be completed
Baseline		FLIE Questionnaire
-1		FLIE Questionnaire (if Day -1 is different from baseline date)
0		Patient Diary
+1		Patient Diary
+2		Patient Diary
+3		Patient Diary
+4		Patient Diary
+5		Patient Diary AND FLIE Questionnaire
+6		Patient Diary

RUSH

CONSENT/AUTHORIZATION FOR PARTICIPATION IN A RESEARCH STUDY

Site Principal Investigator: Amanda Seddon, PharmD
Department: Inpatient Pharmacy
Address and Contact Information: Rush University Medical Center, 1653 W Congress Parkway, 312-947-2406

Protocol Title: Aprepitant- and olanzapine- containing regimens for prevention of acute and delayed nausea and vomiting associated with high dose melphalan and BEAM in autologous stem cell transplant patients

Sponsor(s): Rush University Medical Center

Name of Participant: _____

Key Information:

You are being invited to participate in a research study. Research studies answer important questions that might help change or improve the way we do things in the future.

This consent form will give you information about the study to help you decide whether you want to participate. Please read this form, and ask any questions you have, before agreeing to be in the study.

Taking part in this research study is voluntary. You do not have to participate in this study and may choose to leave the study at any time. If you decide not to participate in this study or leave the study at a later time, your health care, benefits, or relationship with Rush University Medical Center will not change or be affected.

The purpose of this study is to determine whether administration of an aprepitant-containing regimen, an olanzapine-containing regimen, or an aprepitant plus olanzapine containing regimen will prevent nausea and vomiting better for patients undergoing an autologous stem cell transplant with melphalan chemotherapy. Both of these medications are approved by the United States Food and Drug Administration (FDA) for nausea and vomiting.

If you agree to participate in this study, your participation may last up to 7 days after you have completed chemotherapy. The expected minimal study duration would be approximately 7-14 days, all during your hospitalization for your transplant. No additional visits are needed.

During your hospitalization, you will be asked to complete surveys about your nausea and how it

is impacting your comfort level. For a detailed list of study procedures, please see the "*What are the activities you will be doing if you participate in this study?*" section of this consent form.

There are risks to you for participating in this study. In this study, there are risks of side effects with the medications included or you may become uncomfortable answering some of the questions. However, with any medication, side effects are possible.

Very common side effects of aprepitant include fatigue (feeling tired), constipation, diarrhea, hiccups, nausea, hair loss, and anorexia (loss of appetite). Rare but serious side effects include Stevens-Johnson syndrome/toxic epidermal necrolysis (serious skin reaction, potentially life-threatening) and allergic reactions.

Very common side effects of olanzapine include dizziness, postural hypotension (low blood pressure), constipation, somnolence (sleepiness), and tremor (shaking). Other likely side effects include hyperglycemia (high blood sugar), hyperlipidemia (high blood lipids), weight gain, and increased appetite. Rare but serious side effects include seizures, tardive dyskinesia (uncontrolled movement of body parts), neuroleptic malignant syndrome (life-threatening condition, symptoms include fever, sweating, muscle stiffness, confusion, unstable blood pressure etc.), and neutropenia (very low white blood count, which may increase your risk of infection). Boxed warnings for increased risk of death and suicide are reported for patients who are elderly with dementia-related psychosis (a severe mental disorder) who are prescribed olanzapine for treatment.
For a detailed list of risks you should know about, please see the "*What are the risks and discomforts of participating in this study?*" section of this consent form.

You may benefit from taking part in this study. Based on experience with anti-emetic regimens in patients with similar conditions, researchers believe it may be of benefit to people receiving similar chemotherapy or it may be as good as standard therapy with fewer side effects. However, because individuals respond differently to therapy, no one can know in advance if it will be helpful for you.

There are other options available to you if you decide not to participate in this study. You may choose another regimen for prevention of nausea and vomiting with chemotherapy without being in a study such as:

- A regimen not containing either aprepitant or olanzapine
- A regimen containing aprepitant while electing not to participate in the study
- A regimen containing olanzapine while electing not to participate in the study
- A regimen containing olanzapine plus aprepitant while electing not to participate in the study

Detailed Information: Please review the rest of this document for details about the above topics and additional information you should know before making a decision about whether or not you will participate in this study.

Why are you being invited to participate in this study?

You are being asked to take part in this study since you will be receiving an autologous stem cell transplant and will be receiving standard chemotherapy that is known to cause nausea and vomiting.

How many participants will take part in this study?
About 429 study subjects will be taking part in this study, and approximately 75 are expected to be from Rush.

What are the activities you will be doing if you participate in this study?
If you agree to be in this study, it is important that you are completely honest with the doctor and staff about your health history. Before enrollment, your doctor will determine if you would be a candidate for this study. Besides your past medical history, you will need to obtain an electrocardiogram (ECG) to check the electrical activity of your heart. This is routinely done before any autologous stem cell transplant.

Prior to starting and once you begin chemotherapy you will be asked to fill out a patient diary. This diary contains 5 questions to be answered every day for 7 days. These questions will help us asses your nausea, vomiting, and mouth pain. In addition, you will be asked to fill out a questionnaire on quality of life on 2-3 days during the study.

You will be asked to take a specified regimen of medications to prevent nausea and vomiting while hospitalized. No additional visits after your discharge from the hospital are required. No additional procedures will be needed. No additional blood tests are needed.

What are the risks and discomforts of participating in this study?
Side effects, risks, and/or discomforts from participation in this study may include side effects from the anti-nausea medications utilized.

Very common side effects of aprepitant include fatigue (feeling tired), constipation, diarrhea, hiccups, nausea, hair loss, and anorexia (loss of appetite). Rare but serious side effects include Stevens-Johnson syndrome/toxic epidermal necrolysis (serious skin reaction, potentially life-threatening) and allergic reactions.

Very common side effects of olanzapine include dizziness, postural hypotension (low blood pressure), constipation, somnolence (sleepiness), and tremor (shaking). Other likely side effects include hyperglycemia (high blood sugar), hyperlipidemia (high blood lipids), weight gain, and

increased appetite. Rare but serious side effects include seizures, tardive dyskinesia (uncontrolled movement of body parts), neuroleptic malignant syndrome (life-threatening condition, symptoms include fever, sweating, muscle stiffness, confusion, unstable blood pressure etc.), and neutropenia (very low white blood count, which may increase your risk of infection). Boxed warnings for increased risk of death and suicide are reported for patients who are elderly with dementia-related psychosis (a severe mental disorder) who are prescribed olanzapine for treatment.

We are studying the addition of aprepitant and olanzapine to these combination regimens currently used. The additional medications used in the combinations are listed below.

Ondansetron
Side effects include headache, malaise (feeling sick), fatigue (tiredness), constipation, diarrhea, and dizziness. Rare but serious side effects reported include serious allergic reactions, and heart rhythm disorder (QT interval prolongation).

Dexamethasone or other corticosteroids
The side effects reported by patients taking dexamethasone include edema (fluid retention), high blood pressure, sodium retention and/or potassium loss, increased appetite and weight gain, extreme mood swings, tiredness, depression, inability to sleep, nausea, vomiting. Patients may also experience increased sweating, increased blood sugar, irregularities in the menstrual cycle, excess hair, thinning of bone, increased risk of picking up infections or mild infections get worse, hiccups, abdominal pain, stomach ulcers, and skin disorders. Additionally, some patients reported allergic reactions, blood clots, eye disorders including increased eye pressure. Patients with pre-existing schizophrenia (a severe mental disorder), epilepsy (seizures) may experience worsening of their disease; patients with heart disease may experience heart failure. The longer a patient takes these drugs and the larger the dose may increase the incidence of the side effects listed above.

There may be other risks that may happen that we cannot predict.

What are the reproductive risks of participating in this study?
You will be screened for pregnancy prior to enrollment in this study as part of the routine work up for autologous stem cell transplant. Patients who are pregnant are not eligible for autologous stem cell transplant and therefore not eligible for this study.

What if there is new information that may affect your decision to participate in this study?
During this study, you will be told about important findings (either good or bad), such as changes in the risks or benefits of participation in the study or new choices to participation that might cause you to change your mind about being in the study. If new information is shared with you, you may be asked to sign a revised consent form in order to continue participating in this study.

Can you leave or be removed from this study?

You have the right to leave a study at any time without penalty. You are free to withdraw from this study at any time you choose without giving a reason. This will not affect any future care you will receive.

The researchers and sponsor also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interests;
- You do not follow the instructions;
- The study is cancelled for any reason.

What about confidentiality of your medical information?

This authorization is voluntary. Rush University Medical Center and its affiliates ("Rush") will not withhold or refuse your treatment, payment, enrollment, or eligibility for benefits if you sign this authorization. You do not have to sign this authorization, but that means that you cannot be in the study or receive study-related treatment.

By signing this document, you voluntarily authorize (give permission to) Dr. Amanda Seddon, her study team, and other Rush personnel involved with the conduct and review of this study (which may include off-site personnel) to use or disclose (release) health information that identifies you for the study described in this document.

During the study, Dr. Amanda Seddon and her study team will collect Protected Health Information (PHI) about you for the purposes of this research. PHI is your health information that includes your medical history and new information obtained as a result of this study. Some of this information will come from your medical record. The health information that Rush may use or disclose for this research includes:

- All information in a medical record with specific focus on use of nausea and vomiting medications, physical examination results specifically for mucositis or nausea and vomiting, completed patient diaries

Dr. Amanda Seddon and her study team may share your health information and the results of your study-related procedures and tests with people outside of Rush who assist with the conduct and review of this study. The persons who receive your health information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, but only if permitted by the laws governing them. Your health information described above may be used or disclosed to:

- To the Researchers
- Monitoring agencies such as the Food and Drug Administration (FDA), the National Institutes of Health and the Rush Institutional Review Board (IRB).

While you participate in the study you will have access to your medical record, but Dr. Amanda Seddon is not required to release to your study information that is not part of your medical record. Rush is required by law to protect your health information, and study records that identify you will be kept confidential. The results of study tests/procedures performed as part of this study may become part of your medical record. Any study information in your medical

record will be kept indefinitely. Your identity will not be revealed on any report, publication, or at scientific meetings.

You have a right to inspect and copy the information to be disclosed with this authorization and you may obtain a copy of the information by contacting the office listed above.

If you no longer want to be in the study and do not want your future health information to be used, you may change your mind and revoke (take back) this authorization at any time by writing to Dr. Amanda Seddon at 1653 W Congress Parkway, Chicago, IL 60612. If the authorization is revoked, you will no longer be allowed to participate in the study and previously authorized individuals/entities may still use or disclose health information that they have already obtained about you as necessary to maintain the integrity or reliability of the current study.

This authorization is valid for the entirety of this research study. It will expire upon your completion of the study or if you revoke (take back) the authorization.

If you withdraw from this study, the data already collected from you may not be removed from the study records. The study doctor and/or study team may ask you whether they can continue to collect follow-up data on you. If follow-up information will be requested, you will be asked to sign a separate consent form before this information can be collected.

Records of participation in this study will be maintained and kept confidential as required by law. Participants will be assigned an identification number and identifying information will be removed.

The Rush Institutional Review Board (IRB) will have access to your files as they pertain to this research study. The IRB is a special committee that reviews new and ongoing human research studies to check that the rules and regulations are followed regarding the protection of the rights and welfare of human participants.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. This research study can be found by searching for the following Clinical Trial Registry Number (NCT#): NCT02939287.

What are the costs to participate in this study?
There are no costs to you for participating in this research.

Will you be paid for your participation in this study?
You will not be paid for being in this study.

What if you are injured as a result of your participation in this study?
If you get ill or injured from being in the study, Rush University Medical Center will help you get medical treatment. You should let the study doctor know right away that you are ill or injured. If you believe you have become ill or injured from this study, you should contact Dr. Amanda Seddon at telephone number 312-947-2406.

You should let any health care provider who treats you know that you are in this study. If you do seek medical treatment, please take a copy of this document with you because it may help the doctors where you seek treatment to treat you. It will also provide the doctors where you seek treatment with information they may need if they want to contact your study doctor.

You or your health insurance plan will be billed. No money has been set aside to pay the costs of this treatment. Health insurance plans may or may not cover costs of research-related injury or illness. You should check with your insurance company before deciding to participate in this research study.

Rush University Medical Center has no program for financial compensation or other forms of compensation for injuries which you may incur as a result of participation in this study.

By signing this form, you are not giving up any legal rights to seek compensation of injury.

What other information should you know about?
Your transplant team, who are the persons responsible for this research study, are interested in both your clinical care and the conduct of this study. You have the right to discuss this study with another person who is not part of the research team before making your decision whether or not to be in the study.

Who can you contact for more information about this study?
Questions are encouraged. If you have further questions about this study, you may call Amanda Seddon, PharmD at 312-947-2406 or email her at Amanda_N_Seddon@rush.edu.

Who can you contact if you have concerns about your rights as a study participant?
Questions about the rights of research participants may be addressed to the Rush University Medical Center Office of Research Affairs at 1-800-876-0772.

What are your rights as a study participant?
Taking part in this study is voluntary. If you choose not to participate in this study or to leave the study at any time, your health care, benefits or relationship at Rush University Medical Center will not change or be affected.

If you choose to leave this study and you do not want any of your information to be used, you must inform Dr. Seddon in writing at the address on the first page. Dr. Seddon may still use your information that was collected prior to your written notice.

SIGNATURE BY THE PARTICIPANT:
By signing below, you are consenting to participate in this research study. You have read the information given or someone has read it to you. You have had the opportunity to ask questions, which have been answered satisfactorily to you by the study staff. You do not waive any of your legal rights by signing this consent form. You will be given a signed copy of this consent.

Name of Participant	Signature of Participant	Date of Signature

SIGNATURE BY THE INVESTIGATOR/INDIVIDUAL OBTAINING CONSENT:
I attest that all the elements of informed consent described in this consent document have been discussed fully in non-technical terms with the participant. I further attest that all questions asked by the participant were answered to the best of my knowledge.

Signature of Individual Obtaining Consent	Date of Signature