Protocol No. CAN-PRO-NEPA-001

A Phase IV, Real World Observational Study On The Use Of Akynzeo® (netupitant/palonosetron) For The Prevention Of Nausea and Vomiting in Oncology Patients Receiving Highly Emetogenic Chemotherapy (HEC) Over Multiple Cycles.

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Study Product: Akynzeo® (netupitant/palonosetron)

Version: Version 1: 05 June 2018

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Signature of Sponsor Representative **Date: (DD-MMM-YYYY)**

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LIST OF ABBREVIATIONS

5-HT_3	5-hydroxytryptamine type 3
AC	Anthracycline-Cyclophosphamide
AE	Adverse Event
CINV	Chemotherapy-Induced Nausea and Vomiting
CNS	Central Nervous System
CP	Complete Protection
CR	Complete Response
CRO	Contract Research Organization
CRF	Case Report Forms
CTCAE	Common Terminology Criteria for Adverse Events
DMP	Data Management Plan
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
EMA	European Medicine Agency
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-Dose Combination
FLIE	Functional Living Index-Emesis
GCP	Good Clinical Practice
HEC	Highly Emetogenic Chemotherapy
HEOR	Health Economics Outcomes Research

ICH	International Conference on Harmonization
ICF	Informed Consent Form
MAH	Marketing Authorization Holder
MEC	Moderately Emetogenic Chemotherapy
NCCN	National Comprehensive Cancer Network
N/A	Not Applicable
N/D	Not Done
NK-1	Neurokinin-1
PALO	Palonosetron
RCT	Randomized Controlled Trial
PIPEDA	Personal Information Protection and Electronic Documents Act
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Events
VAS	Visual Analog Scale
RWE	Real World Evidence
NEPA	netupitant/palonosetron

INVESTIGATOR AGREEMENT

I have read this protocol and agree to conduct the study according to the procedures and terms provided herein, including all statements regarding confidentiality, and to complete the study within the time designated.

I assume responsibility for the conduct of this study at my study site. I will ensure that I have sufficient resources allocated to this project such that the safety of my patients is protected at all times and that I complete my obligations to the sponsor according to the agreed timelines. I will delegate responsibilities only to those who are qualified by training and experience. I will ensure the integrity of the data generated by my team and that all team members are familiar with the study protocol and the study medication.

I agree that I will grant access to the applicable records, my staff allocated to the conduct of this protocol, and my facilities for the purposes of monitoring, auditing and any required inspections associated with the conduct of this clinical trial.

I agree to ensure that the confidential information contained in the protocol document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

By my signature below, I acknowledge the foregoing covenants, and confirm my understanding of the obligations accorded by the corresponding Clinical Trial Agreement.

_____

Name of Investigator (First Name, Last Name, Title)

_____

Institution*

_____

Address*

_____

_____

Signature of Investigator **Date: (DD, MMM, YYYY)**

* If the address of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor and the appropriate Ethics Review Board and will not require protocol amendment(s).

STUDY SYNOPSIS

TITLE	A Phase IV, Real World Observational Study On The Use Of Akynzeo® (netupitant/palonosetron) For The Prevention Of Nausea and Vomiting in Oncology Patients Receiving Highly Emetogenic Chemotherapy (HEC) Over Multiple Cycles.
SHORT TITLE	Observational study on the use of Akynzeo® in patients receiving HEC
PROTOCOL NUMBER	CAN-PRO-NEPA-001
PHASE	IV
OBJECTIVES OF THE STUDY	To generate Real World Evidence (RWE) on the quality of life by means of the FLIE questionnaire on administration of Akynzeo™ in highly emetogenic chemotherapy (HEC), and to generate Real World Evidence in support of existing clinical trial data. The study will also assess effectiveness and safety of Akynzeo® in the real world setting for the prevention of Chemotherapy Induced Nausea and Vomiting (CINV) in patients receiving highly emetogenic chemotherapy).
INDICATION	Patients with chemotherapy-induced nausea and vomiting who are receiving chemotherapy with high emetogenic potential for a maximum of 2 days on account of various types of cancer.
NUMBER OF PATIENTS	Approximately 200 patients
STUDY DESIGN	Real World, Observational study
STUDY CENTRES	Multi-centre, up to 20 sites
PRIMARY OUTCOME:	• Functional Living Index of Emesis (FLIE) – Quality of Life
SECONDARY OUTCOMES	• Complete Response (CR: no emetic episodes and no use of rescue medication) - overall – 0-120 hours (Day 1 to Day 5) • Severity of nausea (VAS) - daily • Time to failure (time to first emetic episode or time to rescue) • Use of rescue medication - daily • Safety parameters (failure of CR, i.e., nausea and vomiting will not be included in the safety records)

EXPLORATORY OUTCOMES	• HEOR (Health Economic and Outcomes research) parameters:
	  • ER visits
	  • Hospitalizations
	• WPAI-NV (Work Productivity Activity Impairment Scale – Nausea and Vomiting)

METHODOLOGY	• FLIE Questionnaire to be completed by the patient at the end of the observation period (Day 5/120 hours post each cycle) for at least the first 4 consecutive cycles of chemotherapy (cycles 1-4) • Patient Diary to be completed daily starting on the first day of chemotherapy treatment (Day 1) until 5 days post treatment (Day 5/120 hours post each cycle). Diary data for cycles 1 - 4 will be included in the study database • WPAI-NV to be completed by the patient at the end of the observation period (Day 5/120 hours post each cycle) for at least the first four consecutive cycles of chemotherapy (cycles 1-4) • eCRF will be used for data capture
TREATMENT	Akynzeo® (300mg Netupitant/0.5mg palonosetron hydrochloride). In accordance with the approved Canadian Product Monograph; 1 capsule of Akynzeo® administered orally approximately 1 hour prior to the start of each chemotherapy cycle.
INCLUSION CRITERIA	• Patient scheduled to receive a highly emetogenic chemotherapy (HEC). • Patient scheduled to receive antiemetic prevention with Akynzeo® according to the approved Canadian Product Monograph as deemed medically necessary by the participating physician independently from this study. • Age ≥ 18 years. • Women of childbearing potential must use effective contraception during therapy and up to one month after treatment with Akynzeo®. • Patient (and/or patient's authorized legal representative) should understand the nature of the study and provide written informed consent prior to or at the screening visit. • Patient is able and willing to comply with the study protocol for the entire length of the study and will follow all study requirements, procedures and complete all visits as required. • Patient is participating in another clinical trial where antiemetic treatment is not pre-specified by the study protocol.
EXCLUSION CRITERIA (as per Contraindications in the approved Canadian Product Monograph)	• Women of child bearing potential who are pregnant, planning on becoming pregnant or breast feeding. • Hypersensitivity to active substances, excipients or other ingredients of Akynzeo®. • Concomitant use of pimozide, terfenadine, astemizole, or cisapride. • Patient is enrolled in another clinical trial where antiemetic treatment is pre-specified by the study protocol.

STUDY DURATION	This study will last approximately 20 months from 1st patient enrolled until last patient has completed. The observation period for each subject will last 4-6 months.
RECRUITMENT PERIOD	Approximately 12 months
ANALYSIS	Descriptive statistics will be generated for the primary, secondary and exploratory endpoints.

Table 1: Time and event schedule

Activity	Screening/ Visit 1	Visit 2 Cycle 1	Visit 3 Cycle 2	Visit 4 Cycle 3	Visit 5 Cycle 4	Visit 6/Final visit
Time period	-28 days to Day 1, Cycle 1	Day 1 of Cycle 1	Day 1 of Cycle 2	Day 1 of Cycle 3	Day 1 of Cycle 4	Within 28 days of Cycle 4 or prior to start of next chemotherapy cycle
Informed consent	X					
Inclusion/Exclusion	X					
Demographics & Medical History	X					
Nausea assessment - physician	X					
Current treatments/medications	X					
Patient Kit (distribute and provide education on use)	X*					
Patient Assessments:						
Patient diary, including: • Nausea Severity Assessment • Rescue medications • Adverse Events		X[1]	X[1]	X[1]	X[1]	
• Functional Living Index – Emesis (FLIE)		X[2]	X[2]	X[2]	X[2]	
• Work Productivity Activity Impairment Scale – Nausea and Vomiting (WPAI-NV)		X[2]	X[2]	X[2]	X[2]	
Patient Kit - collect and review diary and questionnaires			X	X	X	X
Concomitant medication		X	X	X	X	X
Adverse event		X	X	X	X	X
Study completion assessment/early discontinuation						X

*Patient Kit can be distributed at Screening/Visit 1 or Visit 2. All assessments/training should be completed prior to chemotherapy treatment
[1] Patient completes diary on days 1-5 (0-120 hours) post chemotherapy cycle
[2] Patient completes FLIE and WPAI after day 5 of cycle

1 INTRODUCTION

This document is a protocol for a human research study.

This study will be carried out in compliance with the protocol, international standards of Good Clinical Practice (GCP) (ICH E6), Tri-council Policy Statement on Ethical Conduct for Research Involving Humans (CIHR 2010), applicable regulatory requirements and applicable Institutional research policies and procedures.

1.1 Background Information

Cancer chemotherapy is often associated with nausea and vomiting, which are among the most unpleasant and distressing side effects for subjects [1, 2]. Chemotherapy-induced nausea and vomiting (CINV) reduces patient's health-related quality of life (QoL) [3] and may cause noncompliance or refusal of potentially life-saving chemotherapeutic regimens [4]. The severity and pattern of nausea and vomiting induced by a chemotherapeutic regimen depend on the agents used and the doses employed [4]. Accordingly, chemotherapeutic regimens are classified as highly or moderately emetogenic [4].

CINV is classified as either acute (occurring within the first 24h after chemotherapy) or delayed (occurring after the first 24h, extending until 120h). Nausea and vomiting result from stimulation of a multi-step reflex pathway controlled by the brain. The vomiting reflex involves both central and peripheral components and the emetic response is integrated into the vomiting center [5].

The standard of care for antiemetic prophylaxis now consists of combinations of agents that inhibit several molecular pathways involved in emesis. The concomitant use of these agents is currently recommended for patients receiving chemotherapy of high emetic risk [6]. This regimen consists of a 5-hydroxytryptamine-3 ($5\text{-}HT_3$) receptor antagonist (RA), a neurokinin-1 (NK_1) RA and a corticosteroid, such as dexamethasone. Moreover, the Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology MASCC/ESMO evidence-based guidelines recommend the triplet antiemetic regimen for carboplatin-based regimens [6]. The American Society of Clinical Oncology (ASCO) has also recently recommended the addition of olanzapine to this triplet regimen [7] in HEC.

1.2 Rationale for the Study

Randomized controlled trials (RCTs) are the "gold standard" for generating evidence of the efficacy and safety of a drug. However, enrolment criteria, timelines, and atypical comparators of RCTs limit relevance to standard clinical practice. Real world data (RWD) provide longitudinal information on comparative effectiveness and tolerability of drugs, as well as data on their impact on resource use, medical costs, pharmacoeconomic outcomes, and patient-reported outcomes. While the randomized nature of the RCT ensures its high internal validity by removing bias, their 'controlled' nature casts a doubt on their generalizability to the real-world population. It is for this reason that trials done in a real-life setting post the marketing authorization of a drug are increasingly required [16].

Akynzeo® received authorization from Health Canada in September 2017 for its use in:

- the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy and
- the prevention of acute nausea and vomiting associated with moderately emetogenic cancer chemotherapy that is uncontrolled by a 5-HT_3 receptor antagonist alone

This study is designed to collect clinical data on the real-world use of Akynzeo® in Canada. The aim of the study is to support clinical data from the development program by the generation of real world evidence on the effectiveness, safety and additional parameters of Akynzeo® in a local clinical setting. As a non-interventional study [17], the inclusion of patients will be carried out only after the physician has freely decided – on the basis of the patient's individual situation – that the patient will receive Akynzeo® as antiemetic therapy for the prevention of CINV. The investigation on the effectiveness and safety profile of Akynzeo® is to take place under everyday clinical practice conditions. The parameters of interest for this study will be collected by means of a patient diary and then documented in a dedicated electronic case report form by the appropriate personnel. Moreover, patient exclusion criteria will reflect the Product Monograph (PM), including "Cautions" and "Warnings" and no additional clinical investigations will be performed compared to the routine clinical practice in order to reflect real world use and increase study data generalizability.

This prospective, non-interventional study (NIS) enables the collection of anonymized data feeding a larger global registry reflecting patients' exposure to Akynzeo®. A registry is a database of patients exposed to the same specific drug to determine if that drug has a special impact [17,18], to determine real life effectiveness and quality of care [19].

1.3 Study Drug - Combination of Palonosetron and Netupitant

NEPA (Akynzeo®) was developed as an oral fixed combination of the highly selective NK_1RA, netupitant (300 mg), and the clinically [8] and pharmacologically [9] distinct 5-HT_3RA, palonosetron (0.5mg).

Pivotal clinical studies described in section 1.4, which represented the basis for the marketing authorization of NEPA, have demonstrated superiority of oral NEPA plus dexamethasone over oral palonosetron plus dexamethasone in preventing CINV during the acute (0-24h), delayed (25-120h), and overall (0-120h) phases following both cisplatin- [10] and anthracycline-cyclophosphamide (AC)-based chemotherapy [11,12]. In addition, NEPA was shown to be efficacious over multiple cycles in patients receiving either HEC or moderately emetogenic chemotherapy (MEC) [13].

Akynzeo®, which is the trade name of the medicinal product mentioned above, was approved on 27 May 2015 by the European Medicines Agency for prevention of acute and delayed nausea and vomiting in highly emetogenic cisplatin-based cancer chemotherapy and moderately emetogenic cancer chemotherapy in adults [14] and on 27 September 2017 by Health Canada in combination with dexamethasone, as once-per-cycle treatment in adult patients for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy [15].

1.4 Clinical Studies

Three pivotal clinical studies were published simultaneously in the Journal "Annals of Oncology" in July 2014. The studies demonstrated that a single oral dose of the combination netupitant and palonosetron (NEPA) is efficacious and safe for use in the prevention of CINV.

Study	Design	Patient population & chemotherapy	Treatment arms	Number of CTX cycles	Objective of the study
Study 1: Hesketh et al. [10]	Double-blind, randomized, Phase II dose-finding study	N=694; chemotherapy-naive patients; cisplatin-based HEC	$NEPA_{100mg}$ + Dex $NEPA_{200mg}$ + Dex $NEPA_{300\ mg}$ + Dex $PALO_{oral}$ + Dex (APR + OND_{iv} + Dex; explorative)	One cycle	NEPA dose-finding; efficacy of NEPA
Study 2: Aapro et al. [11]	Double-blind, randomized, Phase III study	N=1455; chemotherapy-naive patients; AC-based CTX	NEPA + Dex $PALO_{oral}$ + Dex	Multiple cycles	Superiority of NEPA compared to PALO
Study 3: Gralla et al. [13]	Double-blind, randomized Phase III study	N=413; chemotherapy-naive patients; all HEC or MEC (except AC)	$NEPA_{300\ mg}$ + Dex $PALO_{oral}$ + Dex APR + $PALO_{oral}$ + Dex (3:1 randomization)	Multiple cycles	Safety of NEPA over multiple cycles, non-inferiority compared to SoC

Study 1: NEPA – dose-finding Phase II (Hesketh et al. 2014)

The dose of netupitant (300 mg) administered in combination with 0.5 mg palonosetron was selected based on the results of a Phase II dose-finding study. This multinational, randomized double-blind study assessed three different single oral doses of netupitant (100 mg, 200 mg and 300 mg) in combination with a fixed oral dose of palonosetron (0.5 mg) and oral dexamethasone compared to oral palonosetron (0.5 mg) and oral dexamethasone, prior to a single cycle administration of cisplatin-based, highly emetogenic chemotherapy (HEC). Solely for exploratory purposes, a treatment arm with the triple combination of aprepitant, ondansetron and dexamethasone were included. The study population consisted of 679 adult male or female chemotherapy-naive patients with a histologically or cytologically confirmed solid tumour. The objective of the study was to determine the optimal dose for netupitant in combination with 0.5 mg palonosetron for effective and safe prevention of CINV, whereby the complete response (CR) rate was measured after 0-120 hours. The highest proportion of patients with CR was in the group treated with 300 mg netupitant plus palonosetron (89.6 %), followed by the group with 200 mg (87.6 %) and the group with 100 mg (87.4 %). The lowest proportion of patients with CR was in the group treated with palonosetron alone (76.5 %). All doses of netupitant in combination with palonosetron were superior to palonosetron monotherapy. The dose of 300 mg netupitant showed an advantage over the lower doses. Compared to the regimen with aprepitant and ondansetron, there was also a higher proportion of responsive patients in the 300 mg netupitant group.

Treatment-related adverse events (AEs) occurred in a total of 333 of the 679 patients (49 %). The total proportion of patients with AEs was comparable in the five treatment groups and not dependent on the netupitant dose (100 mg: 40.7 %; 200 mg: 51.4 %; 300 mg: 50 %; palonosetron monotherapy: 50 %; aprepitant: 53 %). The analysis of AEs, laboratory parameters, vital signs and 12-lead ECG showed no safety concerns for the administration of palonosetron in combination with netupitant at doses of 100 mg, 200 mg or 300 mg.
Based on the results obtained for efficacy and safety in this Phase II dose-finding study, 300 mg oral netupitant in combination with 0.5 mg of oral palonosetron has been identified as the optimum dosage for the combination. [10]

Study 2: Superiority of NEPA in comparison with palonosetron (Aapro et al. 2014)

Based on the results of the dose-finding study by Hesketh et al., the fixed dose combination NEPA, consisting of 300 mg netupitant and 0.5 mg palonosetron, was investigated in a subsequent double-blind, multicentre, randomized Phase III Study with regard to efficacy in comparison with palonosetron. 1455 chemotherapy-naive patients with a median age of 54 years, who received an anthracycline-cyclophosphamide chemotherapy (AC-based) over several cycles, were included. On day 1 of each chemotherapy (CT) cycle, the patients were treated either with NEPA (300 mg netupitant / 0.5 mg palonosetron) + 12 mg dexamethasone or 0.5 mg oral palonosetron + 20 mg dexamethasone. The primary endpoint was complete response defined as "no vomiting, no rescue medication" in the delayed phase (> 24 – 120 h after CT). Of the 724 evaluable patients in the NEPA-arm, 88.4 % showed a complete response in the acute phase and 76.9 % in the delayed phase. In the Palo-arm with 725 evaluable patients, the response rates were 85 % for the acute phase and 69.5 % for the delayed phase of CINV. NEPA showed a statistically significant higher response rate over the overall period with 74.3 % compared to 66.6 % for PALO ($p = 0.001$).

NEPA was also statistically significantly superior to PALO for the secondary endpoints "no vomiting" (a), "no severe nausea" (b) and "complete control" (c), both in the delayed phase and over the entire period for a): 81.8 % and 79.8 % vs. 75.6 % and 72.1 %, for b): 76.9 % and 74.6 % vs. 71.3 % and 69.1 % and for c): 67.3 % and 63.8 % vs. 60.3 % and 57.9 %.
There was no impairment of regular daily activities (based on the Functional Living Index - emesis - questionnaire). Overall, the frequency, nature and intensity of the adverse events were comparable between the two study arms. In 8.1 % of patients treated with NEPA there were treatment-associated side effects (PALO arm: 7.2 %), but there were no serious adverse events, no discontinuations of therapy and no deaths. The most common adverse events were headache and constipation.

The results of the study showed that in all phases after treatment with moderately emetogenic chemotherapy (AC-based considered as MEC at the time of the study), a single oral dose of NEPA in combination with a single dose of dexamethasone leads to better complete response rates than a single oral dose of palonosetron in combination with a single dose of dexamethasone. The authors concluded that future guideline-compliant antiemetic treatment could be simplified on the basis of the fixed dose combination. [11]

Study 3: Safety and efficacy of NEPA over repeated cycles (Gralla et al. 2014)

Another pivotal study for clinical use of NEPA was also published by Gralla and colleagues in 2014. The multicentre, randomized, double-blind phase III study included 413 adult patients with solid tumours of different entities, which had not been previously treated with chemotherapy. Of these patients, 76 % received a non-AC-based MEC (carboplatin, oxaliplatin, doxorubicin,

cyclophosphamide, irinotecan, epirubicin, daunorubicin) and 24 % a HEC (> 90 % cisplatin, the rest dacarbazine, carmustine). Of the 412 evaluable patients in a 3:1 randomization, 308 patients were treated on Day 1 of the CTX with NEPA (300 mg netupitant + 0.5 mg palonosetron) + 12 mg dexamethasone. The remaining 104 patients were treated with 125 mg aprepitant + 0.5 mg palonosetron + 12 mg dexamethasone on day 1 of the CT followed by 80 mg aprepitant + 8 mg dexamethasone (only in case of HEC) on days 2 and 3. The primary endpoint was defined as the safety profile of NEPA administered over at least 6 CT cycles. The efficacy (complete response and prevention of severe nausea) was determined as a secondary endpoint.

Antiemetic treatment was administered in a total of 1961 CT cycles, including 1446 with NEPA and 515 with APR / PALO. 98 % of patients completed cycle 1, 75 % completed 4 cycles and 40 % of patients completed 6 cycles.

The most common treatment-related adverse events were constipation (3.6 % NEPA vs. 1 % AP0R / PALO) and headache (in each case 1 % for NEPA and APR / PALO), whereby the frequency did not increase with increasing number of cycles. Overall, the rate of side effects during treatment in cycle 1 was 5.2 % (n = 308) for NEPA vs. 2.9 % for APR / PALO (n = 104). These rates fell by cycle 6 to 1.6 % for NEPA (n = 124) and 0 % for APR / PALO (n = 43) on account of the decreasing number of cases. There were no concerns with regard to the cardiac safety of NEPA.

Overall, complete response rates (no vomiting, no rescue medication) were high in both study arms over all chemotherapy cycles. NEPA showed a slight, persistent numerical advantage of 2-7 % compared to APR / PALO.

In this study, Gralla et al. were able to demonstrate consistent efficacy of NEPA associated with good tolerability over multiple cycles of highly and moderately emetogenic chemotherapies [13].

1.5 Study Population

This study will enroll adult male or female chemotherapy patients of various cancer types who are scheduled to receive chemotherapy with high emetogenic potential for a maximum of 2 days.

2 STUDY OBJECTIVES

The primary study objective is to generate Real World Evidence (RWE) on the quality of life by means of the FLIE questionnaire on administration of Akynzeo® in highly emetogenic chemotherapy (HEC), and to generate Real World Evidence in support of existing clinical trial data.

The study will also assess effectiveness and safety of NEPA in the real world setting for the prevention of Chemotherapy Induced Nausea and Vomiting (CINV) in patients receiving highly emetogenic chemotherapy).

2.1 Primary Outcome: Functional Living Index - Emesis (FLIE)

The quality of life of patients can be collected by means of the FLIE questionnaire on administration of Akynzeo® during chemotherapy with moderately and highly emetogenic agents.

The Functional Living Index – Emesis questionnaire is a patient reported outcome (PRO) validated tool with the objective of assessing the impact of chemotherapy-induced nausea and vomiting on patient's daily function.

It consists of a nausea domain and a vomiting domain of nine items each where the patient should rate how much nausea and vomiting have affected the quality of life. For each question the patient will rate how much nausea (or vomiting) has affected an aspect of his quality of life during the past five days. Each question uses a visual analogue scale (VAS).

The investigator shall be responsible for explaining to the patient how the questionnaire should be correctly completed.

2.2 Secondary Outcomes

The response to Akynzeo® and the necessity for use of a rescue medication will be recorded to evaluate effectiveness. The medicinal products used as rescue medication will also be recorded. The following parameters will be calculated from information recorded in the patient diary:

- Complete Response (CR): no emetic episode and no use of rescue medication in the overall period (0-120h/Day 1-5)
- Severity of nausea (daily from Day 1 to Day 5) using a VAS scale (Visual Analogue Scale)
- Time to failure (time to first emetic episode or time to rescue)
- Use of rescue medication (daily from Day 1 to Day 5)

The collection of safety data and adverse events AEs in connection with administration of Akynzeo® will be performed.

2.3 Exploratory Outcomes

Health economic and outcomes research data will be collected and recoded on the diary card specifically emergency department (ED) visits and hospitalizations.

Work Productivity Activity Impairment scale for Nausea and Vomiting (WPAI-NV) will be collected on day 5 of each cycle.

3 STUDY DESIGN

3.1 Study Overview

This two year (approximately), multi-centre, prospective, observational real-world study is designed to collect data on the use of Akynzeo® (netupitant/palonosetron) for the prevention of nausea and vomiting in oncology patients receiving highly emetogenic chemotherapy (HEC).

The visit schedule is comprised of 6 study visits (Table 1):

- Visit 1/Screening (4 weeks to 0 weeks prior to Visit 2)
- Visit 2: (Day of/but prior to 1st chemotherapy treatment administration)

- Visit 3: (Day of/but prior to 2nd chemotherapy treatment administration)
- Visit 4: (Day of/but prior to 3rd, chemotherapy treatment administration)
- Visit 5: (Day of/but prior to 4th, chemotherapy treatment administration)
- Visit 6/Final Visit

Visit 1 and 2 can be combined as determined by the investigator. Patients will report the daily occurrence and intensity of nausea and vomiting, rescue medications, adverse events (excluding nausea and vomiting) in a diary from Day 1 (chemotherapy treatment day) to Day 5/time point 0-120 hours post chemotherapy administration of each observation period.

Safety events occurring between chemotherapy cycles will be reported by the patient. Patient will have a follow up period of 28 days post the last-chemotherapy cycle.

3.2 Study Sites

The study will enrol up to 20 Canadian sites.

3.3 Sample Size

The study will include up to **200** patients. No formal sample size calculation has been carried out. The planned number of patients to be enrolled in the study should be adequate for the exploratory purposes and allow a conclusion to be drawn regarding the use of Akynzeo® in the Canadian medical environment.

3.4 Primary Endpoint

The primary endpoint is the FLIE total score for cycle 1.

3.5 Secondary Endpoints

The secondary endpoints are:

- FLIE total score cycles 2-4
- FLIE Nausea domain total score all cycles
- FLIE Vomiting domain total score all cycles
- Complete response-no emesis, no rescue medication during the acute, delayed and overall phase all cycles
- No significant nausea during the acute, delayed and overall phase for all cycles
- Time to failure defined as time to first emetic episode or time to rescue medication use for all cycles
- Use of rescue medication all cycles
- To descriptively asses the patient diary at screening and over time

The response to Akynzeo® and the necessity for use of a rescue medication will be recorded to evaluate effectiveness. Any medicinal products used as rescue medication will be recorded in the patient diary.

3.6 Exploratory Endpoints

- To descriptively assess HEOR parameters (ER visits, hospitalizations)
- To descriptively assess the WPAI-NV

3.7 Safety Assessment

Safety will be evaluated by the incidence and type of adverse events (AEs), serious adverse events (SAEs) and AEs leading to discontinuation of treatment in all patients.

4 SUBJECT SELECTION AND WITHDRAWAL

Protocol waivers will not be provided by the sponsor. All subjects included in this study must meet all of the inclusion criteria and none of the exclusion criteria. Deviations from the protocol will be noted as such and will be addressed by the sponsor as appropriate.

4.1 Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Patient scheduled to receive a highly emetogenic chemotherapy (HEC).
2. Patient scheduled to receive antiemetic prevention with Akynzeo® according to the approved Canadian Product Monograph as deemed medically necessary by the participating physician independently from this study.
3. Age ≥ 18 years.
4. Women of childbearing potential must use effective contraception during therapy and up to one month after treatment with Akynzeo®.
5. Patient (and/or patient's authorized legal representative) should understand the nature of the study and provide written informed consent prior to or at the screening visit.
6. Patient is able and willing to comply with the study protocol for the entire length of the study and will follow all study requirements, procedures and complete all visits as required.
7. Patient is participating in another clinical trial where antiemetic treatment is not pre-specified by the study protocol.

4.2 Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participation in the study:

1. Women of child bearing potential who are pregnant, planning on becoming pregnant or breast feeding.
2. Hypersensitivity to active substances, excipients or other ingredients of Akynzeo®.
3. Concomitant use of pimozide, terfenadine, astemizole, or cisapride.
4. Patient currently enrolled in another clinical trial where antiemetic treatment is pre-specified by the study protocol.

4.3 Subject Recruitment and Pre-Screening

To recruit subjects for this study, any of the following recruitment methods will be acceptable following approval by the Sponsor: review of medical charts from the investigator or sub-investigator's clinical practices, referral from other physicians, any type of media advertisement and community outreach/engagement. All screened subjects will be recorded on a screening/enrolment log.

Any information to be disseminated to potential subjects (handouts, brochures, subject cards etc.) and any advertisements intended to be used for this study (printed ads, posters, flyers, spots etc.) must be approved by the site's REB prior to any use.

4.4 Subject Withdrawal Criteria

Subjects may voluntarily withdraw from the study at any time. If a subject exits the study early all final assessments required at the Final visit should be performed and the study completion/early termination form outlining the reason for withdrawal should be completed. No data will be collected after the early termination visit date. Subjects who withdraw from the study early will not be replaced. The investigator should withdraw subjects from the study if they feel that it is in the best interest of the subject to be terminated from the study. Any administrative or other reasons for withdrawal must be documented and explained to the subject.

The Sponsor's access to the relevant subject data will survive the subject's withdrawal from the study. Withdrawal will be documented in the subject's chart and in the Case Report Form (CRF) with a detailed explanation of the reason for the withdrawal and the date of last dose of study medication.

5 STUDY PRODUCT

Subjects will have access to Akynzeo® as per their usual means for obtaining prescription medications utilizing a study drug access card.

5.1 Dosage and Administration

Following the screening period patients meeting the inclusion/exclusion criteria will receive their dose of Akynzeo® on the day of their chemotherapy administration for each cycle. Each patient will be treated with the recommended dose of Akynzeo® for highly emetogenic chemotherapy, including cisplatin based chemotherapy, as per the Canadian Product Monograph. The recommended dose of Akynzeo® is 1 capsule of Akynzeo® administered orally approximately 1 hour prior to the start of each chemotherapy cycle with dexamethasone 12 mg to be administered orally 30 minutes prior to chemotherapy. Day 2-4 dexamethasone 8 mg orally once daily.

For anthracycline and cyclophosphamide based chemotherapy the recommended dose of Akynzeo is 1 capsule of Akynzeo® administered orally approximately 1 hour prior to the start of each chemotherapy cycle with dexamethasone 12 mg to be administered orally 30 minutes prior to chemotherapy. Administration of dexamethasone on days 2-4 is not necessary.

5.2 Concomitant Medication(s)

Other treatment considered necessary for the subject's welfare may be given at the discretion of the patients treating physician. All such therapy must be recorded in the Case Report Form.

6 STUDY PROCEDURES

The Time and Event Schedule which is found at the end of the protocol synopsis summarizes the type (efficacy, safety, etc.) and frequency of each study procedure to be performed in this study.

No study specific procedure will be performed prior to obtaining written consent of the study subject.

6.1 Visit 1 / Screening (28 to 0 days prior to visit 2)

The following will be performed at visit 1:

- Signed and dated Informed Consent Form
- Medical history (including oncologic history)
- Demographics
- Eligibility assessment
- Nausea Assessment previous or ongoing
- Pregnancy testing in females of childbearing potential will be performed as per the investigators/institutions standard practice for chemotherapy patients
- Assessment of current medications (antiemetic's, anti-tumor drugs, other concomitant medications)
- Patient kit distribution and education on contents (Can also be distributed at Visit 2)

6.2 Visit 2 (1st Day of cycle 1)

- Akynzeo® taken by patient one hour prior to chemotherapy administration
- Diary completed days 1-5 (0-120 hours post chemotherapy administration)
    - Day 1 is defined as a 24-hour period starting at the time chemotherapy is administered (0-24 hours)
    - Day 2 is defined as 25-48 hours after start of chemotherapy
    - Day 3 is defined as 49-72 hours after start of chemotherapy
    - Day 4 is defined as 73-96 hours after start of chemotherapy
    - Day 5 is defined as 97-120 hours after start of chemotherapy
- FLIE is completed after the end of Day 5/120 hours after start of chemotherapy administration
- WPAI-NV completion is completed after the end of Day 5/120 hours after start of chemotherapy administration
- Assessment of adverse events
- Assessment of concomitant medications

6.3 Visit 3 (1st Day of cycle 2)

- Akynzeo® administered, Diary, FLIE and WPAI-NV collection and review
- Distribute diary, FLIE and WPAI-NV for cycle 2
- Assessment of adverse events
- Assessment of concomitant medications
- Note: Patient will complete their daily diary from Day 1 to Day 5

6.4 Visit 4 (1st Day of cycle 3)

- Akynzeo® administered, Diary, FLIE and WPAI-NV collection, review
- Distribute diary, FLIE and WPAI-NV for cycle 3
- Assessment of adverse events
- Assessment of concomitant medications
- Note: Patient will complete their daily diary from Day 1 to Day 5

6.5 Visit 5 (1st Day of cycle 4)

- Akynzeo® administered, Diary, FLIE and WPAI-NV collection and review Distribute diary, FLIE and WPAI-NV for cycle 4
- Assessment of adverse events
- Assessment of concomitant medications
- Note: Patient will complete their daily diary from Day 1 to Day 5

6.6 Visit 6 / Final Visit (should occur prior to start of next chemotherapy cycle)

- Collect completed diary cards, FLIE and WPAI-NV
- Assessment of adverse events
- Assessment of concomitant medications
- Complete study completion/early termination form

6.7 Effectiveness Assessments

The response to Akynzeo® and the necessity for use of a rescue medication will be recorded to evaluate effectiveness. Any medicinal products used as rescue medication will also be recorded in the patient diary.

The following parameters will be recorded in the patient diary:

- Severity of nausea (daily from Day 1 to Day 5) using a VAS (Visual Analogue Scale)

- Time to failure (time to first emetic episode or time to rescue)
- Use of rescue medication (daily from Day 1 to Day 5)

Note: A Complete Response (CR) is defined as no emetic episode and no use of rescue medication during the observational period (Day 1 to Day 5).

6.8 Patient Assessments

6.8.1 Functional Living Index - Emesis (FLIE)

The quality of life of patients will be collected by means of the FLIE questionnaire on administration of Akynzeo® during chemotherapy.

The Functional Living Index – Emesis (FLIE) questionnaire is a patient reported outcome (PRO) validated tool with the objective of assessing the impact of chemotherapy-induced nausea and vomiting on patient's daily function.

It consists of a nausea domain and a vomiting domain of nine items each where the patient should rate how much nausea and vomiting have affected the quality of life. For each question the patient will rate how much nausea (or vomiting) has affected an aspect of his quality of life during the past five days. Each question uses a visual analogue scale (VAS).

The investigator shall be responsible for explaining to the patient how the questionnaire should be correctly completed.

The FLIE will be completed by the patient on Day 5 of chemotherapy cycles 1, 2, 3 and 4.

6.8.2 Patient Diary

The patient diary will be completed daily for the first five days of each cycle (starting on the day chemotherapy is administered). The patient diary will report daily occurrence and intensity of nausea (utilizing a VAS) and vomiting, rescue medications, adverse events (excluding nausea and vomiting), concomitant medication use for CINV.

The patient diary will be included in the Patient Kit will be distributed at Visit 1 and collected at Visits 3 through 6.

6.8.3 WPAI-NV (Work Productivity Activity Impairment – Nausea and Vomiting)

The WPAI-NV is a 7-item questionnaire that assesses the effect of nausea and vomiting on a patient's ability to work and perform regular activities.

The WPAI-NV will be completed by the patient after Day 5 of chemotherapy cycles 1, 2, 3 and 4.

6.8.4 Health Economics Outcome Research (HEOR) Assessments

The following outcomes of health resource utilisation will be collected:

- Hospitalisations
- The number of ER visits

Health resource utilisation will be recorded on the patient diary and collected for all patients participating in the study.

6.9 Safety Assessments

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) from the time of giving written informed consent through to completion of subject participation, including the follow-up period (28 days post Visit 5). Adverse events will be followed by the investigator for a length of time as determined by the sponsor. Specific details on adverse event reporting are provided in section 8 "Safety Assessment".

7 STATISTICAL CONSIDERATIONS

7.1 Overview

This two year (approximately), multi-centre, prospective, observational study is designed to collect clinical data on the real-world use of Akynzeo® in Canada. The aim of the study is to support clinical data from the development program by the generation of real world evidence on the effectiveness, safety and additional parameters of Akynzeo® in a local clinical setting.

This study will enroll adult male or female chemotherapy patients of various cancer types who are scheduled to receive chemotherapy with high emetogenic potential for a maximum of 2 days. Akynzeo® (netupitant/palonosetron) will be used for the prevention of nausea and vomiting in oncology patients receiving HEC.

The primary study objective is to generate RWE on the quality of life by means of the FLIE questionnaire.

7.2 Sample Size Determination

The study is to include up to 200 patients. No formal sample size calculation has been carried out. The planned number of patients to be enrolled in the study should be adequate for the exploratory purposes and allow a conclusion to be drawn regarding the use of Akynzeo® in real life in Canada.

7.3 Efficacy and Safety Analysis

This is a two year (approximately), multi-centre, prospective, observational study designed to collect clinical data on the real-world use of Akynzeo® in Canada. All analyses will be descriptive in nature.

Before beginning data analysis, plausibility checks will be performed. Implausible or ambiguous data will be excluded from analysis.

Prior to database lock, a statistical analysis plan (SAP) defining all details of analysis will be prepared. A table mock-up (TMU) document which will illustrate the details of presentation and analysis for data collected in this study will accompany this document.

The Intent-To-Treat (ITT) population includes all patients who were entered into the study web-based application and have a date of signed informed consent available. This population will be used to provide descriptives for patients enrolled by centre, patient disposition and reasons for screen failure.

The modified Intent-To-Treat (mITT) population includes all patients who were included in the ITT population and fulfilled all entry criteria and received at least one dose of the study treatment (Akynzeo®). Missing questionnaires/assessments will not be imputed. The mITT population will be used for the analysis of the primary, secondary and exploratory endpoints not including health resource utilisation (ER visits, hospitalizations). This population will also be used for demographic, medical history and concomitant medication tables.

The Safety population includes all patients who received at least one dose of the study treatment (Akynzeo®). This population will be used for all safety analyses and health resource utilisation (ER visits, hospitalizations) tables.

Continuous variables will be summarized descriptively by number of observations, number of missing observations, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum and maximum. Categorical variables will be summarized descriptively as frequency counts and percentages.

A number of p-values may be presented in the reported tables for exploratory purposes. Statistical testing will be performed at the two-sided 0.05 significance level unless otherwise specified. P-values will not be adjusted for multiple comparisons.

8 SAFETY ASSESSMENTS

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. Adverse events will be collected from the time a subject has signed an ICF and followed until the end of study-visit 6 (28 days post visit 5/last dose of Akynzeo®).

8.1 Adverse Event Definitions

According to the currently valid Directive of the European Parliament and of the Council relating to the implementation of good clinical practice in the conduct of clinical studies on medicinal products for human use (2001/20/EC), an adverse event (AE) is “Any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment”. An AE could therefore be any unfavourable or unintended sign (for example, an abnormal laboratory finding), symptom or any disorder with a temporal relationship to the use of a medicinal product, regardless of whether or not it is considered to be related to use of the medicinal product.

In the context of this study, all adverse events (AEs) from the time of Akynzeo® administration over a period of 5 days during the chemotherapy cycles which are part of the observation period will be documented on the appropriate pages of the eCRF.

A serious adverse event (SAE) is defined as an AE that:

- results in death;
- is life-threatening;[1]
- requires hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability or incapacity;

[1] This includes every AE that – in the opinion of the investigator – is life-threatening for the study subject. This definition does not include events that may have led to death, if they had occurred in a more severe form.

- is a congenital anomaly or results in a birth defect or
- significant medical events that may endanger patients or require an intervention to prevent the above characteristics or consequences.

An unexpected adverse event is any event for which, with regard to its nature, severity or incidence, no details have been included to date in the current Product Monograph for Akynzeo®. The assessment of the "expectedness" of an AE is performed by the sponsor.

Planned surgical interventions or hospitalizations scheduled before the informed consent form was signed but carried out during the study period (study procedures, chemotherapy cycles, etc.) are not to be regarded as (serious) AEs.

The investigator assesses whether or not an event qualifies as a serious adverse event (SAE, see criteria above).

If an adverse event is classified as serious and there is at least reasonable possibility of a causal relationship to the administration of Akynzeo®, this represents a serious adverse drug reaction (SADR).

All information on Special Situations from the time of Akynzeo® administration will be documented on the appropriate pages of the CRF and transcribed to the AE pages of the eCRF.

Special situations consist of the following:

- exposure during pregnancy, embryo/foetal maternal or paternal exposure (even if uneventful),

- lack of efficacy*,

- off-label use,

- overdose,

- occupational exposure,

- misuse or abuse (symptomatic or not),

- medication errors,

- transmission of infectious agent

*refer to Section 10 for definition of lack of efficacy

8.2 Classification of Adverse Events

The investigator classifies all AEs according to their intensity, seriousness and a potential causal relationship to Akynzeo®.

8.2.1 Intensity

In this study the intensity of an AE is evaluated according to the following definitions:

Mild

A symptom that is barely perceptible by the study subject; does not affect performance or functionality. A prescription medicinal product is usually not required for relief of the symptom, but may be administered depending on the personality of the study subject.

Moderate

A symptom that is so strong that the study subject feels uncomfortable, his performance of everyday activities is restricted; the study subject may continue to participate in the study; treatment of the symptoms may be required.

Severe

The symptom causes severe discomfort. The symptom can be so strong that the study subject is unable to continue participating in the study. The severity may result in termination of treatment with Akynzeo®; the symptom can be treated and/or the study subject may require inpatient treatment.

8.2.2 Causal Relationship to Akynzeo®

The investigator classifies all AEs with regard to a possible causal relationship to administration of Akynzeo®. In this study the assessment of causality is binary, i.e. the question of a potential causal relationship to Akynzeo® is answered by the investigator only with "yes" or "no".

8.3 Adverse Event Reporting

Safety Data Collection:

Should the patient experience any AEs or Special Situations and report these to the investigator during a visit, the investigator will enter all the information available directly into the EDC system within 24 hours. Investigator shall perform a causality assessment (related/not related to CINV prophylaxis/treatment) for each AE. The AE Report Form (Appendix 6a) displays the information that the Investigator is initially required to provide. Investigator's assessment of relatedness to medicinal product for which sponsor is MAH or distributor is included in Appendix 6. Information on related and non-related Serious AEs, Special Situations and Akynzeo® related non-serious AEs will be included on the specified safety report forms (Appendix 6b & 6c).

The Global Reporting Form for SAEs/AESIs/Special Situations and the Akynzeo®-Related Non-Serious Adverse Event Forms will be directed to the sponsor‘s pharmacovigilance address (ProductInfo@purdue.ca), where the report will be processed by the sponsor‘s pharmacovigilance team. An Akynzeo®-related AE that does not meet a seriousness criterion shall be sent by the Investigator to the Sponsor email address (ProductInfo@purdue.ca) within 2 calendar days from Day 0 (investigator adverse event first awareness date). Serious AE, either related or non-related and Special Situations, shall be sent within 24 hours of their detection.

Any follow-up information will be directly requested to the investigator by sponsor. Investigator will provide the requested follow-up information within 10 calendar days from request for non-serious AE and 2 business days for serious ones and special situations. Follow up information obtained should be forwarded to sponsor within the same timelines as the initial AE information. i.e., within 24 hours for Special Situations and Serious AE, whether related or not related, and 2 calendar days for non-serious Akynzeo® related AEs. In the situation that investigator's causality assessment is either missing or unknown, the Global Reporting Form for SAEs/AESIs/Special Situations Report Form will be sent as defined above to the sponsor. Sponsor will perform a provisional causality assessment of all AE and do any reasonable effort to obtain a causality assessment from investigator for any of the drugs for sponsor is MAH or distributor. The AE reports concerning any other drug (sponsor is not MAH or distributor) will be collected in the database and may be sent to the sponsor upon request. For any medicinal products for which another pharmaceutical company holds the Marketing Authorization, investigators are

responsible to report the correspondent safety information to the MAH or Local Competent Authority according to current laws and regulations.

The Global Reporting Form for SAEs/AESIs/Special Situations Report Form included in Appendix 6 will be defined on the basis of the agreement with sponsor and in compliance with the applicable laws.

An emerging safety issue is an issue that may have a potential major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health and the potential need for prompt regulatory action and communication to patients and healthcare professionals. If the investigator identifies any issue meeting this definition, it must be reported to the sponsor immediately and without delay, together with the rationale for which the data are considered to be an emerging safety issue.

9 PREGNANCY REPORTING

If a patient becomes pregnant during the study, as soon as information about the pregnancy is received, the investigator must inform the sponsor within 24 hours (using the Pregnancy Notification Form included in Appendix 7) from the investigational staff becoming aware of it, and the subject must be withdrawn from the study without delay. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10 LACK OF EFFICACY

Lack of efficacy or Unusual Failure in Efficacy is defined as failure of a health product to produce the expected/intended effect, which may result in an adverse outcome for the patient, including an exacerbation of the condition for which the health product is being used. One example of unusual failure in efficacy is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription. Another example of a case that should be reported on an expedited basis is a life-threatening infection where the failure in efficacy seems to be due to the development of a newly resistant strain of bacterium previously regarded as susceptible.

Lack of efficacy should be reported to the sponsor within 24 hours of the investigational staff becoming aware of it using the Global Reporting Form for SAEs/AESIs/Special Situations Report Form (Appendix 6).

11 ETHICAL AND REGULATORY CONSIDERATIONS

The investigator is responsible for ensuring that this study is conducted according to the protocol, current International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (ICH guidelines), applicable government regulations and Institutional research policies and procedures.

All procedures will conform to the latest revision of the "Declaration of Helsinki", the guidelines for the "Conduct of Clinical Investigations" issued by the Therapeutics Products Directorate Canada (1997) and the Tri-Council Policy statement on Ethical Conduct for Research involving Humans (TCPS2-2010).

11.1 Research Ethics Board (REB)

The following documents will be submitted to a properly constituted REB for formal approval before implementation of the study:

- Final protocol and, if applicable, any amendments
- Sponsor-approved Subject Information Sheet and ICF
- Product Monograph (or equivalent information) and amendments
- Any sponsor-approved written information to be provided to the subjects (e.g. subject diaries, subject study participation cards, questionnaires, etc.)
- Sponsor-approved subject recruiting materials (e.g. text for advertisements, flyers, posters, etc.)
- Primary Investigator and Co-Investigator(s)'s up-to-date curriculum vitae (and medical license if required)
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Information on the funding and potential conflicts of interest
- Any other information requested by the REB

Before commencement of the study the investigator must receive from their REB a favorable opinion in writing (signed, dated, and referring to the study by its full title and protocol number) that states which documents (full name, date and version number) have been reviewed and approved.

In order to comply with internationally accepted guidelines governing good clinical research practices, the investigator must also receive a list of the REB's voting members, their titles or occupations, and their institutional affiliations and a statement, that the REB is organized and operates according to GCP and the applicable laws and regulations.

The investigator will provide a copy of this/these document(s) to the sponsor prior to the initiation of their site.

Prior to study implementation the REB must provide the sponsor with a signed and dated attestation, stating that:

1. The membership of the REB complies with the requirements defined in Division 5 of the Food and Drug Regulations.
2. The REB carries out its functions in a manner consistent with GCP.
3. The REB has reviewed and approved the clinical trial protocol and ICF and that the view of the REB has been documented in writing.

During the study the investigator (or sponsor where required) will submit the following documents to the REB for review and approval, if applicable:

- Protocol amendments

- Updates to the ICF
- Updates to any written material that is provided to the subjects during the study
- New or revised sponsor-approved recruiting materials
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Reports of any SAEs or of adverse events which are unexpected, and associated with the study drug
- Any new findings on the study drug that could impact subject safety or the conduct of the study and/or increase the risk to the subjects
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Death of a study subject
- Information about any new investigator(s) at the study site

The investigator agrees to send written summaries of the trial status to the REB annually, or more frequently, if requested by the REB.

At least once a year, or as outlined by the site's REB, the investigator will also seek to obtain written approval from the REB to continue the study. A copy of this written approval, (referring to the study by protocol title, number and date, including the date of any amendment) will be provided to the sponsor.

The investigator will notify the REB of completion of the study not later than one month following study completion or termination.

A copy of all communication between the investigator and the REB regarding this study will be provided to the sponsor's study monitor. The investigator will maintain an accurate and complete record of all submissions made to the REB, including a list of all reports and documents submitted.

11.2 Informed Consent

Before enrolling a subject into the study, and prior to performing any study related procedures, the investigator or an authorized member of the investigational staff must obtain written informed consent from the subject or the subject's legal representative. This consent must be obtained by providing the subject or the subject's legal representative with the current REB-approved subject information sheet and consent form that is written in a language the subject or the subject's legal representative fluently understands. All subjects or their legal representative must have the opportunity to discuss the information provided to them with the investigator / co-investigator / sub-investigator.

During the informed consent process the following will be discussed with the subject or the subject's legal representative and be documented:

- Overall study structure and objectives
- All study visits and procedures (e.g. medication dosing, physical exam, blood taking, subject questionnaires, diaries, etc.)
- Reasonably anticipated benefits and potential hazards of the study

- Subject participation is voluntary and the consent to participate may be withdrawn at any time
- Choosing not to participate or withdrawing consent to participate will not affect the subject's future care
- Collection and processing of personal data (i.e. why the sponsor collects, uses and discloses personal data and who is responsible for protecting their personal information)
- Direct access of authorized health authorities and sponsor staff to confidential subject records
- Any study related questions the subject may have

The subject or the subject's legal representative will then be given the sponsor and REB-approved ICF (printed on the investigator's or institution's letterhead) and sufficient time to read it and discuss the provided information to make an informed decision about their study participation. After all questions have been answered to the subject's or the subject's legal representative's satisfaction the subject or the subject's legal representative will sign and date the ICF. The form will also be signed and dated by the investigator (or investigator-designated research professional obtaining the consent) and a copy of it will be provided to the subject or the subject's legal representative.

The subject or the subject's legal representative will be informed that during the course of the trial they will be provided with any new information or findings that may affect their willingness to participate.

12 DATA HANDLING AND RECORD KEEPING

12.1 Confidentiality and Privacy

Information about study subjects will be kept confidential and managed according to the requirements of the Canadian *Personal Information Protection and Electronic Documents Act (PIPEDA)* (2000).

Only those personal data will be collected and processed that are necessary to investigate the efficacy, safety, quality, and utility of the investigational product(s) used in this study. These data must be collected in an anonymized manner.

As part of the informed consent procedure, explicit consent for the collecting and processing of personal data will be obtained from the study subject prior to any data collection. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of the study subject confidential.

De-identified personal information collected during the study may also be added to research databases and used in the future by the sponsor and other companies and people working for or with the sponsor for scientific research purposes to: (i) develop a better understanding of the safety and effectiveness of Akynzeo®; (ii) study other therapies for patients; (iii) develop a better understanding of diseases included in the study; and (iv) improve the efficacy, design and methods of future studies.

The results of the study may be published in scientific journals and/or presented at scientific meetings. In this case, the personal information will be anonymized.

De-identified personal information may also be disclosed to the following recipients for the purposes identified above: (i) the sponsor and its affiliates; (ii) third service providers engaged to assist the sponsor and the Clinical Trial Site including contract research organizations; (iii) the Institutional Review Board / Ethics Committee which approved the study; (iv) academic research organizations; (v) governmental regulatory agencies and other health authorities; and (vi) the sponsor's business partners and licensing partners. As may be required for the above purposes, Sponsor may disclose certain personal data to third parties recipients also located in countries, which may not have data privacy laws equivalent to those in Canada. In such a case, sponsor will take all necessary steps to ensure the safety of data subjects' personal data in accordance with the requirements of the applicable data protection laws.

The sponsor will ensure that the subject's personal data will be:

- Collected by fair and lawful means
- Collected, used or disclosed reasonably and appropriately, and not used for any purpose other than that to which the subject has consented
- Protected by appropriate security measures
- Handled according to the sponsor's personal information policies. These policies must be clear, understandable and readily available.

The subject has the right to:

- Expect the personal information the sponsor holds about them to be accurate, complete and up-to-date
- Obtain access to their personal information and ask for corrections if necessary
- Complain about how their personal information are handled if they feel their privacy rights have not been respected
- Revoke their authorization for use of their personal data but only under exceptional circumstances which can be shown to cause unwarranted and substantial damage or distress to the subject and only when the data to be removed can be traced back to the subject

In the event that a subject revokes authorization to collect or use personal data, the investigator retains the right to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use personal information, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

12.2 Source Documents

Source data is all information in original records (and certified copies of original records) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Examples of these original documents, data and records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives,

microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

Source data may be collected by the sponsor, e.g., subject's diaries. In such cases, a copy of the source data will remain at the site. Any source data collected by the sponsor will only contain the subjects' initials and subject number as identifiers.

Any data that are directly recorded in the CRFs will be considered as source data (e.g. subject questionnaires, visual analog scales, etc.). If data are recorded directly in the CRF, then it should be noted in the medical records that the assessment was done and by whom and the date it was done.

12.2.1 Direct Access to Source Documents

By signing the ICF, the subject provides permission that their original medical records can be directly accessed for trial-related monitoring, auditing, REB review and regulatory inspection.

The investigator(s) will provide direct access to all source data/documents for study related activities of authorized sponsor personnel, auditors, REB, and regulatory inspectors.

12.3 Subject Screening Form and Subject Identification Form

The investigator will complete a subject screening form which lists all subjects who were evaluated to determine eligibility for study participation. The screening form will list the date of screening, name of the screened subject and their suitability for study inclusion or reason for study exclusion.

The investigator also agrees to complete a subject identification form which allows easy identification of each subject during and after the study. The subject identification form will list the subject's name, initials, contact information, baseline number (if applicable), randomization number, date randomized and date of study completion or withdrawal.

This information should enable the study site to contact the study subjects in the event that the study drug is later found to endanger the health of the subjects or other persons.

To maintain subject confidentiality, the subject screening form and subject identification form are only filed in the site's study file and no copies will be retained in the sponsor's files. Pre-screening logs may be collected by the sponsor from the sites. These logs may only contain subjects' initials but will not contain subjects' names.

12.4 Case Report Forms (CRFs)

A CRF is a printed, optical, or electronic document, designed to record all of the protocol-required information to be reported to the sponsor on each study subject. Case report forms (CRFs) will be supplied by the sponsor. For this study Electronic Data Capture will be used.

All data requested on the CRF must be recorded. Data must be entered into CRFs in English.

The data obtained are entered by the staff at the study site in the data capture screen of the web-based documentation system. According to the data validation plan customized for this study the system validates the data entered online.

The participating physician undertakes to provide all necessary background information to his records upon request. This is particularly important if errors in data entry or data transmission are suspected.

The participating physician assures that the information recorded is accurate and verifiable.

12.5 Record Retention

The investigator shall retain all essential documents (including the subject identification form) for a period of **25 years** or for at least 2 years after the last approval of a marketing application in Canada or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, whatever occurs **later**.

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

13 QUALITY ASSURANCE AND QUALITY CONTROL

13.1 Monitoring

Clinical research personnel from the sponsor or their legally appointed agent will make regular visits to the study site to oversee the progress of the study, and to ensure that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirements.

The purposes of monitoring are to verify that the rights and well-being of the subjects are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements.

The first monitoring visit after study initiation should usually be done as soon as possible after subject recruitment has started.

The investigator will ensure that the monitor or other compliance or quality assurance reviewer is given access to all study-related documents (e.g. source documents, medical records, CRFs, drug accountability records, etc.) and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

The sponsor expects that, during monitoring visits, the relevant investigational staff will be available and allocate adequate time with the monitor for discussion of any issues or questions resulting from the monitoring activities.

13.2 Auditing

The investigator will permit study-related audits by the sponsor's clinical quality assurance department, an independent sponsor selected auditor [e.g. Contract Research Organization (CRO)], or the site's REB of all study related activities, documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.), and applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.). The purpose of an audit is to systematically and independently examine trial-related activities and documents to determine whether the activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable SOPs, GCP and all applicable regulatory requirements.

13.3 Inspecting

The investigator must be aware that a regulatory authority(ies) may be conducting an official review of documents, facilities, records, and other resources that are deemed by the authority(ies) to be related to the clinical study. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable

quality assurance offices. The Principle Investigator is responsible for informing the sponsor of an inspection as soon as he/she becomes aware of it.

14 STUDY FINANCES

14.1 Funding

The sponsor will provide a research grant for the study. A budget will be developed with the investigator and all financial aspects of the study will be documented in a separate agreement between the sponsor and the investigator/institution.

14.2 Insurance

The sponsor maintains a program of comprehensive general liability insurance and product liability insurance for the duration of the study at levels sufficient to support the indemnification obligations assumed under the separate agreement “Investigator Agreement – Study No. CAN-PRO-NEPA-001 Responsibilities and Procedures”.

The investigator also maintains a program of comprehensive general liability insurance for the duration of the study at levels sufficient to support the indemnification obligations assumed under the separate agreement “Investigator Agreement – Study No.CAN-PRO-NEPA-001 Responsibilities and Procedures”.

15 USE OF INFORMATION AND PUBLICATION

Details concerning the procedures to be followed prior to publication are outlined in a separate agreement “Investigator Agreement – Study No. CAN-PRO-NEPA-001 Responsibilities and Procedures”.

Prior to study start, the study will be published in a public study register. The summary of the results and/or the final medical report will be published in a publicly-accessible database no later than one year after study completion (LPO) and may be presented at a scientific congress.

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17 APPENDICES

Appendix 1: Subject Information and Informed Consent Form

Appendix 2: Patient Diary

Appendix 3: FLIE questionnaire

Appendix 4: WPAI-NV questionnaire

Appendix 5: HEC and MEC Emetogenicity

Appendix 6: Safety Reporting Forms

Appendix 7: Pregnancy Notification Form

Appendix 8: Study Drug Access Card

Appendix 1: Subject Information and Informed Consent Form

SUBJECT INFORMATION AND CONSENT FORM

Study Title:	A Phase IV, Real World Observational Study On The Use Of Akynzeo® (netupitant/palonosetron) For The Prevention Of Nausea and Vomiting in Oncology Patients Receiving Highly Emetogenic Chemotherapy (HEC) Over Multiple Cycles.
Study Number:	CAN-PRO-NEPA-001
Study Sponsor:	Purdue Pharma 575 Granite Court Pickering, ON, Canada L1W 3W8
Study Doctor:	TBD
Site Name:	TBD
Site Address:	TBD
Emergency Contact:	**Call** <<24_HOUR_NUMBER>>

INTRODUCTION

You are invited to consider taking part in a real world observational study involving persons with chemotherapy-induced nausea and vomiting. This information and consent form describes the study. It may contain words that you do not understand. If you have any questions, or do not understand anything in this form, please ask the study doctor or nurse to explain. Please take the time to read this form thoroughly, and discuss it with your family, friends and/or regular doctor.

Your participation in this study is entirely voluntary. The study doctor will still treat your chemotherapy-induced nausea and vomiting whether you take part or not. If you decide to take part in the study, you will be asked to sign at the end of this form. Even if you decide to participate in the study, you may withdraw at any time.

WHO IS CONDUCTING THE STUDY?

The study is being conducted/sponsored by Purdue Pharma (Canada). The study doctor is being paid by the study sponsor, Purdue Pharma (Canada), to conduct this medical research study; however, the study doctor is not an employee of Purdue Pharma (Canada).

WHY IS THIS STUDY BEING DONE?

This is a Phase IV study. A Phase IV study is a study of an approved drug or treatment (also called "a post marketing study") which is conducted to obtain additional information regarding the drug's or treatment's, benefits and optimal use.

This study is being done to collect clinical data on the real world use of Akynzeo® in Canada. Akynzeo® is a combination of 2 products called netupitant and palonosetron in a single capsule. It is approved by Health Canada for the treatment of chemotherapy-induced nausea and vomiting. You will receive Akynzeo®, as prescribed by your doctor, regardless of your participation in this study.

If you consent and participate in the study, you will be one of an estimated 200 male and/or female adults with chemotherapy-induced nausea and vomiting, participating in this study, which is taking place at up to 20 study sites in Canada.

A description of this clinical trial will be available on http://www.clinicaltrials.gov.This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

WHAT DOES THE STUDY INVOLVE?
If you take part in the study, you will be required to attend 6 study visits, over a total of 4 to 6 months.

Visit 1 - Screening Visit.

In order to determine if you are eligible to participate in this study, your study doctor will ask you some questions and do some tests. This screening visit is expected to last about 1 hour. The following procedures will be done at this visit:

- Review of your medical history including medications you are currently taking.
- Demographics.
- Nausea assessment – previous and ongoing.
- Pregnancy Test
- Distribution and education regarding the Patient Kit (which includes a Study Pharmacy card, diary card and questionnaires)

Any abnormal result in the assessments or tests mentioned above may affect your eligibility to participate in the study. You will be informed of any significantly abnormal result and, if necessary, you will be referred to another healthcare professional.

Visit 2 – First Day of cycle 1

This visit will occur on the first day of your first chemotherapy cycle. This visit is expected to last about 45 minutes. The following procedures will be done at this visit:

- Review of your health status, medications you are currently taking and any changes since the previous visit.
- The study doctor or nurse or a member of the study staff will ask you about how you have been feeling since the last visit.
- Approximately 1 hour prior to the start of your chemotherapy treatment you will take 1 capsule of Akynzeo®.

Following your visit you must complete the patient diary every day for 5 days after your chemotherapy and the study questionnaires on the 5th day after your chemotherapy, contained in your patient kit

Visits 3 to 5 – First day of cycles 2 to 4

Each visit is expected to last about 30 minutes.

- You will return the patient diary and the study questionnaires.
- The study doctor or nurse or a member of the study staff will review the patient diary and the study questionnaires.
- The study doctor or nurse or a member of the study staff will ask you about any medications you are taking and how you have been feeling since the last visit.
- Approximately 1 hour prior to the start of your chemotherapy treatment you will take 1 capsule of Akynzeo®.

Following your visit you must complete the patient diary every day for 5 days after your chemotherapy and the study questionnaires on the 5th day after your chemotherapy, contained in your patient kit

Visit 6 (Final Visit) - Prior to start of next chemotherapy cycle

This visit is expected to last about 30 minutes.

- You will return the patient diary and the study questionnaires.
- The study doctor or nurse or a member of the study staff will review the patient diary and the study questionnaires.
- The study doctor or nurse or a member of the study staff will ask you about any medications you are taking and how you have been feeling since the last visit.

After this visit your participation in the study will be over.

Early Discontinuation from Study Participation
If you decide to leave the study early, or if you are withdrawn by the study doctor, you will be asked to come to the study doctor's office one more time. The purpose of this visit is to check your health and obtain information for the study. You do not have to come back if you do not agree to do so.

WHAT ARE MY RESPONSIBILITIES?
As a participant in this study, your responsibilities include:

- Following the instructions about the study given to you by your study doctor and staff.
- Complete the patient diaries and study questionnaires as instructed.
- Attending all study visits.
- Taking the study medication as directed.
- Telling the study doctor about changes to your health, and any side effects (unwanted effects or health problems) you experience.
- For your safety, it is very important to tell the study doctor about all medications you are taking, and to check with the study doctor before you begin taking a new medication while in this study.
- If you or your partner becomes pregnant, this must be reported to the study doctor or staff.
- Inform the study doctor or staff if you no longer wish to participate in the study.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?
The most common side effects may include:

- Headache
- Constipation
- Fatigue (feeling tired)

With any medication, there is a risk of allergic reactions, such as hives, swelling of the face, lips, tongue and/or throat which may cause difficulty in breathing or swallowing, and if not treated promptly could become life-threatening. If you experience the symptoms of an allergic reaction, go to the nearest emergency department.

There may be other risks or side effects that are unforeseeable or not listed above. One of the reasons for conducting this study is to see how safe it is to use in people, so there may be other side effects that are not known at this time. In general, these side effects are temporary and will disappear by the end of the study.

Sometimes during a study, we learn about new information about the study drug. If any new information about this study becomes available during the study, your study doctor will let you know as soon as possible. It is possible that this new information may make you change your mind about participating in this research study.

Risks in Pregnancy:

At this time, it is not known if Akynzeo® can harm an unborn child. For that reason, if you are pregnant or breast-feeding, you will not be able to take part in the study. Also, women who are able to become pregnant will be required to use an approved method of birth control while on the study and up to one month after the last dose of Akynzeo®. Acceptable forms of birth control include but are not limited to the abstinence, birth control pills or an intrauterine device. The study doctor will discuss these with you. Even if using an acceptable form of birth control, pregnancy may still occur. Not having sex is the only certain way to prevent pregnancy.

If you do become pregnant, during the study or within 28 days of completing the study, please tell your study doctor. The study doctor may/will ask your permission to follow your pregnancy to see if it is affected at all by your participation in the study.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

No direct benefit is guaranteed to you from taking part in this study. The information gained from this study may help the development of better ways to treat patients with chemotherapy-induced nausea and vomiting in the future.

WHAT ARE THE ALTERNATIVES TO THE STUDY TREATMENT?

You do not have to participate in this study to receive treatment for your condition. You will continue to receive treatment from your doctor.

WHAT HAPPENS IF WE DECIDE TO WITHDRAW?

Your participation in this study is completely voluntary. You have the right to withdraw from the study at any time, without giving a reason, even if you have signed this consent form. If you decide not to take part, or to withdraw, it will not harm your relationship with the study doctor, and you will still receive treatment for your chemotherapy-induced nausea and vomiting. If you do not take part or withdraw from the study, you will not be penalized nor lose any benefits to which you are entitled.

The study doctor may also withdraw you from the study if your condition worsens, if you do not follow the doctor's instructions, if the study doctor feels it is in your best interests to be withdrawn, if

the study sponsor discontinues the study, or the sponsor or a regulatory authority decides to terminate the study. You can be withdrawn without your consent, but the study doctor will tell you why.

WILL MY PARTICIPATION BE KEPT CONFIDENTIAL?

No information that discloses your identity will be released or published without your specific consent.

Study records that identify you will be kept confidential at all times, except where disclosure is required by law. As part of this research, the study doctor will collect the results of your study-related tests and procedures and may also access your personal medical records for health information such as past medical history and test results. Information from this study will be submitted to the sponsor, and may be submitted to Health Canada and possibly to governmental agencies in other countries (e.g. US Food and Drug Administration) where the study medication is marketed or being considered for approval. Information sent from the study site will contain your initials and a code number but will not contain your name. The de-identified personal information collected during the study may also be added to research databases and used in the future by the sponsor and other companies and people working for or with the sponsor for scientific research purposes to: (i) develop a better understanding of the safety and effectiveness of Akynzeo®; (ii) study other therapies for patients; (iii) develop a better understanding of diseases included in the study; and (iv) improve the efficacy, design and methods of future studies.
The results of this research study may be presented at meetings or in publications but your identity will not be disclosed.

To make sure that the health information collected in this study is accurate, it will need to be checked from time to time against your medical records. Some persons may need to see these records in order to monitor the research and verify the accuracy of the study data, including:

- a limited number of representatives from the study sponsoring drug company, (namely its monitors and auditors),
- the research ethics review board - *[name of research ethics board (REB)/institutional review board (IRB)]* (an independent ethics committee that reviewed the ethical aspects of this study to help protect the rights and welfare of study participants),
- government regulatory authorities including Health Canada, the US Food and Drug Administration (FDA) and other foreign regulatory agencies.

Your study records including confidential information about you collected during the study will be kept at a secure location for a period of 25 years following completion of the study.

While every effort will be made to protect the privacy of your information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect your privacy.

The study doctor and the other research team members have no conflicts of interest to declare related to this study.

By signing this information and consent form, you consent to the collection, access, use and disclosure of your information as described above.

Study Costs/Reimbursement:
There is no cost to you, your private medical insurance (if any), or the public health insurance plan, for study procedures. Akynzeo® will be provided free of charge for the duration of the study. You will be given a Clinical Study Drug Access Card that you will use at a pharmacy of your choice to obtain the study medication.

This clinic provides reimbursement for expenses, such as parking or babysitting. You will be reimbursed up to $30.00 for expenses at each study visit.

Compensation for Injury:
This section is to remain as is. If changes are to be made, they must be approved by the Purdue Pharma Legal Department.

If you become ill or are injured as a result of participation in this study, you will receive appropriate medical care. For subjects treated in accordance with the protocol the sponsor will cover necessary medical costs not covered by your government health plan (if applicable) or your private medical insurance (if any). By signing this form, you are not giving up your legal rights, nor releasing the study doctor or sponsor from their legal and professional obligations.

If You Have Questions:
If you have questions, concerns or complaints regarding this study or adverse effects of study medication, you should contact the study doctor or the study staff at the telephone number listed on the first page of this form.

In case of emergency, please go to the nearest hospital emergency department.

This study has been reviewed and approved on ethical grounds by the *[name of REB/IRB]*.

Please contact *[name of REB/IRB]*, which is not affiliated with the research or the research team, if you have questions about your role and rights as a research participant, or have concerns, complaints or general questions about the research, by phone:
[telephone number] or by email: *[REB/IRB email address]*

CONSENT TO PARTICIPATE

I acknowledge I have been given sufficient time to read and ask any question I might have about the information presented in this Informed Consent Form and to consider whether or not to participate in this study. I acknowledge having received satisfactory answers to questions I might have asked. I have been informed of the risks, benefits and alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising my medical care. I know that I may ask now, or in the future, any question I have about the study or the research procedures.

I have been assured that records relating to my care and me will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission unless required by law. I consent to the review of my medical records (which will contain my name) by the sponsor and its representatives, the Research Ethics Board, Health Canada, the FDA and other regulatory authorities where the study drug may be considered for approval for the purposes as described in this Consent Form.

The study doctor has my permission to contact my regular doctor about my participation in this study:

YES _____ NO _____
Initials Initials

By signing this form I voluntarily consent to participate in this research study and have not waived any of my legal rights. I acknowledge that I have received a copy of this consent form.

_____	_____	_____
Subject name (printed)	Signature	Date (dd/mmm/yyyy)
_____	_____	_____
Name of person obtaining consent (printed)	Signature	Date (dd/mmm/yyyy)

INVESTIGATOR STATEMENT

I acknowledge my responsibility for the care and wellbeing of the above subject, to respect the right and wishes of the subject, and to conduct the study according to applicable Good Clinical Practice Guidelines and regulations.

_____	_____	_____
Investigators name (printed)	Signature	Date (dd/mmm/yyyy)

Witness *(If subject is unable to read)*

I attest that:

- the information in the consent form and any other written information was accurately explained to and apparently understood by the subject or the subject's legally acceptable representative; and
- informed consent was freely given by the subject or subject's legally acceptable representative."

_____	_____	_____
Witness name (printed)	Signature	Date (dd/mmm/yyyy)

Appendix 2: Patient Diary

Dear patient,

This booklet contains a diary which you should complete daily during your participation in this study. The patient daily diary will be used to capture the nausea and vomiting you experienced, the medication for the treatment of nausea and/or vomiting you took and to assess the effectiveness of the study treatment in controlling nausea and vomiting. The diary will be collected during study visits and reviewed with you by study personnel.

Please read the instructions carefully before filling the diary. If you have any questions regarding the diary, please contact study personnel.

There are no right or wrong answers. All information you provide will be strictly confidential.

Thank you for your participation in this study.

GENERAL INSTRUCTIONS

- Please bring back the diary at each study visit.
- Please make sure that all writing is clear and readable.
- If you make a mistake, cross it out and make your change readable. Please do not use liquid paper or white out to make your changes.
- Please record the dates and times in the following format:

  Date: dd/mmm/yyyy (i.e., 12/Mar/2018)

  Hour: hh:mm (24-hour clock) (i.e., 18:45)

- Please complete all questions. Do not leave blank spaces.

NAUSEA

To help assess how good or bad your nausea is, we have drawn a scale which ranges from 0 (no nausea) to 100 (nausea as bad as it could be). Each day, for the first 5 days following chemotherapy, we would like you to indicate on this scale how good or bad your nausea was, in your opinion. Please draw a straight vertical line on the scale to indicate how good or bad your nausea was each day. Please see an example below.

Version: May 8, 2018 Confidential Page 1

CAN-PRO-NEPA-001	**PATIENT DIARY** DAILY EVALUATION	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

DAY 1 EVALUATION: 0 - 24 HOURS AFTER START OF CHEMOTHERAPY		
Please complete the page on: (for study personnel only)	☐☐ / ☐☐☐ / ☐☐☐☐ dd mmm yyyy	☐☐ : ☐☐ hh mm

Please remember to record any experience of retching (unproductive vomiting) and/or vomiting on pages 12 to 13 and the medication(s) you took for the treatment of nausea and/or vomiting on pages 14 to 15.

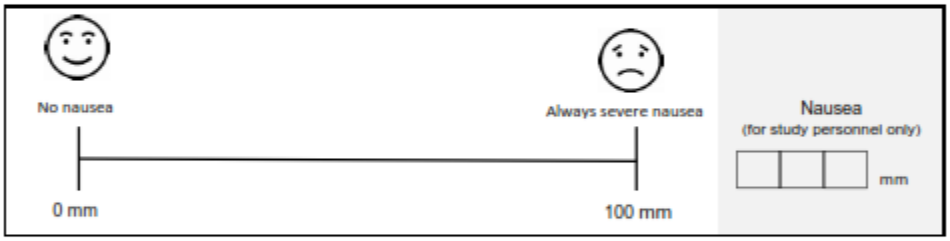
Please evaluate your severity of nausea for the 0 to 24-hour interval after the start of chemotherapy.

Example: Start of chemotherapy – 01June2018 @ 08:00
Period of evaluation = 01June2018 @ 08:00 to 02June2018 @ 07:59

1. NAUSEA

How much nausea did you experience on average during the last 24 hours?

Please mark on the following scale with a straight vertical line:



2. Have you experienced any vomiting in the last 24 hours?

☐ No
☐ Yes → Please record on the Retching and/or Vomiting page (page 12).

3. Has there been a change in your appetite?

☐ No change in appetite
☐ Nausea – lost appetite but able to eat as usual
☐ Nausea – lost appetite but able to eat a reduced amount
☐ Nausea – lost appetite and unable to eat

4. Did you take any medications because of severe nausea?

☐ No
☐ Yes → Please record on the Rescue Medication page (page 14).

CAN-PRO-NEPA-001	**PATIENT DIARY** DAILY EVALUATION	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

DAY 2 EVALUATION: >24 - 48 HOURS AFTER START OF CHEMOTHERAPY

Please complete the page on: (for study personnel only)	☐☐ / ☐☐☐ / ☐☐☐☐ dd mmm yyyy	☐☐ : ☐☐ hh mm

Please remember to record any experience of retching (unproductive vomiting) and/or vomiting on pages 12 to 13 and the medication(s) you took for the treatment of nausea and/or vomiting on pages 14 to 15.

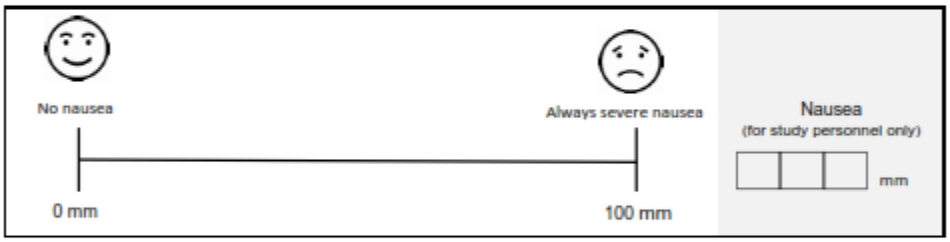
Please evaluate your severity of nausea for the >24 to 48-hour interval after the start of chemotherapy.

Example: Start of chemotherapy – 01June2018 @ 08:00
Period of evaluation = 02June2018 @ 08:00 to 03June2018 @ 07:59

1. NAUSEA

How much nausea did you experience on average during the last 24 hours?

Please mark on the following scale with a straight vertical line:



2. Have you experienced any vomiting in the last 24 hours?

- ☐ No
- ☐ Yes → Please record on the Retching and/or Vomiting page (page 12).

3. Has there been a change in your appetite?

- ☐ No change in appetite
- ☐ Nausea – lost appetite but able to eat as usual
- ☐ Nausea – lost appetite but able to eat a reduced amount
- ☐ Nausea – lost appetite and unable to eat

4. Did you take any medications because of severe nausea?

- ☐ No
- ☐ Yes → Please record on the Rescue Medication page (page 14).

CAN-PRO-NEPA-001	**PATIENT DIARY** DAILY EVALUATION	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

DAY 3 EVALUATION: >48 - 72 HOURS AFTER START OF CHEMOTHERAPY

Please complete the page on: (for study personnel only)	☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy	☐☐ : ☐☐ hh mm

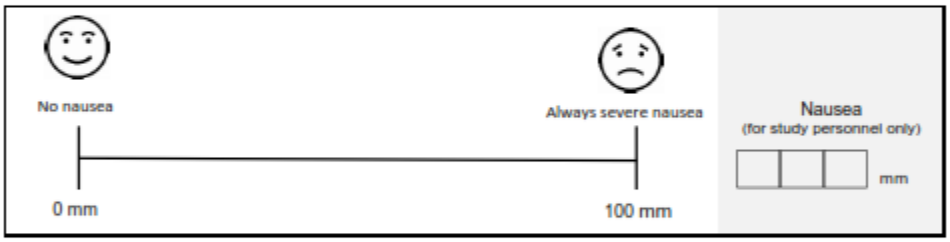
Please remember to record any experience of retching (unproductive vomiting) and/or vomiting on pages 12 to 13 and the medication(s) you took for the treatment of nausea and/or vomiting on pages 14 to 15.

Please evaluate your severity of nausea for the >48 to 72-hour interval after the start of chemotherapy.

Example: Start of chemotherapy – 01June2018 @ 08:00
Period of evaluation = 03June2018 @ 08:00 to 04June2018 @ 07:59

1. NAUSEA

How much nausea did you experience on average during the last 24 hours?
Please mark on the following scale with a straight vertical line:



2. Have you experienced any vomiting in the last 24 hours?

☐ No
☐ Yes → Please record on the Retching and/or Vomiting page (page 12).

3. Has there been a change in your appetite?

☐ No change in appetite
☐ Nausea – lost appetite but able to eat as usual
☐ Nausea – lost appetite but able to eat a reduced amount
☐ Nausea – lost appetite and unable to eat

4. Did you take any medications because of severe nausea?

☐ No
☐ Yes → Please record on the Rescue Medication page (page 14).

CAN-PRO-NEPA-001	**PATIENT DIARY** DAILY EVALUATION	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

DAY 4 EVALUATION: >72 - 96 HOURS AFTER START OF CHEMOTHERAPY		
Please complete the page on: (for study personnel only)	☐☐ / ☐☐☐ / ☐☐☐☐ dd mmm yyyy	☐☐ : ☐☐ hh mm

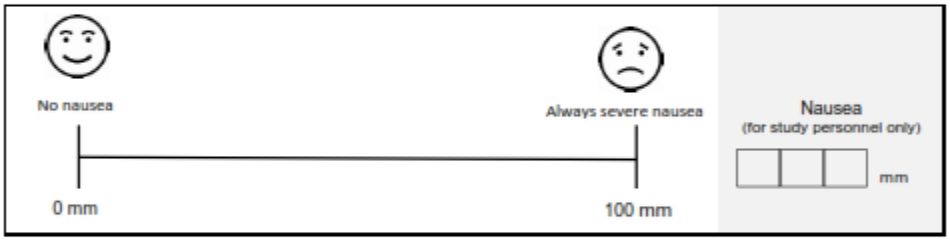
Please remember to record any experience of retching (unproductive vomiting) and/or vomiting on pages 12 to 13 and the medication(s) you took for the treatment of nausea and/or vomiting on pages 14 to 15.

Please evaluate your severity of nausea for the >72 to 96-hour interval after the start of chemotherapy.

Example: Start of chemotherapy – 01June2018 @ 08:00
Period of evaluation = 04June2018 @ 08:00 to 05June2018 @ 07:59

1. NAUSEA

How much nausea did you experience on average during the last 24 hours?
Please mark on the following scale with a straight vertical line:



2. Have you experienced any vomiting in the last 24 hours?

☐ No
☐ Yes → Please record on the Retching and/or Vomiting page (page 12).

3. Has there been a change in your appetite?

☐ No change in appetite
☐ Nausea – lost appetite but able to eat as usual
☐ Nausea – lost appetite but able to eat a reduced amount
☐ Nausea – lost appetite and unable to eat

4. Did you take any medications because of severe nausea?

☐ No
☐ Yes → Please record on the Rescue Medication page (page 14).

CAN-PRO-NEPA-001	**PATIENT DIARY** DAILY EVALUATION	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

DAY 5 EVALUATION: >96 - 120 HOURS AFTER START OF CHEMOTHERAPY		
Please complete the page on: (for study personnel only)	☐☐ / ☐☐☐ / ☐☐☐☐ dd mmm yyyy	☐☐ : ☐☐ hh mm

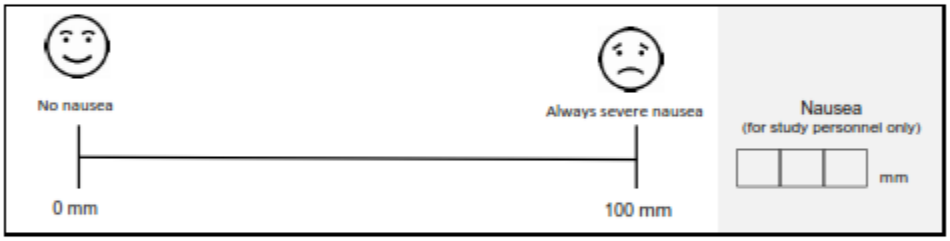
Please remember to record any experience of retching (unproductive vomiting) and/or vomiting on pages 12 to 13 and the medication(s) you took for the treatment of nausea and/or vomiting on pages 14 to 15.

Please evaluate your severity of nausea for the >96 to 120-hour interval after the start of chemotherapy.

Example: Start of chemotherapy – 01June2018 @ 08:00
Period of evaluation = 05June2018 @ 08:00 to 06June2018 @ 07:59

1. NAUSEA

How much nausea did you experience on average during the last 24 hours?
Please mark on the following scale with a straight vertical line:



2. Have you experienced any vomiting in the last 24 hours?

☐ No
☐ Yes → Please record on the Retching and/or Vomiting page (page 12).

3. Has there been a change in your appetite?

☐ No change in appetite
☐ Nausea – lost appetite but able to eat as usual
☐ Nausea – lost appetite but able to eat a reduced amount
☐ Nausea – lost appetite and unable to eat

4. Did you take any medications because of severe nausea?

☐ No
☐ Yes → Please record on the Rescue Medication page (page 14).

At the end of Day 5 evaluation, please complete the following questionnaires: *Functional Living Index – Emesis* and the *Work Productivity and Activity Impairment Questionnaire: Nausea & Vomiting*.

CAN-PRO-NEPA-001	**PATIENT DIARY** Retching and/or Vomiting Log	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

RETCHING (UNPRODUCTIVE VOMITING) AND/OR VOMITING

- *If you experienced a retching (unproductive vomiting) or vomiting episode during the 120 hours (5 days) after the start of chemotherapy, please check "Yes" and record the date, onset time and end time of each episode of retching and vomiting.*
- *Please record the date and onset/end time in the most precise manner.*
- *If you did not experience any retching or vomiting episodes, please remember to check "No" before returning the diary to the Investigator at your next visit.*

	Did you experience any episodes of retching and/or vomiting during the 120 hours (5 days) after the start of chemotherapy?	Yes ☐ No ☐

Retching	Vomiting	Date	Onset Time 00:00 – 23:59	End Time 00:00 – 23:59
☐	X	01 / Jun / 2018 dd mmm yyyy *The first row is pre-filled as an example*	08 : 35 hh mm	08 : 55 hh mm
☐	☐	dd / mmm / yyyy	hh : mm	hh : mm
☐	☐	dd / mmm / yyyy	hh : mm	hh : mm
☐	☐	dd / mmm / yyyy	hh : mm	hh : mm
☐	☐	dd / mmm / yyyy	hh : mm	hh : mm
☐	☐	dd / mmm / yyyy	hh : mm	hh : mm
☐	☐	dd / mmm / yyyy	hh : mm	hh : mm
☐	☐	dd / mmm / yyyy	hh : mm	hh : mm
☐	☐	dd / mmm / yyyy	hh : mm	hh : mm

CAN-PRO-NEPA-001	**PATIENT DIARY** Rescue Medication Log	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

RESCUE MEDICATION

	Did you take medication for the **treatment of nausea and/or vomiting** during the 120 hours (5 days) after the start of chemotherapy?	Yes ☐ No ☐

- ***If you checked "Yes", please record every medication you take for the treatment of nausea and/or vomiting during the 120 hours (5 days) after the start of chemotherapy.***
- *Please record the date and time taken in the most precise manner.*
- *For each medication taken, please record the dose, route and quantity.*

Medication Please list every administration of medication separately	**Dose** (e.g., 10 mg)	**Route** (e.g., oral, rectal, topical, intravenous)	**Quantity** (e.g., 1 tablet)	**Date and Time of Intake of Medication** Please record the date and time of each medication taken. (00:00 – 23:59)
Prochlorperazine	10 mg	Oral	1 tablet	01 / Jun / 2018 (dd / mmm / yyyy) 10 : 25 (hh : mm)
		The first row is pre-filled as an example.		
				dd / mmm / yyyy hh : mm
				dd / mmm / yyyy hh : mm
				dd / mmm / yyyy hh : mm
				dd / mmm / yyyy hh : mm

CAN-PRO-NEPA-001	**PATIENT DIARY** EMERGENCY DEPARTMENT & HOSPITALIZATION	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

EMERGENCY DEPARTMENT VISITS OR OVERNIGHT HOSPITALIZATION

1. Did you visit an Emergency Department during the 120 hours (5 days) after the start of chemotherapy?

☐ No ☐ Yes → If you visited the Emergency Department, please check the applicable box(es) or provide the reason, and record the date, onset time and end time of each visit.

Nausea	Vomiting	Other Reason	Date	Onset Time 00:00 – 23:59	End Time 00:00 – 23:59
☐	☐		☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy	☐☐:☐☐ hh mm	☐☐:☐☐ hh mm
☐	☐		☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy	☐☐:☐☐ hh mm	☐☐:☐☐ hh mm
☐	☐		☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy	☐☐:☐☐ hh mm	☐☐:☐☐ hh mm

2. Were you hospitalized overnight during the 120 hours (5 days) after the start of chemotherapy?

☐ No ☐ Yes → If you were hospitalized overnight, please check the applicable box(es) or provide the reason, and record the date, onset time and end time of each overnight hospitalization.

Nausea	Vomiting	Other Reason	Date	Onset Time 00:00 – 23:59	End Time 00:00 – 23:59
☐	☐		☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy	☐☐:☐☐ hh mm	☐☐:☐☐ hh mm
☐	☐		☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy	☐☐:☐☐ hh mm	☐☐:☐☐ hh mm

CAN-PRO-NEPA-001	**PATIENT DIARY**	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

THANK YOU FOR COMPLETING THE DIARY AND QUESTIONNAIRES.

PLEASE REMEMBER TO RETURN YOUR COMPLETED DIARY & QUESTIONNAIRES TO THE INVESTIGATOR/STUDY COORDINATOR AT YOUR NEXT SCHEDULED STUDY VISIT.

Appendix 3: FLIE questionnaire

CAN-PRO-NEPA-001	PATIENT DIARY FLIE – DAY 5	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

Please complete the FLIE on: (for study personnel only)	☐☐ / ☐☐☐ / ☐☐☐☐ dd mmm yyyy	☐☐ : ☐☐ hh mm

Functional Living Index - Emesis
PATIENT INSTRUCTIONS

In the following questionnaire you are asked to rate to what extent nausea and vomiting have affected your quality of life. The first set of 9 questions refers to nausea and the second set of 9 questions refers to vomiting. The questionnaire should take approximately 10 minutes or less to complete. Please read the instructions before you begin. Think carefully about each question because your answers may help to develop treatments that will improve the quality of life for future patients.

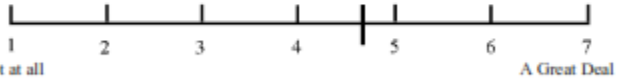
For each question, you will rate to what extent nausea (or vomiting) has affected an aspect of your quality of life during the past five days. Please focus on your experiences **over that time period**. We are interested in **your opinions**, not those of family members or friends. Your answers will remain confidential.

You must answer every question. Use a black ballpoint pen and press firmly so that your mark is clear.

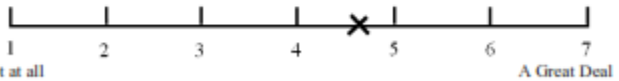
If you are unsure of your answer or do not understand the question, read the question again carefully and make a vertical mark (|) on the line based upon your best understanding of the question. If you want to change your answer, please do the following: make a new vertical mark (|); draw an arrow to the correct mark; initial and date the correction.

Each question uses a visual analogue scale. Think about how you rate your feelings and place a vertical mark (|) on the line at a point corresponding to what extent your nausea (or vomiting) has affected that aspect of your quality of life. **Please read the question carefully because in some questions, a "1" indicates no effect on your quality of life and in other questions a "1" indicates a great deal of an effect on your quality of life.** You may place your vertical mark (|) at any point along the line. Be sure that you make your vertical mark (|) so that it intersects the horizontal line. Do not circle a number. Use a single vertical mark (|) as shown below.

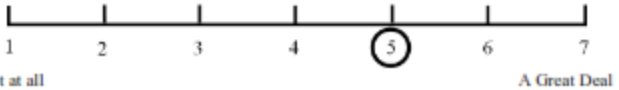
Correct: Vertical mark



Incorrect: "✕"



Incorrect: Circle number



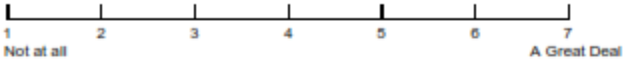
FLIE - Canada/English - Version of 28 Sep 12 - MAPI Institute
ID7093 / FLIE_AU1.0_eng-CA.doc

Version: May 8, 2018 Confidential Page 7

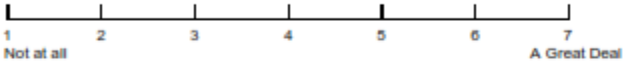
CAN-PRO-NEPA-001	**PATIENT DIARY** FLIE – DAY 5	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

Functional Living Index Emesis

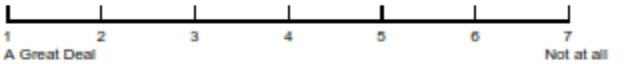
1. Have you had nausea in the past 5 days?



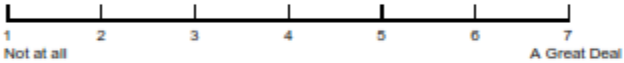
2. Has nausea affected your ability to continue your usual recreation or leisure activities in the past 5 days?



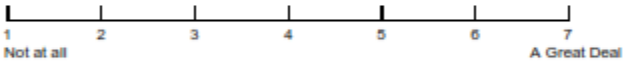
3. Has nausea affected your ability to prepare a meal or do minor household tasks in the past 5 days?



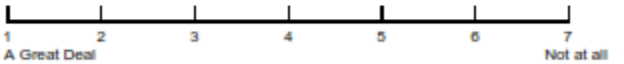
4. How much has nausea affected your ability to enjoy a meal in the past 5 days?



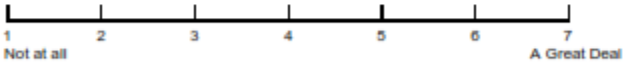
5. How much has nausea affected your ability to enjoy drinking fluids in the past 5 days?



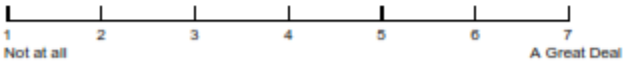
6. How much has nausea affected your willingness to see and spend time with family and friends, in the past 5 days?



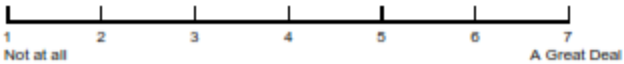
7. Has nausea affected your daily functioning in the past 5 days?



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



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



CAN-PRO-NEPA-001	**PATIENT DIARY** FLIE – DAY 5	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

Functional Living Index Emesis

10. Have you vomited in the past 5 days?

1 2 3 4 5 6 7
Not at all A Great Deal

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

1 2 3 4 5 6 7
A Great Deal Not at all

12. Has vomiting affected your ability to prepare a meal or do minor household tasks in the past 5 days?

1 2 3 4 5 6 7
Not at all A Great Deal

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

1 2 3 4 5 6 7
Not at all A Great Deal

14. How much has vomiting affected your ability to enjoy drinking fluids in the past 5 days?

1 2 3 4 5 6 7
Not at all A Great Deal

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

1 2 3 4 5 6 7
A Great Deal Not at all

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

1 2 3 4 5 6 7
Not at all A Great Deal

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

1 2 3 4 5 6 7
Not at all A Great Deal

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

1 2 3 4 5 6 7
A Great Deal Not at all

Appendix 4: WPAI-NV questionnaire

CAN-PRO-NEPA-001	**PATIENT DIARY** WPAI-NV – DAY 5	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

Please complete the WPAI-NV on: (for study personnel only)	☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy	☐☐ : ☐☐ hh mm

Work Productivity and Activity Impairment Questionnaire: Nausea & Vomiting (WPAI:NV)

The following questions ask about the effect of nausea or vomiting on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated*

1) Are you currently employed (working for pay)?

_____NO _____YES

If NO, check "NO" and go to question 6.

The next questions are about the **past seven days,** not including today.

☐ If you were on vacation/off work in the past seven days, please check the box, and go to question 6.

2) During the past seven days, how many hours did you miss from work because of problems associated with your nausea and vomiting? *Include hours you missed due to sick days, times when you went in late, left early, etc. because of your nausea and vomiting. Do not include time off to participate in this study.*

_____HOURS

3) During the past seven days, how many hours did you miss from work for any other reason, such as holidays or time off to participate in this study?

_____HOURS

4) During the past seven days, how many hours did you actually work?

_____HOURS *(If "0", go to question 6.)*

CAN-PRO-NEPA-001	**PATIENT DIARY** WPAI-NV – DAY 5	☐☐☐ - ☐☐☐ - ☐ Site Number Patient Number Cycle #

5) During the past seven days, how much did your nausea or vomiting affect your productivity while you were working?

Think about days when you were limited in the amount or kind of work you could do, days when you accomplished less than you would like, or days when you could not do your work as carefully as usual. If your nausea or vomiting affected your work only a little, choose a low number. Choose a high number if your nausea or vomiting affected your work a great deal.

Consider only how much nausea or vomiting affected productivity while you were working.

0 1 2 3 4 5 6 7 8 9 10

Nausea or vomiting had no effect on my work — *Nausea or vomiting completely prevented me from working*

CIRCLE A NUMBER

6) During the past seven days, how much did your nausea or vomiting affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, and studying, etc. Think about times when you were limited in the amount or kind of activities you could do and times when you accomplished less than you would like. If your nausea or vomiting affected your activities only a little, choose a low number. Choose a high number if your nausea or vomiting affected your activities a great deal.

Consider only how much nausea or vomiting affected your ability to do your regular daily activities, other than work at a job.

0 1 2 3 4 5 6 7 8 9 10

Nausea or vomiting had no effect on my daily activities — *Nausea or vomiting completely prevented me from doing my daily activities*

CIRCLE A NUMBER

Appendix 5: HEC and MEC Emetogenicity

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Antiemesis

NCCN Guidelines Index
Table of Contents
Discussion

EMETOGENIC POTENTIAL OF INTRAVENOUS ANTICANCER AGENTS[a]

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[b,c]	• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4	• Carmustine >250 mg/m² • Cisplatin • Cyclophosphamide >1,500 mg/m² • Dacarbazine • Doxorubicin ≥60 mg/m²	• Epirubicin >90 mg/m² • Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Streptozocin
Moderate emetic risk (>30%–90% frequency of emesis)[b,c]	• Aldesleukin >12–15 million IU/m² • Amifostine >300 mg/m² • Arsenic trioxide • Azacitidine • Bendamustine • Busulfan • Carboplatin AUC <4[d] • Carmustine[d] ≤250 mg/m² • Clofarabine • Cyclophosphamide ≤1500 mg/m² • Cytarabine >200 mg/m²	• Dactinomycin[d] • Daunorubicin[d] • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Dinutuximab • Doxorubicin[d] <60 mg/m² • Epirubicin[d] ≤90 mg/m² • Idarubicin • Ifosfamide[d] <2 g/m² per dose • Interferon alfa ≥10 million IU/m² • Irinotecan[d]	• Melphalan • Methotrexate[d] ≥250 mg/m² • Oxaliplatin[d] • Temozolomide • Trabectedin[d]

Adapted with permission from:
Hesketh PJ, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-state of the art. Support Care Cancer 2010;19:S43-47.

[a]Potential drug interactions between antineoplastic agents/antiemetic therapies and various other drugs should always be considered.
[b]Proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.
[c]Continuous infusion may make an agent less emetogenic.
[d]These agents may be highly emetogenic in certain patients.

Low Emetic Risk (See AE-3)
Minimal Emetic Risk (See AE-3)
Oral Chemotherapy (See AE-4)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

AE-2

Appendix 6: Safety Reporting Forms

6a. Adverse Event Reporting Form

PURDUE	Adverse Events CAN-PRO-NEPA-001 Case Report Form	☐☐☐ - ☐☐☐ Site Number Patient Number

1. Please complete all fields for each adverse event.

Adverse Event Description	Start Date ☐☐ / ☐☐☐ / ☐☐☐☐ dd mmm yyyy Was the AE Intermittent? ☐ Yes ☐ No AE Duration ☐ < 1 hour ☐ 1 – 24 hrs ☐ > 24 hrs	End Date ☐☐ / ☐☐☐ / ☐☐☐☐ dd mmm yyyy Intensity at Onset ☐ Mild ☐ Moderate ☐ Severe Maximum Intensity ☐ Mild ☐ Moderate ☐ Severe	Was the AE "Serious"? ☐ Yes ☐ No Was the AE a "Special Situation"? ☐ Yes ☐ No (If Yes, please complete the SAE form and forward to Purdue Pharmacovigilance).
Action Taken (check all that apply) (If a medication is given, please add to the Concomitant Medications CRF) ☐ Medication given ☐ None ☐ Procedure performed ☐ Study drug regimen changed ☐ Study drug discontinued	Relationship to Akynzeo® and Dexamethasone. Is the AE related to Akynzeo®? ☐ Yes ☐ No Is the AE related to Dexamethasone? ☐ Yes ☐ No	Outcome ☐ Ongoing ☐ Recovering ☐ Recovered ☐ Fatal ☐ Recovered with sequelae	Did the AE Result in Study Discontinuation? ☐ Yes ☐ No *If YES, please complete the VISIT 6/FINAL VISIT – End of Study Form.*

Adverse Event Description	Start Date ☐☐ / ☐☐☐ / ☐☐☐☐ dd mmm yyyy Was the AE Intermittent? ☐ Yes ☐ No AE Duration ☐ < 1 hour ☐ 1 – 24 hrs ☐ > 24 hrs	End Date ☐☐ / ☐☐☐ / ☐☐☐☐ dd mmm yyyy Intensity at Onset ☐ Mild ☐ Moderate ☐ Severe Maximum Intensity ☐ Mild ☐ Moderate ☐ Severe	Was the AE "Serious"? ☐ Yes ☐ No Was the AE a "Special Situation"? ☐ Yes ☐ No (If Yes, please complete the SAE form and forward to Purdue Pharmacovigilance).
Action Taken (check all that apply) (If a medication is given, please add to the Concomitant Medications CRF) ☐ Medication given ☐ None ☐ Procedure performed ☐ Study drug regimen changed ☐ Study drug discontinued	Relationship to Akynzeo® and Dexamethasone. Is the AE related to Akynzeo®? ☐ Yes ☐ No Is the AE related to Dexamethasone? ☐ Yes ☐ No	Outcome ☐ Ongoing ☐ Recovering ☐ Recovered ☐ Fatal ☐ Recovered with sequelae	Did the AE Result in Study Discontinuation? ☐ Yes ☐ No *If YES, please complete the VISIT 6/FINAL VISIT – End of Study Form.*

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6b. Global Reporting Form for SAEs/AESIs/Special Situations

Global Reporting Form for SAEs/AESIs/Special Situations
(Please refer to completion instructions)

Protocol No. _____ Subject No. _____ ☐ Initial ☐ Follow-up (#) Country of Incidence _____Reporter Country _____

Study Phase at onset of SAE/AESI/Special Situation: ☐ Screening ☐ Run-in ☐ Double Blind ☐ Open Label ☐ Other:_____

1. PRINCIPAL INVESTIGATOR: Name	**Site No.**
Date SAE/AESI/Special Situation became known to the Investigator: ____/_____/_____ DD / MMM / YYYY	
*Investigator's Signature*_____	*Date* ____/_____/_____ DD / MMM / YYYY

2. PATIENT DEMOGRAPHICS (*Please complete this section per CRF*).

Year of Birth	Gender	Height (cm)	Weight ☐ lb. ☐ kg.	Race
_____ YYYY	☐ Male ☐ Female			☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Other

3a. EVENT (S) *The appropriate relationship to investigational medicinal product (IMP) must be entered regardless of cause.*

Event Term	Event Type	Start Date	Stop Date	Outcome	Seriousness Criteria	Dechallenge assessment: Did SAE/AESI/Special Situation partially or completely disappear after Study Drug was withdrawn / reduced?	Rechallenge assessment: Did SAE/AESI/Special Situation reappear or intensify after Study Drug was reintroduced?	Relationship to Study Drug
	1. Adverse Event of Special Interest 2. Special Situation 3. SAE	DD/MMM/YYYY		1. Recovered / Resolved 2. Recovered / Resolved with sequelae 3. Not recovered / Not resolved 4. Fatal 5. Lost to follow-up	1. Death 2. Life Threatening 3. Hospitalization 4. Persistent/significant disability 5. Congenital anomaly/Birth defect 6. Important Medical Event 7. Non-Serious 8. Intervention required (*Devices only*)	1. Yes 2. No 3. Not Applicable		1. Reasonable Possibility 2. No Reasonable Possibility
1.								
2.								
3.								

Global Reporting Form for SAEs/AESIs/Special Situations - Final V1.0 - 10MAR2017

Global Reporting Form for SAEs/AESIs/Special Situations
(Please refer to completion instructions)

3b. CRITERIA FOR SERIOUSNESS *(Enter the criteria for each event in 3a above)*

1. **Death:** Date of Death _____/_____/_____ (DD / MMM / YYYY) Cause of Death _____ (*Please attach a copy of Autopsy report if available*)
2. **Life Threatening**
3. **Hospitalisation:** Initial or Prolonged (*Please attach a copy of discharge summary if available*)

   Admission date: ___/_____/_____ (DD / MMM / YYYY) Discharge date: ___/_____/_____ (DD / MMM / YYYY)
4. **Persistant or Significant Disability**
5. **Congenital Anomaly/Birth Defect**
6. **Important Medical Event**
7. **Non-Serious**
8. **Intervention required** (*Devices only*)

3c. RATIONALE FOR CAUSALITY ASSESSMENT *(Specify SAE/AESI/Special Situation no. at the end of each rational selected -.)*

If the investigator selects "**Yes**" to causal relationship to IMP a rationale should be provided by the investigator by ticking the relevant option below. The "Other" free text field is provided for rationale not listed e.g. drug interactions. *Please note: more than one option may be selected.*

- ☐ Temporal relationship to IMP exposure
- ☐ Event is known to be associated with the IMP drug class.
- ☐ Event improved on discontinuation or dose reduction of study drug
- ☐ Event reoccurred on re-challenge of study drug
- ☐ Biological plausibility
- ☐ Other (*Please Specify*): _____

If the investigator selects "**No**" a rationale should be provided by the investigator by ticking the relevant option below. *Please note: more than one option may be selected.*

- ☐ Event attributed to concomitant medication (*provide details of the concomitant medication in the "Other" free text field*)
- ☐ Event attributed to the concurrent disease (s)/ condition (s) (*provide details of the disease/condition in the "Other" free text field*)
- ☐ Event attributed to non-investigational medicinal product (NIMP) (*specify the NIMP per protocol*)
- ☐ No reasonable temporal relationship to IMP administration
- ☐ Event is expected in the study indication and/or target population
- ☐ Negative de-challenge and/or negative re-challenge
- ☐ Other (*Please Specify*): _____

Global Reporting Form for SAEs/AESIs/Special Situations
(Please refer to completion instructions)

4. INVESTIGATIONAL MEDICINAL PRODUCT *Please complete this section or attach copies of respective dosing pages from the CRF.*

Blind Broken ☐ N/A ☐ No ☐ Yes → Date____/____/____ Reason for breaking blind _____

Product ☐ No IMP taken	**Dates** DD/MMM/YYYY **Start**	**Stop**	**Dose**	**Dose Units** (e.g. mg)	**Dosing Frequency** (e.g. bid)	**Formulation** (e.g. tab)	**Route** (e.g. oral)

5. INVESTIGATIONAL MEDICINAL PRODUCT ACTION TAKEN

Check one box only:

☐ No change
☐ Dose decreased
☐ Dose increased
☐ Withheld transiently
☐ Withdrawn

If Withdrawn or Withheld transiently, give:
Date: __/_____/____
DD/ MMM / YYYY
Reason: _____
Restarted Date: __/_____/____
DD/ MMM / YYYY

6. CONCOMITANT THERAPIES (Including treatment received for the SAEs/AESIs/Special Situations) ☐ **NONE** ☐ **UNKNOWN**

Please complete this section or attach copies of Concomitant Medication pages from the CRF.

Therapy (Drug/Procedure)	**Dose & Units**	**Start Date** DD/MMM/YYYY *(Duration if dates unknown)*	**Stop Date**	**Route** (e.g. oral)	**Frequency**	**Indication for Use**	**Ongoing** (Yes/No)

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(Please refer to completion instructions)

7. RELEVANT MEDICAL HISTORY (Include medical conditions, e.g. allergies, previous drug reactions, alcohol/drug abuse, etc. Specify disease / syndrome for each concomitant therapy listed *Please complete this section or attach copies of Medical History pages from the CRF)* ☐ **NONE**

Disease / Syndrome *(Specify)*	Date of Onset DD/MMM/YYYY	**Ongoing** *(Yes/No)*	Pertinent Details *(Include surgical procedures and dates)*

8. RELEVANT TESTS/LABORATORY DATA *List autopsy, lab tests, ECG results, x-ray findings, etc. Include normal ranges for laboratory findings and date test was performed. For multiple tests, use supplemental page.* ☐ **NONE**

Please attach a copy of the relevant lab report, if available.

DATE OF TEST *DD/MMM/YYYY*	**TYPE OF TEST**	**TEST RESULT & ASSESSMENT**

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Global Reporting Form for SAEs/AESIs/Special Situations
(Please refer to completion instructions)

DESCRIPTION OF EVENT(S): *Provide a clear narrative description of the sequence of events, diagnosis and all relevant details. If additional space is necessary, use supplemental page. Provide subject's state of health prior to* SAE/AESI/Special Situation, *treatment plan for* SAE/AESI/Special Situation, *and the current status of study participation.*

Use supplemental pages to continue above sections when more space is needed: ☐ **Additional documents attached.**

Global Reporting Form for SAEs/AESIs/Special Situations - Final V1.0 - 10MAR2017

6c. Akynzeo®-Related Non-Serious Adverse Event Form

PURDUE	Akynzeo®-Related Non-Serious Adverse Event Protocol No: CAN-PRO-NEPA-001	☐☐☐ - ☐☐☐ Site Number Patient Number

1. Principal Investigator		
Name of Principal Investigator:	_____	
Date Akynzeo®-Related Non-Serious Adverse Event Became Known to the Investigator:	☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy	
Investigator's Signature and Date:	_____	☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy

2. Patient Demographics *(Please complete this section per eCRF)*	
Date of Birth:	☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy
Gender:	☐ Male ☐ Female
Race:	☐ Caucasian ☐ Black ☐ Asian ☐ Hispanic ☐ Aboriginal ☐ Other, specify: _____

3. Event

Event Diagnosis	**Start Date** ☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy	**End Date** ☐☐/☐☐☐/☐☐☐☐ dd mmm yyyy	**Relationship to Akynzeo®** ☐ Yes ☐ No
	Was the AE Intermittent? ☐ Yes ☐ No	**AE Duration** ☐ < 1 hour ☐ 1 – 24 hrs ☐ > 24 hrs	**Intensity at Onset** ☐ Mild ☐ Moderate ☐ Severe
	Maximum Intensity ☐ Mild ☐ Moderate ☐ Severe	**Did the AE Result in Study Discontinuation?** ☐ Yes ☐ No	
	Action Taken (check all that apply) ☐ Medication given ☐ Procedure performed ☐ Study drug regimen changed ☐ Study drug discontinued ☐ None	**Outcome** ☐ Ongoing ☐ Recovering ☐ Recovered ☐ Fatal ☐ Recovered with sequelae	***If YES, please complete the VISIT 6/FINAL VISIT – End of Study Form.***

Reporting Form for Akynzeo®-Related Non-Serious Adverse Event Version 1.0 (06June2018) pg. 1

PURDUE	Akynzeo®-Related Non-Serious Adverse Event Protocol No: CAN-PRO-NEPA-001	___ ___ ___ - ___ ___ ___ Site Number Patient Number

4. Akynzeo® *(Please complete this section or attached copies of dosing pages from CRF)*

Date of Last Dose of Akynzeo® Taken (dd/mmm/yyyy)	Number of Capsules Taken	Action Taken (No change, dose increase/decreased, withheld, withdrawn)

5. Relevant Medical History *(Please complete this section or attach copies of the Medical History pages from the CRF or source)*

Disease/Syndrome (specify)	Onset Date (dd/mmm/yyyy)	Ongoing (Yes or No)	Pertinent Details (Include surgical procedures and dates)

6. Concomitant Medication *(Please complete this section or attached copies of Concomitant Medication CRFs or source)*

Name of Medication	Start Date (dd/mmm/yyyy)	Stop Date (dd/mmm/yyyy)	Amount	Units (e.g., mg)	Frequency (e.g., bid)	Route (e.g., po)

PURDUE	Akynzeo®-Related Non-Serious Adverse Event Protocol No: CAN-PRO-NEPA-001	☐☐☐ - ☐☐☐ Site Number Patient Number

7. **Additional information** *(Please use this area to provide more information to any of the sections above)*

Use supplemental pages to continue above sections when more space is needed: ☐ Check if additional documents attached.

Appendix 7: Pregnancy Forms

Pregnancy Notification Form

Drug Safety & Pharmacovigilance

NOTIFICATION OF PREGNANCY
Subject or Partner Pregnancy

Protocol No.: _____ Subject No.: _____ ☐ Initial ☐ Follow-Up (#_____)

Pregnancy occurred in: ☐ Subject ☐ Subject's partner

1. Investigator Name:_____ **Site No.:**_____

Address: _____

_____ Telephone #: _____

Name of Report Preparer: _____Signature of preparer:_____

Date Pregnancy became known to the Investigator: _____/_____/_____
DD / MMM / YYYY

Investigator's Signature: _____ ***Date:*** _____/_____/_____
DD / MMM / YYYY

2. MATERNAL DEMOGRAPHIC INFORMATION:

Date of Birth _____/_____/_____
DD / MMM / YYYY

ETHNICITY: Select one

☐ Hispanic or Latina
☐ Not Hispanic or Latina

RACE: Select one

☐ White
☐ Black or African American
☐ Native Hawaiian or other Pacific Islander
☐ Asian
☐ American Indian or Alaska Native
☐ Other (Specify) _____

3. MATERNAL PREGNANCY INFORMATION

Last menstrual period: ___/___/____
DD /MMM/ YYYY

Estimated date of delivery by LMP: ___/___/____
DD /MMM/ YYYY

Estimated date of delivery by ultrasound: ___/___/____
DD /MMM/ YYYY

Screen Visit Pregnancy Test	Results and Units	Date of Test(s)
☐ Urine b-hCG	_____	___/___/____ DD /MMM/ YYYY
☐ Serum b-hCG	_____	___/___/____ DD /MMM/ YYYY

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Drug Safety & Pharmacovigilance

Confirmatory Pregnancy Test	Results and Units	Date of Test(s)
☐ Urine b-hCG	_____	___/___/____ DD /MMM/ YYYY
☐ Serum b-hCG	_____	___/___/____ DD /MMM/ YYYY

4. METHOD OF CONTRACEPTION:
Check all that apply

Female:		***Male:***
☐ Barrier Method	☐ Sterilization	☐ Barrier Method
☐ Hormonal Method	☐ Abstinence	☐ Sterilization
☐ Rhythm Method	☐ Intrauterine Device	☐ None
	☐ None	
Other: _____		Other: _____

5. STUDY DRUG: ☐ Run-in Phase ☐ Double Blind Phase ☐Open Label ☐ Other:_____
(Record all dosing schedules below if relevant)

Study Drug	Dates *(DD/MMM/YYYY)*		Dose & Units (e.g. 40mg)	Route (e.g. Oral)	Frequency (e.g. BID)	Dosage Form (e.g. Tablet, Capsule, Solution)
☐ No study medication taken	Start	Stop				

6. MATERNAL CONCOMITANT MEDICATIONS ☐ None ☐ Unknown

Drug	Dose	Dates *(DD/MMM/YYYY)* *Duration if dates are unknown*		Route (e.g. oral)	Indication for Use	Ongoing (Yes/No)
		Start	Stop			

Drug Safety & Pharmacovigilance

7. MATERNAL RELEVANT MEDICAL HISTORY, CONCOMITANT CONDITIONS and SURGICAL PROCEDURES: ☐ None ☐ Unknown *(Complete this section or attach copies of relevant CRF pages).*		
Medical Diagnosis / Surgical Procedures *(For surgical procedures, complete a line for the procedure in addition to the line for the diagnosis.* *Specify each diagnosis / procedure on a separate line.)*	**Date of Diagnosis / Surgical Procedure** *(MMM/YYYY)*	**Was condition current at the start of the study?** *(Yes / No)*

8. PREGNANCY HISTORY:	
Para: _____	**Preterm Deliveries:** _____
Gravida: _____	**Full-Term Deliveries:** _____
Abortion(s) Spontaneous: _____	**No. of Living Children:** _____

9. Please provide pertinent details of abnormalities or complications as well as additional relevant information of this or previous pregnancies.

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Pregnancy Outcome Questionnaire

Drug Safety & Pharmacovigilance

PREGNANCY OUTCOME QUESTIONNAIRE
Subject or Partner Pregnancy

Protocol No.: _____ Subject No.: _____

Pregnancy occurred in: ☐ Subject ☐ Subject's partner

Reasonable attempts should be made to obtain detailed information regarding medical care during labor & delivery.

1. INVESTIGATOR: Name & No.:_____ **Site No.:**_____

Address: _____

_____ Telephone #: _____

Name of Report Preparer: _____Signature of Preparer:_____

Investigator's Signature: _____	***Date:*** ____/____/____ dd / MMM / yyyy

2. PREGNANCY INFORMATION: If yes to any questions below, please provide additional information in Section 6

- Were there infections, illnesses or relevant changes to concurrent conditions during the pregnancy? ☐Yes ☐No
- Was there exposure during pregnancy to:
  - Alcohol Use ☐Yes ☐No
  - Environmental Toxins ☐Yes ☐No
  - Illicit Substances ☐Yes ☐No
  - Other Relevant Exposure ☐Yes ☐No

3. PREGNANCY OUTCOME:

Date of Outcome: ____/____/____ dd / MMM / yyyy

Live Birth: ☐Yes ☐No

Abortion, Spontaneous: ☐Yes ☐No

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Termination, Elective: ☐Yes ☐No
Ectopic Pregnancy: ☐Yes ☐No
Stillbirth: ☐Yes ☐No
*(if **yes** complete & submit a **SAE** Data Form)*

While pregnancy itself is not considered a SAE, any SAEs related to the pregnancy (see below) or SAEs occurring in the child (i.e., congenital anomalies or other conditions present at birth, whether genetically inherited or occurring in utero) must be documented and reported to the Sponsor (or designee) on a separate SAE Data Form. **If applicable, please complete a SAE Data Form for an adverse event occurring in the subject, subject's partner or the fetus/newborn meeting serious criteria.**

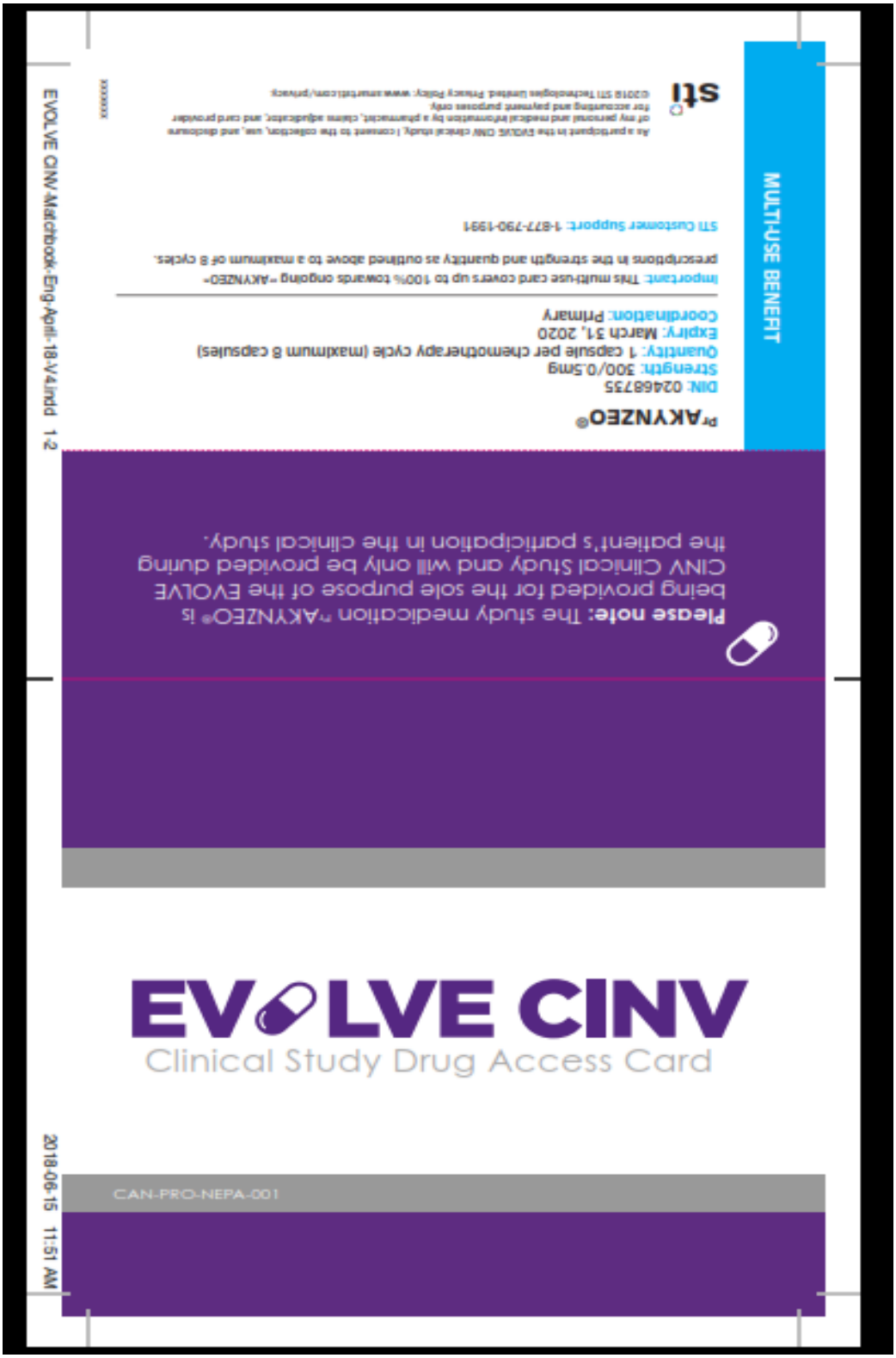
Reportable SAEs associated with **subject or subject's partner** pregnancy include but are not limited to:

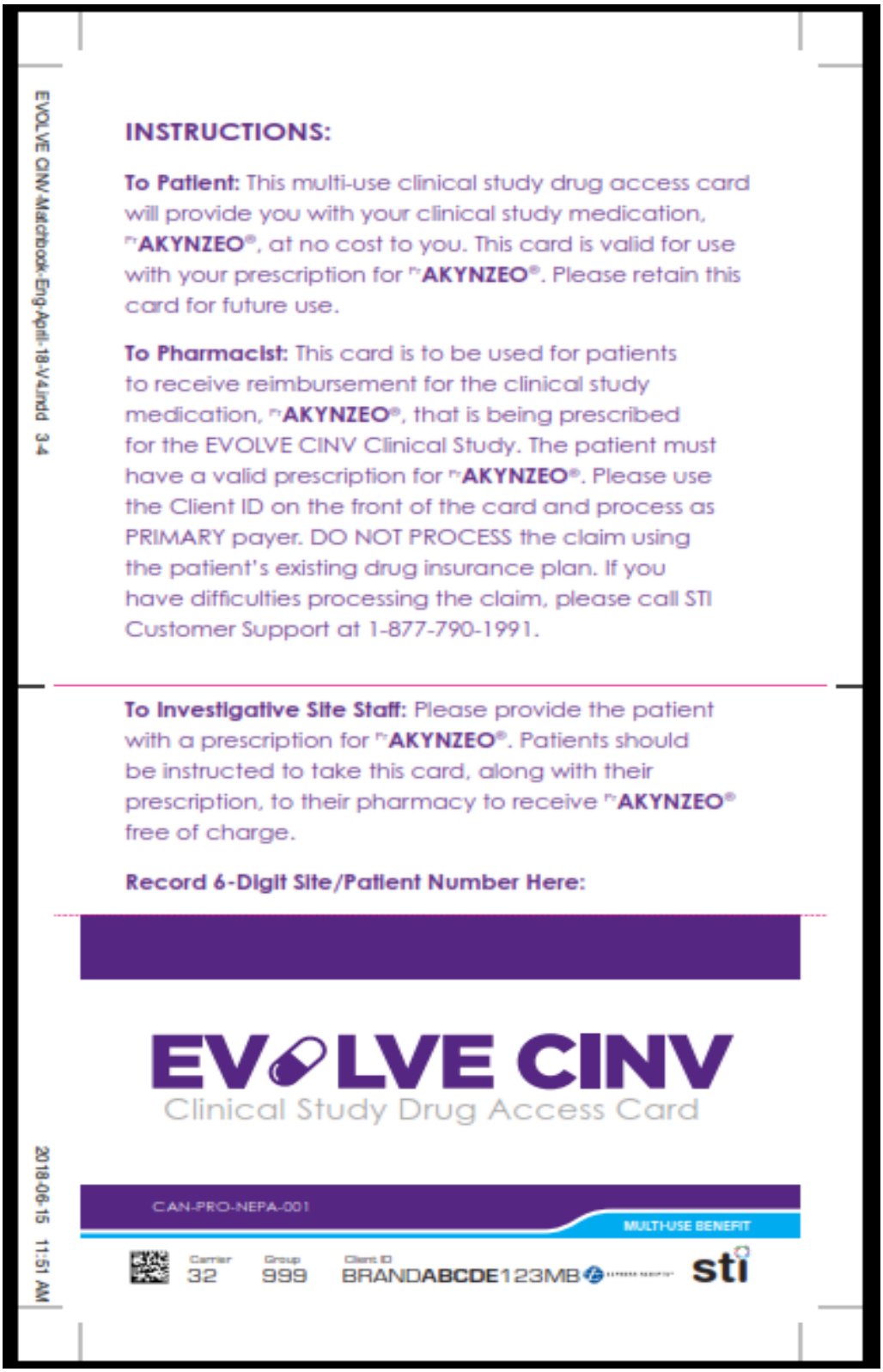
- Pregnancy losses (e.g., spontaneous abortion, late fetal death, elective termination);
- Life threatening developments (e.g., placental abruption, fetal distress);
- Congenital anomalies;
- Neonatal death;
- Any event resulting in maternal death or prolonged maternal hospitalization

4. METHOD OF DELIVERY: Select one

☐ Spontaneous Vaginal ☐ Induced Vaginal
☐ Caesarean Section ☐ Other _____
Gestational Age:_____ (weeks)
Birth Length:_____ cm or inches *(circle one)* Birth Weight: _____kg or lbs *(circle one)*
Apgar Score At: 1 Minute _____ 5 Minutes _____ Sex: ☐M ☐F
Is newborn exam normal? ☐Yes ☐No *(if **no** complete and submit a **SAE** Data Form)*

Appendix 8: Study Drug Access Card




EVOLVE CINV-Matchbook-Eng-April-18-V4.indd 3-4
INSTRUCTIONS:
To Patient: This multi-use clinical study drug access card will provide you with your clinical study medication, rAKYNZEO®, at no cost to you. This card is valid for use with your prescription for rAKYNZEO®. Please retain this card for future use.
To Pharmacist: This card is to be used for patients to receive reimbursement for the clinical study medication, rAKYNZEO®, that is being prescribed for the EVOLVE CINV Clinical Study. The patient must have a valid prescription for rAKYNZEO®. Please use the Client ID on the front of the card and process as PRIMARY payer. DO NOT PROCESS the claim using the patient's existing drug insurance plan. If you have difficulties processing the claim, please call STI Customer Support at 1-877-790-1991.
To Investigative Site Staff: Please provide the patient with a prescription for rAKYNZEO®. Patients should be instructed to take this card, along with their prescription, to their pharmacy to receive rAKYNZEO® free of charge.
Record 6-Digit Site/Patient Number Here:
EVOLVE CINV
Clinical Study Drug Access Card
CAN-PRO-NEPA-001
MULTI-USE BENEFIT
Carrier 32
Group 999
Client ID BRANDABCDE123MB
sti
2018-06-15 11:51 AM