



**Fixed-Dose Combination of Netupitant and Palonosetron (Akynzeo®) in the Treatment of  
Refractory Chemotherapy-Induced Nausea and Vomiting**

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**Study Agent:** Netupitant/Palonosetron (Akynzeo®)

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### Signature Page

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

#### UCSD Principal Investigator

\_\_\_\_\_  
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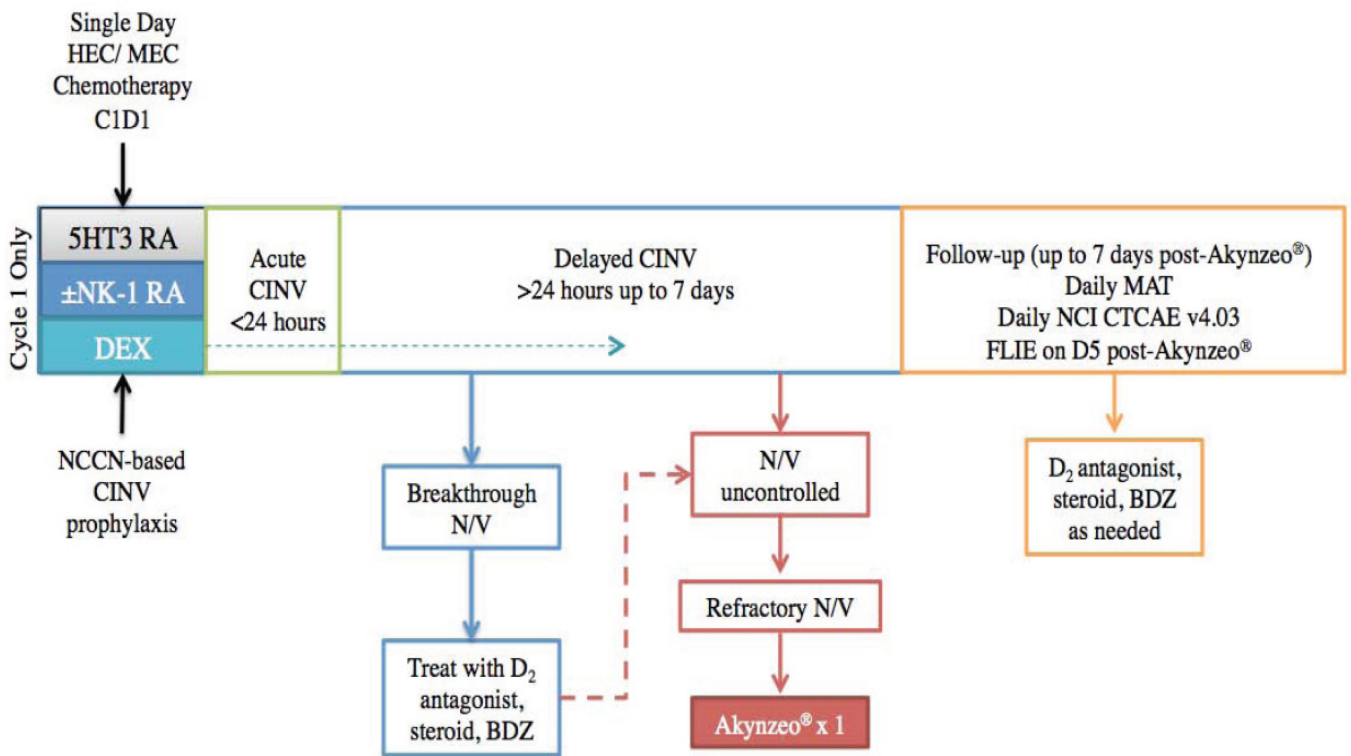
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## LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
CINV	Chemotherapy-Induced Nausea & Vomiting
CTCAE	Common Terminology Criteria for Adverse Events
CTRI	Clinical and Translational Research Institute
CYP3A4	Cytochrome P450
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EKG	Electrocardiogram
FDA	Food and Drug Administration
FLIE	Functional Living Index for Emesis
HEC	Highly Emetogenic Chemotherapy
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protections Program
ICH	International Conference on Harmonization
IDS	Investigational Drug Services
IQR	Interquartile Range
IRB	Institutional Review Board
MASCC	Multinational Association of Supportive Care in Cancer
MEC	Moderately Emetogenic Chemotherapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK1	Neurokinin-1
SAE	Serious Adverse Event
SD	Standard Deviation
5-HT <sub>3</sub>	5-hydroxytryptamine-3

**STUDY SCHEMA**



**STUDY SUMMARY**

<b>Title</b>	Fixed-Dose Combination of Netupitant and Palonosetron (Akynzeo®) in the Treatment of Refractory Chemotherapy-Induced Nausea and Vomiting
<b>Short Title</b>	Akynzeo® in the Treatment of Refractory CINV
<b>Phase</b>	II
<b>Methodology</b>	Single-arm, single-center, open-label study
<b>Study Duration</b>	The anticipated total study duration is 24 months from fully-executed contract and IRB approval. Individual subject participation is limited to approximately 1 week.
<b>Study Center(s)</b>	UC San Diego (UCSD) Moores Cancer Center UCSD Medical Center - La Jolla
<b>Objectives</b>	<p><b>Primary:</b> To determine the feasibility of using a fixed-dose combination of netupitant and palonosetron (Akynzeo®) in the treatment of refractory CINV. For this study, <b>refractory CINV</b> is defined as nausea and/or vomiting that occurs after the first cycle of cancer targeted therapy despite guideline-based prophylaxis and after first-line rescue medication with either a dopamine receptor antagonist, steroid, and/or benzodiazepine.</p> <p><b>Hypothesis:</b> Feasibility, defined as more than 70% of selected study subjects completing all study related procedures, will be achieved.</p> <p><b>Secondary:</b></p> <ul style="list-style-type: none"> <li>• To evaluate the occurrence of adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.<sup>10</sup></li> <li>• To evaluate complete response defined as no emesis and no use of rescue medication for 5 days after Akynzeo® administration.</li> <li>• To characterize 24-hour intervals of CINV using the MASCC Antiemesis Tool (MAT).<sup>11</sup></li> <li>• To evaluate 5-day health related quality of life recall using the Functional Living Index for Emesis (FLIE) scale.<sup>12</sup></li> <li>• To evaluate healthcare resource utilization as defined by the number of emergency room visits, hospitalizations, and infusion center visits encounters regarding signs/symptoms associated with CINV over the seven-day study period.</li> <li>• To evaluate the occurrence of refractory CINV using CINV risk assessment at follow up day 7 compared to treatment day 1.</li> </ul> <p><b>Exploratory:</b> To determine patient preference for use of Akynzeo® for future planned chemotherapy utilizing a five-point Likert scale</p>
<b>Number of Subjects</b>	50
<b>Diagnosis and Main</b>	Patients who have histologically-confirmed cancer, and confirmed refractory CINV will be eligible



**Inclusion Criteria**

**Inclusion Criteria:**

1. Adults greater than or equal to 18 years old.
2. Must have a histologically-confirmed cancer diagnosis.
3. Must have refractory CINV defined as nausea and/or vomiting that occurs after the first cycle of cancer targeted therapy despite guideline-based prophylaxis and after first-line rescue medication with either a dopamine receptor antagonist, steroid, and/or benzodiazepine.
4. Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2.
5. Life expectancy greater than 3 months.
6. Corrected serum calcium level less than or equal to 10.5 mg/dL.
7. Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 14 days following completion of therapy.
  - A) A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
    - i) Has not undergone a hysterectomy or bilateral oophorectomy; or
    - ii) Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has not had menses at any time in the preceding 12 consecutive months)
8. Women of child-bearing potential must have a negative pregnancy test prior to initiating study treatment.
9. Ability to understand and willingness to sign a written informed consent.

**Exclusion Criteria:**

1. Patients with QTc interval greater than 450 ms.
2. Patients with a known hypersensitivity reaction to 5-HT<sub>3</sub> receptor antagonists or NK1 receptor antagonists.
3. Patients who have taken any medication classified as a strong CYP3A4 inducer within one week of Study Day 1 or 5 half-lives (whichever is longer) or use of a strong or moderate CYP3A4 inhibitor within one week of Study Day 1 or 5 half-lives (whichever is longer) (see Appendix 2).
4. Patients with severe hepatic impairment as defined as AST/ALT greater than three times the upper limit of normal, and/or total bilirubin greater than 3 mg/dL, and/or Child-Pugh score >9.
5. Patients with severe renal impairment defined as creatinine clearance of 15-29 mL/min and/or diagnosed with Stage 4 chronic kidney disease.
6. Patients with end-stage renal disease defined as creatinine clearance of <15mL/min and/or diagnosed with Stage 5 chronic kidney disease.

	<p>7. Pregnant or lactating females are excluded from enrollment on this trial.</p> <p>8. Patients unable to swallow oral medications.</p> <p>9. Any other condition that, in the opinion of the investigator, may impact the absorption of oral medications.</p>
<p><b>Study Product(s), Dose, Route, Regimen</b></p>	<p>Subjects will be allowed to participate only once in the study. Study Day 1 will be the day of Akynzeo® dosing. Subjects will receive a single capsule of Akynzeo® (300 mg of netupitant and 0.5 mg of palonosetron) on Study 1</p>
<p><b>Duration of administration</b></p>	<p>Study drug (Akynzeo®) is an oral fixed-dose combination of 300 mg of netupitant and 0.5 mg of palonosetron. Akynzeo® will be administered once as an oral capsule and will be supplied as 300 mg netupitant/0.5 mg palonosetron hard gelatin capsules with a white body and caramel cap with “HE1” printed on the body.</p>
<p><b>Statistical Methodology</b></p>	<p>Ideally, a phase III placebo controlled trial would be completed to demonstrate the efficacy of Akynzeo® in the refractory CINV. However, data regarding pharmacologic interventions for refractory CINV are lacking. Furthermore, it is not established if intervening in the refractory CINV setting is practically feasible. Consequently, we believe a feasibility study is the necessary first step followed by a larger randomized trial.</p> <p><b>Primary outcome measures and sample size</b></p> <p>The proposed study is a prospective, single-center, feasibility trial. The primary aim of this study is feasibility – specifically feasibility will be defined as completion of all study procedures over seven days. For the primary aim, we assume an acceptable completion rate from strata of MEC/HEC or tumor types of all study-related procedures would be at least 70%. Assuming a true completion rate of 85%, a sample size of 50 patients would have an 80% power to detect an absolute difference of 15% at Type I error 0.05.</p> <p><b>Secondary aims</b></p> <p>Secondary outcome measures including (1) the evaluation of adverse events utilizing the NCI CTCATE v4.03,<sup>10</sup> (2) complete response (no emesis and no rescue medication use), (3) characterization of 24-hour CINV using the MAT,<sup>11</sup> (4) five-day health related quality of life utilizing the FLIE,<sup>12</sup> and (5) healthcare resource utilization (emergency room visits, hospitalizations, and infusion center visits over seven days).</p> <p>(1) Adverse events will recorded in detail and the number of events will be described using n and percent. The severity will be described using means (SD) and medians (IQR) of the adverse event grade (which ranges 0-5).</p> <p>(2) The proportion of patients experiencing complete response will be described with descriptive statistics (n and percent) as well as by using a one-sample confidence interval for proportions, applying the normal approximation to the binomial distribution. In addition, a one-sample z test for proportions will be used to determine if the complete</p>

	<p>response rate in this sample is significantly different than the 90% seen in previous studies.<sup>17</sup></p> <ol style="list-style-type: none"><li>(3) CINV will be analyzed using the MAT. The MAT consists of 8 distinct items, 4 of these items are binary and will be described using n and percents the other 4 items are continuous (ranging from 0-10) and will be described using mean and SD. Binary variables will also be described using one-sample confidence intervals for proportions (as described in #2 above) and continuous variables will be described using one-sample confidence intervals for means.</li><li>(4) Quality of life will be analyzed as a binary response, impact on quality of life vs no impact, a score of less than 54 on the FLIE domain scores and a score of less than 108 on the total score indicates an impact on quality of life. Each domain score, and the total score, will be analyzed separately using a 95% confidence interval to describe the proportion of participants with impacted QoL.</li><li>(5) Healthcare resource utilization will be assessed by recording the number of emergency room visits, hospitalizations (with length of stay), and infusion center visits. Each healthcare utilization will be categorized with respect to whether it was specifically related to nausea and vomiting during the seven-day follow up period. A table summarizing the number of each type of utilization related to nausea and vomiting will be provided.</li><li>(6) The occurrence of refractory CINV will be analyzed using CINV risk assessment at follow up day 7 compared to treatment day 1.</li></ol> <p>Patient demographic characteristics (age, sex, and patient reported race/ethnicity) will be described using standard descriptive statistics (n/% or mean/SD).</p> <p>As an exploratory aim, regression analysis will be used to develop a predictive model for CINV, based on age, sex, history of &gt;1 alcoholic beverage per day, history of motion sickness, history of hyperemesis gravidarum, and history of anxiety.</p>
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**SCHEDULE OF EVENTS**

	Screening	Treatment (Study Day 1)	Follow-Up (Study Day 2-3) <sup>2,5</sup>	Follow-Up (Study Day 4-7) <sup>2, 5</sup>
Informed consent	X			
Inclusion/exclusion criteria	X			
Demographics	X			
Medical and surgical history	X			
ECOG Performance Status	X			
Confirmed presence of refractory CINV	X			
Serum pregnancy test <sup>1</sup>	X			
Physical exam with vitals, weight <sup>7</sup>	X		per routine frequency	
Complete metabolic profile <sup>7</sup>	X		per routine frequency	
Complete blood count with differential, platelets <sup>7</sup>			per routine frequency	
EKG QTc evaluation	X <sup>7</sup>		X <sup>3</sup>	
Patient CINV risk factors		X		X
Akynzeo® dispensing and administration		X		
Patient medication diary		X		
Collect hospitalization and emergency room visit data		X	X	X
Concomitant medications	X	X	X	X
Adverse event monitoring		X	X	X
MASCC Antiemesis Tool <sup>8</sup> (MAT)	X	X	X	X
Functional Living Index for Emesis (FLIE) scale <sup>9</sup>	X	X		X <sup>4</sup>
Patient preference Likert-scale				X <sup>6</sup>

<sup>1</sup> Women of childbearing potential only

<sup>2</sup> Subjects will be monitored for a total of 6 days following Akynzeo® dosing

<sup>3</sup> QTc evaluation on Day 3±3 days with single EKG. If patient experiences worsening cardiac symptoms during the study, additional EKG(s) will be performed as clinically indicated

<sup>4</sup> Complete on Day 5 only

<sup>5</sup> Daily unless otherwise indicated. Daily safety assessment and hospitalization/ER visit information on Days 2-7 may occur via in-person visit or telephone call from a study team member. Subjects will also receive a daily reminder (via in-person visit or telephone call) to complete required questionnaires/diaries.

<sup>6</sup> Complete on Day 7 only

<sup>7</sup> EKG, laboratory and physical exam results obtained within 4 weeks prior to the informed consent date may be used to fulfill study requirements. EKG results may be obtained after screening processes yield positive refractory CINV.

<sup>8</sup> To be completed daily for 4 days after CINV prophylaxis or Akynzeo® dosing.

<sup>9</sup> To be completed on the 5<sup>th</sup> day after CINV prophylaxis or Akynzeo® dosing

## 1.0 BACKGROUND AND RATIONALE

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### 1.1 Treatment Guidelines for Chemotherapy-Induced Nausea & Vomiting (CINV)

Current treatment guidelines by the Multinational Association of Supportive Care in Cancer (MASCC), National Comprehensive Cancer Network (NCCN), and the American Society of Clinical Oncology (ASCO), have focused efforts on the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV). A standard approach for highly emetogenic chemotherapy (HEC) is to pretreat with a three-drug regimen, including a neurokinin-1 (NK1) receptor antagonist, a 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptor antagonist, and glucocorticoid. In contrast, moderately emetogenic chemotherapy (MEC) pretreatment usually includes a 5-HT<sub>3</sub> receptor antagonist and a glucocorticoid. These treatment modalities have focused on the acute (<24 hours) and delayed (>24 hours) phases of CINV. As an NCCN designated and ASCO QOPI cancer center, we follow guideline based recommendations for CINV prophylaxis.

### 1.2 Defining Breakthrough Versus Refractory CINV

Little is known about appropriate evidenced-based treatment of refractory CINV. Refractory CINV is distinct from breakthrough CINV. *Breakthrough* nausea and/or emesis can be defined as nausea and/or vomiting that occurs while on prophylactic antiemetics and/or requiring the use of rescue antiemetics.<sup>1</sup> Breakthrough CINV has also been described as nausea and/or vomiting occurring within 5 days of initial chemotherapy and after completion of appropriate prophylactic antiemetic agents.<sup>2</sup> In contrast, *refractory* CINV has been described as occurring during subsequent treatment cycles when prophylactic and rescue antiemetics are not effective.<sup>1,2</sup>

Evidence-based literature regarding treatment of refractory CINV is sparse and represents an unmet medical need. A case report has suggested potential palliation with an NK1 receptor antagonist, but in the non-CINV setting. A 27-year-old patient with breast cancer and meningeal metastases had an 18-month history of poorly controlled nausea/vomiting despite treatment of numerous antiemetics. After two doses of aprepitant 80 mg once daily, there was no recurrence of nausea/vomiting and no observed side effects.<sup>3</sup> In a retrospective study of cancer patients (n=33), olanzapine 5-10 mg daily was studied for the treatment of refractory nausea/vomiting regardless of the chemotherapy emetogenicity.<sup>4</sup> Refractory nausea and vomiting was defined as presence of symptoms after administration of both guideline-recommended CINV antiemetic prophylaxis and after first-line rescue medication.<sup>4</sup> The addition of olanzapine resulted in a 70% overall success rate, which did not differ between HEC and MEC regimens.<sup>4</sup>

### 1.3 Fixed Dose Combination of NK1 Receptor Antagonist and 5-HT<sub>3</sub> Receptor Antagonist

Akynzeo® is an oral capsule containing a fixed-dose combination of 300 mg of netupitant and 0.5 mg of palonosetron. Netupitant is a highly selective NK1 receptor antagonist and palonosetron is a long acting 5-HT<sub>3</sub> receptor antagonist. Palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy. Single-dose administration of Akynzeo®

in healthy subjects, results in peak plasma concentrations in about 5 hours. Mean elimination half-life in cancer patients was 80±29 hours for netupitant and 48±19 hours for palonosetron.<sup>5</sup> Three phase III clinical trials in over 2,500 chemotherapy-naïve patients evaluating Akynzeo® have recently been published for prevention of CINV over repeated cycles of both HEC and MEC regimens.<sup>6-8</sup> Akynzeo® was safe, well tolerated, and showed superiority in preventing CINV from HEC and MEC regimens. However, there is no published literature regarding the use of Akynzeo® for the treatment of refractory CINV.

The overwhelming majority of CINV studies have focused on prevention of nausea and/or emesis. However, 15-30% of patients continue to experience CINV despite receiving guideline-based CINV prophylaxis.<sup>7,8</sup> Refractory CINV represents a an unmet medical need and controlling refractory CINV has the potential to maximize cancer therapy, improve quality of life, and minimize costs associated with healthcare utilization.

## **2.0 STUDY OBJECTIVES**

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### **2.1 Primary**

To determine the feasibility of using a fixed dose combination of netupitant and palonosetron (Akynzeo®) in the treatment of refractory CINV. For this study, refractory CINV is defined as nausea and/or vomiting that occurs after the first cycle of cancer targeted therapy despite guideline-based prophylaxis and after first-line rescue medication with either a dopamine receptor antagonist, steroid, and/or benzodiazepine.

Hypothesis: Feasibility, defined as more than 70% of selected study subjects completing all study related procedures, will be achieved.

### **2.2 Secondary:**

- To evaluate the occurrence of adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.10
- To evaluate complete response defined as no emesis and no use of rescue medication for 5 days after Akynzeo® administration.
- To characterize 24-hour CINV using a modified MASCC Antiemesis Tool (MAT).<sup>11</sup> (**Appendix 1**)
- To evaluate 5-day health related quality of life recall using the Functional Living Index for Emesis (FLIE) scale.<sup>12</sup>
- To evaluate healthcare resource utilization as defined by the number of emergency room visits, hospitalizations, and infusion center visits encounters regarding signs/symptoms associated with CINV over the seven-day study period.
- To evaluate the occurrence of refractory CINV using CINV risk assessment at follow up day 7 compared to treatment day 1.

### **2.3 Exploratory:**

To determine patient preference for use of Akynzeo® for future planned chemotherapy utilizing a five-point Likert scale.

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### **3.0 PATIENT ELIGIBILITY**

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#### **3.1 Inclusion Criteria**

1. Adults greater than or equal to 18 years old.
2. Must have a histologically confirmed cancer diagnosis.
3. Must have refractory CINV defined as nausea and/or vomiting that occurs after the first cycle of cancer targeted therapy despite guideline-based prophylaxis and after first-line rescue medication with either a dopamine receptor antagonist, steroid, and/or benzodiazepine.
4. Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2.
5. Life expectancy greater than 3 months.
6. Corrected serum calcium level less than or equal to 10.5 mg/dL.
7. Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 14 days following completion of therapy.  
A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
  - a. Has not undergone a hysterectomy or bilateral oophorectomy; or
  - b. Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has not had menses at any time in the preceding 12 consecutive months)
8. Women of child-bearing potential must have a negative pregnancy test prior to initiating study treatment.
9. Ability to understand and willingness to sign a written informed consent.

#### **3.2 Exclusion Criteria**

1. Patients with QTc interval greater than 450 ms.
2. Patients with a known hypersensitivity reaction to 5-HT<sub>3</sub> receptor antagonists or NK1 receptor antagonists.
3. Patients who have taken any medication classified as a strong CYP3A4 inducer within one week of Study Day 1 or 5 half-lives (whichever is longer) or use of a strong or moderate CYP3A4 inhibitor within one week of Study Day 1 or 5 half-lives (whichever is longer) (see Appendix 2).
4. Patients with severe hepatic impairment as defined as AST/ALT greater than three times the upper limit of normal and/or, total bilirubin greater than 3 mg/dL, and/or Child-Pugh score >9.
5. Patients with severe renal impairment defined as creatinine clearance of 15-29 mL/min and/or diagnosed with Stage 4 chronic kidney disease.
6. Patients with end-stage renal disease defined as creatinine clearance of <15mL/min and/or diagnosed with Stage 5 chronic kidney disease.
7. Pregnant or lactating females are excluded from enrollment on this trial.
8. Patients unable to swallow oral medications.
9. Any other condition that, in the opinion of the investigator, may impact the absorption of oral medications.

## **4.0 TREATMENT PLAN**

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### **4.1 Subjects and Centers**

A total of 50 subjects, who are 18 years of age or older, have histologically confirmed cancer, confirmed refractory CINV as defined above, an ECOG performance status 0-2, and normal calcium level will be enrolled on this single-center, single-arm study.

### **4.2 Study Design**

This is a Phase II, single-center, single-arm, open-label, feasibility trial using a fixed dose combination of netupitant and palonosetron (Akynzeo®) in the treatment of refractory CINV. The primary aim of this study is feasibility, defined as 70% completion rate of all study procedures over 7 days

## **5.0 Description of Procedures**

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Eligible subjects will be identified in weekly palliative care patient triage meetings. Patients who are 18 years of age or older, have histologically confirmed cancer, and confirmed refractory CINV will be eligible.

After obtaining written informed consent and verifying that the study subject meets all eligibility criteria, the subject will be enrolled in the study through the UCSD Moores Cancer Center Clinical Trials Office. The study coordinator will educate the subject on how to complete the MASCC Antiemesis Tool (MAT), and FLIE scale after CINV prophylaxis. Subjects will be asked to complete the MAT on a daily basis for 4 days and then the FLIE on the 5<sup>th</sup> day after cancer treatment. Subjects will be allowed to participate only once in the study. Study Day 1 will be the day of Akynzeo® dosing. Subjects will receive a single capsule of Akynzeo® (300 mg of netupitant and 0.5 mg of palonosetron) on Study 1. Study drug may be taken with or without food. Subjects will complete a study drug diary to document date and time of Akynzeo® administration. On Study Day 1, the study coordinator will educate the subject on how to complete the written MASCC Antiemesis Tool, and FLIE scale, and medication diary for each day following the Study Day 1. An adequate number of copies of each subject questionnaire and diary will be provided to the subject on Study Day 1 for completion at home during the post-treatment observation portion of the study (Study Days 2-7) as needed.

### **5.1 Patient CINV Risk Factors**

Classifying CINV risk by chemotherapy type has provided a valuable framework for the development of international prophylactic antiemetic guidelines. However, considerable work has revealed a number of patient specific variables that may contribute to emetic risk. Therefore, antiemetic guidelines relying solely on emetogenicity of chemotherapy may potentially undertreat patients at higher individual emetic risk than what the chemotherapy alone suggests. CINV patient-related risk prediction models have been developed.<sup>13-15</sup> Based on data from these models, several key patient risk factors will be collected on Study Day 1 prior to Akynzeo® dosing including: age, sex, alcohol consumption, history and severity of previous CINV, history of morning sickness with pregnancy, history of motion sickness, less sleep the night before chemotherapy, and pre-chemotherapy anxiety.

During the post-treatment observation portion of the study, subjects will receive a daily phone call from a member of the study team to inquire about any adverse event that the subject may



be experiencing and whether they have had any hospitalizations or emergency room visits since the last contact. During these calls, the study team member will also remind the subject to complete the MASCC Antiemesis Tool and medication diary. On Study Day 5 only, the subject will also be instructed to complete the FLIE scale. The subject will be asked to return to clinic on Study Day 3 (+3 days) for a single EKG. Additional clinic visits, physical exams, or laboratory tests performed during the 7-day treatment and follow-up periods will be scheduled according to routine care and according to the subject's treating physician.

Subjects will be asked to return all completed and unused study materials, including subject diaries and questionnaires to a member of the study team at their next routine clinic visit.

A more detailed description of selected assessments is included in the Efficacy Measures and Safety Measures sections.

## 5.2 Removal of Subjects from Study/Study Treatment:

Study subjects may be removed from study treatment or follow-up at any time at their own request or at the discretion of the investigator for any of the following reasons:

- The subject's medical condition worsens or if rescue therapy for subject's CINV fails secondary interventions.
- The investigator believes that study participation is jeopardizing subject's safety.
- The investigator believes that other treatment options may be more beneficial.
- Helsinn or the FDA stops the research due to safety concerns.
- Subject non-compliance with study procedures and requirements.

If a study subject is withdrawn from study participation, the subject will be asked to complete the following study requirements:

- Return unused study materials, including subject diaries and questionnaires.

Discuss future medical care with the investigator

## 5.3 Future Directions

If feasibility is achieved on this study, then future plans would include analysis of secondary and exploratory objectives to determine if there are any trends towards a clinically-meaningful and plausible study endpoint, which would be further developed in a larger Phase II study. We have several key palliative care oncology collaborators, and ultimately plan to propose the Phase II concept through a cooperative group such as the [Palliative Care Research Cooperative Group](#) or the [Alliance in Clinical Oncology Trials](#) Symptom Intervention Committee, both of which Dr. Roeland is an active member.

## 5.4 Other Therapy

Akynzeo® should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. The plasma concentrations of CYP3A4 substrates can increase when co-administered with AKYNZEO. The inhibitory effect on CYP3A4 can last for multiple days.

Length of washout period will be one week prior to Day 1 and/or 5 half-lives whichever is longer for any drug that is a known strong CYP3A4 inducer and/or strong or moderate CYP3A4 inhibitor. A list of known *in vivo* strong CYP3A4 inducers and inhibitors is available from the U.S. Food and Drug Administration.<sup>16</sup> Strong CYP3A4 inducers include, but are not limited to, rifampin, St. John's wort, phenytoin, and efavirenz. Strong CYP3A4 inhibitors include, but are not limited to, ketoconazole, grapefruit juice, clarithromycin, and erythromycin. Use of any drug that is a known weak CYP3A4 inhibitor and/or a known CYP3A4 substrate is permitted. See Appendix 2 for a more comprehensive list of strong and moderate CYP3A4 inhibitors and strong CYP3A4 inducers.

Standard of care for routine CINV prophylaxis at the UCSD Moores Cancer Center follows NCCN guidelines. Routine CINV prophylaxis may be administered concomitantly throughout the 1-week treatment and follow-up period of this study. Patients receiving HEC are pretreated with a three-drug regimen, including an NK1 antagonist, 5-HT<sub>3</sub> receptor antagonist, and glucocorticoid. Patients receiving MEC receive a 5-HT<sub>3</sub> receptor antagonist and a glucocorticoid. Lastly, patients receiving low emetogenic chemotherapy do not receive any standard CINV prophylaxis. For all types of chemotherapy, use of routine breakthrough medication at UCSD, which includes a dopamine antagonist (i.e. prochlorperazine) and/or a benzodiazepine (i.e. lorazepam) will be permitted.

Unless there is a need for urgent intervention, additional medication for refractory CINV will be prohibited. This includes over-the-counter medications, medical marijuana, herbal supplements, and investigational agents for CINV. Other medications, which are considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator.

## **5.5 Efficacy Measures:**

### **5.5.1 Patient Medication Diary**

Subjects will be asked to record all oral and self-administered medications received while on study. This will include any rescue medications used to treat their CINV each day, as well as any vitamins, homeopathic/herbal remedies, nutritional supplements, over-the-counter analgesic medication use, and all other over-the-counter "as needed" medications. Subjects will complete this diary (Appendix 3) on the day of Akynzeo® treatment (Study Day 1) and daily during the post-treatment observation portion of the study (Study Days 2-7).

### **5.5.2 Multinational Association of Supportive Care in Cancer (MASCC) Antiemesis Tool® (MAT)**

The MAT is a validated tool to measure CINV in 24-hour intervals developed by members of Multinational Association for Supportive Care in Cancer (MASCC) to assist patients and oncology professionals in communicating accurately about the prevention and control of nausea and vomiting that may occur with chemotherapy.<sup>11</sup> The concept of the MAT is to provide an easy-to-use and easy-to-evaluate tool to assist in providing the best individual care to patients. Additionally, the tool will aid treatment centers in understanding the effectiveness of their antiemetic strategies. The MAT was first created and posted in 2004. It is now available in eleven languages, obtained by the standard forward/backward translation process. The MAT consists of eight items. Four of these items refer to the occurrence, duration, and frequency of acute nausea and vomiting, and four refer to the occurrence, duration, and frequency of delayed

nausea and vomiting. Dichotomous items are scored “0” (“No”) or “1” (“Yes”) and continuous variables as marked on the 0-10 scale. In total, there are 4 dichotomous variable items and 4 continuous variable items. There is no summing of items; instead, items are evaluated on their own in clinical practice. Each subject will complete a written form of the MAT at approximately the same time each day during the study. The MAT will be completed daily for 4 days after CINV prophylaxis and after Akynzeo® treatment (Study Day 1). Thereafter, it will be completed daily during the post-treatment observation portion of the study at the same time each day starting 24 hours from the time of previous questionnaire completion. English and Spanish versions of the MAT will be made available at study activation. Additional foreign translations will be performed as needed.

### **5.5.3 Functional Living Index Emesis (FLIE) Scale**

The FLIE is a validated patient-reported measure of the impact of CINV on daily life, which measures a 5-day recall. The FLIE is a short, self-administered instrument containing two domains, one for nausea (nine items) and one for vomiting (nine items). Responses to each question are rated on a 100mm visual analog scale that is scored on a one to seven-point scale as described in the FLIE scoring manual. A higher score indicates a better quality of life. Minimal or no impact of CINV on daily life will be defined as an average score of more than six on the seven-point scale (i.e. 108 total score or greater than 54 domain score).<sup>12</sup> The FLIE will be completed on the 5<sup>th</sup> day after CINV prophylaxis, and on the day of Akynzeo® treatment (Study Day 1). During the post-treatment observation portion of the study, the FLIE will be completed on Day 5 only. English and Spanish versions of the MAT will be made available at study activation. Additional foreign translations will be performed as needed.

### **5.5.4 Healthcare Utilization**

CINV healthcare utilization data including information on the number and location of any emergency room visits, hospitalizations, and infusion center visits will be obtained via phone interview assessment on a daily basis over the seven-day treatment and follow-up periods. Phone calls will reference time since last phone interview and review prior responses. Study subjects will be asked to report all symptoms and problems leading up to the health care contact. All non-UCSD emergency room visits, hospitalizations, or infusion center visits will be followed-up with a medical request to verify the symptoms and reasons for such contacts. Records will be reviewed by study staff, and PI will be consulted for any clarifications. The primary and multiple secondary reasons for emergency room visits, hospitalizations, or infusion center visits will be recorded.

### **5.5.5 Patient Preference**

On Study Day 7, subjects will be asked to complete a five-point Likert scale containing the question “On a scale of 1-5, how likely are you to ask your doctor for Akynzeo® to treat your refractory CINV in the future?” Questionnaire results will be used to determine patient preference for future use of Akynzeo® for refractory CINV.

## **6.0 Study Drug Regimens**

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Study drug (Akynzeo®) is an oral fixed-dose combination of 300 mg of netupitant and 0.5 mg of palonosetron. Akynzeo® will be administered once as an oral capsule and will be supplied as 300 mg netupitant/0.5 mg palonosetron hard gelatin capsules with a white body and caramel

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cap with "HE1" printed on the body. All study drug will be supplied by Helsinn, using the current marketed product. IDS will label the study drug with the drug name, study reference number and storage conditions. Study drug will be dispensed to the subject by UCSD Investigational Drug Services (IDS). IDS will be responsible for all study drug shipments and accountability. After refractory CINV is confirmed and all study-related procedures completed on Day 1, subjects will be instructed to take one Akynzeo® capsule. Subjects will be administered a single, oral fixed-dose combination of 300 mg of netupitant and 0.5 mg of palonosetron. Akynzeo® must be kept in a secure place under appropriate storage conditions, as specified on the label and in the Investigator's Brochure. All study drug will be stored in original containers until dispensed to the study patients.

If a patient vomits after taking their Akynzeo® dose within 12 hours and the capsule is expelled from the body intact, it will be considered a missed dose. The patient will be instructed to take a picture of the capsule (if possible) and contact the PI who will determine if the patient should repeat up to one additional dose of Akynzeo®. Any changes from the dosing schedule including missed doses should be recorded in a CRF.

### **6.1 Study Drug Requested Per Patient**

1 capsule (300 mg of netupitant and 0.5 mg of palonosetron) per patient

### **7.0 Safety Measures**

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A physical examination and complete metabolic profile will be assessed at screening to evaluate for the presence of any pre-treatment abnormalities and to confirm eligibility. Physical examination and laboratory testing to evaluate adverse effects that develop during the seven-day treatment and follow-up periods will be performed according to routine frequency for monitoring of the subject's cancer according to the treating oncologist.

Subjects will also be monitored for evidence of QTc interval changes at screening (an EKG will be required prior to Akynzeo® treatment on C2D1) and during the study treatment period on Study Day 3±3 days with a single EKG. If the patient experiences any worsening cardiac symptoms, including, but not limited to dizziness, shortness of breath, or chest pain, during the study period, additional EKG(s) will be performed as clinically indicated.

Daily safety assessments will be performed on the day of Akynzeo® treatment (Study Day 1), and daily during the post-treatment observation portion of the study (Study Days 2-7). All adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.10

### **8.0 Adverse events**

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An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Progression of the cancer under study or events that are unequivocally due to disease

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progression should not be reported as an AE during the study (unless it is considered to be drug related by the investigator).

## 8.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

Adverse events monitoring begins at the time of informed consent signature and ends within 30 days of the last administration of the study drug.

All patients experiencing an adverse event, at least possibly related to the drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any clinically significant abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

## 8.2 Severity

All adverse events will be graded according to the NCI CTCAE version 4.03<sup>10</sup>. The CTCAE v4.03<sup>10</sup> is available at <http://ctep.cancer.gov/reporting/ctc.html>

Per CTCAE v 4.03 when no predefined grading is available, the severity of an AE is graded as follows:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL\*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL\*\*.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.
- \*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- \*\*Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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### 8.3 Seriousness

A “serious” adverse event (SAE) is defined in regulatory terminology as any untoward medical occurrence that:

1. Results in death. If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
2. Is life-threatening. The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires in-patient hospitalization or prolongation of existing hospitalization.  
Note: Hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened does not constitute a serious adverse event.
4. Results in persistent or significant disability or incapacity.
5. Is a congenital anomaly/birth defect
6. Is an important medical event.
  - Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as SAE. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.

### 8.4 Relationship

The relationship to the IP of each AE/SAE will be evaluated by the investigator using the following levels:

- **Not related:** The temporal relationship of the clinical event to the administration of IP makes a casual relationship unlikely; and other drugs, therapeutic intervention or underlying conditions provide a sufficient explanation for the observed event.
- **Related:** The temporal relationship of the clinical event to the administration of the IP makes a casual relationship possible; and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the observed event. A clear-cut temporal association with improvement on cessation of the study drug or recurrence upon re-challenge may also be observed

### 8.5 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in the current known adverse events listed in the agent clinical experience section of this protocol and Akynzeo prescribing information.

### 8.6 Reporting Requirements for Adverse Events

#### 8.6.1 Expedited Reporting

- A. The **Principal Investigator** must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- B. The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of “any unanticipated problems involving risk to subjects or others” (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

**C.** The **FDA** must be notified according to the following timelines:

- within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

**D.** A copy of all SAEs will be submitted to **Helsinn's safety designee** using the approved local regulatory form within 24 hours of the Principal Investigator's awareness by email ([Drug-Safety@Helsinn.com](mailto:Drug-Safety@Helsinn.com)) or fax (732-744-1089).

### 8.6.2 Routine Reporting Requirements

- A.** The **UCSD HRPP** must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.
- B.** The **FDA** must be notified of all non-serious adverse events annually at the time of the annual report.
- C.** **Helsinn** will be notified of all non-serious adverse events in summary or line-item form upon Helsinn's request and at the conclusion of the study.

### 8.6.3 Pregnancy Reporting Requirements

The **Principal Investigator** must be notified within 24 hours of any pregnancies occurring in a female patient or a female partner of a male patient along with pregnancy outcomes. Elective abortions without complications should not be considered adverse events unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered a significant adverse event. Spontaneous abortions should always be reported as significant adverse events.

The Investigator should follow-up with the study patient or the female partner of the study patient until delivery or termination of pregnancy, even if the patient was withdrawn from the clinical study or the clinical study was completed. Helsinn will be informed of all pregnancy outcomes using the contact information provided above.

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## 9.0 Statistical Analysis

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### 9.1 Study Design

Ideally, a phase III placebo controlled trial would be completed to demonstrate the efficacy of Akynzeo® in the refractory CINV. However, data regarding pharmacologic interventions for refractory CINV are lacking. Furthermore, it is not established if intervening in the refractory CINV setting is practically feasible. Consequently, we believe a feasibility study is the necessary first step followed by a larger randomized trial.

### 9.2 Primary outcome measures and sample size

The proposed study is a prospective, single-center, feasibility trial. The primary aim of this study is feasibility – specifically feasibility will be defined as completion of all study procedures over seven days. For the primary aim, we assume an acceptable completion rate from strata of MEC/HEC or tumor types of all study-related procedures would be at least 70%. Assuming a true completion rate of 85%, a sample size of 50 patients would have an 80% power to detect an absolute difference of 15% at Type I error 0.05.

### 9.3 Secondary aims

Secondary outcome measures including (1) the evaluation of adverse events utilizing the NCI CTCATE v4.03,<sup>10</sup> (2) complete response (no emesis and no rescue medication use), (3) characterization of 24-hour CINV using the MAT,<sup>11</sup> (4) five-day health related quality of life utilizing the FLIE,<sup>12</sup> and (5) healthcare resource utilization (emergency room visits, hospitalizations, and infusion center visits over seven days).

- (1) Adverse events will be recorded in detail and the number of events will be described using n and percent. The severity will be described using means (SD) and medians (IQR) of the adverse event grade (which ranges 0-5).
- (2) The proportion of patients experiencing complete response will be described with descriptive statistics (n and percent) as well as by using a one-sample confidence interval for proportions, applying the normal approximation to the binomial distribution. In addition, a one-sample z test for proportions will be used to determine if the complete response rate in this sample is significantly different than the 90% seen in previous studies.<sup>17</sup>
- (3) CINV will be analyzed using the MAT. The MAT consists of 8 distinct items, 4 of these items are binary and will be described using n and percents the other 4 items are continuous (ranging from 0-10) and will be described using mean and SD. Binary variables will also be described using one-sample confidence intervals for proportions (as described in #2 above) and continuous variables will be described using one-sample confidence intervals for means.
- (4) Quality of life will be analyzed as a binary response, impact on quality of life vs no impact, a score of less than 54 on the FLIE domain scores and a score of less than 108 on the total score indicates an impact on quality of life. Each domain score, and the total score, will be analyzed separately using a 95% confidence interval to describe the proportion of participants with impacted QoL.
- (5) Healthcare resource utilization will be assessed by recording the number of emergency room visits, hospitalizations (with length of stay), and infusion center visits. Each healthcare utilization will be categorized with respect to whether it was specifically related to nausea and vomiting during the seven-day follow up period. A table summarizing the number of each type of utilization related to nausea and vomiting will be provided.



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- (6) The occurrence of refractory CINV will be analyzed using CINV risk assessment at follow up day 7 compared to treatment day 1.

Patient demographic characteristics (age, sex, and patient reported race/ethnicity) will be described using standard descriptive statistics (n/% or mean/SD).

As an exploratory aim, regression analysis will be used to develop a predictive model for CINV, based on age, sex, history of >1 alcoholic beverage per day, history of motion sickness, history of hyperemesis gravidarum, and history of anxiety.

#### **9.4 Data and Safety Collection and Monitoring**

All analyses will be conducted using the latest version of R (R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org/>) or SAS (SAS Institute, Cary, NC). The study team will provide support for data monitoring and cleaning.

Records and data to be obtained from the study subjects are detailed above in the Schedule of Events. Subject outcome information will be documented in the electronic medical record and subject's research record. Data for this study will be entered into a password-protected set of electronic case report forms via the Velos eResearch web-based system. Velos eResearch is an integrated software system for managing clinical trials. This system supports several clinical trial functions, including electronic case report forms, tracking and scheduling of subject visits and events, and study reporting. The software links to the UCSD Health System's Epic Electronic Medical Record System to provide improved information and integration for clinical research projects. A robust support team assists investigators in implementing protocols and calendars and building electronic case report forms. Velos provides automated data export procedures for designated users into Excel, and then transferred into SAS and R. Access to the Velos database for this study will be limited to those users required to perform study-specific functions such as data entry and monitoring. A designated study coordinator from the UCSD Moores Cancer Center Clinical Trials Office will be responsible for entering all study data.

In addition to adverse event monitoring and clinical oversight by the principal investigator and co-investigators, the clinical trials office internal monitor and/or a study team member will perform quality assurance of the study. Monitoring will occur once every 3-6 months based upon rate of subject enrollment.

This study will use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. It will be left to the Investigator's clinical judgment whether or not an adverse event is related and of sufficient severity to require the subject's removal from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event.

If the subject was permanently withdrawn from the study or investigational product due to a serious adverse event, the Investigator will notify the IRB of serious adverse events occurring at the site and other adverse event reports received, in accordance with local procedures. Subsequent review of serious, unexpected and related adverse events by the PI, DSMB, IRB, and/or Helsinn may also result in suspension of further trial interventions/administration of study agent at a site. The PI and/or Helsinn retains the authority to suspend additional enrollment for the entire study as applicable. All serious adverse events must be reported within 1 working day of discovery or notification of the event. Serious adverse events will be collected

throughout the study period, beginning with the signing of the informed consent through study completion. For all collected AEs, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories of definitely related, probably related, possibly related, unlikely and unrelated.

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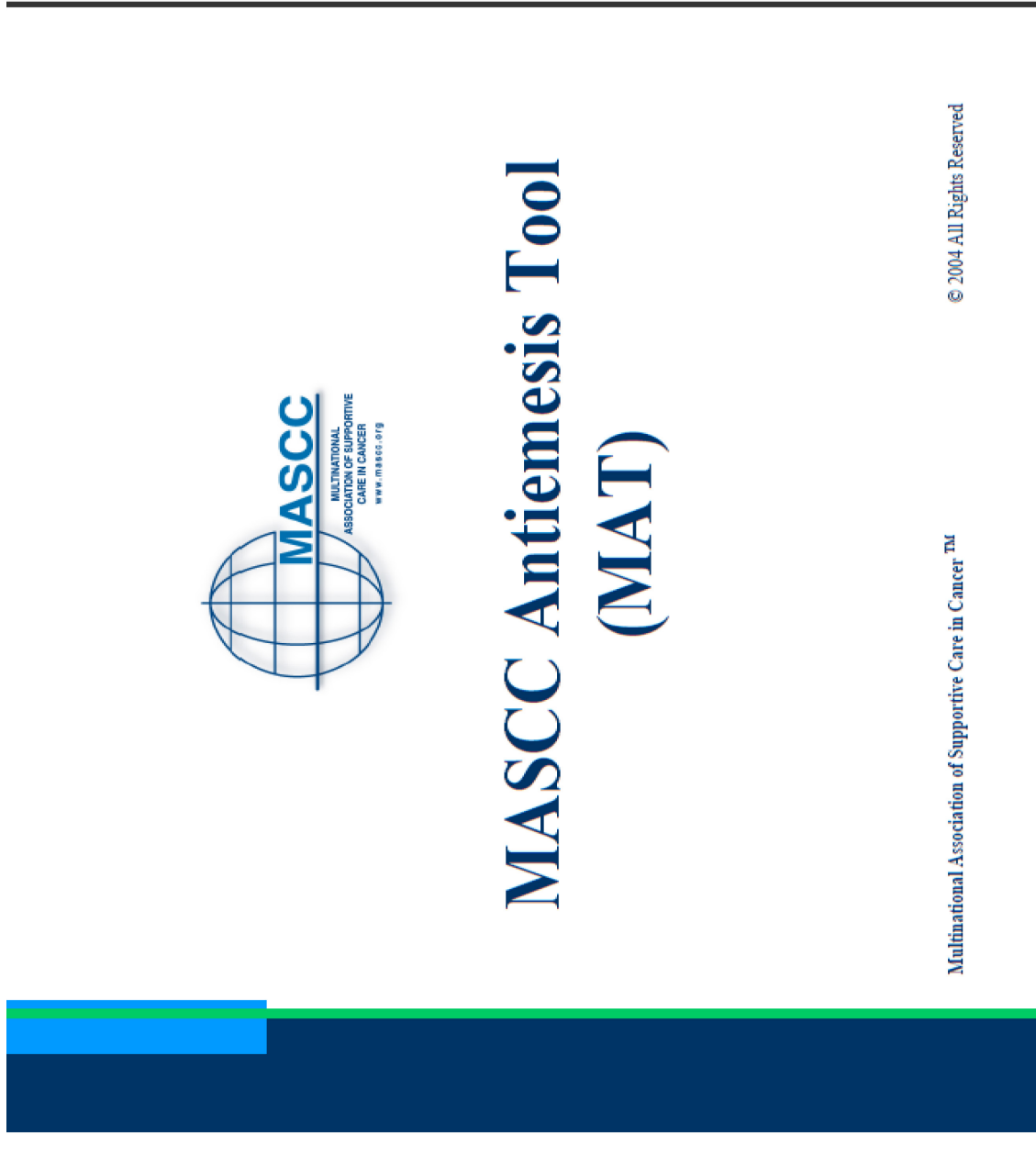
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## 11.0 Appendices

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### 11.1 Appendix 1- MASCC Antiemesis Tool



### MASCC Antiemesis Tool: Instructions

Your Name:

Date of Chemotherapy (this cycle):

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
Day	Month	Day	Day of the Week

Your Oncology Nurse:

Phone:

Your Oncology Physician:

Phone:

#### Information about this brief form:

The MASCC Antiemesis Tool (MAT) is a way to help your doctors and nurses be sure you get the best care there is to prevent nausea and vomiting from chemotherapy. By filling out this form, you can help us make sure that you are having the best control of these possible side effects. Here are the definitions used on this form:

**Vomiting:** The bringing up of stomach contents.

**Nausea:** The feeling that you might vomit.

Please answer all questions. There are no right or wrong answers, only your impression. If you have any concerns about how or when to complete this form, please ask!

Please notice that Question #4 and Question #8 have a different style. These questions are scales. For this type of question, just circle the number from 0 to 10 that most closely resembles your experience with your nausea and vomiting and write the number in the box to the right. An example of this form of question (but dealing with parking) is given below. Feel free to practice with this example or ask one of us to go over it with you.

How much difficulty did you have parking your car today?

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

(Write the number in this box)

Please return the form shortly after completing it, as discussed with us. Thank you!

MASCC Antiemesis Tool

Please fill this out the day after chemotherapy on:

Day  Month  Day of the Week

**Nausea and Vomiting  
during the first 24 hours after chemotherapy:**

(This page refers to the first 24 hours following chemotherapy):

1) In the 24 hours since chemotherapy, did you have any vomiting? Yes  No   
(Select one)

2) If you vomited in the 24 hours since chemotherapy, how many times did it happen?   
(Write the number of times in this box)

3) In the 24 hours since chemotherapy, did you have any nausea? Yes  No   
(Select one)

4) 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?

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

(Write the number in this box)

**MASCC Antiemesis Tool**  
This page asks about the period from the day after to 4 days after chemotherapy.  
So it asks about the time after the first 24 hours.

Please fill this out **four** days after chemotherapy on:

Day	Month	Day of the Week
<input type="text"/>	<input type="text"/>	<input type="text"/>

**Delayed Nausea and Vomiting**

5) Did you vomit 24 hours or more after chemotherapy?      Yes  No   
(Select one)

6) If you vomited during this period, how many times did it happen?        
(Write the number of times in this box)

7) Did you have any nausea 24 hours or more after chemotherapy?      Yes  No   
(Select one)

8) If you had nausea, please circle or enter the number that most closely resembles your experience.  
How much nausea did you have over this time period?

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

(Write the number in this box)

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## **Appendix 2- List of Strong CYP3A4 Inducers and Strong and Moderate CYP3A4 Inhibitors**

### **Strong CYP3A4 inhibitors include the following:**

- Boceprevir
- Clarithromycin
- Conivaptan
- Grapefruit juice
- Indinavir
- Itraconazole
- Ketoconazole
- Lopinavir/ritonavir
- Mibefradil
- Nefazodone
- Nelfinavir
- Posaconazole
- Ritonavir,
- Saquinavir
- Telaprevir
- Telithromycin
- Voriconazole

### **Moderate CYP3A4 inhibitors are the following:**

- Amprenavir
- Aprepitant
- Atazanavir
- Ciprofloxacin
- Darunavir/ritonavir
- Diltiazem
- Erythromycin
- Fluconazole
- Fosamprenavir
- Grapefruit juice
- Imatinib
- verapamil

### **Strong CYP3A4 inducers include the following:**

- Avasimibe
- Carbamazepine
- Phenytoin
- Rifampin
- St. John's wort



**11.2 Appendix 3- Patient Medication Diary**

**Medication Use Diary**

<b>Protocol No.</b>	<b>Participant No.</b>	<b>Participant Initials</b>	<b>Treatment Phase</b>
UCSD XXXXXX			

**Instructions for completion:**

- Please remember to complete this diary **daily** while participating in this study.
- Record each medication you are taking at home on a separate line. For each medication recorded, please list the date or dates that it was taken, how many times it is taken each day, the dose each time it is taken, and the reason why you are taking the medication.
- If there is any information that you do not know, please write "UNK" in the space provided.

<b>Name of Medication</b>	<b>Date(s) Medication Taken (mm/dd/yy)</b>	<b>No. of times taken each day</b>	<b>Dose (each time it is taken)</b>	<b>Reason for Taking Medication</b>

Please sign when all spaces are full and return to the study coordinator during your next clinic visit.

**Patient Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

Herbal supplement use?

- No
- Yes, which one? Dose? Frequency? \_\_\_\_\_

Marijuana use?

- No
- Yes, which one? Dose? Frequency? \_\_\_\_\_

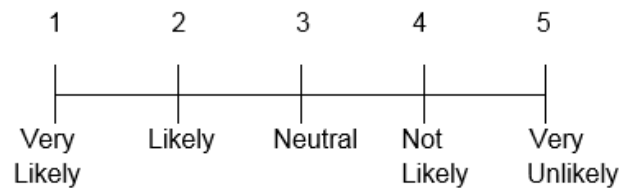
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**Appendix 4- five point Likert scale questionnaire**

**Five point Likert scale questionnaire**

Protocol No.	Participant No.	Participant Initials	Visit	Date
UCSD 161691				

On a scale of 1-5, how likely are you to ask your doctor for Akyzeo® to treat your refractory CINV in the future?

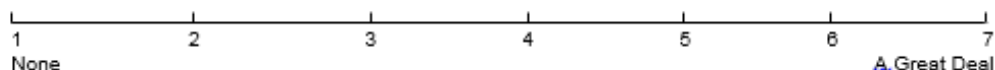


**11.3 Appendix 5 - Functional Living Index for Emesis (FLIE) scale**

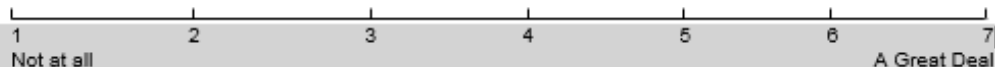
**FLIE Subject Questionnaire**

Protocol No.	Participant No.	Participant Initials	Visit	Date
UCSD 161691				

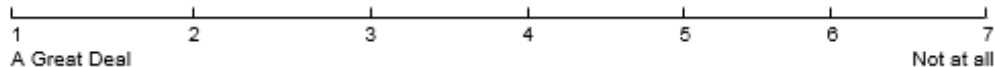
1. How much nausea have you had in the last 5 Days?



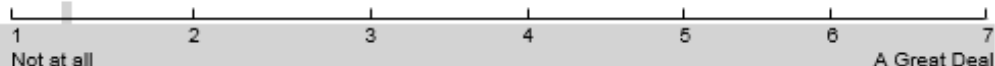
2. Has nausea affected your ability to maintain usual recreation or leisure activities in the last 5 days?



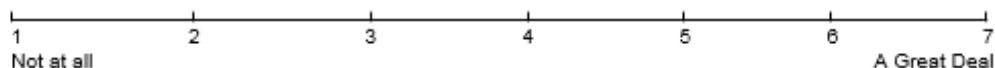
3. Has nausea affected your ability to make a meal or do minor household repairs in the last 5 days?



4. How much has nausea affected your ability to enjoy a meal in the last 5 days?



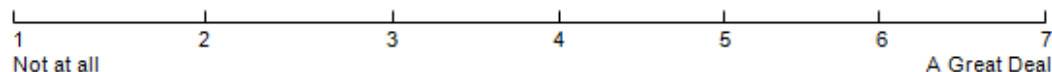
5. How much has nausea affected your ability to enjoy liquid refreshment in the last 5 days?



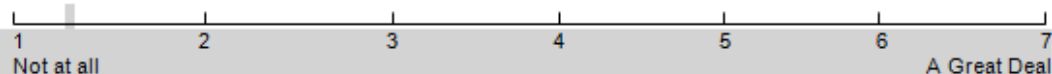
6. How much has nausea affected your willingness to see and spend time with family and friends in the last 5 days?



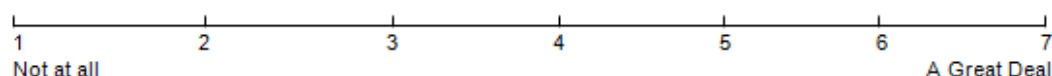
7. Has nausea affected your daily functioning in the last 5 days?



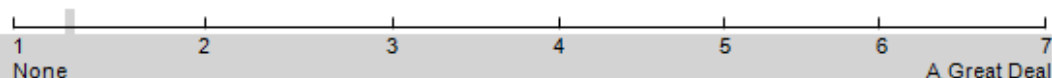
8. Rate the degree to which your nausea has imposed a hardship on you (personally) in the last 5 days.



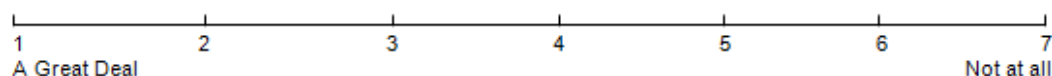
9. Rate the degree to which your nausea has imposed a hardship on those closest to you in the last 5 days.



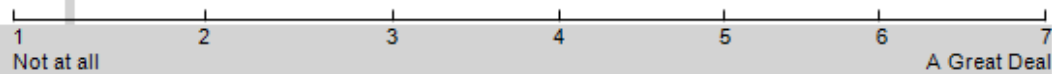
10. How much vomiting have you had in the last 5 days?



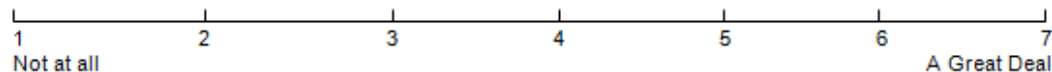
11. Has vomiting affected your ability to maintain usual recreation or leisure activities in the last 5 days?



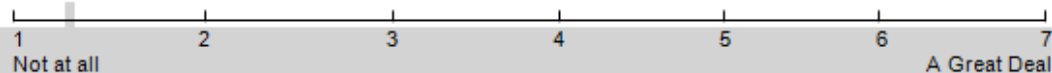
12. Has vomiting affected your ability to complete your usual household tasks in the last 5 days?



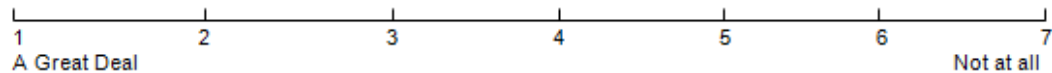
13. How much has vomiting affected your ability to enjoy a meal in the last 5 days?



14. How much has vomiting affected your ability to enjoy liquid refreshment in the last 5 days?



15. How much has vomiting affected your willingness to see and spend time with friends in the last 5 days?



16. Has vomiting affected your daily functioning in the last 5 days?



17. Rate the degree to which your vomiting has imposed a hardship on you (personally) in the last 5 days.



18. Rate the degree to which your vomiting has imposed a hardship on those closest to you in the last 5 days.

