MyRisk: Efficacy and safety evaluation of oral Akynzeo® in patients receiving MEC at high risk of developing CINV based on a prediction tool. A multinational and multicenter study.

PROTOCOL

Date: **05 February 2024 (Version 5.1)**
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Helsinn Healthcare SA

Scientific Lead signature

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Date: 5 February 2024

LIST OF CHANGES

Date	Author	Version	Description of changes
10 October 2018	Simona Parisi	Draft 1	First version
09 January 2019	Simona Parisi	Draft 2	Consolidate suggestions, get advice from HHC GDRP, legal and safety responsibles
22 January 2019	Simona Parisi	Draft 3	List of abbreviations completed, final statistical revision
13 February 2019	Simona Parisi	Draft 4	Safety section inserted
08 April 2019	Simona Parisi	Draft 5	Revision by scientific lead
23 July 2019	Simona Parisi	Draft 6	Revisions by Advisors at MASCC 2019
10 October 2019	Simona Parisi	Final draft	Implementation of the last comments by Advisors and HHC Drug Safety
30 October 2019	Simona Parisi	Final Version	Document Quality Controlled and released
10 December 2019	Simona Parisi	Final Revised version	HEOR parameters revision, EudraCT-number added, Investigator signature page added.
21 September 2020	Simona Parisi	Version 1.2	Signature page of protocol version 1.1. added (page 8) New abbreviations added to List of abbreviations (page 10) Study summary dosage of dexamethasone precisely defined according to MASCC guidelines (Section 1 and Section 3.4) Definition of contraception requirements for WOCBP and male patients with pregnant or non-pregnant WOCBP partner added (section 3.3.1.1) Study treatments (IMP and NIMPs) added (Section 3.4.1) Study visit procedures (Section 3.6.3) updated References (Section 16) reference 22) added Appendix 1 Study Flow Chart updated (pregnancy test added)
05 October 2020	Simona Parisi	Version 1.3	Study summary updated to specify that Standard of care is taken as IMP in the study (Section 1 and Section 3.4) Study treatments updated to specify that Standard of care is taken as IMP in the study (Section 3.4.1)

Date	Author	Version	Description of changes
15 November 2022	Alessandro Alonzi	Version 5.0	Scientific lead affiliation updated Project team and signature page updated (page 9 and 10) New abbreviations added to List of abbreviations (page 11) Primary and secondary objectives and primary and secondary endpoints more accurately defined (Section 1, 2.2 and 3.5) Study population: "Male and Female patients" replaced by "Adult patient" (Section 1 and 3.2) and consequent deletion of "both sexes" in Inclusion criteria (Section 3.3.1.) Randomization and treatment assignment updated (Section 1, 2.2 and 3.5) Risk-benefit assessment chapter added (Section 2.1) Use of Akynzeo® and Standard of care according to SPC added (Section 3.1) Rescue medication section updated (Section 1 and 3.4.3) Study termination added (Section 3.4.4.) Update of recording of symptoms from Patient´s Diary to AE form of eCRF (section 3.6.2) Randomization procedure timing at Visit 0 updated (Section 3.6.3.) and consequent update of the Study Flow Chart (Appendix 1) Typo correction (section 3.6.3.1.) Informed consent chapter updated (Section 4.1) Regulatory requirements updated (Section 4.2) Monitoring methods precisely defined (Section 5) Recording of AEs updated based on the duties of the investigators. Only SAE must be recorded within 24 hours (section 10.3) Appendix 2 Patient´s Diary: inserted version v2.0 Appendix 5 Master Informed Consent Form was deleted, (English version of ICF is approved and it is a separate document), impact on sections 4.1. and 9.1.1.
05 February 2024	Alessandro Alonzi	Version 5.1	Project team and signature page updated (page 9 and 10) Study summary (page 14) Estimated number of subjects and Estimated number of participating sites updated based on the Sample Size re-calculation Sample Size Calculation (page 17) updated Risk factors for CINV: detailed description added (Section 3.3.3.) Number of patients updated based on the Sample Size re-calculation (Section 3.4.5) Sample Size re-calculation (Section 8.2) Efficacy Analysis updated to precisely define the methodology (Section 8.4.) Publication rules updated (Section 13) Detailed description of the CINV calculation was added (Section 3.6.3.1)

STUDY TITLE:

MyRisk: Efficacy and safety evaluation of oral Akynzeo® in patients receiving MEC at high risk of developing CINV based on a prediction tool. A multinational and multicenter study.

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PROTOCOL VERSION: **5.1**

DATE OF PROTOCOL VERSION 5.1: **05th February 2024**

INVESTIGATOR SIGNATURE PAGE

STUDY TITLE: MyRisk: Efficacy and safety evaluation of oral Akynzeo® in patients receiving MEC at high risk of developing CINV based on a prediction tool. A multinational and multicenter study.

Protocol No.: IBA1160 Version date: 05 February 2024

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By signing below, I agree to the conditions relating to this study as set out in this protocol. I have read and understood the study protocol.

I agree to conduct this clinical study according to Good Clinical Practice (ICH GCP) and European Regulatory Requirements.

I fully understand that any changes instituted by me without previous discussion with Helsinn Healthcare SA or their designated representative constitute a violation of the protocol.

I agree to adhere to the protocol in all circumstances other than where necessary to protect the well-being of the patient.

I will ensure that the study product supplied by Helsinn Healthcare SA will be used only for administration to patients included in this study protocol and for no other purposes.

SITE NAME: _____

PRINCIPAL INVESTIGATOR´S

NAME: _____

SIGNATURE: _____ **DATE:** _____

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List of Abbreviations

AC	Anthracycline/cyclophosphamide
ADR	Adverse Drug Reaction
AE	Adverse Event
CAPA	Corrective or/and Preventive Actions
CET	Central European Time
CINV	Chemotherapy-Induced Nausea and Vomiting
CP	Complete Protection
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Chemotherapy
CTCAE	Common Toxicity Criteria for Adverse Events
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Collection
ESMO	European Society for Medical oncology
EU	European Union
FLIE	Functional Living Index-Emesis
FMEA	Failure Mode & Effects Analyses
GCCP	Guideline-Consistent CINV Prophylaxis
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GEE	Generalized estimating equations
GICP	Guideline-Inconsistent CINV Prophylaxis
GLIM	Generalized Linear Model
GP	General Practitioner
HEC	Highly Emetogenic Chemotherapy
FAS	Full Analysis Set
FPI/LPO	First Patient In/Last Patient Out
IBA	Institute of Biostatistics and Analyses
IMP	Investigational Medicinal Product
NIMP	Non-Investigational Medicinal Product
ISO	International Organization for Standardization
ICF	Informed Consent Form
ICH	International Council for Harmonization
IV	Intravenous
LEC	Low Emetogenic Chemotherapy
LOCF	Last Observation Carried Forward
MASCC	Multinational Association for Supportive Care in Cancer™
MAT	MASCC Antiemesis Tool
MAH	Marketing Authorization Holder
MEC	Moderately Emetogenic Chemotherapy

MiE	Minimal Emetogenic Chemotherapy
MVTF	Missing Value Treated as Failure
NEPA	netupitant and palonosetron
PS	Performance Status
RA	Receptor Antagonist
RPN	Risk Priority Number
RSI	Reference Safety Information
QOL	Quality of Life
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
VAS	Visual Analogue Scales
WOCBP	Woman Of Childbearing Potential

1. Study Summary

Study Title

MyRisk: Efficacy and safety evaluation of oral Akynzeo® in patients receiving MEC at high risk of developing CINV based on a prediction tool. A multinational and multicenter study.

Study rationale and background

Despite the availability of effective antiemetics and evidence-based guidelines, up to 40% of cancer patients receiving chemotherapy fail to achieve complete nausea and vomiting control.
Antiemetic guidelines recommendations are based on the emetogenic potential of the chemotherapy. Chemotherapy (CT) agents are divided in Highly, Moderately, Low and Minimally Emetogenic potential (HEC, MEC, LEC, MiE).

In addition to type of chemotherapy, several patient-related risk factors can increase the risk of CINV. Currently, there is limited consensus surrounding the most relevant patient risk factors that may predict the risk of CINV. Based on a recent study by Dranitsaris et al. (Dranitsaris et al. Ann Oncol. 2017 Jun 1; 28(6):1260-1267.), eight (8) predictive factors have been identified and an algorithm has been developed to incorporate these factors into the optimal selection of prophylactic antiemetics:

1. nausea and/or vomiting in the prior cycle of chemotherapy
2. use of non-prescribed antiemetics at home in the prior cycle of chemotherapy
3. platinum or anthracycline-based chemotherapy
4. age < 60 years
5. expectations for (anticipating) nausea and/or vomiting
6. <7 h of sleep the night before chemotherapy
7. history of morning sickness during previous pregnancy
8. cycle of chemotherapy (A negative association between risk and number of cycles was identified where the hazard for CINV was highest in cycles 1 and 2, with a gradual decline and plateau from cycle 3 onward).

The clinical application of this prediction tool has the potential to be an important resource for clinicians and may help to enhance patient care by optimizing the use of the antiemetics in a proactive manner.

Study Objectives

Primary objective:

1. To evaluate if the use of NEPA (netupitant and palonosetron) in patients treated with IV moderately emetogenic chemotherapy and at high risk of CINV is more effective in preventing CINV than standard of care antiemetics, during the overall phase (0-120 hours) post-chemotherapy, over three cycles of chemotherapy

Secondary objectives:

2. Evaluate acute (0 to 24 hours), delayed (>24 to 120 hours), and overall (0-120 hours) CINV indicators in each cycle of chemotherapy

Time 0 is defined as the start time of the chemotherapy administration on Day 1 of each of the three cycles. CINV indicators are nausea and vomiting, their intensity and frequency and Quality of Life in the acute, delayed and overall period.

3. Evaluate the predictive role of potential risk factors in the development of CINV over three cycles of chemotherapy

Potential risk factors for CINV are those thought to be increasing the risk of CINV in patients receiving MEC as reported in section 3.3.3. Risk factors for CINV and in section 3.6.3.1 where the risk score algorithm calculation by using predictive factors for CINV is explained.

4. Evaluate the safety profile of the antiemetic drug over three cycles of chemotherapy

5. Explore the effect of CINV on daily activities and quality of life in patients receiving moderately-emetogenic chemotherapy over three cycles of chemotherapy

6. Evaluate resource utilization and health economic outcome

Study design

This is a phase IV interventional, open label, randomized, active controlled, parallel arms, multicenter and multinational study.

Study population

Adult patients, aged ≥ 18 years, naïve and non-naive to chemotherapy, with diagnosis of any cancer scheduled and intended to be treated for three consecutive cycles with a single dose of any IV MEC regimen, including carboplatin, per cycle. In these MEC-treated patients the use of Standard of Care defined as a 5-HT3 RA + Dexamethasone or equivalent corticosteroids on day 1 of chemotherapy is intended for the prevention of CINV. The use of Standard of Care including an NK-1 RA-based regimen to prevent CINV constitutes an exclusion criterion in the present study.

Estimated number of subjects
410

Estimated number of participating sites
22

Randomization and Treatment assignment

The randomization process will be managed centrally through the eCRF.

At randomization, patients will be stratified for:
- use and non-use of carboplatin
- country

Once assigned to a treatment group before the start of cycle 1, patients will stay on the same treatment group until study completion.

Patients will be randomized according to a computer-generated randomization list before the start of cycle 1 and assigned either to ARM A (test arm) or ARM B (control arm):

ARM A: NEPA

- One capsule of Akynzeo®, a fixed-dose oral combination of the NK1 Receptor Antagonist (RA) netupitant (300 mg) and of the 5-HT3 RA palonosetron (0.5 mg) + Dexamethasone 8 mg (or equivalent corticosteroids) by the oral route on Day 1, approximately 1 hour before chemotherapy

ARM B: Standard of care

- Dexamethasone (or equivalent corticosteroids) 8 mg administered by the oral route (or equivalent IV dose) on Day 1, approximately 1 hour before chemotherapy and one of the 5-HT3-RAs recommended by ESMO and MASCC guidelines (standard of care), i.e. either:
  Granisetron, 2 mg (oral) or 1 mg (IV)
  OR
  Palonosetron, 0.5 mg (oral) or 0.25mg (IV)
  OR
  Ondansetron, 16 mg (oral) or 8 mg (IV)

Applicable to both treatment arms:
In patients receiving moderately emetogenic chemotherapy (i.e.: oxaliplatin, anthracycline and cyclophosphamide) with known potential for delayed nausea and vomiting, the use of dexamethasone 8 mg (or equivalent corticosteroid) on days 2 and 3 post-chemotherapy can be considered.
For all other patients receiving the other moderately emetogenic chemotherapy no routine prophylaxis with dexamethasone (or equivalent corticosteroid) on days 2 and 3 is allowed for delayed nausea and vomiting.

Provision of study drug

Akynzeo® will be provided at national level to each center in a sufficient number of units to cover the need of the enrolled patients' treatment. IMPs will be sourced locally by site pharmacy.

The drugs that may be used as standard of care in Arm B, including dexamethasone that is also used in Arm A, are investigational medicinal products (IMPs) for this study.

The standard of care drugs and dexamethasone (or equivalent corticosteroids) will be provided by the centers as per usual routine practice.

Rescue medication

Rescue medication will be allowed at any time, during every cycle. Patients can ask the investigator for rescue medication. The intake of rescue medications, either prescribed or non-prescribed, must be recorded in the Patient´s diary and in the eCRF.

Study enrollment time: 12 – 18 months

Total number of visits per patient: 5

Efficacy Assessments: primary and secondary endpoints

Definition of the assessment of time-related study efficacy endpoints:

Time-related efficacy study endpoints assessment will start at time 0 defined as the start time of the chemotherapy administration on Day 1 of each of the three cycles.

CINV indicators, such as nausea and vomiting, their intensity and frequency and Quality of Life will be evaluated during the acute phase of emesis, from 0 to 24 hours from the start of chemotherapy, in the delayed phase of emesis, from 24 to 120 hours from the start of chemotherapy, and overall during each day (i.e., day 1, 2, 3, 4 and 5) from the start of chemotherapy.

The primary endpoint will be the proportion of patients with complete response (CR, defined as no emetic episode, no rescue medication) over three cycles of chemotherapy after the start of the MEC administration.

The following clinical secondary endpoints will be evaluated during each cycle:

- Complete response during the acute (0-24h), delayed phase (>24-120h), overall (0-120h) and daily in each cycle;
- No emetic episode during the acute, delayed and overall phase and daily in each cycle;
- Number of vomiting episodes during the acute, delayed and overall phase and daily in each cycle;
- No rescue medication during the acute, delayed and overall phase and daily in each cycle;
- No significant nausea (maximum MAT scale = 2) during the acute, delayed and overall phase and daily in each cycle;
- No nausea (MAT scale = 0) during the acute, delayed and overall phase and daily in each cycle;
- Complete protection (no emetic episode, no rescue medication and no significant nausea) during the acute, delayed and overall phase and daily in each cycle
- Nausea and Vomiting-related quality of life indicators (through the Functional Living Index Emesis scale)
- Collection of chemotherapy delays and/or dose reductions (Delay of chemotherapy administration due to CINV will be also evaluated as part of health economic endpoints, see below)

CINV outcomes data will be prospectively collected over the first 5 days of chemotherapy and for three consecutive cycles using standardized Patient´s diaries translated in local languages.

The following health economic endpoints will be evaluated during the study cycles:

- Number of days and daily doses of rescue medication administered for the treatment of CINV
- Number of re-hydration bags given for at least grade 2 vomiting (CTCAE v5)
- The number of days of unplanned hospitalisations related to CINV and department of hospitalization (type of ward)
- The number of outpatient physician visits and health care consultations due to CINV (e.g., general practitioner)
- The number of unplanned laboratory test including those at unplanned hospitalisations due to CINV
- Discontinuation of chemotherapy treatment due to CINV
- Delay of chemotherapy administration due to CINV
- Days of absence from work

Safety Assessments

The collection and description of AEs, intensity, and relationship to Akynzeo® will be provided. Serious Adverse Events either related or not related to Akynzeo® will be collected and communicated as per law requirements.

Definitions and safety communication loop are advised in section 10. Safety Management of this protocol.

Health Economics and Outcomes Research Assessments:

The health economic component described in this clinical protocol will only focus on resource utilisation linked to CINV and treatment of events (efficacy / safety).

In order to capture event related resource utilisation, patients will be followed for the duration of the study. If one of the following events occurs; death, withdrawal of consent, or lost to follow up, resource utilisation for these patients will be reported up to the point they are withdrawn.

All these parameters will be reported in the eCRF, see 3.7. Health Economic Outcome Research (HEOR) Assessments.

Secondary analysis

An analysis with dependent variable will be performed to identify additional potential risk factors of CINV. A simple logistic regression will be conducted to identify a set of factors with the largest potential contribution to CINV and those with P-value ≤ 0.25 will be taken into further consideration. Generalized estimating equations (GEE), which adjust for patient clustering by chemotherapy cycle, will be then used to determine the final set of additional risk factors. By using reclassification analysis IDI (Integrated discrimination improvement) or NRI (Net reclassification improvement) we will redistribute the patients according to the new set of risk factors. Finally, the set of primary risk factors and the new set of risk factors will be compared. The methods will be detailed in the Statistical Analysis Plan.

Sample Size Calculation

A sample of 410 randomised subjects, each scheduled to be measured 3 times/cycles, achieve a 80% power when using a two-sided Wald test from a GEE analysis to test whether the proportion of Complete response expected in the Test group (71%) differs from that expected in the Control group (60%) at a significance level of 0,050. The subjects are randomly split between a Test group and a Control group, with 50% of the subjects assigned to the Test group. The measurements of each subject will be made at the following times/cycles expressed as proportions of the total study time: {0%; 50%; 100%}. Missing values are assumed to occur completely at random (MCAR) or at random (MAR). These missing value proportions will be combined to form the pairwise observant probabilities using the Independent method. The anticipated proportions missing at each measurement time/cycle are {0%; 7.5%; 15%}. Based on these attrition rate scenario, a sample of 348 completer subjects is expected. The correlation between observations on the same subject is assumed to be 0.5 (ballpark estimate). All computations are performed using PASS 14 software.

Details on the Statistical Methodology and Analysis are given in chapter 8 of the protocol.

2. Introduction

Despite the development of important progress and evidence-based guidelines in chemotherapy-related nausea and vomiting (CINV), CINV management is far from optimal [1-4]. Up to 40% of patients with cancer still present with uncontrolled CINV; CINV remains one of the most unpleasant side effects of chemotherapy [5]. In our previous study, acute nausea and vomiting were reported by 37.3% of patients, while delayed symptoms were experienced by 47.1% of cancer patients [5]. The burden that CINV places on cancer patients is considerable, thereby making it difficult for cancer patients to perform their daily life activities [4]. CINV prevention remains to be an essential aim of antiemesis therapy, because CINV reduces patients' quality of life (QoL), has substantial adverse functional impact and has potential economic consequences in patients with cancer [6].

Antiemetic guideline recommendations are based on the emetogenic potential of chemotherapy and involve 4 levels of classification of intravenous chemotherapy agents, i.e., high, moderate, low and minimal; these have been accepted by major organisations [7]. Moderate emetogenic chemotherapy (MEC) results in acute vomiting in 30% to 90% of cancer patients in the absence of antiemetic therapy [7]. In addition to the chemotherapy type, several patient-related risk factors and clinical characteristics can increase CINV risk [8,9]. These can include use of antiemetics inconsistent with international guidelines, younger age, prechemotherapy nausea, no complete CINV response in an earlier cycle, history of nausea/vomiting, (trait) anxiety, fatigue experience, and expectations of nausea/vomiting[8,9]. Other studies have largely confirmed some of the key risk factors for CINV (history of vomiting during pregnancy, history of motion sickness, age, gender) and added other factors such as (chronic) alcohol consumption, body surface area, fewer hours slept the night prior to infusion, or advanced stage cancer[10,11,12]. Currently, there is a limited consensus surrounding the most relevant patient risk factors that may predict CINV risk. Based on a recent study by Dranitsaris et al. [13] eight predictive factors have been identified, and an algorithm has been developed to combine these patient-related risk factors into the optimal treatment of prophylactic antiemetics. These include:

1. nausea and/or vomiting in the prior cycle of chemotherapy
2. use of non-prescribed antiemetics at home in the prior cycle of chemotherapy
3. platinum or anthracycline-based chemotherapy
4. age < 60 years
5. expectations for (anticipating) nausea and/or vomiting
6. <7 h of sleep the night before chemotherapy
7. history of morning sickness during previous pregnancy
8. cycle of chemotherapy (A negative association between risk and number of cycles was identified where the hazard for CINV was highest in cycles 1 and 2, with a gradual decline and plateau from cycle 3 onward).

It is interesting to see that in a study of 152 patients (484 chemotherapy cycles), the addition of an NK1 receptor antagonist, extended-duration dexamethasone and olanzapine failed to lead to good nausea control

in patients with high risk for CINV due to personal risk factors[14]. A CINV risk model-guided antiemetic trial in 324 early breast cancer patients showed that those at higher CINV risk treated with standard care plus aprepitant with or without olanzapine reported significantly less nausea and vomiting both in the acute and delayed phases compared to those receiving standard antiemetics only[15]. Furthermore, the risk-guided group was associated with higher QALYs gained although higher costs and a probability of the risk-based antiemetics to be cost-effective being >94%[16]. The clinical application of this prediction tool has the potential to be an important resource for clinicians and may help to enhance patient care by optimizing the use of the antiemetics in a proactive manner.

Akynzeo®, an oral combination of the NK1 RA, netupitant and the 5-HT3 RA, palonosetron, is recommended by guidelines for the prevention of CINV [17]. Akynzeo® has been evaluated in a multicentre, randomised, double-blind, double-dummy phase II clinical trial at various dose ranges among 694 cisplatin-treated cancer patients from 44 sites (two countries); each NEPA dose significantly improves CINV prevention in cancer patients[18]. Similar results were obtained in another international, randomised, double-blind and parallel group phase III clinical trial; NEPA prevented CINV in patients receiving MEC [19].

The current study primarily aimed to evaluate whether Akynzeo® leads to a higher response rate compared with standard care in MEC regimen-treated patients who are identified to be at high risk based on the algorithm.

2.1. Risk Benefit Assessment

5HT3-RAs and NK1-RAs are among the drugs of first choice for an optimal antiemetic prophylaxis in cancer patients receiving chemotherapy.

Akynzeo® contains two active substances: Netupitant, a NK1-RA, and Palonosetron, a 5HT3-RA, thus representing a valid and convenient therapeutic option associated with improvement of patient's compliance.

The clinical development program consistently demonstrates that Akynzeo® with dexamethasone provides additional benefit in terms of complete response, both in the delayed, the acute, and the overall phases of CINV in both cisplatin-based chemotherapy (HEC) and AC based chemotherapy (formerly defined as MEC and more recently re-classified as AC HEC).

A single oral dose administered on Day 1 of HEC and MEC regimens is adequate to protect patients from both acute and delayed CINV, as pharmacologically predicted.

The fixed dose combination was shown to be safe and well tolerated in single and multiple cycle studies and there was no increase in AEs observed after repeated cycles. Adverse events most commonly reported were those associated with cytotoxic effects of chemotherapy, or the underlying malignancy. Only headache and constipation, known class effects of the 5-HT3 RAs and NK1 RA, were considered drug-related.

Post-marketing data also provide safe foundation for confident administration of this medicine.

Potential safety concerns include teratogenic effects, serotonin syndrome and Torsade de pointes due to QT/QTc prolongation.

The potential of a teratogenic effect of netupitant in humans is limited and based solely on the preclinical findings observed in rabbits and rats. The incidence of cleft palate in rats occurred at exposures approximately 7-fold greater than exposures seen in humans. Preclinical data showed that palonosetron did not affect pre- or postnatal development, except at high oral doses, unrepresentative of the clinical situation. No substantial evidences are available in clinical studies; therefore, the likelihood of teratogenic effects may represent a safety concern. To mitigate this potential risk advice is given to female patients concerning fertility and pregnancy in the SPC.

The occurrence of Serotonin Syndrome, a potentially life-threatening drug reaction, has been considered a potential class effect of the anti-emetics belonging to the class of the 5HT3 RAs, which includes palonosetron. An increased risk might be evident if antiemetics are administered in combination with other serotoninergic agents. The prospective of an increase in use of Akynzeo® in different cancer settings, also in combination with other serotoninergic drugs, makes the issue of the risk profile important for these drugs. Patient safety would be served if serotonin syndrome is mentioned in the product labelling; therefore, the authorities recommended update of the labelling to inform about this risk.

Torsade de pointes is the most important clinical outcome of QT/QTc prolongation. Integrated review of all available nonclinical and clinical data suggests that Akynzeo® is devoid of any effect on QTc interval or of a proarrhythmic potential. No events of QT prolongation attributable to Akynzeo® have been reported during the post-approval phase. Nevertheless, since cancer patients are a vulnerable population receiving potentially cardiotoxic antineoplastic agents, or with medical history remarkable for hypothyroidism or cardiac diseases on treatment with antiarrhythmics, or may carry electrolytes imbalance, it is reasonable to consider Torsade de pointes due to QT/QTc prolongation an important potential risk. To mitigate this risk, in the SPC an advice is given for monitoring of patients with conditions leading to QT prolongation.

In conclusion, the available efficacy and safety data originated from the clinical development program and the post-marketing experience are suggestive of a favourable benefit-risk profile of Akynzeo®.

2.2. Study Objectives

Primary objective:

1. To evaluate if the use of NEPA (netupitant and palonosetron) in patients treated with IV moderately emetogenic chemotherapy and at high risk of CINV is more effective in preventing CINV than standard of care antiemetics, during the overall phase (0-120 hours) post-chemotherapy, over three cycles of chemotherapy

Secondary objectives:

2. Evaluate acute (0 to 24 hours), delayed (>24 to 120 hours), and overall (0-120 hours) CINV indicators in each cycle of chemotherapy

Time 0 is defined as the start time of the chemotherapy administration on Day 1 of each of the three cycles. CINV indicators are nausea and vomiting, their intensity and frequency and Quality of Life in the acute, delayed and overall period.

3. Evaluate the predictive role of potential risk factors in the development of CINV over three cycles of chemotherapy

Potential risk factors for CINV are those thought to be increasing the risk of CINV in patients receiving MEC reported in section 3.3.3. Risk factors for CINV and in section 3.6.3.1 where the risk score algorithm calculation by using predictive factors for CINV is explained.

4. Evaluate the safety profile of the antiemetic drug over three cycles of chemotherapy

5. Explore the effect of CINV on daily activities and quality of life in patients receiving moderately-emetogenic chemotherapy over three cycles of chemotherapy

6. Evaluate resource utilization and health economic outcome

3. Methodology

3.1. Design

This is a phase IV interventional, open label, randomized, active controlled, parallel arms, multicenter and multinational study.

Akynzeo® will be used in compliance with its Summary of Product Characteristics (SPC).

Standard of care will be used according to SPC and will reflect the consensus of experts in the evidence-based guidelines of MASCC/ESMO resulting from systematic reviews of the published trials of the last two decades.[22]

3.2. Sample and settings

Adult patients, aged ≥ 18 years, naïve and non-naive to chemotherapy, with diagnosis of any cancer scheduled and intended to be treated for at least three consecutive cycles with single doses of any IV MEC regimen per cycle who are able to comply with study requirements and giving signed Informed consent.

3.3. Patients‘ Selection Criteria

3.3.1. Inclusion Criteria

- Adult patients aged ≥18 years
- Patients with a risk score of ≥ 13 as calculated by the algorithm – see 3.6.3.1. Baseline/screening: VISIT 0
- Signed Informed consent
- Patients with diagnosis of any cancer scheduled and intended to be treated for three consecutive cycles with a single dose of any IV MEC regimen, per cycle, including adjuvant or neo-adjuvant chemotherapy
- Patients with ECOG performance status 0, 1 or 2
- Use of Standard of Care defined as a 5-HT3 RA + Dexamethasone (or equivalent corticosteroid) based-regimen on day 1 of chemotherapy for CINV prevention
- Naïve and non- naïve to chemotherapy
- The enrolled women should be a) of non-childbearing potential or b) of childbearing potential using reliable contraceptive measures and having a negative urine pregnancy test done by health care team within 1-24 hours before dosing the antiemetic treatment in both arms and outcome recorded in the medical records
- Able to comply with study requirements

IV Moderately Emetogenic Chemotherapy (MEC) includes any of the following chemotherapy drugs:
-

Alemtuzumab Azacitidine Bendamustine Carboplatin Clofarabine Cyclophosphamide < 1500 mg/m² Cytarabine > 1000 mg/m²	Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan	Oxaliplatin Romidepsin Temozolomide Thiotepa Trabectedin

3.3.1.1 Definition of contraception requirements for WOCBP and male patients with pregnant or non-pregnant WOCBP partner

A woman is considered of childbearing potential (WOCBP) i.e. fertile, following menarche, and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.[22]

A woman of non-childbearing potential is defined as being in a post-menopausal state i.e. no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the post-menopausal state in women not using hormonal contraception or hormone replacement therapy. However,

in the absence of 12 months of amenorrhea, a single FSH measurement is sufficient. [22] Contraceptive measures must be continued up to 1 (one) month after study treatment with Akynzeo®.

Birth control methods which may be considered as highly effective:
Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include: [22]

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal

  progestogen-only hormonal contraception associated with inhibition of ovulation 1:
  - oral
  - injectable
  - implantable

  intrauterine device (IUD)
  intrauterine hormone-releasing system (IUS)
  bilateral tubal occlusion
  vasectomised partner
  sexual abstinence

Acceptable birth control methods which may not be considered as highly effective:
Acceptable birth control methods that result in a failure rate of more than 1% per year include: [22]

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm, or sponge with spermicide

Considering Akynzeo® during the non-clinical study does not indicate teratogenicity/fetotoxicity in early pregnancy and human data are not available or do not contradict these findings, the inclusion of WOCBP is possible using at least acceptable effective contraceptive measures.

Recommendations for male subjects with pregnant or non-pregnant WOCBP partner:
Considering the Study genotoxicity of IMP the male contraception (condom) is recommended to avoid exposure of an existing embryo/fetus. Contraception should be continued until the end of relevant systemic exposure in WOCBP[22].

Contraception after the end of treatment:
Contraception should be continued until the end of relevant systemic exposure in WOCBP. The end of relevant systemic exposure is defined as the time point where the IMP, including any active or major metabolites, has decreased to a concentration that is no longer considered relevant for human teratogenicity/fetotoxicity[22].

3.3.2. Exclusion Criteria

- Patients receiving highly emetogenic chemotherapy (including anthracycline+cyclophosphamide-based chemotherapy)
- Patients receiving oral moderately emetogenic chemotherapy drugs
- Patients receiving opioids within 2 weeks prior to trial enrollment (longer use allowed)
- Use of olanzapine as prophylaxis of CINV

- Patients scheduled to receive radiotherapy concurrently with chemotherapy
- Any illness or condition that, in the opinion of the physician, may confound the results of the study or pose unwarranted risks in administering the investigational product to the patient.
- Patients with mechanical risk factors for nausea (i.e. intestinal obstruction)
- Patients with liver disease (as nausea is a common presenting symptom)
- Patients with metabolic risk factors for nausea (i.e. electrolyte imbalances causing nausea/vomiting)
- Chronic treatment with steroids (with the exception of inhaled or topical steroids)
- Pregnancy and/or breast-feeding women
- Women of childbearing potential refusing to use effective contraception during the whole study treatment and up to one month after study treatment with Akynzeo®
- Use of Standard of Care including an NK-1 RA-based regimen to prevent CINV

3.3.3. Risk Factors for CINV

At the time of the collection of demographic and medical history data at the screening visit (Visit 0, see details below), all the predictive individual factors will be collected and the patients' risk score automatically calculated. These parameters will be used to identify the patients with a CINV risk score ≥ 13 (see 3.3.1., Inclusion Criteria). If the patients comply with all the inclusion and exclusion criteria, they are enrolled into the study. The parameters from 1 to 7 will be used to identify the patients at high risk of CINV:

1. Nausea and/or vomiting in the prior cycle of chemotherapy
2. Use of non-prescribed antiemetics at home in the prior cycle of chemotherapy
3. Platinum or anthracycline-based chemotherapy
4. Age < 60 years
5. Expectation for (anticipating) nausea and/or vomiting
6. History of morning sickness during previous pregnancy
7. Cycle of chemotherapy
8. <7 h of sleep the night before chemotherapy (to be obtained at day of chemotherapy)
9. History of any nausea and vomiting such as motion sickness, vestibular dysfunction…
10. Anticipatory nausea and/or vomiting
11. Anxiety over the past 24hrs (to be obtained at day of chemotherapy)
12. Alcohol intake (number of units per week)
13. Gender
14. Fatigue experience (symptom)
15. Smoking status
16. Weight

Parameters from 8 to 16 are defined as additional risk factors and will not influence the risk score.

The risk factors for CINV are checked at each cycle before chemotherapy and are used for patient´s risk score re-calculation. This result of the re-calculation has no impact on patient´s participation in the study and the randomized group.

The percent of patients using carboplatin will be limited to 20% of the planned number of patients in the study: the maximum number of patients using carboplatin in this study will be 106.

3.4. Intervention and Antiemetic Treatment

Eligible patients will receive before the start of cycle 1 in ratio 1:1 and be assigned either to ARM A (test arm) or ARM B (control arm):

ARM A: NEPA

- One capsule of Akynzeo®, a fixed-dose oral combination (NEPA) of the NK1 Receptor Antagonist (RA) netupitant (300 mg) and of the 5-HT3 RA palonosetron (0.5 mg) + Dexamethasone 8 mg (or equivalent corticosteroids) by the oral route on Day 1, approximately 1 hour before chemotherapy

ARM B: Standard of care

- Dexamethasone (or equivalent corticosteroids) 8 mg administered by the oral route (or equivalent IV dose) on Day 1, approximately 1 hour before chemotherapy and one of the 5-HT3-RAs recommended by ESMO and MASCC guidelines (standard of care), i.e. either:

  Granisetron, 2 mg (oral) or 1 mg (IV)
  OR
  Palonosetron, 0.5 mg (oral), 0.25mg (IV)
  OR
  Ondansetron, 16 mg (oral) or 8 mg (IV)

Akynzeo® will be provided at national level to each center in a sufficient number of units to cover the need of the enrolled patients' treatment. IMPs will be sourced locally by site pharmacy.

The drugs that may be used as standard of care in Arm B, including dexamethasone that is also used in Arm A, are investigational medicinal products (IMPs) for this study.

The 5-HT3-RAs and dexametahsone (or equivalent corticosteroid) will be provided by the centers as per usual routine practice.

In patients receiving moderately emetogenic chemotherapy (i.e.: oxaliplatin, anthracycline and cyclophosphamide) with known potential for delayed nausea and vomiting, the use of dexamethasone (or equivalent corticosteroid) for days 2 and 3 can be considered.
For all other patients receiving the other moderately emetogenic chemotherapy no routine prophylaxis with dexamethasone (or equivalent corticosteroid) for days 2 and 3 is allowed for delayed nausea and vomiting.

3.4.1. Study treatments

The Investigational Medicinal Product (IMP) is defined (Directive 2001/20/EC) as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Akynzeo®, a fixed-dose oral combination (NEPA) of the NK1 Receptor Antagonist (RA) netupitant (300 mg) and of the 5-HT3 RA palonosetron (0.5 mg) is IMP in this study.

The drugs that may be used as standard of care in Arm B, including dexamethasone that is also used in Arm A, are also investigational medicinal products (IMPs) for this study.

Akynzeo® and Standard of care including dexamethasone will be used according to SmPC and will reflect the consensus of experts in the evidence-based guidelines of MASCC ESMO. The dosages are perfectly in the range of dosages specified in SmPC of these products.

Chemotherapy treatment (IV Moderately Emetogenic Chemotherapy) used in the study (alemtuzumab, azacitidine, bendamustine, carboplatin, clofarabine, cyclophosphamide, cytarabine, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin, romidepsin, temozolomide, thiotepa, trabectedin) in both arms A and B does not fall within the definition of an IMP. These products are NIMPs used to assess relevant endpoints in the clinical trial, they will not be tested.

3.4.2. Randomization Procedure

At randomization, patients will be stratified for:

- use and non-use of carboplatin (first stratification factor)
- country (second stratification factor)

Randomization will take place according to a computer-generated randomization list. Randomization will be performed using permuted blocks. The randomization process will be managed centrally through the eCRF.

Randomization will be performed during Visit 1 after the patient is confirmed to be eligible for the study (see section 3.6.3. Study visits procedures).

Once assigned to a treatment group before the start of cycle 1, patients will stay on the same treatment group until study completion.

3.4.3. Rescue medication

Rescue medication will be allowed at any time, during every cycle. Patients can ask the investigator for rescue medication. The intake of rescue medications, either prescribed or non-prescribed, must be recorded in the Patient´s diary and in eCRF.

3.4.4. Study termination

The end of the study for each patient is defined as the day of Visit 4. Visit 4 is a visit on Day 5 of Cycle 3 or before the start of the next programmed chemotherapy cycle. Visit 4 is the final visit of the study.

3.4.5. Premature discontinuation

Patients may withdraw the study at any time at their own willing, without giving further details or justification.
The investigator may also exclude a subject from the study based on his/her clinical judgment:

- general or specific changes in the patient's condition which make the patient ineligible for further assessments according to the inclusion/exclusion criteria
- Non-qualification to perform consecutive cycles (e.g., for toxicity)
- Failure to return for follow-up visits

Number of patients: 410
Study enrollment time: 12 – 18 months
Total number of visits per patient: 5

3.5. Study Endpoints

Definition of the assessment of time-related study efficacy endpoints:

Time-related efficacy study endpoints assessment will start at time 0 defined as the start time of the chemotherapy administration on Day 1 of each of the three cycles.

CINV indicators, such as nausea and vomiting, their intensity and frequency and Quality of Life will be evaluated during the acute phase of emesis, from 0 to 24 hours from the start of chemotherapy, in the delayed phase of emesis, from 24 to 120 hours from the start of chemotherapy, and overall during each day (i.e., day 1, 2, 3, 4 and 5) from the start of chemotherapy.

The primary endpoint will be the proportion of complete responses (no emetic episode and no rescue medication), during the overall phase (0-120h), after the start of the MEC administration over three cycles of chemotherapy.

Clinical secondary endpoints will be evaluated during each cycle:

- Complete response during the acute (0-24h), delayed phase (>24-120h), overall (0-120h) and daily in each cycle;
- No emetic episode during the acute, delayed and overall phase and daily in each cycle;
- Number of vomiting episodes during the acute, delayed and overall phase and daily in each cycle;
- No rescue medication during the acute, delayed and overall phase and daily in each cycle;
- No significant nausea (maximum MAT scale = 2) during the acute, delayed and overall phase and daily in each cycle;
- No nausea (MAT scale = 0) during the acute, delayed and overall phase and daily in each cycle;
- Complete protection (no emetic episode, no rescue medication and no significant nausea) during the acute, delayed and overall phase and daily in each cycle
- Nausea and Vomiting-related quality of life indicators (through the Functional Living Index Emesis scale)
- Collection of chemotherapy delays and/or dose reductions (Delay of chemotherapy administration due to CINV will be also evaluated as part of health economic endpoints, see below)

Health economic endpoints will be evaluated during the study cycles:

- Number of days and daily doses of rescue medication administered for the treatment of CINV
- Number of re-hydration bags given for at least grade 2 vomitings (CTCAE v5)
- The number of days of unplanned hospitalisations related to CINV and department of hospitalization (type of ward)
- The number of outpatient physician visits and health care consultations due to CINV (e.g., general practitioner)
- The number of unplanned laboratory test including those at unplanned hospitalisations due to CINV
- Discontinuation of chemotherapy treatment due to CINV
- Delay of chemotherapy administration due to CINV
- Days of absence from work

3.6. Study Procedures

3.6.1. Calculation of CINV score

Calculation of CINV score will be part of eCRF on factors 1-7 in the above list of predictive factors. Patients with a score of ≥ 13) will be the target population. Factor 8 is part of the model calculating CINV risk score, but as it needs to be completed at the day of the chemotherapy administration it creates significant logistical issues with randomisation, antiemetic prescriptions, and patients' waiting and travel arrangements, hence it will not be used to calculate this score in the present study. Adjustment to the risk score to reflect this change has been considered and hence the predictive score for this study is set to ≥ 13 instead. This score also maximizes appropriate recruitment and increases the sensitivity of the prediction (true positive rate) to 97.4%. This factor, however, alongside several additional others will be measured and will be used in the refinement of the predictive model at the end of the trial.

3.6.2. Data Collection

Data will be collected using the following data collection tools:

MASCC Antiemesis Tool (MAT)
This is an eight-item scale measuring acute and delayed nausea and vomiting in patients receiving chemotherapy. It has shown high reliability, contrasted groups, and concurrent validity, and moderate to high levels of recall[209].

Functional Living Index Emesis (FLIE)
This is an 18-item Likert-type scale measuring the impact of chemotherapy-induced nausea and vomiting on patients' daily function[21]. It is a commonly used scale in antiemetic trials.

Patient´s diaries
Patients will indicate in their diaries the followings from Day 1 to Day 5 of each chemotherapy cycle:

- The intensity of nausea (scale derived from MAT)
- Number of emetic episodes (derived from MAT)
- Rescue medication, either prescribed or non-prescribed
- Adverse events (symptoms of any kind)

Electronic Case Record Form
Patients will be evaluated for 3 consecutive cycles, whichever the duration of their chemotherapy schedule and number of cycles.
All the data will be collected in an electronic Case Record Form (eCRF) by an attending physician, including the data collected by each patient in a Patient´s diary and MAT.
Electronic CRF will contain all the required sociodemographic and clinical data (including information about diagnoses, treatment, rescue medication, medical history, demography, smoking history) divided into particular forms according to the coherence and logical structure to keep a simple and user-friendly data entry system for investigators.
Adverse event data will be collected on a separate form in eCRF and selected data will be automatically reported to the sponsor for pharmacovigilance purposes (see chapter 10). It is at the discretion of the Investigators according to his/her clinical judgment to decide which of the symptoms reported in the patient's diary are to be considered AEs, as defined in the study protocol (see paragraph 10.1) and collected as such in eCRF.

The report will be customized for this project and will contain all the required information.
Data will be collected in an electronic database (eCRF), fully customized to the structure and requirements of the project. Records will be stored under a specific identity number (ID) which will not allow any backward identification of any individual patient. The unequivocal identification of patients will be only known to the treating physician or to an authorized healthcare professional or designated personnel under a contract with a site (on-site data monitoring, see chapter 5.0).
Data will be collected in eCRF by the Investigator(s) or trained study member.
Each patient will fill in the FLIE at the end of each cycle and return this to the attending physician (see below). The collected questionnaires will be then periodically sent to the data management CRO for data entry.
Data from the Patient´s diary and MAT will be digitalized on-site into the eCRF to become part of the electronic database.
The eCRF screen will be available in English and local languages where required (e.g., Chinese, German).

3.6.3. Study visits procedure

No study-specific activities will be completed before signed informed consent form is obtained from patients. Study procedure covers five patient´s visits at the site.

Visit 0
Visit 0 is a screening visit conducted within 2 weeks before chemotherapy administration on cycle 1 or alternatively on Day 1 of chemotherapy Cycle 1. The case of Visit 0 and 1 are combined the patient will still be given adequate time for consideration and consent before the study enrolment.
Investigator considers whether the selected patient meets the predefined eligibility criteria. All predictive individual factors as reported earlier will be collected in eCRF. The risk score will be calculated automatically based on predictive factors No. 1 – 7 (see 3.3.3. Risk Factors for CINV). These parameters will be used to identify the patients with a CINV risk score ≥ 13 (see 3.3.1. Inclusion Criteria). If the patient complies with all the inclusion and exclusion criteria and signs informed consent, he/she is enrolled in the study. If the patient is WOCBP a pregnancy test is done to confirm eligibility. Data from screening visit will be collected in appropriate forms in eCRF.
The randomization procedure can be conducted either during Visit 0, Visit 1 or any time between Visit 0 and Visit 1. The patient is randomized by using an algorithm in eCRF into one of the intervention groups (see sections 3.4. Intervention and antiemetic treatment and 3.4.2. Randomization procedure). If randomization occurs any time before visit 1, it is required to check during Visit 1 that the patient receives the correct treatment assigned according to the intervention groups. The drugs must be correctly stored between the randomization and drug administration at Visit 1.

Visit 1
Visit 1 is a visit on Day 1 of chemotherapy Cycle 1.
WOCBP are tested for pregnancy by a urine dipstick prior to dosing the antiemetic treatment.
The patient is asked about the additional predictive factors (anxiety in the previous 24 hours & <7h of sleep the night before chemotherapy).
The patient is assigned to the treatment and randomized by using an algorithm in eCRF into one of the intervention groups (see sections 3.4. Intervention and antiemetic treatment and 3.4.2. Randomization procedure).
The patient receives antiemetic and chemotherapy at a due time after antiemetic is given.
Data of cycle 1 is collected in eCRF in an appropriate form.
Before the patient leaves the site, he/she receives FLIE, MAT, and a Patient´s diary to answer questions regarding the severity of nausea and vomiting, rescue medication, adverse events. The patient will be instructed by the doctor how to fill in and asked to bring it back at visit 2.

Visit 2
Visit 2 is a visit on Day 1 of chemotherapy Cycle 2.
The patient´s diary, MAT, and FLIE are collected and checked by the investigator. In the case of missing answers, the investigator will need to complete them with the patient. The patient´s eligibility for the chemotherapy is confirmed by checking changes of the screening visit parameters for the algorithm re-calculation. This re-calculation is collected in eCRF. This re-calculation has no impact on patient participation in the study and the randomized group.
Female patients of childbearing potential are tested for pregnancy by a urine dipstick prior to dosing the antiemetic treatment.
The patient receives antiemetic and chemotherapy at a due time after antiemetic is given.
Data of cycle 2 is collected in eCRF in appropriate forms.
Before the patient leaves the centre, he/she receives FLIE, MAT, and a Patient´s diary to answer questions regarding the severity of nausea and vomiting, rescue medication, adverse events. The patient will be instructed by the doctor how to fill in and asked to bring it back at visit 3.

Visit 3
Visit 3 is a visit on Day 1 of chemotherapy Cycle 3. The procedure is the same as described for Visit 2.
The patient´s diary, MAT, and FLIE are collected and checked by the investigator. In the case of missing answers, the investigator will need to complete them with the patient. The patient´s eligibility for the chemotherapy is confirmed by checking changes of the screening visit parameters for the algorithm re-calculation. This re-calculation is collected in eCRF. This re-calculation has no impact on patient participation in the study and the randomized group.
Female patients of childbearing potential are tested for pregnancy by a urine dipstick prior to dosing the antiemetic treatment.
The patient receives antiemetic and chemotherapy at a due time after antiemetic is given.
Data of cycle 3 is collected in eCRF in appropriate forms.
Before the patient leaves the centre, he/she receives FLIE, MAT, and a Patient´s diary to answer questions regarding the severity of nausea and vomiting, rescue medication, adverse events. The patient will be instructed by the doctor how to fill in and asked to bring it back at visit 4.

Visit 4
Visit 4 is a visit ion Day 5 of Cycle 3 or before the start of the next programmed chemotherapy cycle
It is the final visit of the study. FLIE, MAT, and Patient´s diary are collected and recorded information checked.
All patient´s data in eCRF are collected, checked, and validated.

Besides predictive risk factors to calculate the Risk scoring algorithm, further additional factors will be collected and evaluated to confirm the risk scoring algorithm.

Each visit procedure in detail is described in the following chapters. The Study Flow Chart is reported in Appendix 1.

3.6.3.1 BASELINE/SCREENING: VISIT 0

Risk scoring algorithm

Predictive factor	Before a cycle of chemotherapy
Baseline score	10
Impact of patient risk factors	
Patient < 60 age	+1
Expectation (anticipation) of nausea and/or vomiting	+1

Patient has a history of morning sickness during a previous pregnancy	+1
Patient is about to receive platinum or anthracycline chemotherapy	+2
Patient used non-prescribed antiemetics at home in the prior cycle	+3
Patient has nausea or vomiting in the prior cycle	+5
About to receive the 2nd cycle	-5
About to receive ≥ 3rd cycle	-6

VISIT 0 will be conducted within 2 weeks before chemotherapy administration on cycle 1 or alternatively on Day 1 of cycle 1.

- Verify Inclusion/exclusion criteria
- Collect the following information:
  - Demographic data
  - Primary cancer diagnosis
  - Past and recent medical history
  - Number of scheduled cycles
  - Expected time between cycles
  - Eastern Cooperative Oncology Group (ECOG) performance status (0, 1 and 2)
  - Prior radiation therapy and site (within previous 3 months)
- Risk scoring algorithm will be calculated

RISK FACTORS (Risk scoring algorithm calculation)*	**ADDITIONAL RISK FACTORS**
Age	Gender
Expectation of nausea and/or vomiting (YES/NO)	Weight
Morning sickness during previous pregnancy (YES/NO)	Duration of sleep the night before chemotherapy
Chemotherapy type (platinum or anthracycline chemotherapy) and chemotherapy regimen details	History of nausea and vomiting other than morning sickness in females (not-chemotherapy dependent, e.g., motion sickness or vestibular dysfunction)
Use of non-prescribed antiemetics by patients at home in the prior cycle (YES/NO)	Anticipatory nausea/vomiting (CINV before chemotherapy) (YES/NO)
Nausea and/or vomiting in the prior cycle (YES/NO)	Alcohol intake (number of units per week)
Cycle about to be received	Fatigue experience (symptom) (YES/NO)
	Smoking status (YES/NO)
	Anxiety over the last 24 hours (to be inquired right before chemotherapy) (YES/NO)

* Non-naive patient treated outside the study with any chemotherapy regimen at the previous cycles (the next cycle starts 6 months or more later after the previous chemotherapy treatment was finished), will be screened with the following answers to the CINV algorithm questions:
Cycle of chemotherapy about to be received: 1st cycle
Patient used non-prescribed antiemetics at home in the prior cycle: no
Patient has nausea or vomiting in the prior cycle: no

3.6.3.2 VISIT 1: Day 1 of Cycle 1

The patients considered eligible at baseline and showing a risk score ≥ 13 will be randomized.

- WOCBP will perform a urine dipstick pregnancy test, to exclude pregnancy

- Complete the additional risk factor check inquiring "Anxiety over the past 24 hours (YES/NO) and ''Duration of sleep the night before chemotherapy"
- Confirm eligibility of patients to chemotherapy as needed, according to the routine practice
- Administer the assigned antiemetic
- Administer chemotherapy at a due time after antiemetic is given
- Safety findings
- Supply the Patient´s diary for cycle 1 and give instructions to the patient on how to fill it in from Day 1 to 5, and ask to bring it back on Day 1 of cycle 2
- Supply MAT for cycle 1, to be completed by the patient after 24 hours from chemotherapy administration and on Day 5 from chemotherapy administration, give instructions to the patient on how to fill it and ask to bring it back on Day 1 of cycle 2
- Supply FLIE for cycle 1, to be completed by the patient on Day 6 from chemotherapy administration (i.e., collection of data on nausea and vomiting from day 1 to day 5 from chemotherapy dosing), give instructions to the patient on how to fill it in and ask to bring it back on Day 1 of cycle 2
- Call patient between day 3 and 5 from chemotherapy to assess he/she is filling in the daily Patient´s diary

3.6.3.3 VISIT 2: Day 1 of Cycle 2

- WOCBP will perform a urine dipstick pregnancy test, to exclude pregnancy
- Confirm eligibility of patients to chemotherapy according to the routine practice
- Check changes of the following screening visit parameters for the algorithm re-calculation:
    - Expectation of nausea and/or vomiting YES/NO
    - Chemotherapy regimen details
    - Use of non-prescribed antiemetics at home in the prior cycle
    - Nausea and/or vomiting in the prior cycle
    - Number of cycles received
- Confirm the status of the added risk factors:
    - Anticipatory nausea and/or vomiting in the prior cycle (YES/NO)
    - Fatigue experience (symptom) YES/NO
    - Duration of sleep during the night before chemotherapy
    - Anxiety over the past 24 hours YES/NO
- Administer the assigned antiemetic
- Administer chemotherapy at a due time after antiemetic is given
- Safety findings (from diaries and inquiry)
- Rescue medications related to nausea and/or vomiting (from diaries and inquiry)
- Collect chemotherapy delay and/or dose reduction
- Collect and review the Patient´s diary of cycle 1 and digitalize the data in the eCRF
- Collect and review the MAT of cycle 1 and digitalize the data in the eCRF
- Collect and review the FLIE questionnaire relevant to cycle 1
- Supply Patient´s diary for cycle 2 and give instructions to the patient on how to fill it in from Day 1 to 5, and ask to bring it back on Day 1 of cycle 3
- Supply MAT for cycle 2, to be completed by the patient after 24 hours from chemotherapy administration and on Day 5 from chemotherapy administration, give instructions to the patient on how to fill it and ask to bring it back on Day 1 of cycle 3
- Supply FLIE for cycle 2, to be completed by the patient on Day 6 from chemotherapy administration (i.e., collection of data on nausea and vomiting from day 1 to day 5 from chemotherapy dosing), give instructions to the patient on how to fill it in and ask to bring it back on Day 1 of cycle 3
- Call patient between day 3 and 5 from chemotherapy to assess he/she is filling in the daily Patient´s diary

3.6.3.4 VISIT 3: Day 1 of Cycle 3

- WOCBP will perform a urine dipstick pregnancy test, to exclude pregnancy
- Confirm eligibility of patients to chemotherapy according to the routine practice
- Check changes of the following screening visit parameters for the algorithm re-calculation:
    - Expectation of nausea and/or vomiting YES/NO
    - Chemotherapy regimen details
    - Use of non-prescribed antiemetics at home in the prior cycle
    - Nausea and/or vomiting in the prior cycle
    - Number of cycles received
- Confirm the status of the added risk factors:
    - Anticipatory nausea and/or vomiting in the prior cycle (YES/NO)
    - Fatigue experience (symptom) YES/NO
    - Duration of sleep during the night before chemotherapy
    - Anxiety over the past 24 hours YES/NO
- Administered assigned antiemetic
- Administer chemotherapy at a due time after antiemetic is given
- Safety findings (from diaries and inquiry)
- Rescue medications related to nausea and/or vomiting (from diaries and inquiry)
- Collect chemotherapy delay and/or dose reduction
- Collect and review the Patient´s diary of cycle 2 and digitalize the data in the eCRF
- Collect and review the MAT of cycle 2 and digitalize the data in the eCRF
- Collect and review the FLIE questionnaire relevant to cycle 2
- Supply the Patient´s diary for cycle 3 and give instructions to the patient on how to fill it in from Day 1 to 5, and ask to bring it back at the last visit on Day 5 of cycle 3 or before the start of the next programmed chemotherapy cycle
- Supply MAT for cycle 3, to be completed by the patient after 24 hours from chemotherapy administration and on Day 5 from chemotherapy administration, give instructions to the patient on how to fill it and ask to bring it back at the last visit on Day 5 of cycle 3 before the start of the next programmed chemotherapy cycle
- Supply FLIE for cycle 3, to be completed by the patient on Day 6 from chemotherapy administration (i.e., collection of data on nausea and vomiting from day 1 to day 5 from chemotherapy dosing), give instructions to the patient on how to fill it in and ask to bring it back at the last visit on Day 5 of cycle 3 or before the start of the next programmed chemotherapy cycle
- Call patient between day 3 and 5 from chemotherapy to assess he/she is filling in the daily Patient´s diary

3.6.3.5 FINAL VISIT (VISIT 4): DAY 5 OF CYCLE 3 or before the start of the next programmed chemotherapy cycle

- Verify the general health status of the patient according to clinical routine
- Safety findings (from diaries and inquiry)
- Rescue medications related to nausea and/or vomiting (from diaries and inquiry)
- Collect and review the Patient´s diary of cycle 3 and digitalize the data in the eCRF
- Collect and review the MAT of cycle 3 and digitalize the data in the eCRF
- Collect and review the FLIE questionnaire relevant to cycle 3.

3.7. Health Economics Outcome Research (HEOR) Assessments

The health economic component described in this clinical protocol will only focus on resource utilisation linked to CINV and treatment of events (efficacy/safety).

To capture event-related resource utilisation, patients will be followed for the duration of the study. If one of the following events occurs; death, withdrawal of consent, or lost to follow up, resource utilisation for these patients will be reported up to the point they are withdrawn.

3.7.1. Resource Utilisation and Costs

The economic data will be collected primarily in physical units of health care resources used per patient and per event (efficacy/safety). The health economic endpoints are reported in section 3.5. Study endpoints.

Health resource utilisation will be collected for all patients participating in the clinical trial while resource costing, with costs collected outside the clinical study, will be performed in selected countries. No direct patient cost will be requested from institutions or patients.

3.7.2. Perspectives

The perspective is the viewpoint from which costs and monetary benefits are considered.
The payer's (health insurance) perspective estimates costs from the "third-party payer" point of view. This perspective considers only the part of health care expenses (both inpatient and outpatient care) that are charged to or reimbursed by the health insurance.
This economic evaluation, based on direct medical costs, will be performed according to the payer's perspective.

All resource consumption data analysis will be specified in a separate Health Economics Analysis Plan.

4. Ethical consideration

4.1. Informed Consent Form

Patient´s participation in the study is voluntary. The patient's consent may be withdrawn at any time, without giving reasons and without prejudice to further medical care.
The study participants will be informed in writing and orally before the start of the study about the nature and scope of the planned investigation, in particular about the possible benefits for their health and possible risks, and their consent will be documented by signing the consent form.

Informed Consent Form (ICF) consisting of two documents (Informed consent with participation in the Study and Patient´s personal data protection Inform consent) will be obtained from each patient prior to study initiation. Two original documents will be signed by the patient. One original Informed Consent Form (ICF) will be filed with the patient´s documentation in the clinical center and the second original Informed Consent form will be given to the patient.

IBA will prepare the Master Informed Consent Form in English according to the European requirements.
The Master Form will be then distributed to all the coordinators of the respective countries (local CROs). Each coordinator (local CRO) will have to review the Master Informed Consent Form and add in track changes the sentences or expressions possibly required by the local Health Authorities and local legislative.
The document with tracked changes (including deletions if applicable) will have to be sent back to IBA for the translation in the local language.

4.2. Regulatory Requirements

The study will be conducted in accordance with the Helsinki Declaration in its current version and all local laws or regulations.
Submission to Ethics Committee and local Health Authorities and relevant approvals are required and will be performed at the local national level by the coordinator of the respective country (local CRO).

4.3. Legislative Requirements

Local legislative requirements of the countries in which the study takes place will be applied.
Legislative requirements regarding personal data protection are described in the following section 9. Confidentiality. The study protocol and the study results will be posted in EUDRACT and ClinicalTrials.gov in accordance with regulatory requirements and timelines.
Notification to Data protection Authorities in individual countries will be applied according to the local regulatory and legislative requirements.

5. Monitoring

The purposes of trial monitoring are to verify:

1) The rights and well-being of human subjects are protected
2) The trial data are accurate, complete, and corresponding with the source documents (medical records)
3) The study is conducted in compliance with the currently approved protocol and its amendments, GCP requirements, and with the relevant regulatory requirements.

ICH E6 (R2) provides for flexibility in how trials are monitored, advising sponsors to consider "the objective, purpose, design, complexity, blinding, size, and endpoints of a trial" in determining the extent and nature of monitoring for a given trial.
Quality risk-based monitoring approaches can be highly effective in phase IV and are supported by regulatory guidance.

Generally applying the integrated approach of Quality Risk-Based Monitoring in conjunction with procedures, such as investigators' training, and written guidance can assure appropriate conduct of a post-approval study in accordance with ICH GCP requirements.

This clinical study is post-registration clinical study phase IV where the medicinal product is used in accordance with SPC. The only intervention is randomization, so this kind of monitoring will be implemented in this study.

Quality Risk-Based Monitoring enables focused attention of risk while promoting efficient utilization of time, resources, and budget. Risk management including the used procedure within this study is described in chapter 5 (Risk management and Risk assessment).
Due to the extent, budget, and nature of the study the remote monitoring (remote evaluation of collected data, performed in a timely manner supported by appropriately qualified and trained persons (data managers, biostatisticians) will be primarily applied. The processes of data control and data review are described in the following chapters of this document. The effectiveness and efficiency of this strategy will be regularly monitored in compliance with the Risk management plan.

In the event the controls will disclose the system error at the site, the following process will depend on the scope and difficulty to eliminate the discrepancy. Correction by the distant way (teleconference with IBA HelpDesk assistant or data manager) will be prioritized if possible.
If the controls indicate the high error rate, or it will be necessary to solve the problem at the study site, the issue will be escalated to the sponsor and local CRO. The Local CRO will arrange a visit to the site to solve the issue on-site (on-site data monitoring to verify the process and data).

Risk assessment (chapter 6) is applied throughout the Study lifecycle and involved in all its parts from the Study design through preparation (protocol development, …) and execution to the final evaluation.
Based on Risk assessment results, the following monitoring methods are applicable throughout the whole Study: centralized statistical monitoring and on-site-monitoring. Details are described in the Monitoring Plan.

6. Risk Management and Risk Assessment

Risk management will be applied on all processes (contracts management, recruitment management, training of investigators, data collection and data processing, data review, data analyses, etc.) throughout all trial lifecycle to ensure human subject protection and the reliability of the trial results in compliance with requirements of ICH E6 Guideline for Good Clinical Practice.
The trial will be based on a Risk-based approach, it means that:

- All critical processes, that are essential for human subject protection and reliability of results will be identified (methods of operation and setting of the study, crucial processes such as ICF collecting, regulatory processes, SOPs/manuals, and their training, budget risks, etc).
- Risks will be evaluated on the base of a probability of occurring, their detectability and severity, and considered with the predefined quality tolerance limits.
- If nonacceptable risk will be defined, the corrective or/and preventive actions will be implemented to reduce the risk to an acceptable level. Detected risks, CAPA, responsibilities, and the schedule of risk monitoring will be summarized in the document Risk assessment report.
- The risks will be communicated with interested participated subjects (sponsor, cooperating CROs, investigators) adequately.
- The risks will be reviewed periodically according to the Risk management Plan, which is a part of the Risk assessment report and Quality Control Plan, that will be prepared as separate documents on the base of Risk analyses.

The Risk management is illustrated on the following figure:

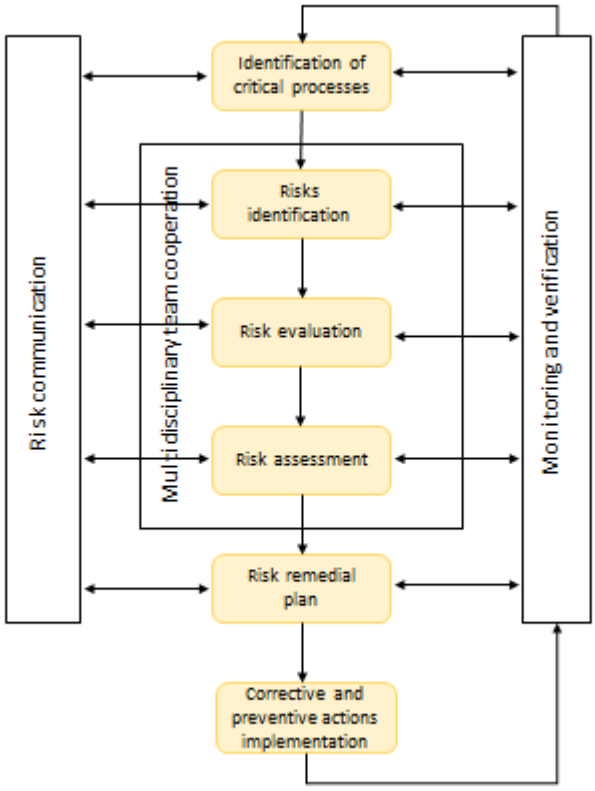

Figure 1 The scheme of Risk management in the trial

For risk analyses, a methodology FMEA (Failure Mode and Effects Evaluation) will be used. It is a risk management tool to proactively identify and assess the causes and effects of potential failures in a system, thereby preventing them from happening. All considered risks are assessed according to Risk priority number (RPN) considering severity (how severe is the consequence if the process fails), occurrence or probability (how often or how is probable, that process fails), detection (how easily can failure be detected).
This Risk analysis will be processed as a separate document according to IBA's Working instruction. FMEA is a multidisciplinary method, so the sponsor and IBA experts will participate in its processing, evaluation, and implementation of preventive actions.

7. Data Collection and Data Management

IBA will manage all data management activities for the study.
Data will be collected into the database behind the EDC system **CLADE-IS** (see Appendix 6). The system has been specifically designed for the collection of large amounts of data in clinical trials and/or clinical registries. It will be fully customized to the structure and requirements of the project. The online application is accessible to users via any internet browser. Records are stored under a specific identity number (ID) which does not allow any backward identification of any individual patient. The unequivocal identification of the patient is only known to the treating physician or authorized healthcare professional.

Clinical management of the patient reflects the standard clinical practice in each country/center. Data (no patient´s initials, no full date of birth will be collected) from all patients who meet inclusion criteria will be consecutively entered in the project database.
Each patient will fill the Patient´s diary for 5 consecutive days after each chemotherapy administration, MAT questionnaire during the first 24 hours following chemotherapy, and four days after chemotherapy, and FLIE quality of life (QoL) questionnaire on 6th day after each chemotherapy. FLIE QoL questionnaire and MAT questionnaire will be available in validated translation for each country. Patient diaries will be available in local languages for each country. Patients included in the study shall undergo 3 consecutive chemotherapy cycles. Data from the Patient´s diary and MAT will be digitalized onsite to become part of the electronic database. IBA will do the quality control process of digitalized patient diaries and MAT data. FLIE QoL questionnaires will be periodically sent to IBA for digitalization and following quality control.
Specific data management documentation will be prepared by IBA. Firstly, it will be the Data Management Plan containing detailed information about database setup (form statuses, user roles, type of validations, reporting, and database specialties) and detailed information about consequential data management processes and relevant documents (Quality Control Plan, Translation, and Coding or SAE Reconciliation Plan). Secondly, it will be the Data Validation Plan containing the plan of all checks planned to be performed on collected data. All particular documents will be prepared by IBA and approved separately. Data management plan and Data validation plan will be issued prior to data collection beginning. Data will be collected in eCRF by the Investigator(s) or trained study member. Every person authorised to enter project data into eCRF will receive a login and password granted exclusive access to him/her. Data will be entered into the system according to the technical manual that will be provided to all users by IBA in the same languages as eCRF (English and local languages where required (e.g., Chinese, German).

Control of data correctness will be performed in several steps.

1) Automatic validations: The first and most extensive step is automatic control performed according to pre-programmed checks based on Data Validation Plan. The system will generate queries based

on these checks and investigators will have to answer them. Most of system queries could be generated in local languages.

2) Manual queries: The second step is the possibility to create manual queries based on specific findings realised by any member of the project team (especially after the data review process). These queries will be created in English and answers will be requested in English too.
3) Data review: Data review process will be organised regularly (quarterly) and will be one of the key project milestones focusing on the quality of collected data and accuracy of data collection and data cleaning process (details of the data review process in the paragraph below).
4) Quality Control of Patient´s diaries and MAT data. Patient´s diaries and MAT data will be digitalized on clinical sites. The patient´s diaries and MAT questionnaires will be sent to IBA then and submitted to the quality control process (details of the quality control process in the paragraph below).
5) Quality Control of FLIE data. FLIE data will be sent to IBA and then digitalized. The quality control process will be applied to them too.

Data Review Process

The goal of the data review process is to review collected data during the course of the project in order to verify data quality, confirm the accuracy of data collection and data cleaning processes, and eventually to update the established process. The data review process will be organised regularly. At each time data review will be performed, an agenda containing a list of actions will be prepared. The following items will be considered for review:

- A global overview of subjects and their database statuses. This overview will present detailed enrolment and how rigorously investigators are working with the EDC system. The data manager will prepare this overview.
- Medical review of specific predefined consistencies of medical information. The Scientific Lead will be in charge to review key medical data in order to provide information on whether collected data are all right from the medical perspective (review of used medication, adverse events, etc.). The Scientific Lead will work with data provided by the data manager in advance to the data review meeting.
- The total number of outstanding queries in particular sites compared to the global number of open queries. The number of totals/open queries can show how rigorously investigators are working with the EDC system and their will to correct found inconsistencies. The list of queries will be prepared by the data manager.
- List of specific data inconsistencies. In addition to system queries raised during the data collection process, there might be inconsistencies found during medical coding, SAE reconciliation, or analytical data review. These issues will be prepared by the project manager and will be discussed too.
- Plan of remaining steps until the nearest milestone. A review of the study calendar will be part of each data review meeting. Following on enrolment status, plan of enrolment for the next study period will be discussed as well as the number of participating countries, planned FPI/LPO milestones, the status of patient diaries tracking, etc. This item will be prepared by the project manager.
- Overview and classification of protocol deviations as defined by the Sponsor and the Scientific Lead. Based on already collected data there might be information about existing protocol deviations. The data analyst will prepare a list of all known protocol deviations in order to discuss all relevant patients. The following deviations will be considered:
    - fulfillment of inclusion criteria
    - violation of exclusion criteria
    - study visits not corresponding to the study design

Data Review Process will be built on the agenda prepared by the project manager according to the above-mentioned points and containing all details to be discussed during the meeting. It is important to invite all relevant people in order to arrange a constructive discussion leading to appropriate conclusions, at least Helsinn representative, Scientific Lead, and IBA project manager will participate. All the decisions made during the meeting will be written, reviewed by all participants, and approved. Meeting minutes will include all the tasks resulting from the meeting and solutions of discovered issues.

Quality Control Process

The principle of the quality control process is to compare original data with data transferred into the clinical database. This process will be applied on FLIE QoL questionnaires (as these are only data being entered into the clinical database out of clinical site) and Patient´s diaries and MAT questionnaires (as these data will be digitalized as well). Initially, a Quality Control Plan will be created to plan the frequency of quality control process, list of items to be checked, permitted error rate, and other processing details. The results of the quality control process will be presented in the Quality Control report.

7.1. Data Quality Control

The purpose of data control in the clinical trial is to verify that:

- The rights and well-being of human subjects are protected
- The reported data are accurate, complete, and verifiable with source documents
- The conduct of the trial is in accordance with the current protocol, GCP, and regulatory requirement

Within this trial, the risk-based approach to data quality control of clinical trial will be implemented. There will be no on-site monitoring involved from the IBA side. Data verification will be set by using the EDC system. There will be no monitoring of source documentation. The potential risks of this approach will be considered within the Risk assessment and the necessary measures will be implemented. The key points in this approach are:

- The standard operating procedures
- Contracts with the sites/investigators
- Qualification and training of participating subjects (investigators/local CROs/IBA….)
- eCRF and validation of the EDC system
- Risk management and communication of risks
- Data review (the quality of processed data will be verified by a process of Data review)
- Quality Control is performed on digitalized data (will be described in the Quality Control Plan).

Data review

The purpose of regular data reviews as well as single use before analysis is:

a) Identify missing data, inconsistent data, data outliers, unexpected lack of variability, and protocol deviation
b) Examine data trends such as the range, consistency, and variability of data within and across sites.
c) Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
d) Analyse site characteristics and performance metrics.
e) Select sites and/or processes for targeted on-site monitoring.

8. Statistical analysis

The data will be statistically processed, analyzed, and evaluated centrally by the Institute of Biostatistics and Analyses, Ltd., Poštovská 68/3, 602 00 Brno.

8.1. Statistical Analysis Plan

Detailed data processing procedure will be described in the Statistical Analysis Plan (SAP) with regard to the nature of the primary and secondary endpoints of the study and all the other data collected via the Electronic Data Collection (EDC) system. The SAP will be implemented as soon as the protocol will be finalized.

8.2. Sample Size Analysis

A sample of 410 randomised subjects, each scheduled to be measured 3 times/cycles, achieve a 80% power when using a two-sided Wald test from a GEE analysis to test whether the proportion of Complete response expected in the Test group (71%) differs from that expected in the Control group (60%) at a significance level of 0,050. The subjects are randomly split between a Test group and a Control group, with 50% of the subjects assigned to the Test group. The measurements of each subject will be made at the following times/cycles expressed as proportions of the total study time: {0%; 50%; 100%}. Missing values are assumed to occur completely at random (MCAR) or at random (MAR). These missing value proportions will be combined to form the pairwise observant probabilities using the Independent method. The anticipated proportions missing at each measurement time/cycle are {0%; 7.5%; 15%}. Based on these attrition rate scenario, a sample of 348 completer subjects is expected. The correlation between observations on the same subject is assumed to be 0.5 (ballpark estimate). All computations are performed using PASS 14 software.

8.3. Analysis Populations Sets

The Full Analysis Set (FAS) will consist of all randomized patients to whom the investigational drug is dispensed. It will be the primary basis for the analyses of efficacy. Following the intent-to-treat principle, patients in the FAS population will be analyzed according to the treatment to which they were randomized.
A Per Protocol (PP) population will consist of all patients in the FAS population who complete the study fully compliant with the protocol and without any major deviation. Patients in the PP population will be analyzed according to the treatment they received. Efficacy analyses based on the PP population will be considered supportive.
The Safety population is defined as the set of all randomized patients with at least one documented application of any study drug. It will be the basis for the analyses of safety. Patients in the Safety population will be analyzed according to the treatment they received.

8.4. Efficacy Analysis

All efficacy analyses will be performed on the FAS population. Also, analysis of the primary and secondary efficacy variables will be carried out on the Per Protocol population to assess the robustness of the findings. Safety outcomes will be analyzed on the Safety population.

The primary efficacy endpoint "Proportion of complete responses over three cycles of chemotherapy after the start of the MEC administration" will be analyzed by means of a generalized linear model (GLIM) with logit link function, binomial distribution, and with "study treatment" (NEPA + Dex or Standard of care), "carboplatin use" (yes or no) and "country" as factors. Moreover, the GLIM model will be parameterized with generalized estimating equations with an exchangeable working correlation matrix to take into account clustered data (i.e. three repeated measures corresponding to as many cycles of chemotherapy within each subject). Results will be reported as odds ratios with associated two-sided 95% confidence intervals and p-values.
The same statistical approach will be used for all the secondary efficacy endpoints except for the following outcomes "delay and/or dose reduction" which will be analyzed using a Stratified Wilcoxon Rank Sum test blocking for carboplatin use and country.
Missing data on the primary efficacy endpoint will be imputed using conventional Multiple Imputations approach. The SAS® MI procedure will be employed to perform multiple imputation in order to obtain Maximum Likelihood estimates which, by definition, are unbiased under a MCAR and MAR mechanism for missing values. Details on Multiple Imputations will be provided with the SAP.
Missing data on secondary efficacy endpoints will be imputed using last observation carried forward (LOCF).
The overall type I family-wise error rate for testing the primary and the secondary efficacy parameters is controlled at the 0.05 significance level without the need for adjustments since the study is planned with a single primary endpoint and since secondary endpoints are only supportive of primary endpoint findings. All statistical analyses will be performed using SAS version 9.4 or later.

8.5. Health Economic Analysis

The analytical approach will be a cost-efficacy analysis. This approach combines measures of costs over time with efficacy measures.

Resource Utilisation and Costs

The analysis of medical consumption will be performed by comparing the number of resources consumed per treatment group. Health care resource consumption will be expressed in units for each selected resource (e.g. number of days of hospitalisation, the number of physicians' consultations). For each selected resource unit, both the frequency of use (i.e., % patient usage) and intensity of use (i.e., the average amount used) will be presented. The costs by treatment group will be presented in an aggregate manner and by subgroups.

The pooling of resource utilisation patterns will be undertaken unless any country effect or country × treatment interaction effect has been noted in the primary efficacy criteria.

Cost Estimates

The resource consumption will be valued by country, using average national charges/costs collected outside the clinical study by resource items; detailed valuation methods will be country-specific.

Efficacy

Efficacy criteria, as defined in Section 3.5. Study endpoints will be compared across groups.

Cost-efficacy Analysis

The incremental cost-efficacy ratio will be calculated in case a difference in efficacy is found between groups and if the costs in the Akynzeo® group are higher. If that is not the case, then incremental costs (or savings) results across groups will be presented as cost-minimisation or cost-consequence results.

The different options are summarised in Table 1.

Table 1: Cost-Efficacy Analysis

	Difference in Efficacy	No difference in Efficacy
Akynzeo® group costs lower	Savings	Savings
Akynzeo® group costs higher	Cost-efficacy	Incremental Costs

All resource consumption data analysis will be specified in a separate Health Economics Analysis Plan.

9. Confidentiality

The data collected within the database will be pseudonymised.

Each patient will be enrolled in the study electronic database under a unique Identification Number (ID) and henceforth will be identifiable only via this ID code. Re-identification of patients from the patient number in the study will not be possible. The unique ID of the individual patient is only known to collaborating physician or qualified medical personnel involved in the project.
In order to respect patient privacy, all patient records, study reports, and communications will identify the patient by the assigned unique patient number. The patient's confidentiality will be maintained and will not be made publicly available, to the extent permitted by the applicable laws and regulations. The study sponsor of this study is the owner of all data and any information or material collected in the database.

9.1. Personal Data Protection

The processing of personal data of natural persons involved in the study is carried out in accordance with any applicable "Data Protection Laws", including without limitation the Regulation (EU) 2016/679 of the European Parliament and of the Council on the protection of nature persons with regard to the processing of personal data and on the free movement of such data (hereinafter „GDPR"), as well as any country legislation in relation to the protection of personal data. Both the controller and the processor are obliged to observe the rules and obligations coming from the applicable Data Protection Laws, as well as to set up the relevant processes for data subjects' rights fulfilment.
Whether personal/pseudonymous or anonymous data is processed within the study, it is always protected information processing. Therefore, IBA has established the ISMS Information Security Management System in compliance with the standard ISO/IEC 27000. By this way IBA has accepted and implemented appropriate technical and organisational security measures required by standard and Regulation.

9.1.1. Patients´Personal Data Processing

The controller of personal data, who determines the purposes and means of processing within the overall study is the Sponsor (Helsinn Healthcare SA, Via Pian Scairolo 9, 6912 Pazzallo-Lugano, Switzerland). The patient can´t be included in the study without signed **explicit informed consent**. The responsible for acquiring and storing of patient informed consent for statistical and scientific purposes is the investigator/Provider of health services (site) according to conditions stated in the contract with the participating site. The specific

purposes are described in the informed consent form. Information that the patient gave the consent with processing of his/her data should be confirmed in the EDC system. Without this confirmation, the new patient can´t be entered.
The processing of identifiable personal data of the patient in the study, before pseudonymisation, is allowed only to an investigator/ Provider of health services (site). The investigator/Provider of health services (site) shall enter the patient´s data into the EDC system under a unique ID, the investigator is the only person who can identify the patient based on his/her ID. Other persons accessing the study are unable to identify a patient in the EDC system. The physician is the contact person for the patient´s rights fulfillment. The physician shall be familiarized with rules for personal data processing.
Further data processing in the study is in the pseudonymous regime, where the persons accessing the registry based on their access rights are unable to identify the patient (directly or indirectly).

9.1.2. Investigators´ Personal Data Processing

Within the study, the personal data of cooperating investigators are processed by IBA on the base of the creation of access accounts and communication during the study course. On the base of the legitimate purpose of the controller, the investigator´s data might be communicated to, and processed by, the controller as a processor to ensure the smooth running of the study and high quality of collected data.

Should the Sponsor receive any information on investigators, the Controller of investigators personal data is Helsinn. The processors are IBA, local CROs and permitted sub-processors managing the investigators for the study.

In such a case, the investigators are properly informed about their data processing; IBA, local CROs and permitted sub-processors to undertake to provide adequate notices to the investigator (in a form provided by and on behalf of the Sponsor) and undertake to ensure that all investigators have acknowledged to the processing of their personal data as required for the following purposes: (a) the conduct of the Study; (b) review by governmental or regulatory agencies, public authorities or pharmaceutical industries associations, IBA, the Sponsor, and their agents and affiliates; and (c) compliance with legal or regulatory requirements including those on disclosure of transfers of values from pharmaceutical companies to healthcare professionals and healthcare organizations; and (d) storage in databases for use in selecting investigators, study staff, and institutions for future clinical trials.

9.1.3. Ensuring of Personal Data Protection

IBA has implemented the following measures in compliance with the ethical and legal requirements to ensure the maximal possible safety of collected data:

- Technical measures of EDC system
- Internal standards form personal data processing, risks management, incident management, training system
- Access policy – access to the data only for the authorized person on the base of their access rights
- Training of investigators

9.1.4. Description of Archiving and Disposal of Data after Finishing the Study

Unless prohibited law or otherwise required by the applicable law to be preserved, IBA will securely delete all personal data in its possession or under its control upon the termination of the study according to the requirements of the Data Protection Laws, with the exception of personal data that in accordance with the applicable laws, regulations and/or guidelines in force must be conserved by the IBA.

10. Safety Management

All Adverse Events (AEs) occurring after signing the informed consent through the AE reporting period are to be recorded on the AE pages of the eCRF irrespective of its relatedness to the study drug.

10.1. Definitions

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

AEs include the following types of occurrences:

- Other medical experiences, regardless of their relationship to the study drug, such as injury, surgery, accidents, increased severity of pre-existing symptoms, apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, physiological testing, or physical examination findings;
- Reactions from drug overdose, abuse, misuse, medication errors, withdrawal, hypersensitivity, or toxicity;
- Clinically relevant abnormal findings, including laboratory abnormalities, as well as worsening of any pre-existing condition at each visit;
- Adverse drug reactions.

Planned surgical interventions or planned hospitalizations scheduled prior to the informed consent but performed during the study (e.g. corrective procedures, biopsy, additional chemotherapy cycles, etc.) should NOT be considered AEs.

An Adverse Drug Reaction (ADR) is any noxious and unintended response associated with the investigational medicinal product at any dose. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

A Serious Adverse Event (SAE) is any event that suggests a significant hazard, contraindication, side effect, or precaution, whether or not it is considered to be associated with the study drug. A SAE is an AE that meets any of the following criteria:

- Results in death. This includes any death that occurs during the conduct of a clinical study, including deaths that appear to be completely unrelated to the study drug (e.g. car accident);
- Is life-threatening. This includes any AE during which the subject is, in the view of the Investigator, at immediate risk of death from the event as it occurs. This definition does not include events that may have caused death if they had occurred in a more severe form; Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Other medical events that based upon appropriate medical judgment are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining a SAE.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a serious ADR that is unexpected or for which the development is uncommon (unexpected issue) observed during a clinical trial and for which there is a relationship with the experimental drug, whatever the tested drug or its comparator.

The drugs that may be used as standard of care in Arm B, including dexamethasone that is also used in Arm A, are investigational medicinal products (IMPs) for this study.

Section 4.8 of the relevant SmPC of each IMP used in the Study will serve as the reference safety information (RSI) for determining expectedness of serious adverse reactions (SARs) that occur with these products.

Any serious and unexpected AE that the Investigator or the Sponsor considers to be at least possibly related to study drug is subject to expedited reporting to the appropriate Health Authorities. AEs for which causality is not assessed by the Investigator are related to the study drug by the Sponsor.

10.2. Classification of AEs

The Investigator will classify AEs about severity and relationship to the investigational medicinal product. Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study drugs. If the Investigator's causality assessment is missing or unknown, the AE must be considered as related to the product.

10.2.1. Severity

The severity of an AE will be rated by the Investigator according to the descriptions and grading scales of the Common Terminology Criteria for Adverse Events (CTCAE) version 5, as follows:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate Instrumental Activities of Daily Living (ADL)*
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4 Life-threatening consequences; urgent intervention indicated
- Grade 5 Death related to AE

(*) Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. (**) Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.2.2. Relationship to the investigational product and/or additional study drug

For this study, a causal relationship of an AE with the study drug will be classified as either:

- RELATED

or

- NOT RELATED

10.3. Recording of AEs

All AEs (including SAEs) starting from the time of informed consent signature up to the end of the study must be collected in the eCRF, irrespective of relatedness to the study drug.

SAE should be collected and reported within 24 hours.

Any related SAE (based on Investigator judgment) beyond the end of the study may be recorded on the SAE Reporting Form.

SAEs must be followed up by the Investigator until symptom resolution or until the condition stabilizes or the patient is lost to follow-up.

Non-serious AEs must be followed up by the Investigator until the end of the study. At the end of this follow-up period, all unresolved non-serious AEs will be documented on the eCRF as “not recovered”.

Clinically relevant abnormal findings, including laboratory abnormalities, as well as worsening of any pre-existing condition at each visit shall be recorded as an AE.

Any abnormalities seen at baseline should not be recorded as an AE.

The Investigator will be responsible for ensuring that the correct information concerning all AEs is entered on the appropriate eCRF pages and in the SAE Reporting Form as applicable.

10.3.1. Reports of Lack of efficacy

Lack of efficacy will be recorded in the eCRF and classified according to its seriousness. Whenever the signs and symptoms considered as lack of efficacy are nausea and vomiting and occurring during the study (up to 5 days after the study drug(s) and dexamethasone administration), these will not be recorded in the AE section of the eCRF, unless it meets the criteria for a SAE or the Investigator considers the episode(s) of nausea and vomiting to be caused by a reason other than lack of efficacy of study treatment.

If at any time during the study, a sign /symptom of lack of efficacy meets a SAE criterion, it is to be reported to the Sponsor and recorded in the AE/SAE section of the eCRF. The report shall clearly state “lack of efficacy” as an SAE.

10.3.2. Pregnancy

In the unlikely event that a patient becomes pregnant during the study, the Investigator will be requested to complete the Pregnancy Report Form (Appendix 8) and forward it to the ethics committee (EC) / Institutional review board (IRB) and the Sponsor immediately (within 24 hours) of becoming aware of the pregnancy. Pregnant patients will be followed by the Investigator and Sponsor until the fetus /newborn is delivered. The Investigator will request the subject’s primary care physician (or obstetrician) to provide further information. A new Pregnancy Report Form will be filled with follow-up information on the pregnancy. The form duly completed by the primary care physician (or obstetrician) should be sent by email or fax to the Sponsor.

If pregnancy occurs while the patient is on the study, the subject will be discontinued from the study.

If a female partner of a male patient becomes pregnant during the male patient’s participation in this study and gives consent to collect information, the investigator must fill the SAE form and forward it as described above.

10.4. Reporting of SAEs

The Investigator should record any SAEs using the electronic SAE Reporting Form which is a part of eCRF. The investigator should complete all mandatory questions of SAE Reporting Form either by the selection of the response in the dropdown or by writing a text to the relevant text field. Manually entered text is required in case of SAE description (diagnosis or main symptoms), medical history of the patient-relevant to the event, concomitant medications, clinical description of the event, cause of death in case SAE is fatal. This text needs to be written in English.

As soon as possible, but no later than 24 hours after first knowledge by the Investigator, the Investigator will send via automatically generated e-mail in eCRF the SAE Reporting Form to IBA.

It is the responsibility of the Investigator to inform his Ethics Committee (EC) about SAEs according to the local EC requirements. Reporting of SUSARs to the relevant EC and Local Competent Authority, in accordance with the EU Clinical Trial Directive 2001/20/EC, ICH E6 Guidance on GCP and ICH E2A10 Guidance on Clinical Safety Management, will be the responsibility of the Sponsor and IBA.

Deaths and life-threatening related events should be reported to IBA immediately by the completed electronic SAE Form. When the Investigator receives any information about a SAE, which changes or adds to the information on the initial SAE Form, a new SAE Reporting Form (the ”follow-up” form) should be filled in and automatically emailed to IBA within 24 hours, especially if the new information has an impact on the seriousness, relatedness or expectedness of the SAE.

11. Insurance

This clinical study is post-registration clinical study phase IV where the medicinal product is used in accordance with SPC and Marketing Authorisation. The only intervention is randomization.

Due to intervention post-registration study type insurance of the study is required.

Specialist clinical trial liability insurance will be designed to provide financial protection for those sponsoring and conducting the trials as well as to provide a suitable compensation to the volunteers should they suffer harm as a result.

The validity of clinical trial insurance will be the study Sponsor’s responsibility. Proof of insurance will be submitted to the approving Local Competent Authority before approval is given. The purpose of clinical study insurance is to ensure the public/products liability as well as no-fault compensation.

12. Sites Training and Start of Data Collection

Training of the eCRF users will be done before the start of data collection in order to ensure a unified approach to data entry. Instructions for completing the records and controlling of the system will be described in the user guide, which will be distributed to each participating physician involved in the registry. The user guide will be also part of the eCRF. To answer additional questions regarding working with the EDC system and the rules of data entry, there will be helpdesk operating every working day between 8 am and 4 pm CET.

Training will be performed as an audio/video conference. An audio/video conference is a very popular and efficient way to train many people with very limited costs. It is also time-effective.

Training will be held before the start of the study and also in the special situations like training new staff in an already-running study or training several new functionalities after the database is updated in order to guarantee consistent work with the database system throughout the study’s duration for all database users.

13. Publication Rules

According to the agreement, the global data are owned by the Sponsor of the study – Helsinn Healthcare SA. Data property will be treated in individual contracts with physicians/medical centers. Data collected in the MyRisk study will be passed to the study sponsor, Helsinn Healthcare SA after processing the final data analysis.

Each country can process its own data prior to running the analysis of global data. The scope of these analyses will be described in the SAP. The individual country analysis will be processed and provided to the Sponsor. The Sponsor can use the country analytical outputs to be published separately and locally as congress participation as soon as available.
A full manuscript of the local data can be prepared and published only after global data will be published.

The scope and form of data will always be used in accordance with the legislation on the protection of personal data and medical secrecy in Europe.

14. Investigators Fee

The local CRO will sign an agreement with individual physicians/medical centers involved in the study. In the agreement, there will be specified the amount of remuneration which is appropriate to compensate for the time spent by the investigator on this study.

Individual physician/medical centre will be rewarded for the data delivery for all three patient cycles including digitalization of Patient´s diaries and MAT data and providing completed FLIE questionnaires in paper to IBA through local CRO. The condition is that the data will be complete and correct and checked by data review and all data quality procedures described in chapter 5 (Monitoring) and chapter 7 (Data management).
Data ownership will be specified as part of the contracts.

15. Quality Assurance and Control

Quality management, all processes of quality control and quality assurance, will be implemented and described within the Standard Operating Procedures to ensure the trial is conducted and data are generated, documented, and reported in compliance with this protocol, GCP, and regulatory requirements.
The processes critical to ensuring human subject protection and reliability of trial results will be assessed within the Risk assessment (see chapter 5 Risk management).
The data collection and their processing in the EDC system will be carried in accordance with IBA internal quality management system and procedures. IBA has established its quality system in compliance with the requirements of international standards EN ISO 9001:2015 Quality management and ISO/IEC 27 001:2013 Information Security Management System and Good Clinical Practice.

16. References

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Appendix 1 Study Flow Chart

	Screening visit Visit 0	Day 1 Cycle 1 Visit 1	Day 1 Cycle 2 Visit 2	Day 1 Cycle 3 Visit 3	Day 5 Cycle 3 Final visit Visit 4
	Visit 0 can be alternatively included into Visit 1				
ENROLMENT					
Eligibility screen (risk score patients' pre- selection)	x				
Informed consent	x				
Inclusion/exclusion criteria	x				
Baseline form	x				
Final patients' selection	x				
Pregnancy test	x	x	x	x	
INTERVENTION					
Randomization	x				
Intervention A group	x		x	x	
Intervention B group	x		x	x	
ASSESSMENT					
Cycle 1 form		x			
Cycle 1 Patient´s diary, MAT and FLIE forms given to patient		x			
Cycle 1 Patient´s diary, MAT and FLIE collection and eCRF form completion			x		
Cycle 2 form			x		
Cycle 2 Patient´s diary, MAT and FLIE forms given to patient			x		
Cycle 2 Patient´s diary, MAT and FLIE collection and eCRF form completion				x	
Cycle 3 form				x	
Cycle 3 Patient´s diary, MAT and FLIE forms given to patient				x	
Cycle 3 Patient´s diary, MAT and FLIE collection and eCRF form completion					X

Appendix 2 PATIENT´S DIARY (English Master Version)

MyRisk

PATIENT´S DIARY

Patient ID (generated by MyRisk database system):

…….

Study chemotherapy cycle no: **1** **2** **3**

(please circle the number of study cycle)

Date of chemotherapy

Day/Month/Year: (DD/MM/YYYY)	Day of the Week:

PLEASE RETURN THE DIARY AT YOUR NEXT VISIT

Dear Patient,

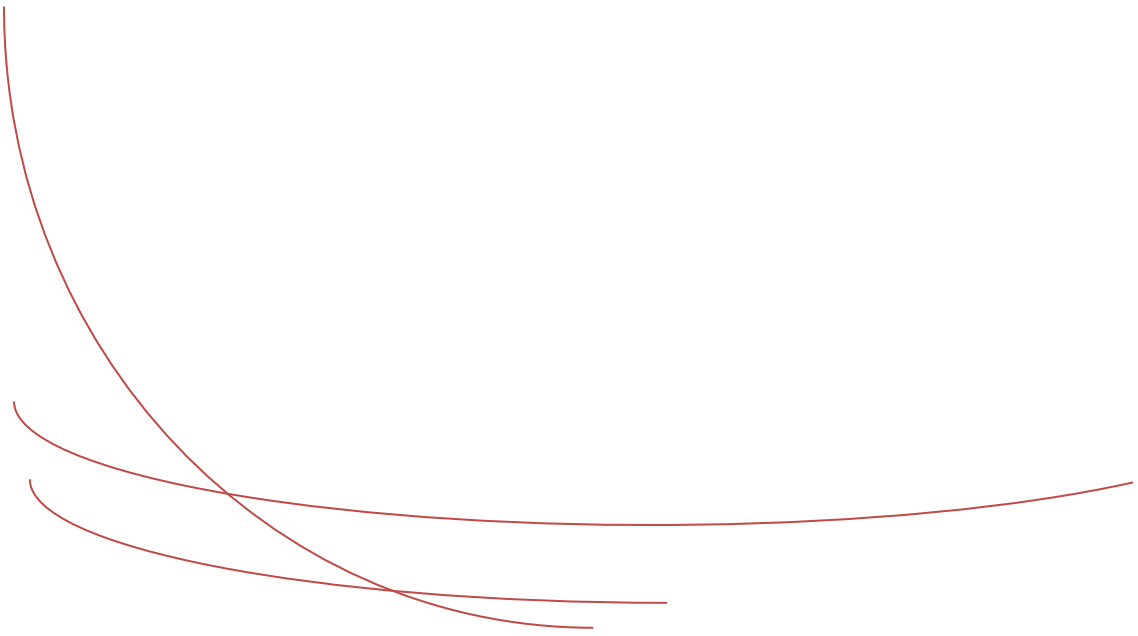
*This is a diary which we ask you to complete **daily** after each chemotherapy cycle during your participation in MyRisk study. The patient diary is used to quantify the medication for the treatment of nausea and/or vomiting you take, other concomitant medication you take during the treatment, adverse events and symptoms of any kind that you suffer from and to assess the effectiveness of the treatment in controlling nausea and/or vomiting.*

The diary will be collected during study visits and reviewed with you by your study doctor. If you have any questions regarding your diary please contact your study doctor.

The answers that you will provide will help us to understand the effectiveness of the treatment. This information will help us to improve treatment and support for patients like you. Please be ensured that there are no right or wrong answers.

All information you provide will be strictly confidential.

Thank you for your participation.



DAY 1
Nausea and Vomiting during the first 24 hours after chemotherapy
(this page refers to the first 24 hours after chemotherapy)

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

If you vomited in the 24 hours since chemotherapy, how many times did it happen?

(Write the number of times in this box)

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

How much nausea did you have in the last 24 hours?
If you had nausea, please circle or enter the number that most closely resembles your experience.

0	1	2	3	4	5	6	7	8	9	10

None **As much as possible**

(Write the number in this box)

I needed to use rescue medication against nausea and/or vomiting prescribed by my doctor.

Yes ☐ **No** ☐ (Select one)

If yes, please fill in the drug name(s): .....

How many pills of the drug have you taken? .....

Drug active ingredient:

mg/per day:

(to be filled by investigator)

I needed something else because of nausea and/or vomiting.

Yes ☐ **No** ☐ (Select one)

If yes, please describe what:

.....

Please re-write in English.

(to be filled by investigator)

I suffered from adverse event or symptoms of any kind in 24 hours after chemotherapy.

Yes ☐ **No** ☐ (Select one)

If yes, please describe any symptom you suffered from:

.....

.....

Please follow described AE and complete SAE/AE form in eCRF based on these data and patient's data you get at visit.

(to be followed by investigator)

DAY 2
Nausea and Vomiting during the 2nd day after chemotherapy
(this page refers to the second day after chemotherapy)

In the 2nd day after chemotherapy, did you have any vomiting? **Yes** ☐ **No** ☐ (Select one)

If you vomited in the 2nd day after chemotherapy, how many times did it happen?

(Write the number of times in this box)

In the 2nd day after chemotherapy, did you have any nausea? **Yes** ☐ **No** ☐ (Select one)

How much nausea did you have in the last 24 hours?
If you had nausea, please circle or enter the number that most closely resembles your experience.

0	1	2	3	4	5	6	7	8	9	10

None **As much as possible**

(Write the number in this box)

I needed to use rescue medication against nausea and/or vomiting prescribed by my doctor.

Yes ☐ **No** ☐ (Select one)

If yes, please fill in the drug name(s): .....

How many pills of the drug have you taken? .....

Drug active ingredient:

mg/per day:

(to be filled by investigator)

I needed something else because of nausea and/or vomiting.

Yes ☐ **No** ☐ (Select one)

If yes, please describe what:

.....

Please re-write in English.

(to be filled by investigator)

I suffered from adverse event or symptoms of any kind in the 2nd day after chemotherapy.

Yes ☐ **No** ☐ (Select one)

If yes, please describe any symptom you suffered from:

.....

.....

Please follow described AE and complete SAE/AE form in eCRF based on these data and patient's data you get at visit.

(to be followed by investigator)

DAY 3
Nausea and Vomiting during the 3rd day after chemotherapy
(this page refers to the third day after chemotherapy)

In the 3rd day after chemotherapy, did you have any vomiting? **Yes** ☐ **No** ☐
(Select one)

If you vomited in the 3rd day after chemotherapy, how many times did it happen?

(Write the number of times in this box)

In the 3rd day after chemotherapy, did you have any nausea? **Yes** ☐ **No** ☐
(Select one)

How much nausea did you have in the last 24 hours?
If you had nausea, please circle or enter the number that most closely resembles your experience.

0	1	2	3	4	5	6	7	8	9	10

None **As much as possible**

(Write the number in this box)

I needed to use rescue medication against nausea and/or vomiting prescribed by my doctor.

Yes ☐ **No** ☐ (Select one)

If yes, please fill in the drug name(s): .....

How many pills of the drug have you taken? .....

Drug active ingredient:

mg/per day:

(to be filled by investigator)

I needed something else because of nausea and/or vomiting.

Yes ☐ **No** ☐ (Select one)

If yes, please describe what:

.....

Please re-write in English.

(to be filled by investigator)

I suffered from adverse event or symptoms of any kind in the 3rd day after chemotherapy.

Yes ☐ **No** ☐ (Select one)

If yes, please describe any symptom you suffered from:

.....

.....

Please follow described AE and complete SAE/AE form in eCRF based on these data and patient's data you get at visit.

(to be followed by investigator)

DAY 4
Nausea and Vomiting during the 4th day after chemotherapy
(this page refers to the fourth day after chemotherapy)

In the 4th day after chemotherapy, did you have any vomiting? **Yes** ☐ **No** ☐
(Select one)

If you vomited in the 4th day after chemotherapy, how many times did it happen?

(Write the number of times in this box)

In the 4th day after chemotherapy, did you have any nausea? **Yes** ☐ **No** ☐
(Select one)

How much nausea did you have in the last 24 hours?
If you had nausea, please circle or enter the number that most closely resembles your experience.

0	1	2	3	4	5	6	7	8	9	10

None **As much as possible**

(Write the number in this box)

I needed to use rescue medication against nausea and/or vomiting prescribed by my doctor.

Yes ☐ **No** ☐ (Select one)

If yes, please fill in the drug name(s): .....

How many pills of the drug have you taken? .....

Drug active ingredient:

mg/per day:

(to be filled by investigator)

I needed something else because of nausea and/or vomiting.

Yes ☐ **No** ☐ (Select one)

If yes, please describe what:

.....

Please re-write in English.

(to be filled by investigator)

I suffered from adverse event or symptoms of any kind in the 4th day after chemotherapy.

Yes ☐ **No** ☐ (Select one)

If yes, please describe any symptom you suffered from:

.....

.....

Please follow described AE and complete SAE/AE form in eCRF based on these data and patient's data you get at visit.

(to be followed by investigator)

DAY 5
Nausea and Vomiting during the 5th day after chemotherapy
(this page refers to the fifth day after chemotherapy)

In the 5th day after chemotherapy, did you have any vomiting? **Yes** ☐ **No** ☐
(Select one)

If you vomited in the 5th day after chemotherapy, how many times did it happen?

(Write the number of times in this box)

In the 5th day after chemotherapy, did you have any nausea? **Yes** ☐ **No** ☐
(Select one)

How much nausea did you have in the last 24 hours?
If you had nausea, please circle or enter the number that most closely resembles your experience.

0	1	2	3	4	5	6	7	8	9	10

None **As much as possible**

(Write the number in this box)

I needed to use rescue medication against nausea and/or vomiting prescribed by my doctor.

Yes ☐ **No** ☐ (Select one)

If yes, please fill in the drug name(s): .....

How many pills of the drug have you taken? .....

Drug active ingredient:

mg/per day:

(to be filled by investigator)

I needed something else because of nausea and/or vomiting.

Yes ☐ **No** ☐ (Select one)

If yes, please describe what:

.....

Please re-write in English.

(to be filled by investigator)

I suffered from adverse event or symptoms of any kind in the 5th day after chemotherapy.

Yes ☐ **No** ☐ (Select one)

If yes, please describe any symptom you suffered from:

.....

.....

Please follow described AE and complete SAE/AE form in eCRF based on these data and patient's data you get at visit.

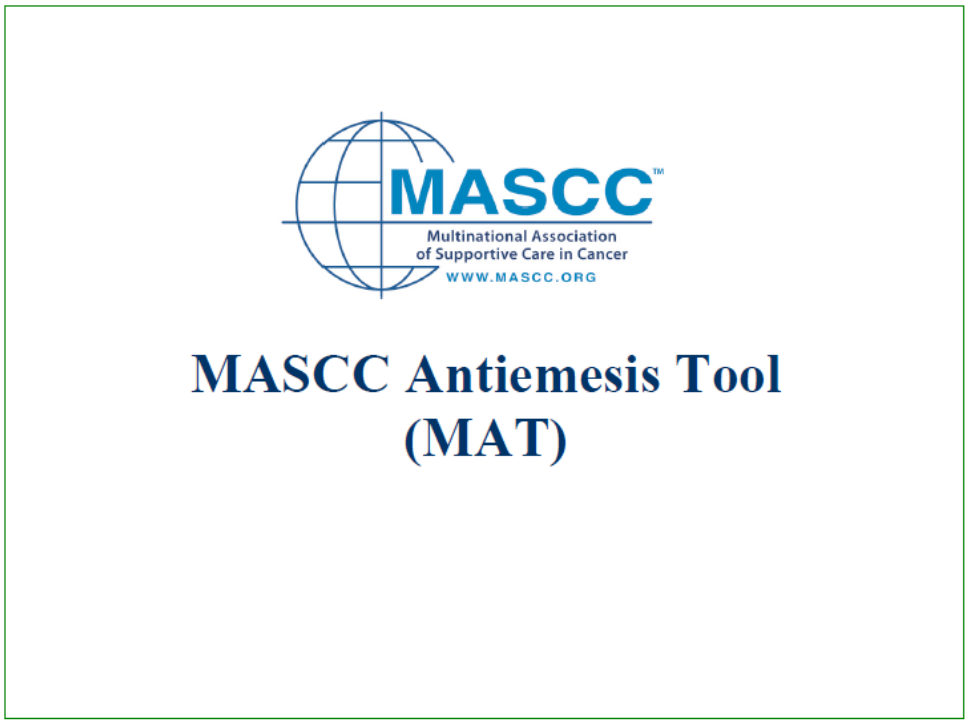
(to be followed by investigator)

I, THE UNDERSIGNED INVESTIGATOR, DECLARE THAT I HAVE CHECKED AND REVIEWED THE PRESENT DIARY FOR COMPLETENESS AND ACCURACY.

_____ _____

NAME OF INVESTIGATOR DATE AND SIGNATURE

Appendix 3 MASCC Antiemesis Tool (MAT) (English Version)



MASCC Antiemesis Tool: Instructions

Your Name:			
Date of chemotherapy (this cycle):	Day:	Month:	Day of the Week:
Your Oncology Nurse:		Phone:	
Your Oncology Physician:		Phone:	

Information about this brief form:

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

Here are the definitions used on this form:

Vomiting: The bringing up of stomach contents.

Nausea: The feeling that you might vomit.

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

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

How much difficulty did you have parking your car today?

(Write the number in this box)

0 1 2 3 4 5 6 7 8 9 10

None — As much as possible

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

 1

MASCC Antiemesis Tool

Please fill this out the day after chemotherapy on:

Day: Month: Day of the Week:

Nausea and Vomiting during the first 24 hours after chemotherapy:

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

1) In the 24 hours since chemotherapy, did you have any **vomiting?**	**Yes** ☐ **No** ☐ (Select one)
2) If you vomited in the 24 hours since chemotherapy, how many **times** did it happen?	(Write the number of times in this box) ☐
3) In the 24 hours since chemotherapy, did you have any **nausea?**	**Yes** ☐ **No** ☐ (Select one)
4) If you had nausea, please circle or enter the number that most closely resembles your experience. How much nausea did you have in the last 24 hours? **0 1 2 3 4 5 6 7 8 9 10** None — As much as possible	(Write the number of times in this box) ☐

 2

MASCC Antiemesis Tool

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

Please fill this out four days after chemotherapy on:

Day: Month: Day of the Week:

Delayed Nausea and Vomiting

5) Did you **vomit** 24 hours or more after chemotherapy?	**Yes** ☐ **No** ☐ (Select one)
6) If you vomited during this period, how many **times** did it happen?	(Write the number of times in this box) ☐
7) Did you have any **nausea** 24 hours or more after chemotherapy?	**Yes** ☐ **No** ☐ (Select one)
8) If you had nausea, please circle or enter the number that most closely resembles your experience. How much nausea did you have over this time period? **0 1 2 3 4 5 6 7 8 9 10** None — As much as possible	(Write the number of times in this box) ☐

 3

Appendix 4 FLIE questionnaire (English version)

Functional Living Index - Emesis
PATIENT INSTRUCTIONS

In the following questionnaire you are asked to rate how much 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.

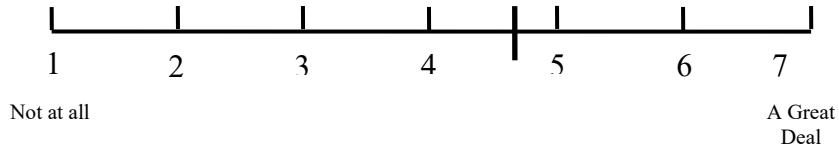
For each question, you will rate how much nausea (or vomiting) has affected an aspect of your quality of life during the past five days. Please focus on your experiences **over that time period**. We are interested in **your opinions**, not those of family members of friends. Your answers will remain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

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

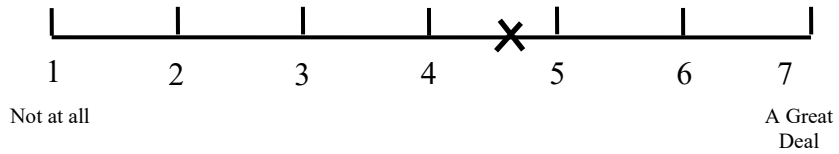
If you are unsure of your answer or do not understand the question, read the question again carefully and make a vertical mark (**|**) on the line based upon your best understanding of the question. If you want to change your answer, please do the following: make a new vertical mark (**|**); draw an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

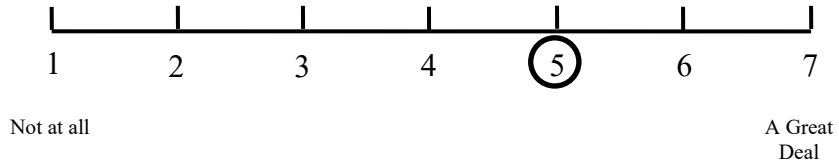
Correct: Vertical mark



Incorrect: Single "✕"

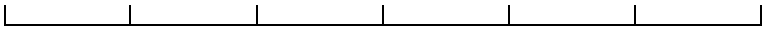


Incorrect: Circle number



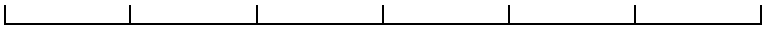
Functional Living Index Emesis

1. How much nausea have you had in the past 5 days?



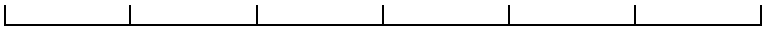
1 2 3 4 5 6 7
None A Great Deal

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



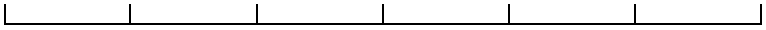
2 3 4 5 6 7
Not at all A Great Deal

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



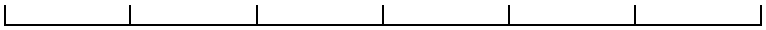
1 2 3 4 5 6 7
A Great Deal Not at all

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



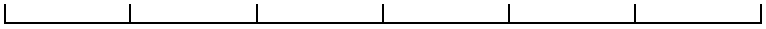
1 2 3 4 5 6 7
Not at all A Great Deal

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



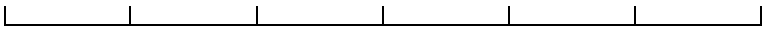
1 2 3 4 5 6 7
Not at all A Great Deal

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



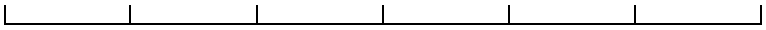
1 2 3 4 5 6 7
A Great Deal Not at all

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



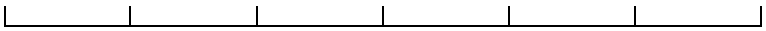
1 2 3 4 5 6 7
Not at all A Great Deal

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



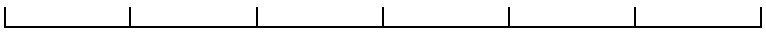
1 2 3 4 5 6 7
Not at all A Great Deal

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



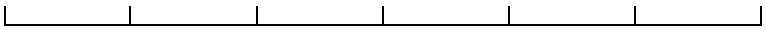
1 2 3 4 5 6 7
Not at all A Great Deal

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



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

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

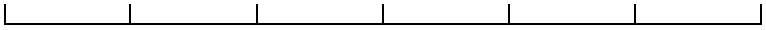


1 2 3 4 5 6 7
A Great Deal Not at all

12. Has vomiting affected your ability to make a meal or do minor household repairs during the past 5 days?

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

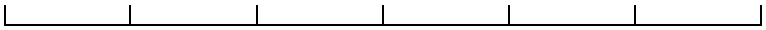
13. How much has vomiting affected your ability to enjoy a meal in the past 5 days?



1 2 3 4 5 6 7

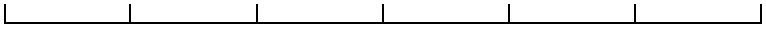
Not at all A Great Deal

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



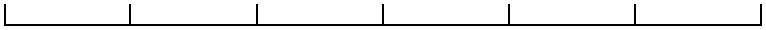
1 2 3 4 5 6 7
Not at all A Great Deal

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



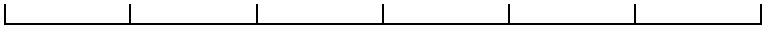
1 2 3 4 5 6 7
A Great Deal Not at all

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



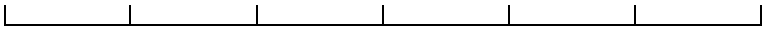
1 2 3 4 5 6 7
Not at all A Great Deal

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 5 Emetogenic potential of single antineoplastic agents

	IV chemotherapy		Oral chemotherapy[a]
High	Anthracycline/cyclophosphamide combination[b] Carmustine Cisplatin Cyclophosphamide ≥1500 mg/m^2 Dacarbazine Mechlorethamine Streptozocin		Hexamethylmelamine Procarbazine
Moderate	Alemtuzumab Azacitidine Bendamustine Carboplatin Clofarabine Cyclophosphamide <1500 mg/m^2 Cytarabine >1000 mg/m^2 Daunorubicin Doxorubicin	Epirubicin Idarubicin Ifosfamide Irinotecan Oxaliplatin Romidepsin Temozolomide[c] Thiotepa[d] Trabectedin	Bosutinib Ceritinib Crizotinib Cyclophosphamide Imatinib Temozolomide Vinorelbine
Low	Aflibercept Belinostat Blinatumomab Bortezomib Brentuximab Cabazitaxel Carfilzomib Catumaxumab Cetuximab Cytarabine ≤1000 mg/m^2 Docetaxel Eribulin Etoposide 5-Fluorouracil Gemcitabine	Ipilimumab Ixabepilone Methotrexate Mitomycin Mitoxantrone Nab-paclitaxel Paclitaxel Panitumumab Pemetrexed Pegylated liposomal doxorubicin Pertuzumab Temsirolimus Topotecan Trastuzumab-emtansine Vinflunine	Afatinib Axatinib Capecitabine Dabrafenib Dasatinib Everolimus Etoposide Fludarabine Ibrutinib Idelalisib Lapatinib Lenalidomide Olaparib Nilotinib Pazopanib Ponatinib Regorafenib Sunitinib Tegafur uracil Thalidomide Vandetanib Vorinostat
Minimal	Bevacizumab Bleomycin Busulfan 2-Chlorodeoxyadenosine Cladribine Fludarabine Nivolumab Ofatumumab	Pembrolizumab Pixantrone Pralatrexate Rituximab Trastuzumab Vinblastine Vincristine Vinorelbine	Chlorambucil Erlotinib Gefitinib Hydroxyurea Melphalan Methotrexate l-phenylalanine mustard Pomalidomide Ruxolitinib Sorafenib 6-Thioguanine Vemurafenib Vismodegib

[a]Classified emetic potential of oral agents based upon a full course of therapy and not a single dose.
[b]The combination of an anthracycline and cyclophosphamide in patients with breast cancer should be considered highly emetogenic.
[c]No direct evidence found for temozolomide i.v.; as all sources indicate a similar safety profile to the oral formulation, the classification was based on oral temozolomide.
[d]Classification refers to individual evidence from paediatric trials.

Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy-and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Annals of Oncology. 2016;27(suppl_5):v119-v133.

Appendix 6 CLADE-IS – Data Management System description

The data management system **CLADE-IS** is used for this study. Its basic characteristics:
Authorized access:

- Robust system of access control: authentized/authorized users only (login, password).
- Centralized user account management (Helpdesk IBA).
- Multilevel authorization procedure (DAM).
- Automatic log-off after a predefined period of user´s inactivity.

Encryption:

- Encrypted communication between the user and the central database (HTTPS protocol, SSL – Secure Socket Layer encryption).

Data consistency, data security – backup procedures:

- Data are validated on client and server side.
- There are also additional validations — any detected problems are reported (queries).
- Each server is automatically backed up before any changes to the system are carried out (every night).
- Procedures and safeguards are enforced to ensure that backup data cannot be accidentally overwritten.
- Latest copies of data from servers are always available in case of an adverse event to ensure a quick resumption of the service.
- Database contains data auditing — every change is saved to another schema.

Physical security:

- Servers run in IBA own data center with restricted access (with chip cards).
- Servers are protected using security system connected to security desk & non-stop camera monitoring.
- Servers are backed up by UPS with SMS warnings.
- Each server has dedicated firewall and is behind central university network traffic monitoring.
- Servers have dedicated subnet.
- Detector of fire.
- Temperature detector.
- Movement detector.
- We have two independent distant server rooms interconnected by 100Mbps.

Additional web protections:

- System is protected against SQL injection.
- System contains Cross-site scripting protection.

All data entered into CLADE-IS passes through several steps of validation.

All checks are programmed and validated into the system. This process is performed simultaneously with the creation of the database. In the first step, the structure of the eCRF is created together with format checks. There are two options how to implement coherence checks into the database:
In case Data Validation Plan is approved before creation of database, coherence checks are implemented together with creation of database and format checks.
If Data Validation Plan is not approved yet, it is possible to firstly create only database and consequently program coherence checks once database structure is approved.

Appendix 7 Serious Adverse Event Report Form (AE)

Report information

- Report type
  - Initial
  - Follow-up
- Date of form creation
- Date of last form modification
- Country
- Investigator's name

Patient information

- Site
- Patient ID
- Date of birth
- Gender
  - Male
  - Female
- Weight [kg]
- Height [cm]

AE information

- AE description (diagnosis or main symptoms)
- Start date and time
- Stop date and time
- Ongoing
  - Yes
  - No
- Serious Adverse Event?
  - Yes
  - No
- If YES, SAE criteria
  - Fatal
  - Life Threatening
  - Required or Prolonged Hospitalization
  - Persistent or significant Disability or Incapacity
  - Congenital Anomaly/Birth defect
  - Other Important Med Event
- Severity (CTCAE v.5.0)
  - Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
  - Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate Instrumental Activities of Daily Living (ADL)
  - Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or indicated; disabling; limiting self-care ADL
  - Grade 4 Life- threatening consequences; urgent intervention indicated
  - Grade 5 Death related to AE
- Outcome
  - Recovered

- Recovering
- Recovered with Sequelae
- Not recovered/Ongoing
- Fatal
- Unknown

- Relation to Study Medication
  - Related
  - Not related

Additional AE/SAE information

- Was the AE/SAE associated with a Trial Procedure?
  - Yes
  - No
- Was the AE/SAE associated with Chemotherapy?
  - Yes
  - No
  - Not applicable (if not receiving chemo)
  - Unknown
- Was SAE associated with other causes?
  - Yes
  - No
- If YES, specify the cause
  - Concomitant disease
  - Concomitant medication
- Other
  - If OTHER, specify

If patient hospitalized, please provide following:

- the admission date
- the discharge date
- still hospitalized?
  - Yes
  - No

If fatal, provide the following:

- Date of Death
- Cause of Death
- Autopsy done
  - Yes
  - No

Study Medication

- Name of the actual drug administered
  - Akynzeo + Dexamethasone 8 mg
  - Granisetron, 2 mg (oral) or 1 mg (IV) + Dexamethasone 8 mg
  - Palonosetron, 0.5 mg (oral) or 0.25 mg (IV) + Dexamethasone 8 mg
  - Ondansetron, 16 mg (oral) or 8 mg (IV) + Dexamethasone 8 mg
  - Dolasetron 100 mg (oral) + Dexamethasone 8 mg
  - Tropisetron 5 mg (oral or IV) + Dexamethasone 8 mg
- Administration start date and time

- Last dose prior to AE/SAE – date and time
- Study Medication Action Taken
    - No Action Taken
    - Interrupted
    - Withdrawn
- If interrupted, date when interruption started
- If interrupted, date when interruption ended
- If withdrawn, date of last dose
- Did the event improve or disappear after stopping study drug?
    - Yes
    - No
    - Not applicable
- Did the event reappear or worsen after restarting study medication?
    - Yes
    - No
    - Not applicable

Concomitant Medications

(Only provide details of those medications the patient was taking during the study period prior to the event. Chemotherapy regimen should be included in this section, if applicable. Do not include medications used to treat the reported SAE)

- Medication (brand name or generic name)
- Indication (Indicate treatment diagnosis (please note this diagnosis for treatment should match the patient's history)
- Unit Dose (report single dose administration (e.g.500)
- Unit (give unit)
- Frequency
    - S=SINGLE
    - QD = once per DAY
    - BID =TWICE PER DAY
    - TID=3 TIMES PER DAY
- Route
    - IV=INTRAVENOUS
    - PO=ORAL
    - IM=INTRAMUSCULAR
    - RECTAL=RECTAL
    - INH=INHALATION
    - TOPIC=TOPICAL
    - NAS=NASAL
    - SC=SUBCUTANEOUS
- Start date
- Stop date
- Ongoing
    - Yes
    - No
- Co-suspect drug information?
    - Yes
    - No

Management of AE/SAE

- Specific treatment of the AE/SAE?
    - None
    - Non- drug Treatment
    - Drug Treatment
- If non-drug treatment, specify

If drug treatment

- Medication (brand name or generic name)
- Indication
- Start date
- Stop date
- Ongoing
    - Yes
    - No

<u>Medical history/Risk factor(s) relevant to the event</u>

- Relevant medical history
    - Yes
    - No

If YES

- Disease
- Onset date
- Stop date
- Ongoing
    - Yes
    - No
    - Unknown

<u>Clinical description of event</u>

<u>Diagnostic tests</u>

- Diagnostic tests performed
    - No
    - Yes

If YES

- Test performed
- Date
- Findings/Results (Units)
- Normal Range (Units)

Appendix 8 Pregnancy Form

Report information

- Date of form creation
- Date of last form modification
- Country
- Investigator's name

Patient information

- Site
- Patient ID
- Date of Birth
- Start date of last menses
- Date pregnancy confirmed
- Number of fetuses
- Estimated date of delivery

Drug exposure during pregnancy

- Study Medication start date and time
- Study Medication stop date and time
- Concomitant Medication drug (generic name)
- Concomitant Medication indication
- Concomitant Medication start date
- Concomitant Medication stop date
- Concomitant Medication ongoing
    - No
    - Yes

Pregnancy Outcome

- Outcome
    - Not known at this date
    - Induced abortion
    - Stillbirth
    - Neonatal death
    - Uneventful (normal/healthy baby)
    - Miscarriage/ Late
    - Birth defects
    - Ectopic pregnancy
    - Spontaneous abortion
- If induced abortion, date of termination planned or undertaken
- If induced abortion, reason for termination
- If neonatal death, cause of neonatal death
- If late, number of weeks late
- If birth defects, specify
- Patient consented for pregnancy monitoring?
    - Yes
    - No