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**Randomized Controlled Trial of Olanzapine for the Control of Chemotherapy-induced Vomiting
in Children Receiving Highly Emetogenic Chemotherapy**

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ABSTRACT

Background: Chemotherapy-induced nausea and vomiting (CINV) are among the most distressing cancer treatment-related symptoms. Chemotherapy-induced vomiting (CIV) control in children with cancer is poor. Most children receiving highly emetogenic chemotherapy (HEC), including those receiving hematopoietic stem cell transplant (HSCT) conditioning, experience CIV despite receiving antiemetic prophylaxis. Olanzapine improves CINV control in adult cancer patients, has a track record of safe use in children with psychiatric illness, does not interact with chemotherapy and is inexpensive. We hypothesize that the addition of olanzapine to standard antiemetics will improve CIV control in children receiving HEC

Objectives: Primary: To compare acute phase CIV control provided by olanzapine plus standard antiemetics (ondansetron/granisetron/palonosetron with or without dexamethasone) versus placebo plus standard antiemetics in children receiving HEC. Secondary: In these patients: 1) to compare CIV in the delayed and overall phases; chemotherapy-induced nausea (CIN) control and CINV control during the acute, delayed and overall phases; 2) to describe the safety of olanzapine and 3) to assess the correlation between nausea severity assessed by patients using tools validated for use in children and adults.

Methods: This is a multi-centre, blinded, placebo-controlled, pragmatic superiority trial conducted over a single chemotherapy block. In addition to standard antiemetics, eligible children will receive either placebo or olanzapine (0.1 mg/kg/dose; maximum 10 mg/dose) by mouth once daily starting before the first dose of chemotherapy or HSCT conditioning and for 4 doses after the last dose of chemotherapy or HSCT conditioning.

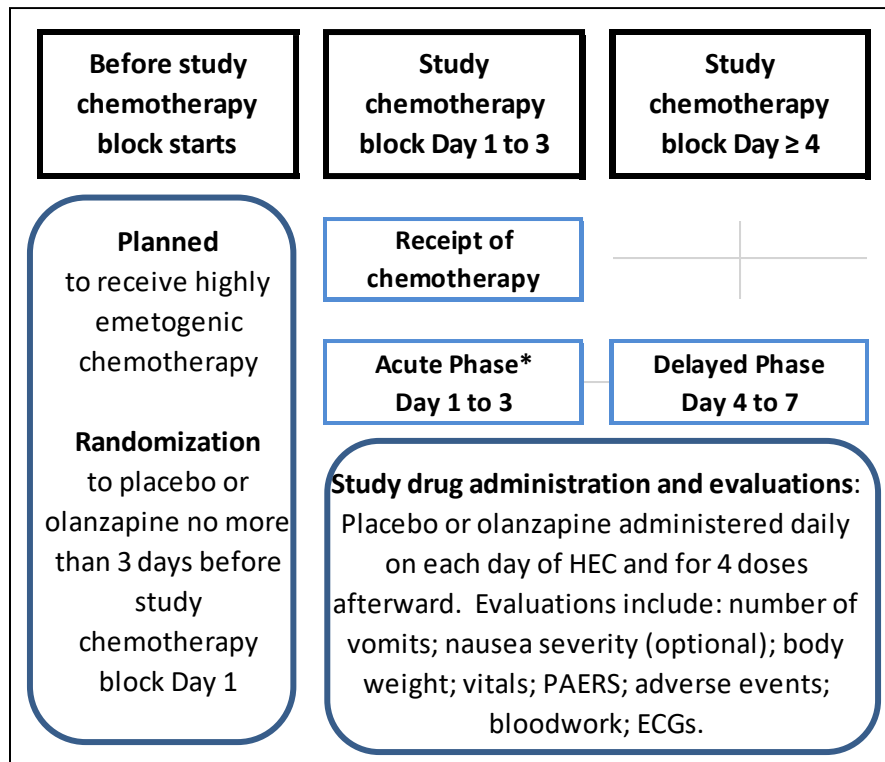
The primary outcome measure is complete or partial control of CIV during the acute phase. Complete control is defined as no use of breakthrough anti-emetic agents and no vomiting/retching. Partial control is defined as no more than two vomits or retches during any 24-hour period. The acute phase starts from the time of administration of the first dose of chemotherapy or HSCT conditioning and continues until 24 hours after administration of the last dose of chemotherapy or HSCT conditioning.

Secondary CINV outcome measures are: complete and partial CIV control during the delayed phase (starting from the end of the acute phase and continuing for 4 days); complete and partial CIN control during each of the acute and the delayed phases; and complete and partial CIV, CIN and CINV control in the overall phase (acute and delayed phases). Other secondary outcome measures include: change in body weight, modified Pediatric Adverse Event Rating Scale (PAERS) score, plasma amylase, creatine phosphokinase, glucose, prolactin, fasting triglyceride concentrations, or hepatic function; incidence of ECG abnormalities including QTc prolongation and non-hematologic adverse effects (CTCAEv4, spontaneous reports); and, for HSCT patients, neutrophil engraftment (attainment, time) and incidence of veno-occlusive disease and acute GVHD (including maximum grade and stage).

Summary: This trial will provide high quality evidence for or against the addition of olanzapine to standard antiemetic prophylaxis in children receiving HEC.

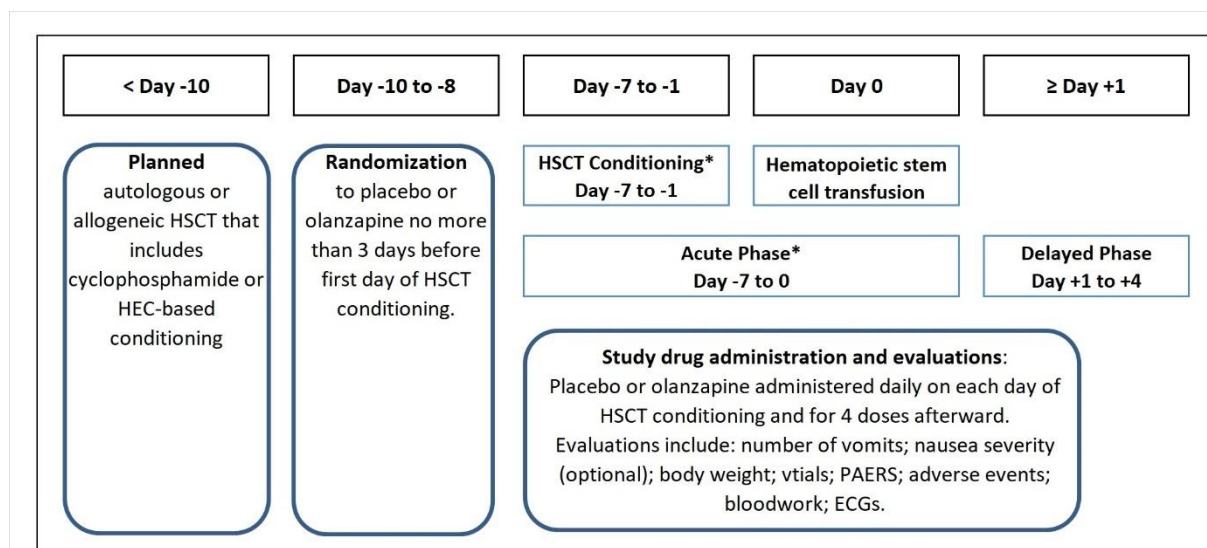
EXPERIMENTAL DESIGN SCHEMA

Patients receiving HEC (non-HSCT):



*Based on a 3-day chemotherapy block. Actual duration of acute phase will vary on duration of chemotherapy block.

Patients receiving HEC as HSCT conditioning:



*Based on a 7 day HSCT conditioning regimen. Actual duration of acute phase will vary depending on duration of HSCT conditioning.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Objective

To compare the control (complete plus partial control vs. failed control) of chemotherapy-induced vomiting (CIV) provided in the acute phase by olanzapine plus standard antiemetics (ondansetron/granisetron/palonosetron with or without dexamethasone) versus placebo plus standard antiemetics in children receiving highly emetogenic chemotherapy (HEC).

The acute phase is defined as starting from the administration of the first chemotherapy dose of the chemotherapy block or the first dose of HSCT conditioning and continuing until 24 hours after the last dose of chemotherapy of the chemotherapy block or HSCT conditioning.

1.2 Secondary Objectives

1.2.1 In each of the two study arms, to compare the control of:

- Complete CIV control in the acute phase
- CIV (complete and complete plus partial) in the delayed and overall phases
- chemotherapy-induced nausea (CIN) in the acute, delayed and overall phases and
- chemotherapy-induced nausea and vomiting (CINV) in the acute, delayed and overall phases.

The delayed phase is defined as starting at the end of the acute phase and continuing for 4 days (96 hours) or until the start of the subsequent chemotherapy block or, for HSCT patients, administration of cyclophosphamide after Day 0, whichever is first. The overall phase encompasses both the acute and delayed phases.

1.2.2. To describe the safety profile of olanzapine in children receiving HEC

1.2.3 To assess the correlation between nausea assessment scores of the Pediatric Nausea Assessment Tool (PeNAT) and of the Multi-national Association of Supportive Care Antiemesis Tool (MAT), a nausea severity measure validated for use in adult cancer patients, in children aged 13 to <18 years.

2.0 BACKGROUND

2.1 Trial Importance

Chemotherapy-induced nausea and vomiting (CINV) is one of the most distressing treatment-related symptoms according to children with cancer and their parents. CINV reduces quality of life and may lead to medical complications and increased health care utilization.¹⁻³ Even when antiemetic prophylaxis is given to children receiving highly emetogenic chemotherapy, only about half experience complete control of vomiting.^{4,5}

Chemotherapy that is classified as HEC is associated with a > 90% rate of vomiting when antiemetics are not given. Most children who receive HEC experience CINV, even if they receive CINV prophylaxis.⁶⁻⁸ The lack of high quality evidence of the efficacy and safety of antiemetic agents in children receiving chemotherapy makes CINV control in children challenging. Children receiving HEC deserve study since they are known to experience a heavy CINV burden despite prophylaxis and, for those who are hospitalized throughout the study evaluation period data integrity is likely to be high since they will be hospitalized throughout the study evaluation period. Olanzapine was chosen as the study antiemetic intervention because of its favourable safety profile and efficacy for CINV control in adults, a track record

of safe use in children with mental illness and, unlike other possible agents, its lack of drug-drug interactions with chemotherapy and low cost.

2.1.1 Prevention of CINV

CINV prophylaxis aims for complete CINV control, defined as no vomiting, retching or nausea and no use of 'as needed' (PRN) antiemetic agents for breakthrough CINV. Current evidence-based guidelines for antiemetic prophylaxis for children receiving (HEC) recommend the use of ondansetron or granisetron plus dexamethasone and aprepitant during the acute phase.^{4,5} The place of palonosetron in CINV prevention in children is unclear since preliminary pediatric data have only recently become available.⁹⁻¹⁷

We conducted 9 systematic reviews on the subject of CINV in pediatric cancer patients as the foundation to 4 clinical practice guidelines.^{4,7,19-22} These reviews have demonstrated that CINV is poorly controlled in children and that the quality of evidence to support recommendations regarding CINV prophylaxis and treatment is generally low. These systematic reviews have also highlighted many research gaps in this area including the lack of high quality evidence of the efficacy of antiemetic agents.

2.1.2 CINV in children receiving HEC

Children receiving HEC experience CINV despite receipt of prophylaxis. Complete acute phase CIV control rates of 12 to 92% have been reported in pediatric studies evaluating palonosetron, ondansetron or granisetron prophylaxis.^{16,22a} Administration of multi-day chemotherapy and inability to administer adjunctive antiemetics such as dexamethasone or aprepitant because of adverse effects, co-morbidities, or interaction with chemotherapy are barriers to achieving complete CIV control in pediatric patients.

Children undergoing HSCT typically receive chemotherapy for 2 to 7 days prior to receipt of stem cells. HSCT conditioning usually includes HEC and may include total body irradiation, also highly emetogenic.^{23,24} Despite receipt of prophylaxis, most children experience CINV during (acute phase) and after (delayed phase) HSCT conditioning.^{6,7,25} Hewitt et al evaluated vomiting in children receiving cyclophosphamide plus total body irradiation and given ondansetron.⁶ Only 45% of children experienced complete CIV control during conditioning. In another study involving 25 children undergoing HSCT given ondansetron and dexamethasone for CINV prophylaxis, only 8% and 22% achieved complete CINV control in the acute and delayed phase, respectively.⁷ In a prospective, observational study performed at SickKids, we found that only 24% and 22% of children receiving myeloablative HSCT conditioning had complete CIV control in the acute and delayed phases, respectively.^{25,26}

2.2 Selection of Study Medication

Olanzapine is an atypical antipsychotic agent with antiemetic properties whose efficacy and safety for CINV prophylaxis and treatment has been demonstrated in adult cancer patients.^{1,27-40} In adults receiving highly emetogenic chemotherapy, the addition of olanzapine to standard CINV prophylaxis (e.g. ondansetron plus dexamethasone) has resulted in complete control of vomiting in almost all patients on days that chemotherapy is given. It has been recognized by adult oncologists as a new strategy for improving CINV control.^{23,24} Rigorous study is required to determine if olanzapine can convey the same benefit to children with cancer.

2.2.1 Olanzapine as an antiemetic in adults

Olanzapine, an atypical antipsychotic agent, is recommended for treatment of breakthrough CINV²³ and prevention of acute CINV in adult cancer patients.^{24,41} In adult cancer patients receiving HEC, the addition of olanzapine to CINV prophylaxis with ondansetron plus dexamethasone has resulted in complete CIV control in almost all patients on days that chemotherapy is given. Furthermore, in adults receiving highly emetogenic chemotherapy, the contribution of olanzapine to CIV control is equivalent to that of aprepitant.^{31,38}

Hocking et al conducted a systematic review of randomized controlled trials evaluating olanzapine for CINV control in adults.⁴² Six randomized controlled trials met study eligibility criteria: 3 for CINV prophylaxis (488 patients) and 3 for the treatment of breakthrough CINV (323 patients). The authors of this systematic review concluded that olanzapine should be considered as an alternative to aprepitant in the CINV prophylaxis regimens recommended for adults receiving HEC. Wang et al conducted a meta-analysis of prospective trials evaluating the use of olanzapine for prevention of CINV and published in English or Chinese.⁴³ Six trials in adult cancer patients were included in this analysis. The odds ratio of complete CINV control (no vomiting and no use of rescue antiemetic agents) on the first day of chemotherapy in patients who received olanzapine-containing CINV prophylaxis was 1.95 (95% confidence interval (CI): 1.71 to 3.23; p = 0.01) and 2.65 (95% CI: 1.36 to 5.15; p = 0.004) in the delayed phase. Indeed, olanzapine is now recommended for CINV prophylaxis²⁴ and for treatment of breakthrough CINV^{23,24} in adult clinical practice guidelines.

2.2.2 Safety of olanzapine in adults

When given to adults for prolonged periods (> 6 weeks) to treat mental illness, the most common adverse effects of olanzapine are sedation, weight gain, postural hypotension, constipation, dizziness, and restlessness.²¹ An association with the onset of insulin-resistant diabetes mellitus has been suggested, but no causal relationship established.⁴⁴ Olanzapine has a black box warning regarding its use in elderly patients with dementia-related psychosis.²¹ Neuroleptic malignant syndrome has been reported rarely with olanzapine.

The side effect profile of short courses of olanzapine such as for CINV prevention is less certain. No Grade 3 or 4 toxicities attributable to olanzapine have been reported in studies evaluating its use for CINV control in adults.^{1,27,29,31,33,35,38,39,45,46} In a phase I trial for CINV prophylaxis in adults, dose-limiting toxicities were: depressed level of consciousness and fatigue.⁴⁶

2.2.3 Use of olanzapine in children

Olanzapine is approved for treatment of schizophrenia and manic or mixed episodes of bipolar I disorder in adolescents ages 13-17 years in the USA.^{21,47} Atypical anti-psychotic agents such as olanzapine have replaced the older typical agents as the standard of care in children and adolescents with mental illness and behavioural disorders.⁴⁸⁻⁵² Pediatric olanzapine doses ranging from 2.5 to 20 mg daily have been used for these indications.

Olanzapine is being used off-label in some pediatric institutions for CINV control. We undertook a retrospective review of the safety and efficacy of olanzapine use for CINV control in children in 4 institutions.⁵³ Sixty children (age range: 3.1-18 years) who received olanzapine during 158 chemotherapy

blocks (4 HSCT conditioning) were identified. The median initial olanzapine dose was 0.09 mg/kg/day (range: 0.026-0.210 mg/kg/day). Most children (65%) who received olanzapine daily for the entire acute phase experienced complete acute CIV control. Given that olanzapine was most often initiated due to a history of poorly controlled CINV, this level of CIV control suggests that olanzapine may be beneficial. Furthermore, olanzapine was well tolerated; safety is discussed below.

There are no published trials describing the contribution of olanzapine to CINV control in children receiving HSCT conditioning or conventional chemotherapy (MEDLINE, Embase to November 27, 2015). Long et al have described the preliminary results of a pilot randomized cross-over study comparing ondansetron and dexamethasone plus either aprepitant or olanzapine in children receiving HEC.⁵⁴ Olanzapine was dosed in increments of 1.25 mg (1.25 to 10 mg) according to body weight. Of the 14 patients have received olanzapine, 2 experienced grade 1 agitation. No other adverse events were reported.

We have recently completed a Health Canada-approved, multi-centre, single arm feasibility study of olanzapine use in 15 children aged 4 to 18.⁵⁵ This single arm feasibility study included, but did not focus on, children receiving HSCT conditioning, the target population in this study. This study met the feasibility endpoints.

The contribution of olanzapine to control of CINV in children and its safety in this setting are unknown. High quality evidence from a randomized controlled trial is required so that pediatric clinicians can make fully informed decisions regarding its use for CINV prophylaxis.

2.2.4 Safety of olanzapine in children

Olanzapine is approved for use in adolescents with schizophrenia or bipolar disorder in the USA,²¹ although it has been used off-label for other mental illnesses and in younger children. The most common adverse effects reported in adolescents receiving olanzapine for 3 or 6 weeks are sedation, increased weight, and increased appetite.²¹

In order to evaluate the safety profile of olanzapine in children, we conducted a systematic review and meta-analysis. We included 47 studies describing olanzapine use in children < 13 years old. 387 children receiving olanzapine for up to 1 year for the treatment of psychiatric or behavioural conditions were evaluated.⁵⁶ Results from prospective studies were synthesized in a meta-analysis. The most common adverse events attributed to olanzapine were weight gain and sedation. The proportion of children receiving olanzapine who were reported to experience weight gain or sedation in these trials was 78% (95% CI: 63 to 95%) and 41% (95% CI: 29 to 59%), respectively. Extrapyramidal symptoms or electrocardiogram (ECG) abnormalities were reported in 9% (95% CI: 4 to 21%) and 14% (95% CI: 7 to 26%), respectively. QTc prolongation was not observed in any of the 9 children for whom descriptions of ECG abnormalities are available. Potentially serious adverse events were either not attributed to olanzapine and/or were reversible. Nine case reports of olanzapine poisoning in children aged 1 to 12 years were included in this systematic review. After ingestion of olanzapine 7.5 to 100 mg, drowsiness/lethargy/somnolence (8/9 patients), agitation/combativeness (7/9 patients) and tachycardia (6/9 patients) were reported. All children recovered completely after olanzapine poisoning with the

exception of a child who had mild upper extremity tremor 13 days later. There were no fatalities attributed to olanzapine in studies describing its therapeutic use in younger children or in cases of poisoning.

We also conducted a retrospective, multi-centre review of the safety and efficacy of olanzapine use for CIV control in children as previously mentioned.⁵⁷ The adverse events reported in these children were of minor clinical significance. Grade 1-2 sedation was reported in 11/158 (7%) of chemotherapy blocks. Of the 25 chemotherapy blocks where liver function tests were evaluable, transient grade 1-3 elevations in plasma transaminase concentrations were observed in 5; all resolved uneventfully. Bilirubin was unaffected. Changes in body weight were able to be assessed in 31 patients: the mean weight change was 0% (range: -22 to +18%). No serious adverse events were attributed to olanzapine.

In the previously mentioned multi-centre, retrospective review of olanzapine use for CIV control in children, the mean initial olanzapine dose administered was 0.10 ± 0.051 mg/kg/dose (range: 0.026 to 0.256 mg/kg/dose).⁵⁷ In this uncontrolled study, no relationship was observed between olanzapine dose and CIV control. However, children who were reported to have experienced sedation received a significantly higher olanzapine dose than did children who were not reported to have experienced sedation (0.14 ± 0.033 vs. 0.09 ± 0.051 mg/kg/dose; OR: 1.17; 95% CI: 1.08 to 1.27; $p = 0.0001$).

An initial olanzapine dose of 0.14 mg/kg/day once daily was given in the single-arm feasibility study described earlier. Of the 15 children who participated, 5 experienced sedation. The olanzapine dose was moved to bedtime for 1 patient while the olanzapine dose was decreased in the remaining 4. Another patient experienced sedation and dizziness. The olanzapine dose was reduced in this patient but later increased to the initial dose due to poor CIV control. Olanzapine was discontinued in one patient who experienced transient blurred vision and in another with increased plasma GGT values. Based on this experience the olanzapine dose given in this trial is lowered from 0.14mg/kg/day to 0.1mg/kg/day.

3.0 STUDY ENROLLMENT PROCEDURES AND PATIENT ELIGIBILITY

The main coordinating site for this multi-center, randomized controlled trial is The Hospital for Sick Children, Toronto, Canada.

3.1 Study Enrollment

3.1.1 Research Ethics Board (REB) Approval

Local REB approval of this study must be obtained prior to site enrolling patients. Each site must submit REB documents to the study PI: Dr. Lee Dupuis at lee.dupuis@sickkids.ca and the US national coordinating site PI: Dr. Christopher Dvorak at Christopher.dvorak@ucsf.edu.

The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements in Canada (REB and Health Canada) and the United States (IRB and the Food and Drug Administration (FDA)).

3.1.2 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. A unique patient ID number will be assigned.

3.1.3 Measures to Minimize Bias: Randomization and Blinding

Sites will obtain each participant's randomization assignment via randomize.net.

Placebo tablets are identical in appearance to olanzapine tablets. Subject treatment allocation will be concealed from all subjects, site investigators and site clinicians throughout the entire time that the study is conducted. The Investigational Drug Service, University of Pennsylvania School of Medicine will provide olanzapine and placebo to the Pharmacy Department of each participating site.

If emergency un-blinding is required, the site investigator will contact the nominated principal applicant or delegate who will authorize the site's Department of Pharmacy to provide the information directly to the patient's treating physician. The principal applicant, co-applicants, and study team members at the coordinating site and participating sites will remain blinded.

3.2 Patient Eligibility Criteria

3.2.1 Inclusion Criteria

Planned receipt of HEC or cyclophosphamide $\geq 1 \text{ g/m}^2/\text{day}$ ($\geq 33 \text{ mg/kg/day}$) for cancer treatment or autologous or allogeneic HSCT conditioning.^{81,82} Examples of HEC are: busulfan IV (myeloablative dosing), carboplatin $\geq 175 \text{ mg/m}^2/\text{dose}$, cisplatin $\geq 12 \text{ mg/m}^2/\text{dose}$, cytarabine $\geq 3 \text{ g/m}^2/\text{day}$, melphalan $> 140 \text{ mg/m}^2$, methotrexate $\geq 12 \text{ g/m}^2/\text{dose}$ and thiotepa $\geq 300 \text{ mg/m}^2/\text{dose}$.

Plan for inpatient admission from administration of first study drug dose until 24 hours following administration of last study drug dose.

Body weight of at least 12.5 kg

2.5 to < 18 years of age. Note that the minimum age requirement corresponds to an approximate body weight of 12.5 kg.

Samples for all laboratory tests will be obtained within one week prior to administration of the first chemotherapy dose of the study chemotherapy block or the first HSCT conditioning dose:

- Plasma creatinine within 1.5 times the upper limit of normal for age.
- Amylase within age-appropriate limits
- Plasma conjugated bilirubin within $\leq 3\text{x}$ upper limit of normal for age unless attributable to Gilbert's Syndrome
- ALT $\leq 5\text{x}$ upper limit of normal for age

A baseline ECG within the month prior to study drug administration without known clinically significant abnormalities including pathologic prolongation of QTc.

A plan for scheduled, round-the-clock receipt of ondansetron, granisetron or palonosetron for antiemetic prophylaxis during administration of chemotherapy or HSCT conditioning.

Negative pregnancy test if female of childbearing potential

Patients of childbearing potential must consent to use adequate contraception (males and females) or agree to practice abstinence

Parent or child able to speak a language in which the modified Pediatric Adverse Event Rating Scale (PAERS) is available.

Optional: Child participants in the optional assessment of nausea severity must be 4 to 18 years of age. Child and a parent/guardian must be English, Spanish or French-speaking. The Pediatric Nausea Assessment Tool⁵⁸ (PeNAT) is validated in English-speaking children 4 to 18 years old with an English-speaking parent/guardian and has been translated into Spanish and French. The MAT is available in English, Spanish and French.

3.2.2 Exclusion Criteria

CNS malignancy, either primary CNS tumor or CNS metastases not in remission. A history of CNS leukemia, in remission at study entry, is allowed.

Pre-existing seizure disorder requiring treatment with anticonvulsants; known cardiac arrhythmias; known clinically significant ECG abnormalities at baseline including QTc prolongation; uncontrolled diabetes mellitus; history of neuroleptic malignant syndrome; known hypersensitivity or allergy to olanzapine.

Treatment within 14 days prior to the first day of study drug administration with olanzapine or other anti-psychotic agents (e.g. risperidone, quetiapine, aripiprazole, clozapine, butyrophenone) including those used to control CINV (e.g. chlorpromazine, prochlorperazine, promethazine) (see Appendix I).

Scheduled administration (i.e. not PRN) of antiemetics other than dexamethasone and ondansetron, granisetron or palonosetron is **not** permitted. However, at the discretion of the treating physician, scheduled aprepitant and fosaprepitant may be initiated in the acute phase in patients who experience failed CIV control in the acute phase (see section 4.2.1).

Scopolamine patches, phenothiazines (e.g. chlorpromazine, prochlorperazine), or acupuncture are not permitted during the acute and delayed phases. Methylprednisolone and hydrocortisone are permitted during the acute and delayed phases for prevention or treatment of reaction (e.g. thymoglobulin, alemtuzumab, blood products) and, for HSCT patients, during delayed phase for

GVHD prophylaxis. Administration of olanzapine other than ordered as per study procedures is not permitted. However, other antiemetics may be administered as needed (PRN) for treatment of breakthrough CINV. For patients receiving busulfan, scheduled administration of benzodiazepines such as lorazepam for seizure prophylaxis is permitted on the days that busulfan is given and for 24 hours after.

For HSCT patients, receipt of cranial boost radiation within 14 days prior to the first day of HSCT conditioning.

Planned co-administration of citalopram, amifostine, or medications known to alter the metabolism of olanzapine (e.g. ciprofloxacin, valproic acid⁵⁹) (see Appendix II).

Previous participation in this study.

Participants in the optional assessment of nausea severity must be free of cognitive, hearing or visual impairment that preclude completion of the PeNAT.⁶⁰

4.0 TREATMENT PLAN

4.1 Overview of Treatment Plan

This is a multi-center, randomized, blinded, placebo-controlled, pragmatic, superiority trial conducted over a single block of HEC or a single course of HSCT conditioning.

The primary study outcome measure is complete or partial control of vomiting during the acute phase. Complete control of vomiting is defined as no use of breakthrough anti-emetic agents and no vomiting/retching. Partial control of vomiting is defined as no more than 2 vomits or retches during any 24-hour period.

For secondary objectives, the following will be described for each study arm:

1. the proportion of patients experiencing complete, partial and failed CIN and CINV control in the acute phase and complete, partial and failed CIV, CIN and CINV in the delayed and overall phases
2. changes in: body weight, modified PAERS^{61,62} score (Appendix IV), plasma amylase, creatine phosphokinase, glucose, prolactin, fasting triglyceride concentrations, or hepatic function
3. incidence of ECG abnormalities, including QTc prolongation, and non-hematologic adverse effects (CTCAEv4, spontaneous reports)
4. for HSCT patients: incidence of veno-occlusive disease, acute graft-versus-host disease (GVHD; including maximum grade and stage) and neutrophil engraftment (attainment, time) and
5. correlation between the MAT nausea score and the highest daily PeNAT score

4.1.1 Standard antiemetic prophylaxis

All patients will receive standard, scheduled antiemetic prophylaxis consisting of ondansetron, granisetron or palonosetron intravenously (IV) or by mouth (PO) on a schedule (not PRN) during the acute

phase. Ondansetron or granisetron will be given in doses recommended by a pediatric acute CINV prophylaxis guideline.⁴

Dexamethasone may be prescribed as a scheduled antiemetic (not PRN) at the discretion of the treating physician. Since only weak recommendations for dexamethasone dosing are available, dexamethasone (if given) will be dosed as per institutional standards.⁴ Similarly, palonosetron will be dosed as per institutional standards.

Breakthrough antiemetic agents (e.g. lorazepam, metoclopramide, dimenhydrinate) may be given as needed in doses as per institutional standards. However, PRN doses of phenothiazines (e.g. chlorpromazine, methotrimeprazine, prochlorperazine, and promethazine), aprepitant, fosaprepitant, dexamethasone or olanzapine may not be administered during the study period.

At the discretion of the treating physician, fosaprepitant or aprepitant may be initiated during the acute phase of the study chemotherapy block in patients with failed CIV control. Failed CIV control is defined as more than 2 vomits or retches in a 24-hour period.

4.1.2 Administration Schedule: Olanzapine or Placebo

Patients will be randomized to receive either olanzapine or placebo once daily starting before the first dose of chemotherapy or HSCT conditioning and continuing for 4 doses after the last dose of chemotherapy or HSCT conditioning or until, for chemotherapy patients, the next chemotherapy block starts or, for HSCT patients, administration of cyclophosphamide after Day 0, whichever occurs first.

The time of day that the first dose of chemotherapy or HSCT conditioning is given will be determined by the clinical team.

Study drug is administered based on the olanzapine dosing schedule regardless if randomized to olanzapine or placebo. Olanzapine 0.1 mg/kg/dose (maximum 10 mg/dose) will be administered by mouth as a single daily dose based on actual body weight. The dose will be rounded to the nearest half tablet (1.25 mg). For children who require oral liquid dosage forms, the study drug may be disintegrated in water prior to administration.⁶³ Should a child vomit within 30 minutes of study dose administration, the study dose will be repeated. An algorithm for the selection of the initial olanzapine dose is presented in Table 1.

Table 1: Study drug dosing algorithm

Actual Body Weight (kg)	Initial Olanzapine Dose (mg/day as a single daily dose)	Initial Placebo Dose (# tablets/day as a single daily dose)
12.5 to < 19	1.25	½
19 to < 32	2.5	1

32 to < 44	3.75	1½
44 to < 58	5	2
58 to < 69	6.25	2½
69 to < 82	7.5	3
82 to < 94	8.75	3½
≥ 94	10	4

If CIV is not controlled at the initial study drug dose, the patient's daily study drug dose may be increased by 1.25 mg or a ½ tablet (max: 10 mg/dose or 4 tablets/dose) if adverse effects are absent or not troublesome at the discretion of the site study team.

4.1.3 CINV outcome measurement

Each child/family will be instructed on the use of a CINV diary⁶⁴ (Appendix V). Patients and parents will record the time of vomit and retch on each day of chemotherapy or HSCT conditioning administration and for 5 days after completion of chemotherapy or HSCT conditioning or the start of the next chemotherapy block or, for HSCT patients, until administration of cyclophosphamide after Day 0, whichever occurs first.

Patients and parents may participate in the optional nausea assessment. Children will self-report the severity of their own present nausea using the PeNAT at minimum twice daily (upon rising in the morning and at bedtime), as well as whenever the child feels nauseated, requests PRN antiemetic agents or the child's health care provider/parent believes the child may be nauseated. Nausea severity will be assessed on each day of the acute and delayed phases. A parent or a health care provider may assist the patient in completing the nausea severity assessments but will serve only to transcribe the information provided by the child on to the CINV diary. They will not make a proxy assessment of the severity of the child's nausea. Site research personnel will be taught to administer the PeNAT using a standardized training package and will teach parents and children how to use the PeNAT. Site research personnel will collect completed diary pages several times over the study period.

Children 13 years to < 18 years of age who agree to participate in nausea assessment will complete the PeNAT twice daily at minimum as described above. They will also complete the MAT once daily at bedtime. (Appendix VI)

In addition to the information provided by the patient/family, the number of vomits recorded by the nursing staff and the name, dose, and time of administration of all antiemetic agents administered to study patients will be abstracted from the patient's health record.

4.1.4 Safety outcome measurement

The expected duration of chemotherapy or HSCT conditioning ranges approximately from 1 to 10 days; thus, the expected duration of study drug administration will range approximately from 5 to 14 days.

The following assessments will be made on each day of study drug administration (see 4.1.5.5 Table 2): plasma glucose concentration, and maximum and minimum blood pressure. Conjugated bilirubin and ALT will be obtained at minimum 3 times weekly during the acute and delayed phases. Body weight and plasma prolactin, amylase, creatine phosphokinase and fasting triglyceride concentrations will be obtained on the first day of conditioning and within 24 hours of administration of the last dose of study drug. Results of ECGs obtained for clinical care and study purposes, during study drug administration will be recorded. Chart review to identify possible olanzapine-associated adverse events will continue for 30 days after administration of the last dose of study drug.

Patients or parents will complete the modified PAERS prior to administration of the first dose of the study drug, once between days 3-6, and again on the last day of study drug administration. Should the last day occur on a weekend or statutory holiday, the PAERS can then be completed up to three days prior to the last dose. This will ensure that all patients are receiving study drug at the time of the second assessment and it accommodates study staffing challenges. Symptoms which are scored as “quite” or “very” bothersome on the modified PAERS will be brought to the attention of the treating physician.

For patients receiving HSCT conditioning, chart review to assess study-related HSCT outcomes will continue for 100 days after HSCT. The following will be recorded through the first 100 days: day post-HSCT of neutrophil engraftment, diagnosis (Yes/No) of veno-occlusive disease,⁶⁵ and acute GVHD (maximum stage and grade) (see Appendix III for definitions).

4.1.5 Study Procedures

Subject Enrolment and Treatment Assignment

Sites will obtain each participant’s randomization assignment via randomize.net. Allocation is 1:1. Randomization will use varying block sizes and stratification by center, receipt of HSCT conditioning and known determinants of CIV: inclusion of total body irradiation^{23,66} in the conditioning regimen (HSCT patients) and receipt of dexamethasone as an antiemetic.⁶⁷⁻⁶⁹

Assessments

One month prior to initial study drug administration:

- Baseline ECG within the month prior to study drug administration

0 to 7 days prior to initial study drug administration:

- Obtain informed consent
- Review inclusion/exclusion criteria
- Medical and medication history (accepted antiemetic prophylaxis ordered, history of CNS malignancy and other excluding medical history, treatment with excluded medication, history of motion sickness)
- Body weight

- Laboratory assessments [plasma glucose, blood counts, conjugated bilirubin, ALT, plasma prolactin, amylase, creatine phosphokinase, and fasting triglyceride concentrations]

On initial day of study drug administration:

- Plasma pregnancy test, where applicable. If the test obtained as a standard of care was negative prior to admission and patient denies sexual intercourse in the interim, this test can be omitted.
- Completion of modified PAERS by parent/guardian or by patient within 12 hours prior to administration of initial study drug dose
- For participants in optional CIN assessment: completion of PeNAT and MAT (if applicable) within 2 hours prior to the first dose of chemotherapy or HSCT conditioning

On second and subsequent days of study drug administration, prior to study drug administration:

- Determination of need to increase or decrease study drug dose. That is, if:
 - o unexplained, excessive somnolence or depressed level of consciousness (CTCAEv4 Grade 3; difficult to arouse; obtundation or stupor) or dizziness (CTCAEv4 Grade 3; severe unsteadiness or sensation of movement) is present, see section 5.1
 - o the participant has vomited or retched since the last dose of study drug (CIV is not controlled), see section 4.1.2.

For HSCT patients, on day of HSCT:

- Stem cell source
- Whether product was cryopreserved with dimethylsulfoxide (DMSO)

Study Drug Administration

- Study drug (olanzapine or placebo) dispensed and taken by patient 1 to 2 hours prior to administration of the first dose of chemotherapy or HSCT conditioning
- Study drug administered daily on each day of chemotherapy or HSCT conditioning including total body irradiation and for 4 doses afterward or until next chemotherapy block is started or, for HSCT patients, administration of cyclophosphamide after Day 0, whichever occurs first.

Treatment Assessments

- Parent/patient: record time of vomiting and retching on diary on each day of chemotherapy or HSCT conditioning and for 5 days after completion of chemotherapy or HSCT conditioning
- For participants in optional CIN assessment: assessment of nausea severity at least twice daily on each day of chemotherapy or HSCT conditioning and for 5 days after completion of chemotherapy or HSCT conditioning using PeNAT for participants less than 13 years old. Participants between 13 and < 18 years old will complete both PeNAT and MAT nausea assessments.
- BP, heart rate, and respiratory rate will be obtained at minimum every 6 hours during the study drug administration period
- Plasma glucose (daily until last day of study drug administration)
- Urine glucose (qualitative – dipstick or quantitative) will be obtained daily during study drug administration
- Blood counts, conjugated bilirubin, ALT (3 times weekly during acute and delayed phases)
- Body weight (last day of study drug administration)
- PAERS (last day of study drug administration, or up to 3 days prior to the last dose if last dose

is on the weekend/statutory holiday)

- Plasma prolactin, amylase, creatine phosphokinase and fasting triglyceride concentrations (last day of study drug administration)
- An additional ECG once between day 3-6 of study drug administration
- Adverse Events (daily until 30 days after administration of last study drug dose)
- For HSCT patients: attainment and date of engraftment, incidence of veno-occlusive disease, ECG abnormalities and frequency of acute graft versus host disease (until 100 days post-HSCT)

Day of HSCT	HSCT Conditioning (chemotherapy administration)	Informed Consent	Inclusion/Exclusion review	Medical and Medication History	Study drug administration	Study drug dose adjustment assessment	CINV diary – PeNAT and MAT are optional	Body Weight	ECG	Plasma glucose and urinalysis	Blood counts, conjugated bilirubin, ALT	Prolactin, amylase, creatine phosphokinase fasting triglyceride concentrations	Blood pressure, heart & respiratory rates	PAERS	AE ^y	HSCT outcome
	Pretreatment	x	x	x			x	x	x	x	x	x		x		
Day -7	X				x		x			x			x			
Day -6	X				x	x	x			x	x		x			
Day -5	X ^β				x	x	x			x			x			
Day -4	X ^β				x	x	x			x	x		x			
Day -3	X ^β				x	x	x			x			x			
Day -2	X ^β				x	x	x		x ^Ω	x	x		x	x ^Ω		
Day -1	X ^β				x	x	x			x			x			
Day 0	Transplant Day				x	x	x			x			x			
Day +1					x	x	x			x	x		x			
Day +2					x	x	x			x			x			
Day +3					x	x	x	x		x	x	x	x	x ^α		
Day +4							x									
Day +30																
Day +100																x

Ω - Obtain PAERs & ECG between days 3-6 of study administration

α - Obtain PAERs on the last day of study drug administration. There is a +3 day window

β - HSCT conditioning may run from 2-7 days.

y - Adverse events will be collected from study drug admin up to day 30 after conditioning.

Table 2a: Procedure table representing a 7-day HSCT conditioning regimen

Table 2b: Procedure Table representing a 3-day chemotherapy block

Study chemotherapy block day	Receipt of chemotherapy	Informed Consent	Inclusion/Exclusion review	Medical and Medication History	Study drug admin	Study drug dose adjustment assessment	CINV Diary- PeNAT and MAT are optional	Body Weight	ECG	Plasma glucose and urinalysis	Blood counts, direct bilirubin, total bilirubin, ALT	Prolactin, amylase, creatine phosphokinase, fasting triglyceride concentrations	Blood pressure, heart & respiratory rates	PAERS	AE ^v
Pretreatment		X	X	X					X						
Day 1	X				X		X	X		X	X	X	X	X	↓
Day 2	X				X	X	X			X			X		
Day 3	X				X	X	X		X ^Ω	X	X		X	X ^Ω	
Day 4					X	X	X			X			X		
Day 5					X	X	X			X	X		X		
Day 6					X	X	X			X			X		
Day 7					X	X	X	X		X		X	X	X ^α	
Day 8							X								
Day +34															

Ω - Obtain PAERs & ECG between day 3-6 of study drug administration

α - Obtain PAERs on the last day of study drug administration. There is a 3-day window.

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Sedation

The most common adverse effect of olanzapine when used short-term, as is the case in this study, is sedation. Olanzapine or placebo will be discontinued in any child who experiences depressed level of consciousness CTCAEv4 Grade 4 (coma) of uncertain etiology. Furthermore, the olanzapine/placebo dose will be halved in children who experience unexplained, excessive somnolence or depressed level of consciousness (CTCAEv4 Grade 3; difficult to arouse; obtundation or stupor) or dizziness (CTCAEv4 Grade 3; severe unsteadiness or sensation of movement). The lowest olanzapine dose to be administered is 1.25 mg (half a 2.5 mg tablet). The administration time of the olanzapine or placebo dose may also be moved to bedtime at the discretion of the clinical team. If clinically significant symptoms continue despite dose reduction, or dose time adjustment, olanzapine or placebo will be discontinued.

6.0 DRUG INFORMATION

6.1 Olanzapine

Olanzapine is an atypical antipsychotic drug that blocks many neurotransmitters including many of those involved in nausea and vomiting. It is metabolized hepatically but is neither an inducer nor an inhibitor of cytochrome P450 (CYP) isoenzymes. Therefore, no interaction with drugs commonly given in HSCT (e.g. busulfan, cyclosporine or tacrolimus) is expected. However, the dose intensity of olanzapine may decrease if given together with CYP1A2 inducers (e.g. barbiturates, carbamazepine, fluvoxamine, and rifampin) or increase when given together with CYP1A2 inhibitors (e.g. ciprofloxacin). Smoking and concurrent administration of valproate also decrease the dose intensity of olanzapine.⁵⁹ No antineoplastic agents used in HEC or HSCT conditioning regimens (e.g. busulfan, fludarabine, thymoglobulin) including cyclophosphamide, induce or inhibit CYP1A2.

The pharmacokinetics of olanzapine have been described in 8 non-smoking children aged 10 to 18 years and are similar to those observed in adult non-smokers.⁷⁰ The mean time to maximum olanzapine plasma concentration was 4.7 ± 3.7 hours and the mean elimination half-life was 37.2 ± 5.1 hours. Another study evaluated the pharmacokinetic disposition of olanzapine in 22 patients aged 5 to 14 years. (Eli Lilly Canada, personal communication, May 6, 2011) Again, the mean pharmacokinetic parameters and the overall range of plasma olanzapine concentrations observed in these children were similar to adults when compared on the basis of the mg/kg dose administered.

Toxicity: Rarely, olanzapine may be associated with potentially serious adverse effects. The reported incidences of neuroleptic malignant syndrome (hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia), tardive dyskinesia hypoglycemia, and hyperprolactinemia in patients receiving olanzapine is less than 1%. Body temperature regulation may also rarely occur; patients who are dehydrated are at increased risk. The reported incidence of orthostatic hypotension in patients receiving olanzapine is 1 to 10%. Reversible increases in transaminase concentrations have been reported in 12% of adolescents. The risk of most adverse effects associated with olanzapine increases with high doses and prolonged

durations of administration. No serious adverse effects have been reported in adult cancer patients taking olanzapine short-term for CINV control as will be the case in this study.

Formulation and Stability: Tablets 2.5 mg. Stability on the original bottle will be assigned by the manufacturer.

Guidelines for administration: Patients will receive olanzapine once daily starting just before the first dose of chemotherapy within the study chemotherapy block or the first dose of HSCT conditioning and continuing for a maximum of 4 doses after the last dose of chemotherapy or until the next chemotherapy block begins or, for HSCT patients, administration of cyclophosphamide after Day 0, whichever occurs first.

Olanzapine will be dosed at 0.1 mg/kg/dose (maximum 10 mg/dose) as a single daily oral dose rounded to the nearest increment of a half-tablet (1.25 mg). Olanzapine tablets can be disintegrated in tap or sterile water immediately prior to administration to patients who are unable to swallow tablets whole.

The olanzapine dose may be halved in patients who experience undesirable, acute adverse effects potentially attributable to olanzapine (e.g. sedation) but who elect to continue olanzapine therapy. The administration time of the second or subsequent olanzapine doses may be moved to bedtime at the discretion of the clinical team. See section 5.1.

In consultation with the patient, the patient's guardian (if relevant) and the clinical team, the olanzapine dose may be increased by a half-tablet (1.25 mg) if a patient experiences uncontrolled CIV (vomits or retches).

Olanzapine can be given with or without food.

Supplier: The University of Pennsylvania will supply olanzapine to each site's Pharmacy Department.

Product disposal: Any unused or expired product vials will be returned to the respective Pharmacy Department. After accountability and reconciliation have been performed, the drug will be destroyed locally.

6.2 Placebo

Toxicity: None to report

Formulation and Stability:

Tablet Weight	Not to exceed 200 mg
Olanzapine Content	None
Release Profile	None
Appearance	White to off-white tablet with markings similar to 2.5 mg olanzapine tablet.
Hardness	> 40 N
Disintegration	Not more than 15 minutes
Friability	Less than 1% for 6.5 g of tablets after 100 drops

Stability	achieve 60 months, stored at room temperature conditions (less than 28 C and 60% RH), with ongoing stability testing done by the University of Pennsylvania
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Guidelines for administration: Patients will follow administration guidelines as if they were receiving olanzapine.

Supplier: The University of Pennsylvania will provide placebo to each site's Pharmacy Department.

Product disposal: Any unused or expired product vials will be returned to the respective Pharmacy Department. After accountability and reconciliation have been performed, the placebo will be destroyed locally.

7.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

7.1 Criteria for Removal from Protocol Therapy

- a) Development of depressed level of consciousness CTCAEv4 Grade 4 sedation (coma) of uncertain etiology
- b) Patient unable to tolerate or refuses oral medications
- c) Refusal of further protocol therapy by patient/parent/guardian.
- d) Completion of planned therapy.
- e) Physician determines it is in the patient's best interest.

7.2 Off Study Criteria

- a) Death
- b) Lost to follow-up
- c) Withdrawal of consent for any further data submission
- d) HSCT patients: Completion of Day 100 evaluation
- e) Non-HSCT patients: Completion of evaluation 30 days following administration of last study drug dose

8.0 STATISTICAL CONSIDERATIONS

8.1 Justification for Methodological Choices

8.1.1 CINV Diary

This method of CINV diary completion has been shown to be feasible in several studies.^{25,71,72} CINV diary completion and retrieval rates are high when patients are admitted to hospital as will be the case in the proposed study. In a recently completed study of CINV in children receiving IV methotrexate, CINV diary completion rate was 100% while children were in-patients.⁷³ In a prospective, observational study in HSCT patients at SickKids, the CINV diary completion rate was 93%.²⁶

The number of vomiting and retching episodes will be determined from the patient diary and from the health record. On days that these numbers are available in both the patient diary and the health record,

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the higher number of the 2 data sources will be used as the outcome. Otherwise, the single available source will be used or, if neither are available, the outcome will be deemed missing for that day.

8.1.2 Nausea assessment tool in adolescents

The PeNAT is validated for use in English-speaking children with English-speaking parents aged 4 to 18 years. It has also been translated into Spanish and French. It consists of a script and a faces scale and is designed to allow children to rate the severity of the nausea they are experiencing at the time of assessment. Although not raised as an impediment to the use of the PeNAT during the validation or subsequent studies and trials, it is possible that adolescents may find the faces scale of the PeNAT to be juvenile. An instrument validated for use by adult cancer patients may be better received by this age group.

The method of nausea severity assessment validated and widely used in adults is a VAS that allows adults to assess the maximum severity of nausea over the past 24 hours.⁷⁴ This instrument, the Multi-National Association of Supportive Care in Cancer Antiemesis Tool (MAT) was chosen to evaluate as a possible alternative to the PeNAT in adolescents.

8.1.3 Safety Outcome Measurement

Patients or parents will complete the modified PAERS (Appendix IV) three times:

1. prior to administration of the first dose of the study drug,
2. once between days 3-6, and
3. on the last day of study drug administration.

The PAERS is a psychometrically validated child self-report or parent report measure developed by the Child and Adolescent Psychiatry Trials Network, National Institute of Mental Health, to identify adverse events related to psychotherapeutic agents used in pediatric psychiatry.^{61,62} It takes less than 15 minutes to complete. We have retained elements of the PAERS relevant to this trial.

There is no reason to believe that olanzapine will influence HSCT outcomes. Nevertheless, since these patients are highly vulnerable and these data will be available through routine monitoring, we will record the following through the first 100 days post-HSCT: day post-HSCT of neutrophil engraftment, diagnosis (Yes/No) of veno-occlusive disease, and acute GVHD (maximum stage and grade).

8.1.4 Olanzapine Dosing

Several approaches using actual body weight, body surface area and allometric models have been applied to estimate safe and effective pediatric drug doses based on adult doses. Body surface area or allometric models based on body weight have been recommended for dose scaling for children beyond infancy.⁷⁵ Using these methods and the oral olanzapine dose which has demonstrated efficacy and safety in adult cancer patients (10 mg/dose as a single daily dose), the predicted safe and effective pediatric olanzapine dose ranges from 0.12 to 0.26 mg/kg/day; maximum 10 mg/day.

We have taken a conservative approach and based the initial olanzapine dose in the proposed study on the experience with olanzapine in children for mental conditions⁵⁶ and for CINV prophylaxis,⁵³ the experience with adult cancer patients,⁴³ allometric scaling methods of pediatric dose derivation⁷⁵ and the comparable pharmacokinetic properties of olanzapine in older children and adults with an appreciation for the possible relationship between the dose and sedation.⁵³ The number of children for whom the dose of the study drug is reduced, increased or discontinued due to adverse effects will be reported for each study arm.

8.1.5 Inclusion and Exclusion Criteria

The lowest possible initial olanzapine dose able to be delivered is 1.25 mg. Therefore, the requirement that children weigh at least 12.5 kg will permit a maximum initial olanzapine dose of 0.1 mg/kg/dose.

Participation in the optional CIN assessment is limited to:

- 1) those families with either an English, Spanish or French-speaking, and Hindi in Indian sites, parent and child because the study patient-report measure (PeNAT) has been validated in these languages and
- 2) children 4 to 18 years of age because the PeNAT is validated in this age range.

8.1.6 Endpoints

The choice to describe the primary and secondary CIV and CIN endpoints as proportions during the acute, delayed and overall phases is based on CINV interventional trial design recommendations and is currently the standard method for reporting the performance of antiemetic prophylaxis strategies in adult supportive care trials.^{77,78}

8.2 Statistical Analysis Methods

Participant and cancer therapy will be summarized by arm:

- Patient demographic and diagnosis data (age; sex; cancer diagnosis or diagnosis leading to HSCT)
- Information regarding:
 - antiemetic regimen
 - chemotherapy or HSCT conditioning regimen and
 - for HSCT patients, information regarding the HSCT (stem cell source and degree of match, acute GVHD prophylaxis regimen).

8.2.1 Study Endpoints

Table 3: Definition of CIV and CIN Outcome Measures⁷⁹

Outcome Measures	Definition
Chemotherapy-induced vomiting control:	
Complete	• no vomiting/retching and no use of breakthrough antiemetic agents during the phase* of interest
Partial	• 1-2 vomiting/retching episodes during any 24-hour period during the phase* of interest
Failure/No control	• 3 or more vomiting/retching episodes during any 24-hour period during the phase* of interest
Chemotherapy –induced nausea control:	
Complete	• No nausea (< 18 yrs: maximum PeNAT score = 1) during the phase* of interest
Partial	• Mild nausea (maximum PeNAT score = 2) during any 24-hour period during the phase* of interest
Failure/No control	• moderate-severe nausea (maximum PeNAT score=3-4) during any 24-hour period during the phase* of interest

*acute, delayed or overall phase

Primary endpoint

The primary analysis will be based on the intention-to-treat principle with respect to study arm allocation and will include all eligible and evaluable patients, regardless of protocol treatment compliance. Analysis will be conducted once, after accrual of 160 evaluable patients. No subgroup analyses are planned.

An evaluable patient will provide data for the primary endpoint (vomiting or retching episodes and breakthrough medication usage) on each day of the acute phase. The number of vomiting and retching episodes each day will be determined from the patient diary and from the health record. On days that these numbers are available in both the patient diary and the health record, the higher number of the 2 data sources will be used as the outcome. Otherwise, the single available source will be used or, if neither are available, the outcome will be deemed missing for that day.

If more than 5% of participants are missing the complete records (i.e., for every day) for the primary outcome, the analyses described under “Missing data (a)” below will constitute the primary analysis of the primary outcome. Otherwise, only those with complete data will be included in the primary analysis and analyses addressing missing data will be considered to be sensitivity analyses.

Details of primary statistical analysis model: In the acute phase, each participant will be classified as having either (a) control, defined as complete plus partial control, or (b) no control, defined as failure/no control, using the definitions in the table above. The percentages of participants in each arm with control will be calculated. However, a simple comparison of proportions ignores an important

feature of the anticipated data: The longer the acute phase for a participant, the higher the chance of failure and the lower the chance of control.

If the rate (per unit time) of nausea and vomiting events for a participant is R , the probability of no events in time t , under the Poisson assumption is:

$$P(\text{events} = 0) = \exp(-R * t)$$

So, the probability of an event is one minus this:

$$P(\text{events} > 0) = 1 - \exp(-R * t)$$

The complementary log-log function is defined as

$$\text{cloglog}(p) = \log(-\log(1-p))$$

Applying this to the probability of an event:

$$\begin{aligned} & \text{cloglog}(P(\text{events} > 0)) \\ &= \text{cloglog}(1 - \exp(-R * t)) \\ &= \log(-\log(\exp(-R * t))) \\ &= \log(R * t) \\ &= \log(R) + \log(t) \end{aligned}$$

We use these relationships to decide on the model for the primary outcome. The comparison between arms will use failure (i.e., no control) as the outcome, and the natural logarithm of the duration of the acute phase as an offset, in a binomial regression model using the complementary log-log link; predictors will be the treatment arm and stratification variables from randomization: center (AIIMS vs non-AIIMS), receipt of HSCT conditioning, receipt of total body irradiation and receipt of dexamethasone as an antiemetic.

To assess whether the intervention reduces the rate of vomiting and nausea (i.e., increases control), we will estimate the rate ratio (RR) from this model, along with a 90% CI and associated p-value for a one-sided test of benefit:

H_0 : Vomiting increased with Olanzapine, $RR > 1$

H_1 : Vomiting decreased with Olanzapine, $RR < 1$

The choice of a one-side 90% CI means that rejection of H_0 will coincide with the CI excluding a RR of 1.

Missing data: The primary analysis will be rerun on all randomized patients, using two different methods to deal with incomplete outcome data:

(a) In a multiple imputation scheme, patients' missing outcome data will be predicted from partial data (i.e., other CIV diary days), treatment, and patient characteristics; the result of multiple imputations will be combined using standard methods.

(b) in two separate sensitivity analyses, days without assessments will be assigned as days with or days without CINV.

Secondary endpoints

The following four groups of secondary outcomes will be compared between intervention groups:

- 1 Complete CIV control in the acute phase
- 2 CIV (complete; complete plus partial)
 - a. delayed phase
 - b. overall phase
- 3 Chemotherapy-induced nausea (CIN)
 - a. acute phase
 - b. delayed phase
 - c. overall phase
- 4 Chemotherapy-induced nausea and vomiting (CINV)
 - a. acute phase
 - b. delayed phase
 - c. overall phase

For secondary aims comparing CIV, CIN and CINV control during the delayed and overall phases, analyses similar to those on the primary endpoint of CIV will be performed.

Comparison of complete or partial CIV control rates observed during the acute phase between study arms is the accepted method of evaluation in modern antiemetic trials. This method is most often applied to single-day chemotherapy regimens as is the norm in adult oncology. However, chemotherapy is most often administered on multiple, consecutive days in pediatric oncology and in HSCT conditioning. Thus, evaluation of CIV control as a binary endpoint (controlled vs. uncontrolled) over a period of several days may lack the discriminatory ability to identify clinically meaningful improvements in CIV control in patients receiving multiple-day chemotherapy. To be considered evaluable in terms of the secondary CIN/ CINV study aims, patients must provide a diary with at least 1 nausea severity assessment on each day of either the acute or delayed phase, or both.

We will use the standard accepted approach (combining all days in a phase into a single binary variable), but also conduct secondary analysis using repeated measures analyses where the outcomes are the daily measures of CIV/CIN control. These may be more sensitive in identifying smaller treatment effects between treatment arms and can include patients who might have been excluded from the standard analysis due to missing daily assessment, or who might necessitate more complicated analyses including imputation.

In these secondary analyses, the daily CIV/CIN outcome may be modeled as a binary outcome of complete control (yes/no), or as an ordinal outcome with three levels: complete/partial/no control. The daily complete control outcome will be compared between the 2 randomized arms with a generalized linear mixed model for the binary outcome or a mixed proportional odds models for the ordinal outcome. The treatment effect will be estimated as the odds ratio associated with olanzapine for the binary outcome or the common odds ratio associated with olanzapine for the ordinal outcome. Stratification variables from randomization (as listed above) will be include in these models.

For the secondary aim describing the safety profile of olanzapine including, AEs, PAERs scores and, for HSCT patients, impact on HSCT outcomes (day post-HSCT of neutrophil engraftment, diagnosis (Yes/No) of veno-occlusive disease,⁶⁵ and acute GVHD (maximum stage and grade)), analyses will primarily be descriptive such as using counts and frequencies for summarizing categorical data. For AEs, we will calculate the percentages in each arm experiencing any AE and, if there are sufficient AEs of several particular types, provide this summary by AE type. Using the 5-point PAERs score, we will calculate percentages of patients with quite bothersome or severely bothersome symptoms at any time point or with increased bother from baseline. The number of patients who reduced the study drug dose or discontinued study drug administration due to toxicity will be calculated.

For the secondary objective exploring the association between the PeNAT and MAT scores among patients aged 13 to < 18 years, descriptive statistics and plots will be used. Since PeNAT is administered multiple times per day while MAT is administered once per day for the maximum nausea experienced, the maximum daily PeNAT scale will be compared to the MAT score. Spearman's rho will be used to quantify the degree of association between PeNAT and MAT on each study day, so that results are not weighted towards participants with longer chemo blocks.

8.2.2 Sample Size

The study will enrol a minimum of 160 evaluable patients.

Considering that up to 20% of patients will be ineligible or not evaluable for the primary endpoint, the maximum enrolment for the trial will be 200 patients. This sample size will have at least 82% power – across plausible baseline percentages - to detect a 20% increase^{78,80} in complete or partial acute phase CIV control at a 0.05 significance level. Power is exactly 82% for an increase in complete or partial CIV control from 40% to 60%. An increase in acute phase CIV control of 10% or more is considered to be clinically significant. As the comparison is between standard antiemetics plus olanzapine vs. standard antiemetics plus placebo, we expect and are only interested in increases in the rate of control. Therefore, power is based on a 1-sided, two-sample Z-test of proportions with α level of 0.05. With 80 evaluable patients per arm, power is 80% for the following pairs of control group and intervention group values: an increase from 30% to 49%, an increase from 50% to 69% and an increase from 70% to 86%. Power for analyses of secondary CIV endpoints during the delayed and overall phases is similar to that for the primary analysis.

9.0 ADVERSE EVENTS

9.1 Evaluation Criteria

9.1.1 Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize version 4.0 of the CTCAE of the National Cancer Institute (NCI) for toxicity and performance reporting (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Toxicities are to be reported on the appropriate data collection forms.

9.1.2 Data Safety Monitoring Board (DSMB)

An interdisciplinary and interprofessional DSMB will be formed and will include a pediatric psychiatrist, a pediatric oncologist with HSCT experience, a pediatric pharmacist and a pediatric cardiologist. The DSMB will be informed of all SAEs and any grade 3-4 non-hematological AEs within 72 hours of PI notification and will be sent an AE summary quarterly. The information received by the DSMB will be unblinded.

The DSMB will meet quarterly by teleconference to review all AE data (including the PAERS data (the proportion of participants who experience QTc prolongation, neurological toxicity, suicidal ideation, depression, etc.), data on any seizure, depressed level of consciousness of CTCAEv4 Grade 4 of uncertain etiology and any SAE occurring during the acute and delayed phases). They will also meet on receipt of notification of any non-hematological grade 3-4 AEs that are, in the opinion of the site PI, unexpected and at least possibly related to the study drug, and/or as needed to ensure participant safety and study integrity. Based on this information, the DSMB will provide timely direction to the Trial Steering Committee regarding the need for protocol revision including olanzapine dose adjustment. Additional information can be found in the Olanzapine RCT SickKids DSMB Charter.

9.1.3 Premature Study Termination or Suspension

This study may be temporarily suspended or prematurely terminated if sufficient reasonable cause is identified by the DSMB or the PI. If the study is prematurely terminated or suspended, the coordinating PI will promptly inform the PI of each site, and Health Canada/the FDA. Each site's PI will inform their local REB/IRB. Possible reasons for study suspension or premature termination include, but are not limited to: determination of unexpected, significant or unacceptable risk to participants; inadequate compliance with protocol requirements; or determination of futility of enrolment into the trial.

The study may resume once issues leading to study suspension have been addressed to the satisfaction of the DSMB, sites' REBs/IRBs, Health Canada and the FDA.

9.2 Reporting Requirements

9.2.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents.

9.2.2 Adverse Event Reporting

Routine reporting is accomplished via the Adverse Event (AE) log and Case Report Form (CRF). For this study, routine reporting will include all serious adverse events (SAEs) as defined below and non-hematological grade 3-4 AEs.

Grade 3-4 AEs that are non-hematological are entered on the AE log, described in the AE CRF and, if in the opinion of the site PI are unexpected and at least possibly related to the study drug, reported to the DSMB within 72 hours of awareness.

9.2.3 Serious Adverse Events (SAEs)

Any AE that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect is considered an SAE. Each site is responsible for reporting SAEs to their respective Research Ethics Board in accordance with local reporting requirements.

9.2.4 SAE Reporting

All SAEs must be reported to the study PI, Lee Dupuis at lee.dupuis@sickkids.ca within 24 hours of awareness. The PI is available via e-mail or fax.

SAEs are recorded on the Study AE form and described using the AE CRF.

The study PI will report SAEs to The Hospital for Sick Children's Research ethics Board and the University of California, San Francisco Institutional Review Board according to their AE reporting requirements. All external (off-site), unexpected SAEs deemed to be at least possibly related to the study medication will be reported to the University of California, San Francisco and the Hospital for Sick Children within 10 working days or, for death or life-threatening events, within 5 working days. In the latter case, a follow-up report must be filed within 8 calendar days. The PI and global sponsor will also distribute expedited reports to each site investigator for submission to their local ethics board within 15 days.

SAEs will be managed according to The University of California, San Francisco's and the Hospital for Sick Children's standard clinical management practices. The DSMB will be informed by telephone, fax or email of all SAEs, within 72 hours of PI notification. Dr. Christopher Dvorak will provide expedited reports of SAEs to the FDA according to applicable guidelines and regulations for US study sites. Dr. Lee Dupuis will provide these reports to Health Canada for Canadian sites.

Administration of study drug will cease if patients experience any SAE (for example a seizure or severe allergic reaction) thought to be attributable to olanzapine as determined by their primary physician.

11.0 RECORDS AND REPORTING

11.1 Case Report Forms and Submissions

Institutions will be provided with electronic copies of data collection forms, PAERs (Appendix IV), PeNAT (Appendix V), and MAT (Appendix VI) to print, complete and to give to participant to complete. The completed forms will then be sent electronically to the coordinating site (SickKids) for data review, quality assurance, and data entry.

Sites will maintain and archive study material for 25 years in order to harmonize with Health Canada regulations.

11.2 Research Ethics Board

Study procedures will not be initiated until local REB/IRB and Health Canada/FDA have approved the study. Patients or patient representatives will consent to the study prior to study activities initiating. At any time, a patient may withdraw consent to all or parts of the study.

11.3 Confidentiality

All participant-participating related information including Case Report Forms, laboratory values, and questionnaires will be kept strictly confidential. All records will be kept in a secure, locked storage unit only accessible by access card, and only research staff will have access to the records. Participants will be identified only by means of a coded study number. The local study database will identify participants by numeric codes only, and will be in a password protected folder on a SickKids shared drive.

Upon request, source documents will be made available to The Hospital for Sick Children, the study sponsor, monitor, and applicable regulatory agencies.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study Monitoring Plan

Due to geographical issues, resources, and personnel, the monitoring plan for this study is two-fold: in-person and remote. All monitoring of sites within Canada will be completed by a designated study staff member from The Hospital for Sick Children. Additionally, this same monitor will complete all remote monitoring within the United States. Domestic, in-person or remote monitoring will be completed by a designated study site staff member from the coordinating center (The Hospital for Sick Children or UCSF). A study monitor will visit (in-person or remote) each participating site at least twice during the lifespan of the study: once shortly after site activation and again for the site close-out visit.

This plan will identify key documentation that the monitor will verify both on-site and remotely. This process ensures that trial related data are accurate, complete, and verifiable from source documents and that participant rights and safety are protected. The monitor will verify compliance with the regulatory requirements, protocol, GCP, study specific procedures, and participant eligibility. In addition to evaluating the reported data for accuracy and completeness, the monitor will identify any trends in data that may be indicative of insufficient documentation or protocol deviations.

The principal investigator will supervise the training of all study personnel at each site with respect to study procedures. Site personnel are responsible for the maintenance of their own site's Regulatory Binder and Essential Documents.

Addition information can be found in the detailed Monitoring Plan.

12.2 Data Monitoring

The Hospital for Sick Children will be responsible for the auditing of completed forms sent from all other participating sites, prior to data entry. All queries will be responded to in a timely matter. Any queries that remain outstanding for greater than 30 days will be forwarded to the Trial Steering Committee.

12.3 Trial Steering Committee

The Principal Applicant, Co-Applicants and the Clinical Research Manager at the coordinating site will constitute the Trial Steering Committee. The Steering Committee will teleconference monthly to review site activation and patient accrual, to review serious, unexpected, drug-related adverse events and to resolve issues regarding study procedures.

Teleconferences will be held monthly with the Project Manager at the coordinating site and study team members at all participating sites. Training regarding study procedures will be updated and issues regarding study procedures will be discussed at these teleconferences.

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14.0 APPENDICES

APPENDIX I: Examples of anti-psychotic drugs

- Aripiprazole
- Asenapine maleate
- Clozapine
- Iloperidone
- Lurasidone hydrochloride
- Olanzapine, Olanzapine pamoate
- Paliperidone
- Quetiapine fumarate
- Risperidone
- Ziprasidone

APPENDIX II: Drugs which may interact with olanzapine via CYP1A2 induction or inhibition

Note: This list is not exhaustive.

CYP1A2 Inducers	CYP1A2 Inhibitors
Carbamazepine	Amiodarone
Phenobarbital	Cimetidine
Rifampin	Ciprofloxacin
Ritonavir	Clarithromycin
	Erythromycin
	Fluvoxamine
	Isoniazid
	Mexiletine
	Sildenafil

APPENDIX III: Definition of HSCT Outcomes

1. Time to neutrophil engraftment:

- the first of 2 consecutive days post-HSCT that an absolute neutrophil count $\geq 0.5 \times 10^9/L$ is achieved

2. Acute Graft-vs-Host Disease: Modified Glucksberg scale

(Bone Marrow Transplantation 1995;15, 825–82)

aGVHD Grade	Skin	Liver	Gut
I	1-2	0	0
II	1-3	1	1
III	2-3	2-3	2-3
IV	4	4	4

2.1 Organ Staging – Skin

1	Maculopapular rash < 25% BSA*
2	Maculopapular rash 25 to 50% BSA
3	Generalized erythroderma
4	Erythroderma with bullae and desquamation

*BSA: body surface area

Contributions of body components to BSA - Age independent Components:

Anterior trunk: 13% Posterior trunk & buttocks: 18%

Upper limbs: 10% each Feet: 5% each

Contributions of body components to BSA - Age dependent:

	< 1 yr	1 yr	5 yr	10 yr	15 yr
Head	19%	17%	13%	11%	9%
Thigh	5.5%	6.5%	8%	8.5%	9%
Lower leg	5%	5%	5.5%	6%	6.5%

2.2 Organ Staging – Liver

1	Total bilirubin > 34 and < 54 µmol/L
2	Total bilirubin ≥ 52 and < 103 µmol/L
3	Total bilirubin ≥ 103 and < 256 µmol/L
4	Total bilirubin ≥ 256 µmol/L

2.3 Organ Staging – Gut. Note: Use mL/m²/day value until value exceeds that provided in mL/day.

	Stool volume	
	mL/m ² /day	mL/day
1	> 280 and ≤ 555	> 500 and ≤ 1000
2	> 555 and ≤ 883	> 1000 and ≤ 1500
3	> 833	> 1500
4	Severe abdominal pain ± ileus	

3. Hepatic Veno-occlusive disease: modified Seattle criteria (Bone Marrow Transplant. 1992;10:197-214)

Presence, before day 20 after transplant of at least two of the following features:

- Bilirubin ≥ 2 mg/dl
- Hepatomegaly and right upper quadrant pain
- Ascites and/or unexplained weight gain > 2%

APPENDIX IV: Modified PAERs – Parent and Youth Reports – English*

Study Site #: _____

Study Patient # _____

Adverse Event Rating Scale – Parent Report						
Today's date: _____ (dd/mm/yy)						
This form asks about problems that your child or teen may have experienced recently. Please indicate how much the following things have bothered or been a problem for her/him by checking the appropriate box. Please answer every question.						
If present, please indicate to what extent it was bothersome or a problem by placing a <u>checkmark</u> in the appropriate column...						
#	Please answer every question	Not present	A little bit bothersome / a <u>mild</u> problem	Somewhat bothersome / a <u>moderate</u> problem	Quite bothersome / a <u>severe</u> problem	Very bothersome / an <u>extreme</u> problem
1	Trouble thinking clearly					
2	Muscle cramps or spasm					
3	Feeling withdrawn or numb					
4	Trouble paying attention					
5	Muscle weakness					
6	Trouble falling or staying asleep					
7	Nervous, tense, uptight					
8	Trying to hurt self					
9	Muscle tremors or shaking					
10	More thirsty					
		Not present	A little bit bothersome / a <u>mild</u> problem	Somewhat bothersome / a <u>moderate</u> problem	Quite bothersome / a <u>severe</u> problem	Very bothersome / an <u>extreme</u> problem
11	Headache					
12	Racing or jumbled thoughts					
13	Irritable / in a bad mood					
14	Feeling restless or keyed up					
15	Tired all the time					

		Not present	A little bit bothersome / a <u>mild</u> problem	Somewhat bothersome / a <u>moderate</u> problem	Quite bothersome / a <u>severe</u> problem	Very bothersome / an <u>extreme</u> problem
16	Dizzy or light headed					
17	Brittle mood/easily upset					
18	Sleeping too much					
19	Sad or low mood/unhappy					
20	Can't sit or stand still					
		Not present	A little bit bothersome / a <u>mild</u> problem	Somewhat bothersome / a <u>moderate</u> problem	Quite bothersome / a <u>severe</u> problem	Very bothersome / an <u>extreme</u> problem
21	Drowsy or out of it					
22	Not interested / no enthusiasm					
23	Angry or hostile					
24	Thinking about or wanting to hurt self					
25	Chest pain					
26	More hungry					
27	Waking up tired					
28	Muscles stiff or tight					
29	Dry mouth					
30	Other:					
31	Other:					
32	Other:					

Study Site #: _____

Study Patient # _____

Adverse Event Rating Scale - Youth self-report						
Today's date: _____ (dd/mm/yy)						
This form asks about problems that you have experienced recently. Please indicate how much the following things have bothered or been a problem for you by checking the appropriate box. Please answer every question.						
If present, please indicate to what extent it was bothersome or a problem by placing a <u>checkmark</u> in the appropriate column...						
#	Please answer every question	Not present	A little bit bothersome / a <u>mild</u> problem	Somewhat bothersome / a <u>moderate</u> problem	Quite bothersome / a <u>severe</u> problem	Very bothersome / an <u>extreme</u> problem
1	Trouble thinking clearly					
2	Muscle cramps or spasm					
3	Feeling withdrawn or numb					
4	Trouble paying attention					
5	Muscle weakness					
6	Trouble falling or staying asleep					
7	Nervous, tense, uptight					
8	Trying to hurt self					
9	Muscle tremors or shaking					
10	More thirsty					
		Not present	A little bit bothersome / a <u>mild</u> problem	Somewhat bothersome / a <u>moderate</u> problem	Quite bothersome / a <u>severe</u> problem	Very bothersome / an <u>extreme</u> problem
11	Headache					
12	Racing or jumbled thoughts					
13	Irritable / in a bad mood					
14	Feeling restless or keyed up					
15	Tired all the time					

		Not present	A little bit bothersome / a <u>mild</u> problem	Somewhat bothersome / a <u>moderate</u> problem	Quite bothersome / a <u>severe</u> problem	Very bothersome / an <u>extreme</u> problem
16	Dizzy or light headed					
17	Brittle mood/easily upset					
18	Sleeping too much					
19	Sad or low mood/unhappy					
20	Can't sit or stand still					
		Not present	A little bit bothersome / a <u>mild</u> problem	Somewhat bothersome / a <u>moderate</u> problem	Quite bothersome / a <u>severe</u> problem	Very bothersome / an <u>extreme</u> problem
21	Drowsy or out of it					
22	Not interested / no enthusiasm					
23	Angry or hostile					
24	Thinking about or wanting to hurt self					
25	Chest pain					
26	More hungry					
27	Waking up tired					
28	Muscles stiff or tight					
29	Dry mouth					
30	Other:					
31	Other:					
32	Other:					

* Versions of the PAERs in multiple languages will be made available to all participating sites

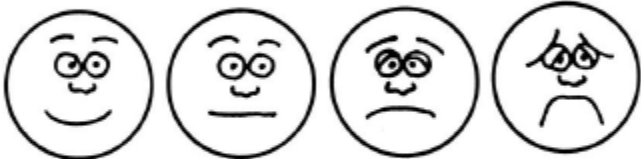
Study ID # _____

Date: _____

Patient Diary

Nausea

- Use the faces to describe how bad your nausea or _____ is. Check the box that describes how you feel.
- Write down the time that you rated your nausea.



1 2 3 4

Time					
Other Times	Morning				
	Bedtime				

Vomiting

Time of Vomit or Retch		

- Write down the time of each vomit, dry heave, and _____.
- If each vomit or dry heave is more than one minute apart, write down the time.

Less than 13 yo optional diary

Study ID #: _____

Vomiting Patient Diary

Date: _____

Vomiting

Time of Vomit or Retch		

- Write down the time of each vomit, dry heave, and _____.
- If each vomit or dry heave is more than one minute apart, write down the time.

<13 ans journal optionnel

Numéro de l'étude _____

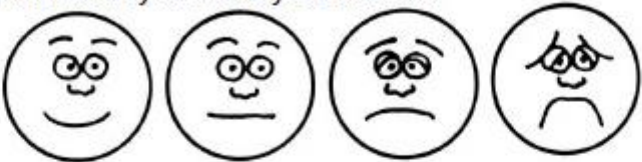
<13 años diario opcional

Study ID #: _____ Date: _____

Patient Diary

Nausea

- Use the faces to describe how bad your nausea or _____ is. Check the box that describes how you feel.
- Write down the time that you rated your nausea.



1 2 3 4

Time					
Other Times	Morning				
	Bedtime				

Vomiting

Time of Vomit or Retch		

- Write down the time of each vomit, dry heave, and _____.
- If each vomit or dry heave is more than one minute apart, write down the time.

MAT Nausea

- Complete before bedtime.

In the 24 hours since chemotherapy, did you have any nausea?	Yes ☐ No ☐ (Select one)
If you had nausea, please circle or enter the number that most closely resembles your experience. How much nausea did you have in the last 24 hours?	 (Write the number in this box)

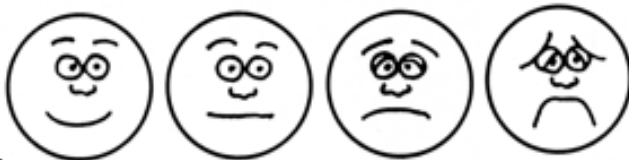
0 1 2 3 4 5 6 7 8 9 10
None As much as possible

13-17.9 yo optional patient diary

Journal du patient

Nausée

- Sers-toi des visages pour décrire à quel point tu te sens nauséux ou _____. Coche la case qui représente ce que tu ressens.
- Note à quel moment tu as évalué ta nausée.



Moment		1	2	3	4
Autres moments	Lever				
	Coucher				

Vomissements

Heure du vomissement ou du haut-le-cœur		

- Note l'heure de chaque vomissement, effort pour vomir et _____.
- S'il se passe plus d'une minute entre chaque vomissement ou effort pour vomir, note l'heure.